DECLARATION OF AUTHORSHIP

This thesis has been my own work. Material presented While part of Chapter 2 has its origins in material submitted for the M.Sc. (Epidemiology), the sections have been substantially developed and expanded. Nine Towns Study of Blood Pressure in Children I was responsible for the design and funding of the study (including the supplementary methodological studies), the recruitment of schools and the organization of fieldwork, including the supervision of the field study nurses. While I received computing support with the analysis, which was carried out using SAS on the University of London Amdahl Computer, I was directly responsible for specifying the precise details of all analyses conducted, and for their interpretation.

Peter H. Whincup

A STUDY OF BLOOD PRESSURE IN CHILDREN IN NINE BRITISH TOWNS

THESIS

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ABSTRACT

The age at which differences in blood pressure between populations emerge may have important implications for the primary prevention of high blood pressure. This thesis describes a study of blood pressure in childhood, conducted in nine British towns in 4056 children aged between 5.00 and 7.50 years to determine whether the pattern of geographic differences previously described in middle-aged men was also present in childhood. Standardization of blood pressure measurement was facilitated by the use of an automated oscillometric blood pressure recorder, the Dinamap 1846SX. Cuff bladder size had a marked effect on blood pressure measurement and was taken into account in the analyses.

Significant differences between the mean systolic and diastolic blood pressures of children in the different towns were observed. The pattern of town mean blood pressures was related both to the blood pressure pattern in adults in the same towns and to standardized mortality ratios for adult cardiovascular disease. However, these findings were strongly dependent on the observations in Guildford, a town with exceptionally low average blood pressure levels both in children and in adults.

Blood pressure levels were strongly related to age, weight and height but not to social factors. Birth weight was inversely related to blood pressure at 5-7 years but only when standardized for current body build. Maternal age, birth order and a parental history of hypertension were all strongly related to blood pressure; average blood pressures were higher in subjects with higher maternal age, in firstborn children and in those with a parental history of high blood pressure. These effects were largely independent of one another and of age and social class.

The results suggest that geographic differences in blood pressure in British men may have their origins in the first years of life. The relationship between birthweight and blood pressure in childhood may reflect the influence of either intrauterine or factors or, more likely, weight gain in infancy. New studies to investigate these findings further are outlined.

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Chapter 1

There are striking variations in the average blood pressure levels of different populations in middle age. Studying the emergence of these variations may contribute to an understanding of aetiological factors and the optimal timing of preventive measures. The Nine Towns Study of Blood Pressure in Children set out to examine whether variations in the average blood pressure levels of middle-aged men in different towns observed in the British Regional Heart Study were established by 5-7 years of age. The study also provided an opportunity to explore the individual determinants of blood pressure of children in this age-group, both current factors (for example age, height and weight) and those factors which might denote influences acting early in life (for example birthweight).

Chapter 2

This review provides the background to the geographic and individual hypotheses explored in the later chapters of the Thesis. First, the evidence of earlier studies on the age at which geographic differences in population blood pressures emerge is examined. While geographic patterns are likely to be present at the end of the second decade, some evidence suggests that they may already be present in the first decade. Second, the determinants of blood pressure during the first decade of life are reviewed. The concluding section describes the development of the study hypothesis and summarizes the potential confounding factors taken into account in the Nine Towns Study of Blood Pressure in Children.

Chapter 3

This chapter describes the aims, objectives and the methodology of the Nine Towns Study of Blood Pressure in Children. Selection of the study population and the measurement procedures used are described in detail.

Chapter 4

In this chapter the factors related to blood pressure levels in individuals are examined. Strong relationships between age, body build and blood pressure are described. Pulse rate and a parental history of hypertension are also related to blood pressure in childhood, while social factors show little or no association. Circumstances of measurement, particularly anxiety in the subject and the presence of a parent, are also related to blood pressure level. In the final section, the methods of standardization employed in subsequent analyses, particularly for age and body build, are described.

Chapter 5

This chapter describes the geographic aspects of the study results. Evidence for the presence of significant between-town differences in childhood blood pressure levels, and for relationships between town mean childhood blood pressure levels and adult blood pressure levels and adult cardiovascular mortality rates, is presented. The validity of the results are examined critically, taking account of the potential contributions of bias and confounding factors.

Chapter 6

In this chapter the relationships between factors which may be indicators of early life influences and blood pressure in childhood are examined. These factors include birthweight, birth order, maternal age and infant feeding pattern. The influence of a parental history of hypertension is also taken into account. Birthweight is inversely related to blood pressure once the effects of current body build are taken into account. Birth order, maternal age and parental history of hypertension are all independently related to blood pressure while infant feeding pattern shows no relationship. The significance of these relationships is discussed and possible mechanisms outlined.

Chapter 7

In this chapter the main implications of the study findings, both for public health and for further research, are drawn. Particular emphasis is given to the observation that population differences in blood pressure may be present in the first decade of life and to the associations between body build, birthweight and blood pressure. The implications of each of these findings for the aetiology and prevention of high blood pressure is discussed. Ways in which geographic variation in childhood blood pressure and the relationship between birthweight and blood pressure might be investigated further are discussed.

<u>Appendix I</u> discusses the rationale for the sampling and measurement procedures used in the study and presents data on the validity of the sampling method and on response rates. Methodological aspects of blood pressure measurement in the study, including the performance of the Dinamap blood pressure recorder and the influence of observer and cuff bladder size on measurement, are also examined.

CHAPTER 1

INTRODUCTION

1.0 SUMMARY

The primary prevention of high blood pressure, a major contributory cause of cardiovascular disease, is an important priority. Studying the emergence of patterns of blood pressure, particularly between populations, may contribute to an understanding both of the aetiological factors responsible and of the optimal timing for preventive measures. The Nine Towns Study of Blood Pressure in Children set out to address this question in a geographic context, by examining whether variations in the average blood pressure levels of middle-aged men in different towns observed in the British Regional Heart Study were established by 5-7 years of age. The study also provided an opportunity to explore the individual determinants of blood pressure at 5-7 years, including both current factors (for example age, height and weight) and factors which might denote influences acting early in life (for example birthweight).

1.1 THE IMPORTANCE OF HIGH BLOOD PRESSURE

Diseases of the circulatory system constitute the single most important cause of death in developed countries (World Health Organization, 1987). The majority of these deaths are attributed to two conditions, ischaemic heart disease and cerebrovascular disease. In England and Wales, circulatory disease currently accounts for almost half of all deaths, of which almost 60% are attributed to ischaemic heart disease and some 25% to stroke (Table 1.1). While the majority of deaths from these conditions occur in the elderly, an appreciable number of deaths from both conditions occur much earlier in life (Table 1.2). Mortality rates for ischaemic heart disease in middle-age in the United Kingdom are among the highest in the world, while cerebrovascular mortality rates compare unfavourably with those of many other countries in the developed world (Figure 1.1). Moreover, while mortality rates for cerebrovascular disease have been falling in Britain for many years (Editorial, 1983; Royal College of Physicians, 1989), mortality rates for ischaemic heart disease in the United Kingdom have shown relatively little decline, in contrast to the striking falls observed in the United States and some other countries (World Health Organization, 1987).

High blood pressure (hypertension) is an important risk factor for both ischaemic heart disease and cerebrovascular disease, as well as being responsible for a smaller number of deaths attributed directly to high blood pressure (Table 1.1). In the case of cerebrovascular disease, high blood pressure is the most important single risk factor (Royal College of Physicians, 1989). In the case of ischaemic heart disease, high blood pressure is one of a group of major risk factors which also include diet, serum total cholesterol and cigarette smoking (Joint Working Party of the Royal College of Physicians and the British Cardiac Society, 1976). Although forms of secondary hypertension are well recognized these are uncommon and primary, essential, hypertension is responsible for the greater part of the problem of high blood pressure, both in Great Britain and worldwide (Rose G, 1985b). There is therefore a strong case for measures to prevent high blood pressure and its complications, either by removing its source, or by preventing its consequences. Possible approaches to prevention are considered in the following section.

1.2 <u>STRATEGIES FOR THE PREVENTION OF HIGH BLOOD PRESSURE AND ITS COMPLICATIONS</u>

1.2.1 PRIMARY AND SECONDARY PREVENTION

Within the framework of current terminology (Barker DJP and Rose G, 1984), two approaches to the prevention of the consequences of high blood pressure could be advocated. <u>Primary prevention</u> is concerned with the prevention of exposure to the factors responsible for the development of high blood pressure. <u>Secondary prevention</u> is concerned with the use of measures to prevent the progression or development of complications once high blood pressure has developed. In practice, this would imply the reduction of elevated blood pressure levels, either by non-pharmacological means (for example by reduction in weight or alcohol intake), or by the use of antihypertensive drugs. The distinction between primary prevention and non-pharmacological forms of secondary prevention is often difficult, because the point at which high blood pressure begins may be hard to define.

Consistent evidence has suggested that the risk of stroke can be markedly reduced by treatment with antihypertensive drugs (Veterans Administration Cooperative Study Group on Antihypertensive Agents, 1967 and 1970; Reader R et al, 1980; IPPPSH Collaborative Group, 1985; Medical Research Council Working Party, 1985). Secondary prevention by antihypertensive drugs has therefore become a prominent, probably the most prominent, strategy for prevention of the complications of high blood pressure. However, used alone, the effectiveness of this strategy may be limited, for three main reasons. First, the benefits of antihypertensive drug treatment have not been demonstrated in all subjects whose blood pressure puts them at risk of cardiovascular disease. Second, the reversal of risk resulting from drug treatment of high blood pressure appears to be limited. Third, the widespread use of antihypertensive drug treatment may be undesirable in its own right. Each of these limitations is considered in detail below.

1.2.1.1 Benefits of antihypertensive treatment: relation to the population at risk

While the benefits associated with treatment of more severe levels of hypertension (a sustained diastolic blood pressure of 110 mmHg or more) are considerable (Veterans Administration Cooperative Study Group on Antihypertensive Agents, 1967), those associated with treatment for mild to moderate hypertension (sustained diastolic blood pressure of 90 to 109 mmHg) are small (Medical Research Council Working Party, 1985). The limited benefits of drug therapy in milder cases are reflected in current treatment recommendations, which advise that diastolic blood pressure levels of less than 100 mmHg should not normally be managed with antihypertensive drug treatment (Amery A et al, 1986; British Hypertension Society working party, 1989). However, the cardiovascular risk associated with high blood pressure develops continuously from low levels and is already marked by a diastolic pressure level of 90 mmHg, a level well below that at which conclusive benefits of drug treatment can be demonstrated. Moreover, the number of people with blood pressure levels below the drug treatment threshold, but at increased risk of cardiovascular events due to their blood pressure, is substantial. It has been calculated from data in the Whitehall Study that, of deaths attributable to hypertension, half of those caused by ischaemic heart disease and a quarter of those from stroke occur in subjects with diastolic blood pressures below 100 mmHg (Rose G, 1981). Similar calculations for the British Regional Heart Study suggest that the proportion of all cardiovascular events occurring at blood pressure levels below the treatment threshold may be even higher (60% for ischaemic heart disease and 50% for stroke). Moreover, these figures (based on epidemiological studies in which blood pressures were measured on a single occasion) may underestimate the proportion of cases occurring below the drug treatment threshold in clinical practice, where repeated readings form the basis for diagnosis and drug treatment (British Hypertension Society working party, 1989).

1.2.1.2 Reversal of risk with antihypertensive drug treatment

A recent analysis has compared the reduction in stroke and ischaemic heart disease observed in the 14 published randomized placebo controlled trials of antihypertensive drug therapy (Collins R et al, 1990) with those expected from the findings of observational epidemiological studies (MacMahon SW et al, 1990). The results suggested that the treatment of hypertension may reverse the epidemiologically expected risk of stroke almost completely within five years of starting treatment. However, while the risk of ischaemic heart disease appeared to be reduced by antihypertensive treatment, the reduction extended to only just over half the epidemiologically expected risk. Although the confidence limits on this estimate are wide, the findings nonetheless suggest that the effectiveness of antihypertensive drug treatment in the reversal of risk of ischaemic heart disease is limited. This limitation is an important one, because (as illustrated in Figure 1.2, using data from the British Regional Heart Study) ischaemic heart disease accounts for a much greater proportion of the cardiovascular events associated with high blood pressure than does stroke. A limitation of 50% in the reversal of risk of ischaemic heart disease associated with high blood pressure therefore constitutes an important limitation on the effectiveness of drug treatment in the overall reduction of cardiovascular risk.

1.2.1.3 Side-effects and risks of antihypertensive drug treatment

The widespread use of antihypertensive drug treatment may be undesirable in its own right. Apart from considerations of cost, drug treatment carries risk of side-effects, some of which may be distressing or disabling (Medical Research Council Working Party, 1981). Moreover, recent studies have suggested that low blood pressure levels on antihypertensive drug treatment may be associated with an increased risk of myocardial infarction (Cruickshank JM et al, 1987). In addition, the processes of being identified and labelled as a hypertensive individual may carry important psychological consequences, including loss of self esteem, depression and anxiety about health (MacDonald LA et al, 1984).

1.2.2 PRIMARY PREVENTION OF HIGH BLOOD PRESSURE

The limitations of a drug treatment strategy for the control of high blood pressure emphasize the need for an alternative strategy for the prevention of high blood pressure and its consequences. The application of primary prevention, particularly in the context of the whole population, offers particular advantages; it is radical, safe and of considerable potential benefit to the population as a whole, although not to the individual (Rose G, 1985a). However, effective primary prevention requires a clear understanding of the cause or causes of the condition to be prevented. Although high blood pressure has been widely studied and many potential causal factors have been proposed, considerable uncertainty still exists about the aetiology of the condition. However, before aetiological questions about high blood pressure can be addressed, it is important to consider exactly what is meant by the term 'high blood pressure'.

1.3 DEFINING THE PROBLEM OF HIGH BLOOD PRESSURE

1.3.1 HIGH BLOOD PRESSURE AND THE INDIVIDUAL

The observation that the variation of blood pressure within a population follows a continuous, unimodal, distribution (Hamilton M et al, 1953) took several years to be accepted (Pickering G, 1968) but was of profound importance for the understanding of high blood pressure. The implication of this observation is that there is no clear-cut division between a normal blood pressure and a high blood pressure and that the distinction must be made on quantitative, rather than qualitative, grounds. Barker and Rose (Barker DJP and Rose G, 1984) identified four possible diagnostic criteria which could be used to distinguish subjects with high blood pressure from those with normal blood pressure. These criteria included (i) statistical (for example, a value more than two standard deviations above the mean, or above the 95th percentile of the distribution), (ii) clinical (i.e. the presence of symptoms or signs of clinical disease), (iii) prognostic (i.e. a measurable effect on outcome) and (iv) operational (i.e. a level at which clinical action is likely to be beneficial). In clinical practice, operational criteria are the most helpful because they relate closely to the principal dilemma which the clinician faces, whether or not to introduce measures to reduce the blood pressure. Current operational definitions of high blood pressure in adults have been well summarized in a recent report (British Hypertension Society working party, 1989).

While operational definitions are valuable in defining the hypertensive individual requiring treatment <u>within</u> a population, they have important limitations in defining the problem of high blood pressure as a whole. They do not take into account the observation that some blood pressure levels below the operational threshold for treatment are associated with an increased risk of cardiovascular disease (see section 1.2.1.1). Moreover, none of the definitions described here takes into account the marked variation in average blood pressure (and in the prevalence of operationally defined high blood pressure) described between different population groups, particularly on a geographic basis. This subject is considered in more detail in the next section.

1.3.2 HIGH BLOOD PRESSURE AND THE POPULATION

In Western societies it has long been observed that blood pressure rises with age in adult life (Figure 1.3). The levels of blood pressure reached in middle-age are sufficiently high to be associated with increased cardiovascular risk in an appreciable proportion of the population of such societies (Rose G, 1981). However, high average levels of blood pressure in middle-age and a rise in blood pressure with age during adult life are not inevitable. In particular, several populations have been identified in which average blood pressure levels are low and blood pressure rises little if at all during adult life

(Figure 1.3). This observation has been confirmed in studies examining complete population groups (Maddocks I, 1961), suggesting that the observation is not an artefact of sample selection. Moreover, strong support for the validity of the finding has been provided by the observation that the blood pressure levels of subjects from these 'low blood pressure populations' tend to rise markedly on migration (Shaper AG et al, 1969; Poulter N et al, 1985). Such populations tend to have low rates of cardiovascular disease and have certain physical characteristics in common (Shaper AG, 1974). These include lean body build (with correspondingly low levels of obesity), high levels of physical activity, low blood cholesterol levels and low salt intake intakes. In addition, the social structure of these communities differs markedly from those of Westernized societies (Henry JP and Cassel JC, 1969).

The average blood pressure levels of different populations in middle-age (like those of individuals within a population) appear to follow a continuous, rather than a bimodal, distribution (Intersalt Cooperative Research Group, 1988; Figures 2.1 and 2.2). The absence of a clear-cut distinction between those populations which have relatively high and relatively low mean blood pressures emphasizes that quantifying differences between populations, rather than defining abnormality, is likely to provide the most constructive approach to examining these differences.

1.3.3 AETIOLOGICAL DIMENSIONS OF HIGH BLOOD PRESSURE

Each of the two types of variation in blood pressure described above, within-population and between-population, raises a distinct aetiological question (Figure 1.4). Variation within a population poses the question of why some individuals have relatively high blood pressure levels while others have relatively low levels. Variation between populations poses the question of what determines the average blood pressure level of the population (Rose G, 1985a). Both of these dimensions are fundamental to the study of the causes of high blood pressure, although the contribution of different aetiological components, particularly the relative importance of genetic and environmental factors, is likely to differ between the two settings.

The determinants of blood pressure level <u>within</u> a population are likely to include an important genetic component. The strongest evidence for this view has come from twin studies showing that monozygotic twins have less within-pair variance than dizygotic twins (Feinlieb M et al, 1975) and from adoptive studies showing significant parent-natural child correlations, but negligible parent-adoptee correlations (Biron P and Mongeau JG, 1978). However, the precise magnitude of the genetic component has been the subject of debate. While some investigators have estimated from twin studies in adolescents and adults that the proportion of variance in blood pressures explained by genetic factors may be as high as 60% (McIlhaney ML et al, 1975; Feinlieb M et al, 1975), Annest and his colleagues, in a study of familial blood pressure patterns in adopted and natural children, suggested that more conservative estimates of approximately 30% might be appropriate (Annest JL et al, 1979a and b).

In contrast, the determinants of blood pressure level <u>between</u> populations are likely to be predominantly environmental. The strongest evidence for this conclusion is provided by the results of studies of migration between populations with different mean blood pressure levels. In particular, the blood pressure levels of subjects from populations with low mean blood pressure levels (usually unacculturated, rural populations) tend to be higher after migration into the army (Shaper AG et al, 1969) or into an urban, Westernized setting (Joseph JG et al, 1983; Poulter NR et al, 1985). Such changes do not appear to be the result of selection effects (Joseph JG et al, 1983). Other studies have demonstrated that the extent to which migrants adopt the blood pressure pattern of their new community is related to the degree of acculturation (Scotch NA, 1963; Maddocks I, 1967; Prior IAM et al, 1968).

In order to clarify the nature of high blood pressure, an understanding is needed both of the variation in blood pressure within a population group and of the variation in blood pressure between population groups. However, in order to study the <u>environmental</u> factors involved in the development of high blood pressure, between-population differences in blood pressure are likely to be particularly important. The inclusion of populations with different mean blood pressure levels in studies of environmental factors is therefore likely to be particularly valuable.

1.4 THE ORIGINS OF HIGH BLOOD PRESSURE

The study of the origins of high blood pressure, aiming to determine the point at which the process begins, is likely to be complementary to the study of aetiological factors in developing an understanding of the problem of high blood pressure. Identification of the age at which the process starts to develop could help to identify likely aetiological factors, acting at a time when their effect might be reversible, and suggest the optimal time for the introduction of preventive strategies. In addition, identifying the origins of the process may help in understanding the pathogenesis of the condition. However, defining the point at which high blood pressure begins is not easy. While it would be possible to identify the point at which a particular blood pressure level is reached, either in an individual or in a specified proportion of a population group, an arbitrary procedure of this sort would throw little light on the problem. A more constructive approach would be to start with the blood pressure in middle-age, which is associated with cardiovascular risk both in individuals (Kannel WB and Higgins M, 1990) and in populations (Keys A, 1980). The beginnings of the process might then be defined as the point at which the pattern of blood pressure variation observed in middle-age first develops. While such a definition would ignore any latent period in the development of adult patterns, it would at least provide a starting point for further investigation. However, such a definition can be applied in each of the settings discussed above, within-population and between-population. Application of this definition is each of these contexts is described in the following sections.

1.4.1 DEVELOPMENT OF ADULT PATTERNS OF BLOOD PRESSURE WITHIN POPULATIONS

Several longitudinal studies of individuals within populations have studied the consistency of blood pressure rank in individual subjects within a population over time (a phenomenon known as 'tracking'). The results have suggested that the development of consistency of blood pressure rank in the individual probably begins in the first year of life, although the correlation coefficient indicating the extent of agreement in the rank of readings one year apart at that age is very small (0.1 or less) (Levine RS et al, 1978; de Swiet M et al, 1980a). The tracking coefficient for a one year interval rises from the first year to exceed 0.4 between 3 and 4 years (de Swiet M et al, 1980a). From there it continues to rise until the end of the second decade (Rosner B et al, 1977), at which point stable values of approximately 0.7 are established. The early establishment of blood pressure rank within a population would be consistent with the importance of the genetic component in this type of blood pressure variation (section 1.3.3). However, the consistency of blood pressure rank in childhood is too weak to permit confident identification in childhood of individuals who will develop high blood pressure in adult life (Hofman A et al, 1983b; de Swiet M, 1986).

1.4.2 DEVELOPMENT OF ADULT PATTERNS OF BLOOD PRESSURE BETWEEN POPULATIONS

The study of the development of adult blood pressure patterns between populations has received less critical attention than that within populations. While many authorities have concluded that differences in blood pressure between populations emerge in adult life (Peart WS, 1979) and that blood pressures are similar in childhood in all populations (Rose G, 1985b), it is difficult to find an adequate review of this question. Do the differences in blood pressure of different population groups already described in middle-age emerge in adult life, or are they apparent earlier, in adolescence or even in childhood? The distinction between these possibilities, which are illustrated in Figure 1.5, is important, because, as discussed above, between-population blood pressure differences are likely to include a strong environmental component. If differences between populations emerge in adult life, this implies that the factors responsible for differences in population blood pressure levels are either not present, or are not influencing blood pressure levels, before that point. If, on the other hand, population differences in blood pressure first appear not in adult life but in childhood, or even earlier, the implications are quite different. This would imply that the determinants of blood pressure differences between populations were acting <u>before</u> adult life and would suggest that the study of potential determinants of blood pressure levels in childhood might be particularly important. It would also imply that the timing of measures aiming for primary prevention of high blood pressure would need to begin in the early years of life. Finally, the early development of population differences would have important implications for the pathophysiological processes involved in the early phases of high blood pressure at the population level. Of particular interest in this context is the relationship between initial blood pressure and subsequent change in blood pressure, which appears to change with age (Hofman A, 1984). In adult life, initial blood pressure is strongly related to subsequent change in blood pressure, even after allowing for regression to the mean (Svardsudd K and Tibblin G, 1980; Wu M et al, 1980). However, in childhood an inverse association between initial blood pressure level and subsequent change has been demonstrated, which becomes weaker with increasing age (Hofman A and Valkenburg HA, 1983). It has been proposed (Hofman A, 1984) that this may represent a homeostatic mechanism restoring blood pressure to the mean of the distribution, which fails at a certain stage. The development of differences in population blood pressure in early childhood might indicate a failure of such mechanisms; studying the relationship between initial pressure and change in blood pressure in populations with differing blood pressure levels in childhood might be of considerable interest in this context.

1.5 OPPORTUNITIES FOR THE STUDY OF THE DEVELOPMENT OF BLOOD PRESSURE DIFFERENCES BETWEEN POPULATION GROUPS

In order to study the development of blood pressure differences between populations, it is necessary to compare the blood pressure patterns of progressively younger age-groups in populations with marked differences in average blood pressure in middle-age. The large differences in blood pressure observed between countries (Marmot MG, 1984; Intersalt Cooperative Research Group, 1988) have made international differences in blood pressure an obvious and important starting point for studies of between-population differences in blood pressure. Such studies provide most of the existing evidence on the patterns of differences in blood pressure between populations and on the aetiological factors which are responsible (Intersalt Cooperative Research Group, 1988). However, the use of international comparative studies as a tool for the investigation of the aetiology of blood pressure poses certain problems. The standardization of sampling methods and techniques of blood pressure measurement between populations may be difficult, although many of these difficulties may be overcome (Intersalt Cooperative Research Group, 1988). More difficult, however, are the marked cultural differences which exist between different countries and the possibility of confounding by confounding factors which may be difficult to recognize and to quantify (Marmot MG, 1984). For these reasons, the study of blood pressure variation between population groups <u>within</u> a single country may offer considerable advantages. Although differences in blood pressure within a single country are unlikely to be as large as those occurring between countries, standardization of population sampling and blood pressure measurement are likely to be easier to achieve. They also offer the advantage that the contribution of confounding factors may be less marked than in an international setting. Geographic variations in blood pressure <u>within</u> a single country would therefore provide particular opportunities to study the development of between-population differences in blood pressure and their aetiology.

1.5.1 GEOGRAPHIC VARIATION IN BLOOD PRESSURE LEVELS IN MIDDLE AGE WITHIN GREAT BRITAIN

The possibility of geographic variation in blood pressure levels within Great Britain is of particular interest because there are marked geographic variations in cardiovascular mortality (Office of Population, Censuses and Surveys, 1990a). Mortality rates from cardiovascular disease are lowest in the South East of England and rise progressively to the North and West, with the highest rates being found in the conurbations in Scotland, North-West and Northern England and in the South Wales valleys. The most comprehensive survey of adult blood pressure levels in Britain has been the British Regional Heart Study, which set out to examine the extent of cardiovascular disease and its determinants in middle-aged men in 24 British towns, selected to represent all major British regions and to include towns with a wide range of mortality, both from ischaemic heart disease (Figure 1.6) and from cerebrovascular disease. The findings of the British Regional Heart

Study, which are fundamental to the study described later in this thesis, are described in some detail below.

1.5.2 THE BRITISH REGIONAL HEART STUDY

1.5.2.1 Aims and methodology The British Regional Heart Study is a prospective study of cardiovascular disease in middle-aged British men in 24 British towns. One of its main aims has been to explain the reasons for the marked geographical variations in cardiovascular mortality in Britain. The study is based on 7735 men, aged 40-59 years at screening, drawn at random from the age-sex register of one representative General Practice in each of the study towns. Towns were selected on the basis of their size (population 50,000 to 100,000) and were chosen to ensure that the full range of cardiovascular mortality and all major British regions were represented. Wherever possible these were representative of their region both in socioeconomic terms and in their cardiovascular mortality rates. The General Practice selected in each town had a social class distribution which was closely representative of the men in that town, as indicated by Census data. Although subjects with severe mental and physical disability were excluded, no attempt was made to exclude subjects with cardiovascular disease or other specific illnesses. In each practice a sample of 450 men, stratified by 5-year age-group, was selected randomly from the practice list and invited to participate. An overall response rate of 78.2% was obtained.

On entry to the study all participants completed a questionnaire administered by one of three research nurses, who also carried out measurements of height, weight, respiratory function and blood pressure, recorded an electrocardiogram and took a blood sample. The nurses visited the study towns in succession between January 1978 and June 1980, with each nurse carrying out approximately one third of the measurements in each town. Blood pressure measurements All observers received repeated training and testing in blood pressure measurement using standard training tapes (Rose G, 1965; Bruce NG et al, 1988). All measurements were made with a single London School of Hygiene sphygmomanometer (Rose GA et al, 1964). Two consecutive measurements of blood pressure were made in the right arm with the subject seated after a period of rest. Daily outdoor temperature measurements were obtained for each town from the relevant local weather station. The study questionnaire provided information on subjects' longest held occupations for social class coding and also on current alcohol intakes.

1.5.2.2 Observations on blood pressure

Striking differences in the average blood pressures of middle-aged men in the different towns were observed. Age-adjusted town mean systolic pressures (Table 1.3) varied between 135.8 mm Hg in the lowest town (Shrewsbury) and 152.4 mm Hg in the highest (Dunfermline) - a range of 16.6 mm Hg. Marked variation in town mean diastolic pressures was also apparent, with a range of 12.5 mm Hg in diastolic pressure between 76.0 mm Hg in the lowest town (Lowestoft) and 88.5 mm Hg in the highest (Dunfermline). A strong correlation between town mean systolic and diastolic pressures was observed ($r = 0.78$; $p < 0.0001$). The differences in average blood pressure described were associated with differences in the prevalence of hypertension (Shaper AG et al, 1988).

1.5.2.3 Validity of blood pressure observations

The validity of these large and highly statistically significant differences in blood pressure between towns has been explored in some detail. The variation in blood pressure could not be explained by observer differences in measurement, nor by differences in ambient temperature between the towns. Since no prior hypothesis was specified to the observers, observer bias seems an unlikely explanation. The interspersal of high and low blood pressure towns in the order of examination made the explanation of systematic measurement drift improbable. Support for the validity of the findings included the observation that town mean blood pressure levels (both systolic and diastolic) were associated with the standardized mortality ratios for all cardiovascular diseases (Figure 1.7). A strong positive association was observed for mean systolic pressure ($r = 0.55$; $p < 0.01$) with a weaker, non-significant, association for diastolic pressure ($r = 0.30$).

Additional support for the validity of these observations has been provided by the results of a second survey of blood pressure, the Nine

Towns Study (Adults), carried out in 1986-7 in nine of the original 24 British Regional Heart Study towns - three with high, three with intermediate and three with low adult blood pressure levels (Bruce NG et al, 1990a). The same general practices were used in these towns to provide samples of men and on this occasion also women. A stratified random sample of subjects in two five-year age-bands (40-44 years and 55-59 years) was selected to permit direct comparison with the original 40-59 year age-group and in addition a sample of subjects aged 25-29 years was selected to provide data on a younger age-group. Two observers carried out all blood pressure measurements using a Dinamap 1846SX automated oscillometric blood pressure recorder to minimize measurement drift and observer bias in measurement. The response rates in the older two age-strata were similar to those in the British Regional Heart Study (76%). On this occasion the range of mean town blood pressure levels in men in these older two age-groups was less than in the British Regional Heart Study (9.0 mmHg systolic, 5.0 mmHg diastolic). However, the average systolic blood pressures (treatment-adjusted medians) were significantly correlated with those of the previous study ($r = 0.66$, $p = 0.05$). Moreover, strong correlations between town mean blood pressure and cardiovascular SMR were observed both for systolic pressure ($r = 0.81$) and for diastolic pressure ($r = 0.87$). Between-town differences in mean blood pressure were also observed in women, which were of a similar pattern to those observed in men and which also showed a positive relationship with standardized mortality ratios for cardiovascular disease. In the 25-29 year age-group (in which a much lower overall response rate of 55% was obtained), relationships between town mean blood pressures and cardiovascular mortality of similar magnitude and direction to those in the older groups were observed for both men and women.

1.5.2.4 Opportunities for study of the origin of population differences in blood pressure

The results of the British Regional Heart Study and of the Nine Towns Study (Adults) suggested that geographic variations in blood pressure were present within Great Britain, and that these differences were apparent in the third decade of life. A geographic study of blood pressure in childhood, the Nine Towns Study of Blood Pressure in

Children, was conceived, designed and conducted to determine whether the geographic blood pressure patterns described in adults were apparent in children 5-7 years of age. The rationale, design, conduct and results of this study are described in detail in this thesis.

1.6 AIMS AND STRUCTURE OF THE THESIS

The first aim of this thesis is to examine the age at which geographic differences in blood pressure between population groups emerge. This aim is addressed in two ways. First, a review of earlier relevant literature is conducted (section 2.2). This examines the question of whether there are differences in the average blood pressure of different populations before adult life, and whether the differences observed are related to those in middle-age. Second, the conception, design and results of a study examining geographic variation in blood pressure levels in childhood in Great Britain and comparing them with established patterns of variation in adults are described (chapters 3 and 6).

The second aim of the thesis is to examine the determinants of individual blood pressure levels in the first decade. This aim is addressed, first, by reviewing the findings of earlier studies on the major determinants of blood pressure level in childhood (chapter 2) and, second, by presenting the findings of the present study in the context of these earlier investigations. The determinants of blood pressure examined include 'current' determinants, for example age and weight, which are considered in chapter 4. In addition, the relationship between factors which may be markers of early life experience (for example, birthweight and birth order) and blood pressure in individuals are considered in chapter 6.

The design of the study posed several methodological problems, particularly in the development of appropriate sample selection and in blood pressure measurement. The ways in which these problems were addressed and the extent to which these solutions were successful are reviewed in Appendix I.

1.7 A NOTE ON THE DEFINITION OF HIGH BLOOD PRESSURE IN CHILDREN

Defining high blood pressure in childhood poses difficulties similar to those already referred to in adults. As in adults, blood pressure in childhood follows a continuous distribution, so that there is no clear divide between normality and abnormality. The principal justification for identifying individual children with high blood pressure is to enable treatable cases of secondary hypertension to be detected; such cases often have blood pressure levels which would be regarded as hypertensive in an adult (Still JL and Cottom D, 1967; de Swiet M, 1986). There is little evidence that individuals who will go on to develop essential hypertension in adult life can be reliably detected in childhood. The predictive value of a high blood pressure reading in childhood for high blood pressure later in life is very low (Hofman A et al, 1983b). Moreover, the benefits of intervention to lower a high blood pressure level occurring in childhood due to essential hypertension have yet to be established (de Swiet M and Dillon MJ, 1989). In this thesis, no attempt will be made to provide definitions of high blood pressure levels in children. The purpose of the analyses presented is to compare blood pressure patterns in children, both on a geographic and on an individual basis. The use of arbitrary definitions of abnormality would be unhelpful in this context and will therefore be avoided.

TABLE 1.1 DEATHS FROM CIRCULATORY DISEASE IN ENGLAND AND WALES, 1989

Category and ICD-9 code		Male	Female	Both sexes	Percentage of all circulatory deaths
		NUMBERS OF DEATHS			
Acute rheumatic fever & chronic rheumatic heart disease	390-398	573	1751	2324	0.8
Hypertensive disease	401-405	1575	1951	3526	1.3
Ischaemic heart disease	410-414	82847	67947	150794	57.0
Diseases of pulmonary circulation	415-417	819	1101	1920	0.7
Other forms of heart disease	420-429	7127	12251	19378	7.3
Cerebrovascular disease	430-438	25210	43482	67692	25.6
Diseases of arteries and veins	440-459	9284	9682	18966	7.2
					Percentage of all deaths
All diseases of the circulation	390-459	127435	137165	264600	45.9
All causes other than circulatory disease	---	153855	158417	312272	54.1

Data for men and women, all ages.
(Source: Office of Population, Censuses and Surveys, 1991)

TABLE 1.2 DEATHS FROM ISCHAEMIC HEART DISEASE AND CEREBROVASCULAR DISEASE IN ENGLAND AND WALES, 1989, BY 10 YEAR AGE-GROUP

ISCHAEMIC HEART DISEASE (ICD-9 410-414)

Age group (yrs)	Death rate/million population		Number of deaths	
	Men	Women	Men	Women
25-34	31	7	119	25
35-44	355	54	1244	190
45-54	1658	299	4700	843
55-64	5460	1711	13861	4545
65-74	13307	5999	26613	14840
75-84	27404	15958	27789	28038
85 +	44913	34427	8504	19457

CEREBROVASCULAR DISEASE (ICD-9 430-438)

Age group (yrs)	Death rate/million population		Number of deaths	
	Men	Women	Men	Women
25-34	26	19	98	73
35-44	69	66	242	230
45-54	209	165	592	465
55-64	812	601	2061	1597
65-74	3123	2431	6245	6013
75-84	10895	10197	11048	17916
85 +	25742	28563	4874	16143

(Source: Office of Population, Censuses and Surveys, 1991)

TABLE 1.3 BRITISH REGIONAL HEART STUDY: AGE-STANDARDIZED MEAN SYSTOLIC AND DIASTOLIC PRESSURES IN THE 24 STUDY TOWNS.

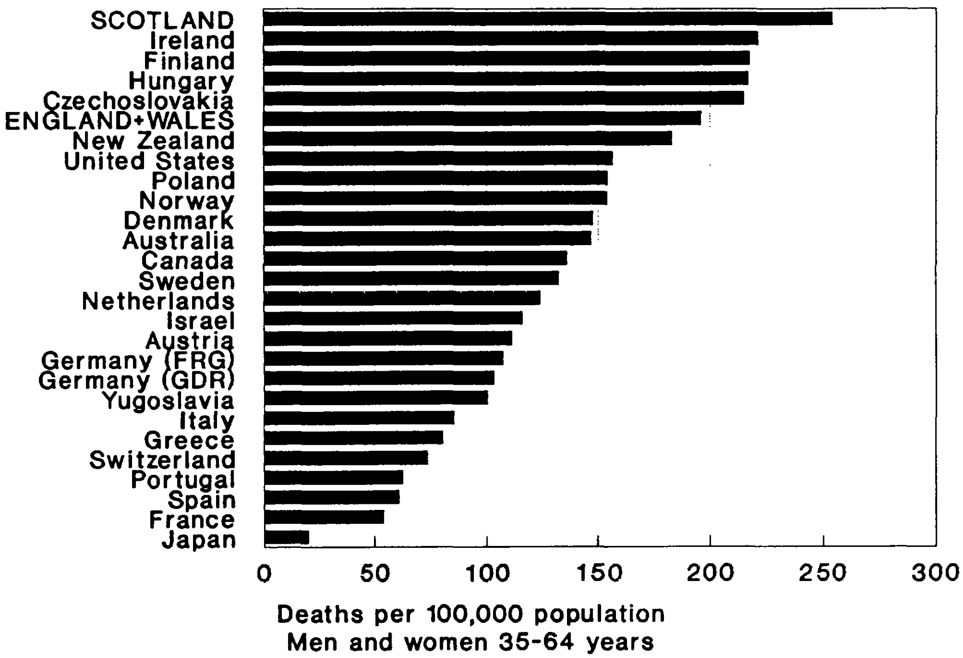
BLOOD PRESSURE (mmHg)

TOWN	SYSTOLIC		DIASTOLIC	
	Mean	(s.e.)	Mean	(s.e.)
Shrewsbury	135.8	(1.1)	77.4	(0.7)
Guildford	135.9	(1.1)	77.6	(0.7)
Harrogate	138.6	(1.2)	82.6	(0.8)
Exeter	138.9	(1.1)	78.5	(0.7)
Scunthorpe	140.4	(1.1)	78.2	(0.6)
Lowestoft	142.2	(1.1)	76.0	(0.7)
Ipswich	142.6	(1.0)	79.3	(0.7)
Ayr	143.4	(1.3)	81.2	(0.8)
Mansfield	143.7	(1.3)	79.0	(0.7)
Gloucester	144.8	(1.4)	81.2	(0.9)
Burnley	146.0	(1.2)	84.5	(0.8)
Maidstone	146.3	(1.1)	83.4	(0.7)
Darlington	146.6	(1.2)	84.0	(0.7)
Southport	147.2	(1.3)	82.0	(0.7)
Hartlepool	147.7	(1.1)	85.8	(0.7)
Wigan	147.9	(1.2)	82.4	(0.7)
Falkirk	147.9	(1.3)	85.5	(0.8)
Bedford	148.0	(1.3)	85.0	(0.8)
Grimsby	148.4	(1.1)	85.9	(0.7)
Merthyr Tydfil	148.8	(1.4)	82.1	(0.8)
Newcastle-u-Lyme	149.0	(1.3)	82.1	(0.9)
Carlisle	149.9	(1.1)	88.2	(0.6)
Dewsbury	150.8	(1.2)	82.7	(0.8)
Dunfermline	152.4	(1.3)	88.5	(0.8)

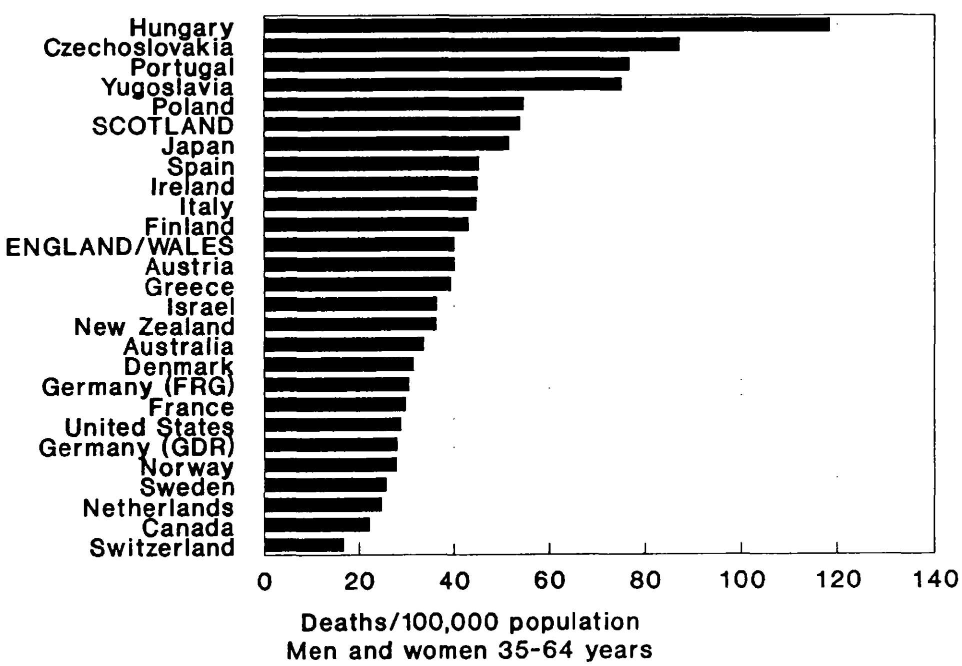
(Towns are ranked in descending order of mean systolic pressure).

Figure 1.1 MORTALITY RATES FOR ISCHAEMIC HEART DISEASE AND CEREBROVASCULAR DISEASE: BY COUNTRY

ISCHAEMIC HEART DISEASE

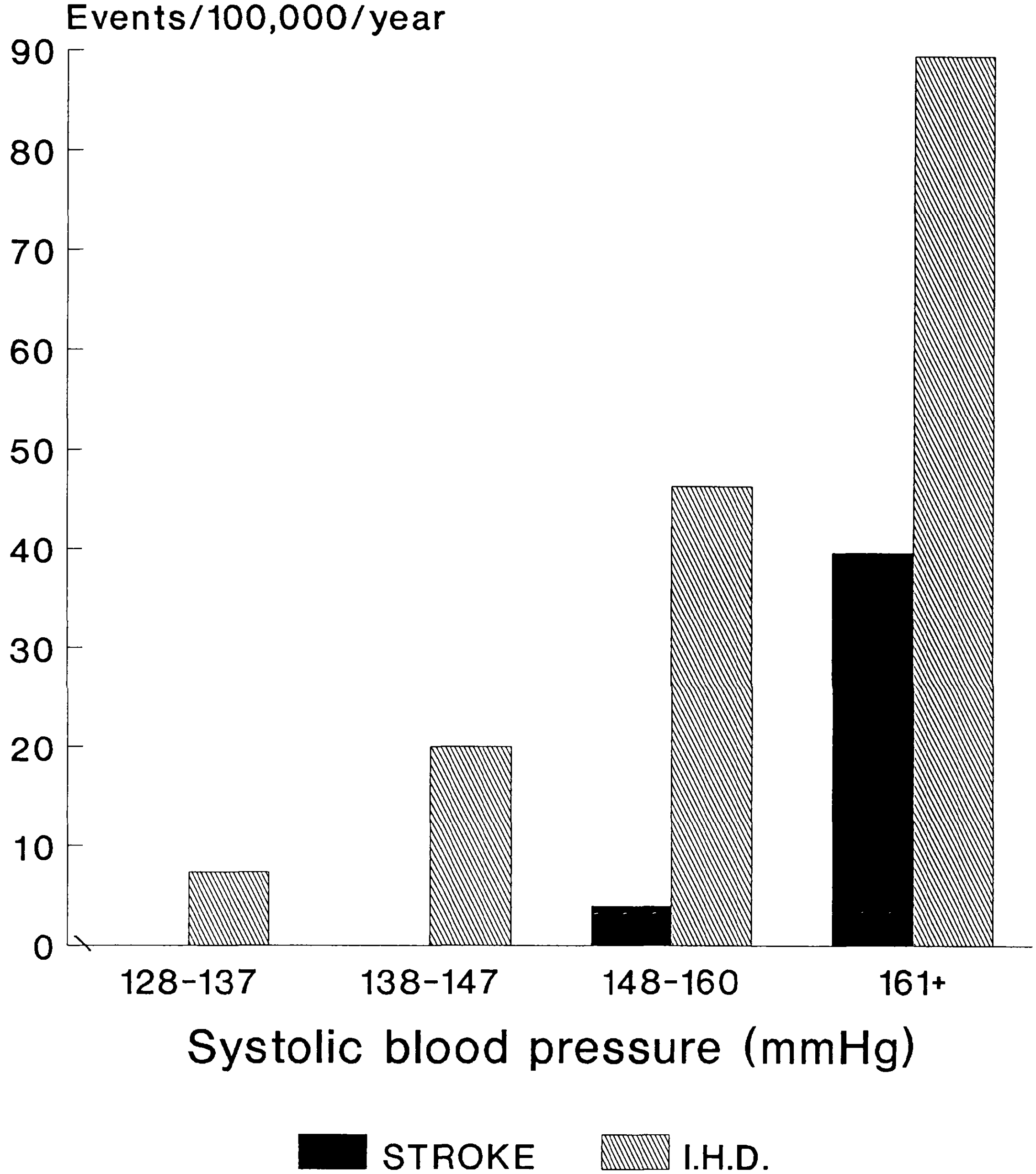


CEREBROVASCULAR DISEASE



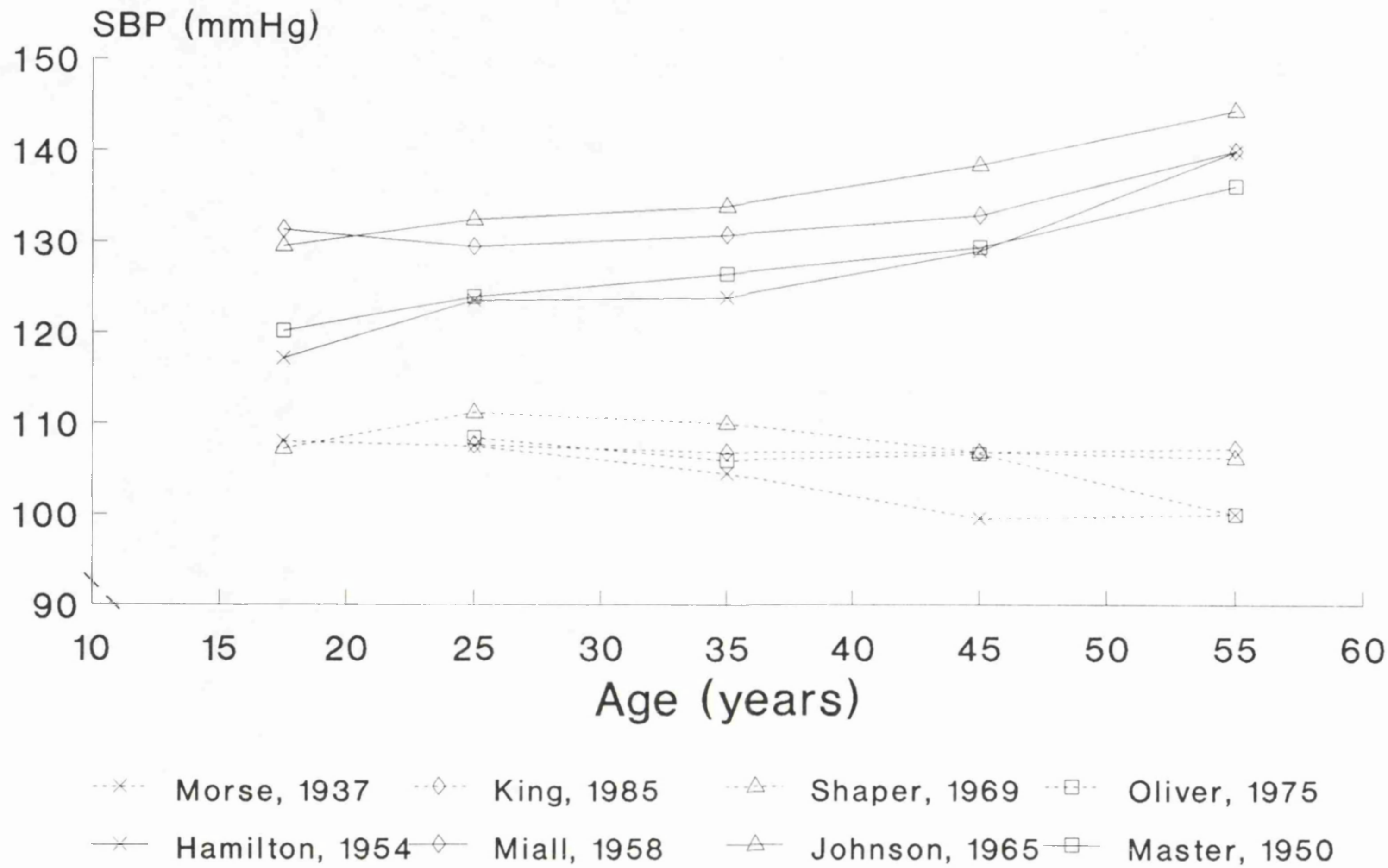
Data shown are for 1984-1985
Source: World Health Organization, 1987

Figure 1.2 I.H.D. AND STROKE EVENTS ATTRIBUTABLE TO HYPERTENSION



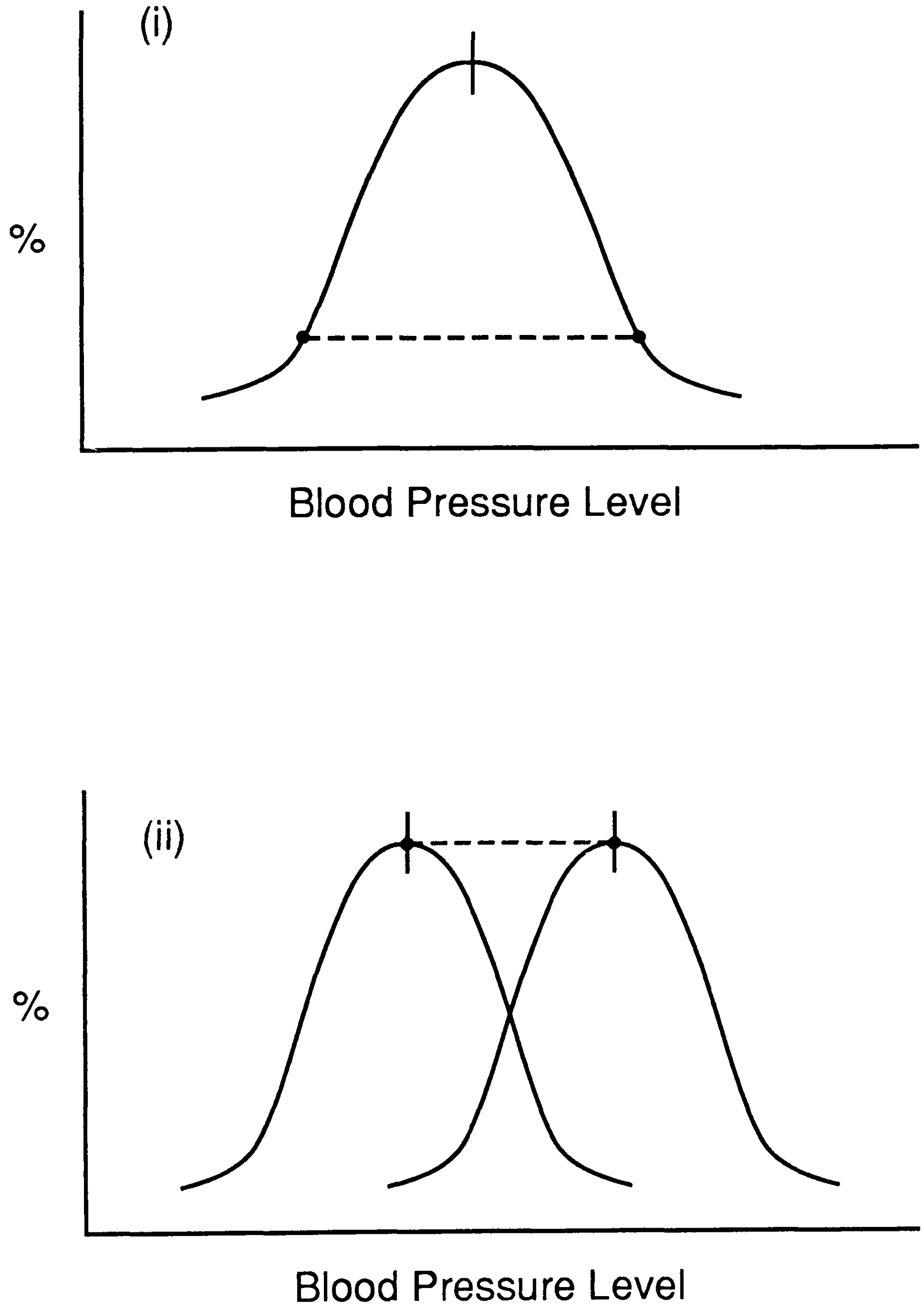
Numbers of events/100,000/year based on men aged 40-59 years (BRHS)

Figure 1.3 AGE AND SYSTOLIC BLOOD PRESSURE IN VARIOUS POPULATIONS



STUDY POPULATIONS
Morse, Chinese aboriginals; King, Papua New Guinea natives;
Shaper, Kenyan nomads; Oliver, Yanomamo Indians;
Hamilton, Londoners; Miall, South Wales populations;
Johnson, Michigan population; Master, Chicago population.

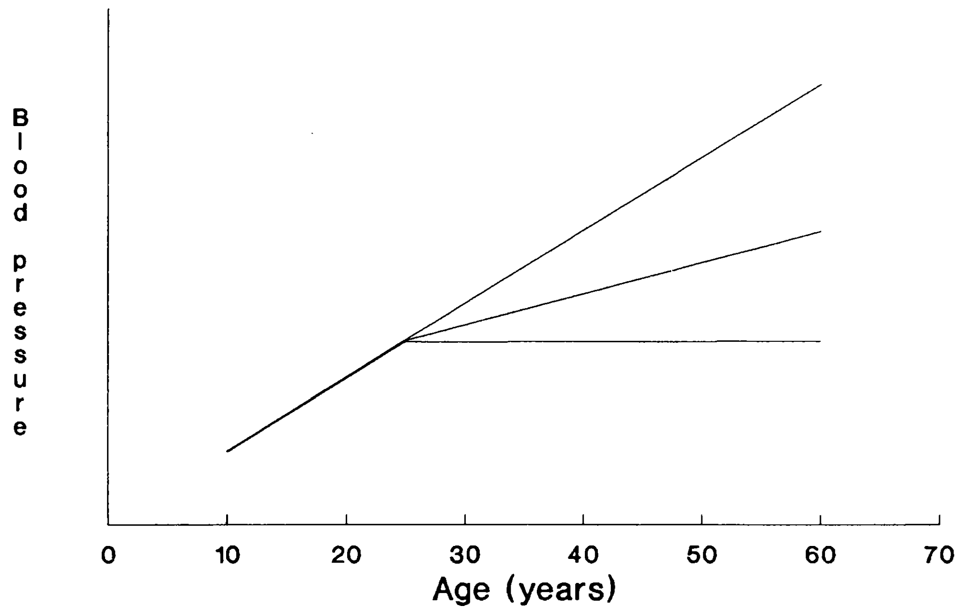
Figure 1.4 BLOOD PRESSURE DISTRIBUTIONS: TWO AETIOLOGICAL QUESTIONS



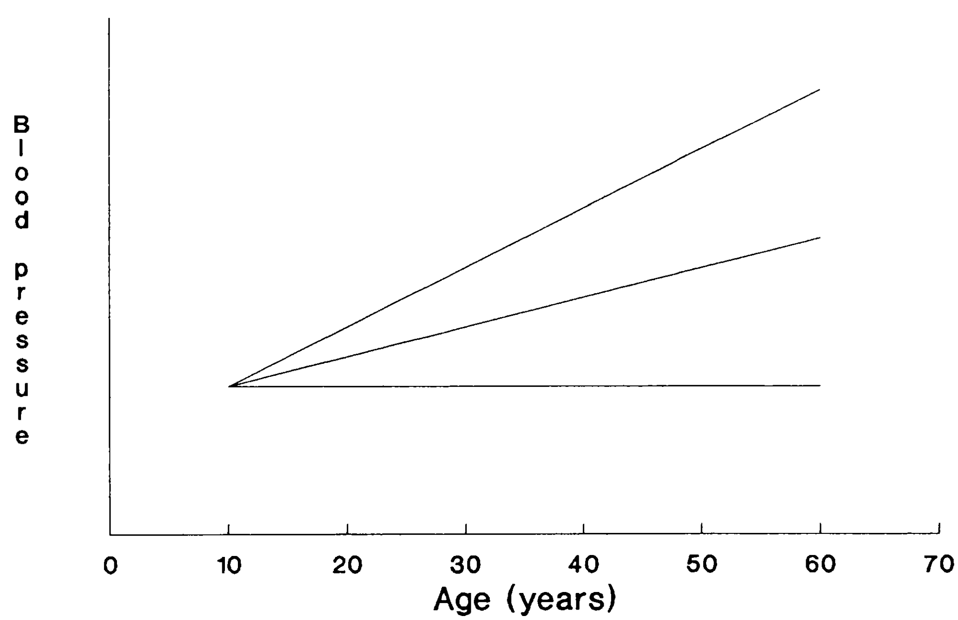
(i) variation within population
(ii) variation between populations

Figure 1.5 DEVELOPMENT OF BLOOD PRESSURE DIFFERENCES BETWEEN POPULATIONS: TWO POSSIBILITIES

(i)



(ii)

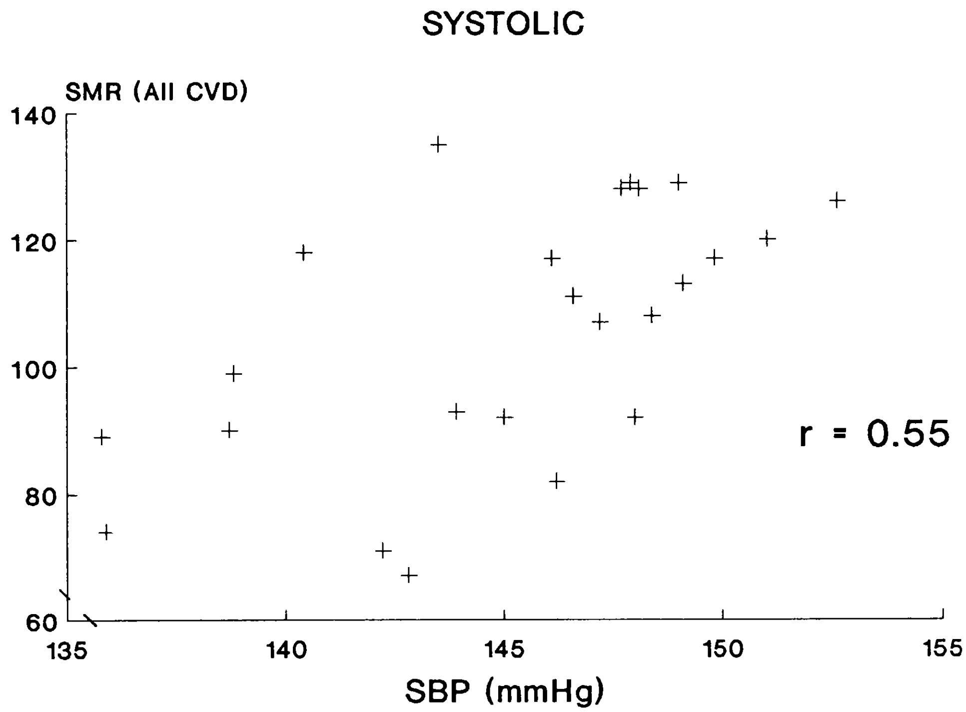


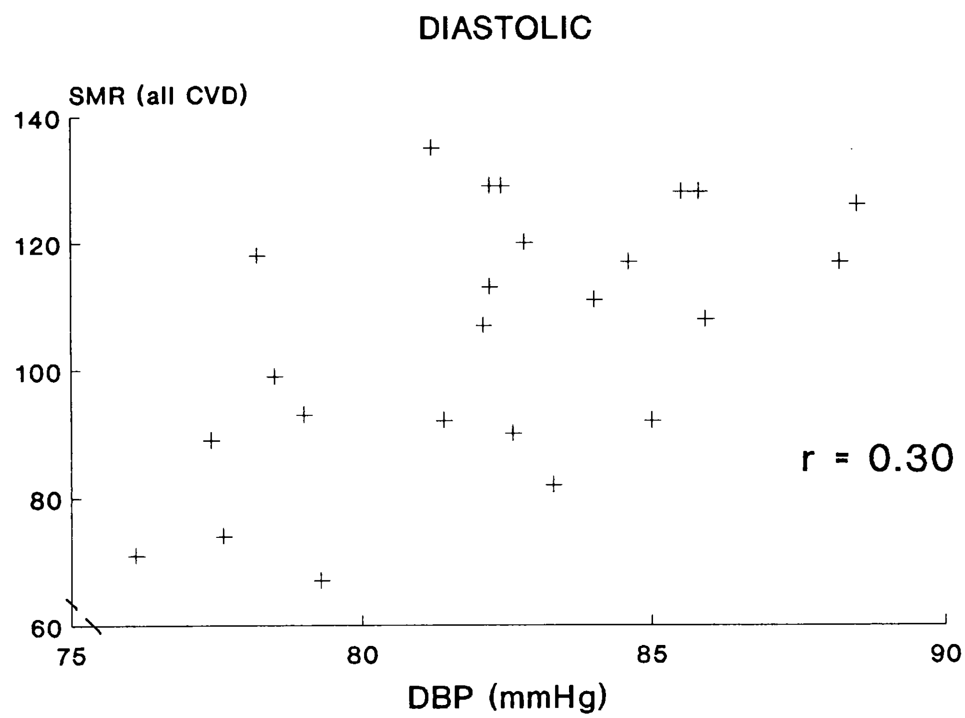
In (i) population differences emerge in adult life
In (ii) population differences emerge in childhood

Figure 1.6 BRITISH REGIONAL HEART STUDY: GEOGRAPHIC LOCATION OF 24 TOWNS

(Figures are SMRs for ischaemic heart disease, men 35-64 years, 1979-1983)

Figure 1.7 BRITISH REGIONAL HEART STUDY: MEAN BLOOD PRESSURE LEVELS AND SMRS FOR CARDIOVASCULAR DISEASE IN THE 24 TOWNS





CHAPTER 2

REVIEW

2.0 SUMMARY

This review provides the background to the geographic and individual hypotheses explored in this thesis. First, the age at which geographic differences in blood pressure emerge is studied by examining patterns of blood pressure in young people from populations with differing blood pressure levels in middle-age. A review of population studies including both middle-aged and young subjects suggests that between-population differences are likely to be established by 15-19 years. However, evidence from studies of migration and dietary intervention in younger children provides some support for the presence of population differences in the first decade of life. Second, the principal individual determinants of blood pressure in childhood (including age, body build, social class and factors related to blood pressure measurement) are reviewed. The development of the hypotheses to be examined in a geographic study of blood pressure in childhood and the main confounding factors to be taken into account are summarized.

2.1 INTRODUCTION

This chapter sets out to review those aspects of the epidemiology of blood pressure which have a direct bearing on the development and testing of the hypotheses put forward in the thesis. The first part (section 2.2) explores the age at which adult differences in blood pressure levels between populations begin to emerge. The second part (section 2.3) reviews current knowledge on the individual determinants of blood pressure in the first decade of life. The third and final part (section 2.4) describes the development of the specific hypotheses examined in the study, together with the main potential confounding factors which need to be taken into account.

2.2 DIFFERENCES IN BLOOD PRESSURE BETWEEN POPULATIONS: AGE OF DEVELOPMENT

2.2.1 INTRODUCTION: PREVIOUS STUDIES

The age at which differences in average blood pressure levels between populations first emerge has received little critical attention. Reviewers have often held that the emergence of these differences occurs during adult life (Peart WS, 1979) and that blood pressure patterns in childhood are essentially similar in all populations (Fixler DE, 1985; Rose G, 1985b). However, direct evidence to support these contentions are limited. Two types of study have been carried out which are particularly relevant to this question. One is the systematic study of blood pressure patterns in childhood in different population groups. This has been explored directly in the multicentre studies by Wynder and colleagues (Wynder E et al, 1981) and by Knuiman and colleagues (Knuiman JT et al, 1988) and indirectly, using data from earlier studies in different populations, by Labarthe and colleagues (Labarthe DR, 1983 and 1986; Brotons C et al, 1989). A second approach, taken by Epstein and Eckoff (Epstein FH and Eckoff RD, 1967) has been to examine the relationship between blood pressure levels in childhood and subsequent change in blood pressure. These different approaches are considered in detail below.

2.2.2 SYSTEMATIC STUDY OF BLOOD PRESSURE LEVELS IN CHILDHOOD IN DIFFERENT POPULATIONS

2.2.2.1 Direct studies of children in different population groups

While many investigators have measured blood pressure in children in individual countries, few have attempted to make standardized measurements in different geographic settings. Two systematic studies of blood pressure levels of children in different countries have been reported.

(i) The first study, which was part of the "Know Your Body" Programme, involved the measurement of 5,331 children 13 years of age by participant investigators in 15 countries representing Europe, Africa and Asia during 1978 and 1979 (Wynder EL et al, 1981). However, procedures for the selection of subjects were not specified and the number of participants varied widely between locations (from 60 in Nigeria to 1459 in Finland). Moreover, no observer training was undertaken and different types of sphygmomanometer were used in different locations. The lack of standardization in selection and measurement procedures makes the results of the study very difficult to interpret. Although no blood pressure values were presented, there appeared to be a range of more than 10 mmHg in the mean systolic blood pressures of children in different countries. The highest mean blood pressure levels were observed in France, Finland and Greece and the lowest in Yugoslavia, Thailand and Nigeria (Table 2.1). However, this variation in blood pressure may be accounted for, at least in part, by the lack of measurement standardization. Differences in the onset of puberty in different locations may also influence the blood pressure patterns observed. However, this is unlikely to provide a complete explanation because the relationships between attained height and blood pressure in the study locations (based on the rankings provided) are weak.

(ii) The second study involved the measurement of children aged 8 and 9 years in each of 19 locations in 13 European countries during 1986 (Knuiman JT et al, 1988). Three schools were selected in each location to provide a sample of approximately 60 children who were invited to take part. The response rate varied between 42% and 100% in the different centres. Considerable attention was paid to standardization of blood pressure measurement in the study. Although different observers carried out measurements in different locations, centralized observer training took place and Hawksley random zero instruments were used throughout. Considerable variation in mean blood pressure levels was observed between the study centres (Table 2.2), with ranges of 14 mmHg for systolic and 8 mmHg for diastolic pressure. While sampling variation and residual measurement bias may contribute to these differences, the results would nonetheless be consistent with a degree of geographic variation in childhood blood pressure levels. However, the geographic pattern is not straightforward; there is particularly wide variation <u>within</u> countries (8 mmHg systolic between Rome and Milan; 6 mmHg systolic between Catania and Santiago) and no consistent pattern of variation between countries. If the variations in blood pressure between countries are real, their relationships to variations in adult blood pressure level or adult stroke mortality rate are of potential importance. Although no information is available on adult blood pressure patterns in all the specific locations in which these children were sampled, contemporary data on adult blood pressure levels in ten of the thirteen countries are available from Intersalt Study data (Intersalt Cooperative Research Group, 1988) and recent data on mortality rates for cerebrovascular disease are available for all thirteen countries studied (World Health Organization, 1987). However, the correlation between childhood systolic blood pressure level and adult systolic blood pressure level is negative ($r = -0.69$), as is that for cerebrovascular mortality rate ($r = -0.56$). The low mean childhood blood pressure levels observed in Hungary and Portugal (two countries in which adult blood pressure levels and stroke mortality rates are high) make an important contribution to these findings. This study therefore provides some evidence for the presence of geographic variation in blood pressure during childhood, but provides no support for a positive relationship between blood pressure level in childhood and either adult blood pressure level or adult stroke mortality pattern.

In the first of the two studies described here little attempt was made to standardize blood pressure measurement, making the results of that study difficult to interpret. However, in the second study, considerable efforts were made to ensure standardization of blood pressure measurement. While the results of that study suggested that blood pressure levels vary in childhood between locations, they do not suggest that blood pressure levels in childhood are higher in those populations in which adult blood pressure levels and cerebrovascular mortality rates are high. However, it should be noted that all the populations included in that study were developed European populations, all with appreciable cerebrovascular mortality rates. Moreover, all ten of the thirteen countries in the study which were also included in the Intersalt Study showed a marked rise of blood pressure with age during adult life. This study therefore provided little evidence on childhood blood pressure levels in which the blood pressure rise during adult life was small or absent. The information available on children from such populations is considered in the following sections of this review.

2.2.2.2 Systematic reviews of studies of blood pressure in childhood in different locations

The studies of blood pressure carried out in many different countries over the past sixty years provide an important source of information about the extent of variation in childhood blood pressure levels between populations. However, caution is needed in interpreting the results obtained by different investigators using different methodologies. This is emphasized by the findings of a review (Fixler DE et al, 1980) which examined the marked variation in childhood blood pressure levels reported by different investigators in the United States (Weiss NS et al, 1973; Roberts J and Maurer K, 1977; Berenson GS et al, 1980) and concluded that much if not all of the variation was likely to be explained by the different measurement protocols employed in different studies. Childhood blood pressure patterns in childhood in different populations have been reviewed by Labarthe and his colleagues in a series of reports (Labarthe DR, 1983 and 1986; Brotons C et al, 1989). In the most recent and most extensive review (Brotons C et al, 1989), a total of 129 studies from different countries were identified by a comprehensive literature search. Europe (49 studies), the United States (30 studies) and the Western Pacific (22 studies) were the regions most heavily represented, with Africa, South-East Asia and other parts of the Americas also included. The results of 79 of these studies, which provided adequate details of blood pressures and subject numbers, were pooled; in the pooled data set it was observed that blood pressure tended to rise with age in both systolic and diastolic pressure. While the reviewers commented on the presence of differences in blood pressure patterns between studies, they made no attempt to establish whether there was genuine heterogeneity in childhood blood pressure between the populations examined - nor did they make any systematic attempt to relate childhood blood pressure patterns to adult blood pressure or cardiovascular mortality in the populations from which the children were drawn. In particular, no attempt was made to establish whether childhood blood pressure patterns differ between those populations in which average blood pressure levels in middle-age are high and those in which they are low. The only attempt to provide such an overview, that by Epstein and Eckoff, is described in the next section.

2.2.3 RELATIONSHIP BETWEEN BLOOD PRESSURE LEVEL IN CHILDHOOD AND BLOOD PRESSURE CHANGE IN ADULT LIFE IN DIFFERENT POPULATIONS

Epstein and Eckoff set out to devise a framework into which existing data on blood pressure patterns throughout life in different populations could be placed (Epstein FH and Eckoff RD, 1967). They began by categorizing systolic blood pressure levels in an age-group described as 'a little below 10 years' into three groups (105-115, 115-125 and 125-135 mmHg) and then defined five grades of slope representing increasing degrees of blood pressure rise with age (from 0 to 50 mmHg) between the childhood age-group and 70 years. This framework provided fifteen possible combinations of childhood blood pressure level and rate of rise, into which the data from earlier blood pressure surveys of 34 different populations could be sorted. The distribution of populations between the 15 combinations (Table 2.3) did not suggest that there was any systematic relationship between initial blood pressure level and the extent of blood pressure change with age, either in males or females. The authors took an empirical approach to the interpretation of their findings, proposing different explanations for the particular patterns found in different locations.

While the results of Epstein and Eckoff's analysis suggested that blood pressure levels might differ between populations in the first decade, the absence of a relationship between initial blood pressure and subsequent blood pressure change does not suggest that the initial differences in pressure are related to developments in adult life. However, on closer examination the analyses presented by Epstein and Eckoff are seriously flawed by a lack of comparability in the age-groups of the different populations studied. Table 2.4 shows the youngest and the oldest age-groups of each of the 28 published studies included in their review. While Epstein and Eckoff referred to their youngest age-group as being under 10 years, in only five of the 28 published studies reviewed did the youngest group conform with this definition. In most studies (18) the youngest age-group was between 10 and 20 years; in five studies the youngest age-group included subjects over the age of 20 years. Similarly, in the upper age-group, only 11 of the published studies included an age-group of 70 years or more, while in three the oldest age-group included no subjects over 60 years. This lack of comparability between different studies in the age-groups on which comparisons have been based makes the interpretation of Epstein and Eckoff's groupings effectively impossible. The lack of standardization in the youngest age-groups, in which blood pressure changes rapidly with age, is particularly serious, undermining the comparability of data both on variation in childhood blood pressure level and on the rate of blood pressure change in the different study groups.

Despite the shortcomings of Epstein and Eckoff's analysis, their review was an important and much needed attempt to relate blood pressure patterns in childhood to those in adult life, including both populations in which blood pressure rose steeply in adult life and those in which the rise was minimal or absent, which has not been repeated. In the next section an attempt is made to draw together the results of studies carried out in different populations, to examine the extent of variation in blood pressure between populations (both in early adult life and in adolescence and childhood) and to establish whether population differences in these age-groups are related to blood pressure patterns later in adult life.

2.2.4 POPULATION BLOOD PRESSURES IN EARLY ADULT LIFE AND ADOLESCENCE: RELATIONSHIPS WITH BLOOD PRESSURES IN MIDDLE-AGE

2.2.4.1 Introduction

An investigation of blood pressures in early adult life and adolescence and their relationships with levels in middle-age on a population basis can be conducted in two settings. The first is provided by the many separate studies of blood pressure which have been carried out in different population groups around the world during the last seventy years or so. These studies cover a wide range of geographic settings and many include data on subjects of a wide age-range, often including children. However, the absence of standardization in the methodology of blood pressure measurement between these studies places limits on the comparability of these separate studies, which are referred to hereafter as 'unstandardized studies'. The second setting is provided by the recent Intersalt Study, in which blood pressures of adults aged between

20 years and 59 years of age were measured in 52 different population groups in 32 different countries around the world during 1985 and 1986 (Intersalt Co-operative Research Group, 1988). Considerable attention was paid to the standardization of blood pressure measurement, with centralized observer training, a strict measurement protocol and the use of pre-checked Hawksley random zero sphygmomanometers throughout. This study therefore provides an important additional opportunity to examine population blood pressure patterns in early adult life in a standardized setting. However, the use of different observers in different centres (unavoidable for practical reasons) leaves open the possibility of a residual degree of measurement error between populations which cannot be completely discounted.

In all analyses presented, the 50-59 year age-group has been used to represent blood pressure levels in middle-age. Blood pressure in this age-group is known to be strongly related to cardiovascular mortality both on an individual basis (Kannel WB and Higgins M, 1990) and on a population basis (Keys A, 1980). The age-groups representing early adult life and adolescence are 20-29 years (on which information is available both from the unstandardized studies and the Intersalt Study) and 15-19 years (information only from the unstandardized studies).

2.2.4.2 <u>Studies and methods</u>

(a) <u>Data from unstandardized studies</u>

(i) <u>Selection of studies</u> An attempt has been made to identify all population-based studies of blood pressure reported in the English language literature, either longitudinal or cross-sectional, which examined blood pressures in both in middle-age and in young adult subjects. Earlier studies were identified from reviews (Epstein FH and Eckoff RD, 1967; Shaper AG, 1974). A literature search was used to identify all population studies of blood pressure reported in the English language literature between 1960 and 1990.

(b) <u>Criteria for inclusion of studies</u> In order to be included, studies had to have been based on a population sample drawn from a specified geographic location (or locations) and must have included subjects over at least the age-range 20 to 59 years, with a minimum of ten subjects in each 10 year age-sex group. Those studies which also include data on 15-19 year-olds form the basis for the analyses of that age-group. To be included, measurements of blood pressure must have been carried out using either an aneroid or a mercury sphygmomanometer (including the random-zero and London School of Hygiene modifications). No studies with automated instruments were included; blood pressure measurement with early automated instruments was often unreliable (Labarthe DR et al, 1973) and measurements with modern automated instruments are not always comparable with the sphygmomanometer (see Appendix I). Those studies in which subjects were selected on the basis of their blood pressure, or in which subjects in any particular age-group were reported to be selected or examined differently from those in other age-groups, were excluded. No populations have been excluded on the basis of ethnic origin. The search process yielded a total of 65 studies of which 47 could be included, providing data on males in 62 locations (50 countries) for the age-range 20-59 years; corresponding data on women were available for 54 locations from 43 studies. Data for the 15-19 year age group were available for 35 locations in males and 28 in females. A full list of these studies is included in Appendix II.

(c) <u>Handling of data</u>

Data for males and females have been treated separately. In those studies presenting data in five-year age cells, unweighted means for 10-year periods have been calculated. In those studies presenting data on 10-year age groups different from those used in the present review (e.g. 15-24 years, 25-34 years) an assumption of linearity in blood pressure change with age has been made in order to calculate an unweighted mean blood pressure at 17.5, 25.0 and 55.0 years. Where data are presented for different subgroups within a study report (e.g. populations of separate islands, rural and urban groups), all subgroups which fulfil the inclusion criteria in their own right have been included. Equal weight has been given to all studies, whatever their size, in the regression and correlation analyses presented.

(ii) Data from Intersalt Study

As described above, the Intersalt Study carried out standardized blood pressure measurements in 52 population groups from 32 countries around the world. Europe (23 groups) and the United States (6 groups) had the most extensive representation, while the Soviet Union, China, Japan, India, Africa and the West Indies were also included. Within each population group, an attempt was made to recruit twenty-five subjects of each sex in each of four ten year age-groups between 20 and 59 years, using a variety of sampling methods. Results used for the analyses below are drawn from published mean systolic and diastolic blood pressures for each ten-year age group, which have been published for men and women separately (Intersalt Co-operative Research Group, 1989). In 42 of the 52 groups, at least 190 subjects were included, while in the other ten at least 160 subjects took part. The relatively small variation in the numbers of subjects between different groups has been ignored in the analyses, with equal weight being given to all centres in the regression and correlation analyses presented.

(d) Independent assessment of the prevalence of hypertension in population groups

When interpreting the results of the review, an assessment of the prevalence of hypertension in the populations studied which is independent of the measured blood pressure level would be of considerable value. Stroke mortality rates provide one simple indicator for separating 'high blood pressure populations' from other populations. However, information on stroke mortality is normally only available for highly developed countries, where rates tend to be high. For those isolated populations in which surveys have suggested that blood pressure levels are particularly low, independent validation of blood pressure levels is often impossible, unless separate studies have been carried out on other occasions, preferably by other investigators. The only other indicator that low blood pressure levels in middle-age are likely to be valid is provided by the estimate of the change in blood pressure with age. In populations in which average blood pressures are low in middle-age the rise in blood pressure with age tends to be small or absent (Shaper AG, 1974). Estimates of the rise of blood pressure with age in cross-sectional studies tend to be largely independent of blood pressure level (Evans JG and Rose GA, 1971).

Certain populations in the unstandardized and Intersalt study groups can be independently identified as 'high blood pressure populations' on the basis of stroke mortality. In the unstandardized studies, those populations in the United States, the United Kingdom and the West Indies, all countries with high rates of stroke and other hypertensive diseases at the time these studies were conducted (World Health Organization, 1960 to 1975; World Health Organization, 1987), are classified as 'high blood pressure populations'. In the Intersalt Study, those populations in which standardized stroke mortality rates at the time of study exceeded 100/million/year, based on the standard W.H.O. European population (World Health Organization, 1987), are classified as 'high blood pressure populations'. The classification of 'low blood pressure populations', as discussed above, is difficult and unsatisfactory. In the unstandardized studies, the only criteria which can be established are (i) a reported absence of hypertension in the population studied <u>and</u> (ii) a rise in systolic blood pressure between 20-29 and 50-59 years of less than 10 mmHg in both men and women. In the Intersalt Study populations, four populations can be identified as 'low blood pressure populations' on the basis of (i) earlier studies showing low mean levels of blood pressure in middle-age in the same or a closely related population <u>and</u> (ii) a rise in systolic blood pressure of less than 10 mmHg between 20-29 and 50-59 years in both men and women in the present study. These population groups include those in Brazil (Yanomamos and Xingus), Kenya and Papua New Guinea.

2.2.4.3 <u>Results and interpretation</u>

(i) <u>Population blood pressures at 20-29 years and their relationships to blood pressures at 50-59 years</u>

The mean, ranges and standard deviations of both systolic and diastolic blood pressures in men and women aged 20-29 and 50-59 years in different locations for both the unstandardized studies and for the Intersalt Study are presented in Table 2.5. Mean blood pressures are slightly higher in the unstandardized study group than in the Intersalt study group. In both cases mean levels are higher at 50-59 years than at 20-29 years. The greater rise between these age-groups observed in women is consistent with earlier reports (Whelton PK, 1985). While the considerable variation in mean blood pressure levels between studies at 50-59 years is expected, the important observation in this table is the marked variation in mean blood pressure levels (both systolic and diastolic) at 20-29 years, both in the unstandardized study populations and (to a marginally smaller degree) in the closely standardized Intersalt populations. In the unstandardized studies, the use of different observers and measurement protocols make some degree of systematic error in blood pressure measurement inevitable. However, the persistence of marked variation in mean blood pressure levels at 20-29 years in the very carefully standardized Intersalt study populations implies that a component of the variation in blood pressure between populations in the 20-29 year-age group is likely to be genuine.

The importance of the differences in blood pressure observed at 20-29 years depends on the way in which they relate to the differences observed at 50-59 years. These relationships are presented for the unstandardized study populations in Figure 2.1 and for the Intersalt Study populations in Figure 2.2. The corresponding regression coefficients, for both systolic and diastolic pressure, are presented in Table 2.6A. Strong and highly statistically significant positive associations are apparent between average blood pressures at age 20-29 years and those at 50-59 years, in both the unstandardized and Intersalt study populations, for both sexes and for both systolic and diastolic pressure. Regression coefficients are higher for women than for men and are higher for the unstandardized studies than for the Intersalt study, generally being approximately twofold greater in the unstandardized studies.

In considering the interpretation of these associations it is again necessary to consider the potential contribution of systematic error (bias) in blood pressure measurement between populations in interpreting the results of these analyses. Error of this type could influence the blood pressure levels recorded at all ages in a particular population, and account for associations between blood pressures at 20-29 years with those at 50-59 years with a regression coefficient close to unity. However, if measurement bias is entirely responsible for these associations between population blood pressures at 20-29 and 50-59 years, two inferences can be drawn. First, because measurement bias would not be expected to relate to the true blood pressure level of a population, the position of populations on the regression scatter should show no relationship to any independent indicators of the extent of high blood pressure in a population, such as the stroke mortality rate. If, on the other hand, the association is valid, those populations in which stroke mortality is high would be observed to have relatively high blood pressure levels both at 20-29 years and 50-59 years, and be found in the upper right quadrant of the scatter diagram, while those populations in which stroke mortality is low might be expected to occupy the lower left quadrant of the scatter diagram. Second, because the measurement of blood pressure change with age is largely independent of the measurement of blood pressure level (Evans JG and Rose GA, 1971), blood pressure level at 20-29 years should be completely unrelated to blood pressure change in subsequent adult life (30-39 to 50-59 years). If, on the other hand, the relationship between blood pressure at 20-29 years and 50-59 years is valid, it might be expected that initial blood pressure level at 20-29 years in a population would be positively related to subsequent blood pressure change with age, as observed in studies of individuals in adulthood (Svardsudd K and Tibblin G, 1980; Wu M et al, 1980).

Both of these inferences can be examined. The first is explored in Figure 2.3, in which the regression plots for systolic pressure from Figures 2.1 and 2.2 are presented; however, on this occasion those populations which can be classified on independent grounds as 'high blood pressure populations' and (on less secure evidence, as discussed above) 'low blood pressure populations' are identified. In all the figures, the 'high blood pressure populations' are seen predominantly in the upper right quadrant of the regression scatter, while 'low blood pressure populations' are in the lower left quadrant. In the unstandardized studies the mean systolic differences between 'high' and 'low' blood pressure populations at 20-29 years are 13.1 mmHg for males (s.e. 2.1 mmHg, df 40, $p < 0.0001$) and 9.8 mmHg for females (s.e. 1.7 mmHg, df 29, p

<0.0001). A similar pattern of differences is seen with Intersalt data, although the very small number of low blood pressure populations (N = 4) make estimates of blood pressure differences between low blood pressure populations and high blood pressure populations extremely unstable. Results for diastolic pressure (not presented) show a similar pattern to those for systolic.

The second inference is examined in Figure 2.4, which presents the relationship between systolic blood pressure level at 20-29 years and the change in systolic blood pressure between 30-39 and 50-59 years, for both the unstandardized studies and the Intersalt Study. The corresponding regression coefficients, together with those for diastolic pressure, are presented in Table 2.6B. In the unstandardized studies, mean systolic blood pressure levels at 20-29 years are strongly related to the systolic difference between 30-39 and 50-59 year age-groups. A weaker, non-significant, association in the same direction is observed for women in the Intersalt study, but not for men. The relationships between diastolic pressure level at age 20-29 and diastolic differences between 30-39 and 50-59 years are weak and inconsistent.

The results of these supplementary analyses therefore suggest, first, that the associations between population blood pressure levels at 20-29 and 50-59 years are not the result of measurement bias, because blood pressure patterns both at 50-59 years and 20-29 years are related to independent measures of the extent of high blood pressure in the study populations. Second, systolic blood pressure levels at 20-29 years are positively related to subsequent systolic blood pressure change in three of the four analyses conducted, although there are no consistent relationships for diastolic pressure. These findings are unaffected by the exclusion of studies with small numbers of subjects and by the exclusion of particular ethnic groups. The observations therefore provide some support for the validity of population differences in blood pressure levels at 20-29 years and their relationship to blood pressure differences at 50-59 years. In the next section the extent to which these population differences are present at 15-19 years will be examined.

(ii) Population blood pressures at 15-19 years and their relationships to blood pressures at 50-59 years

The examination of population blood pressure levels at 15-19 years and their relationships to blood pressure in middle-age is restricted to those unstandardized studies which provide information on the 15-19 year age-group (28 studies and 35 populations in males; 22 studies and 28 populations in females). No data are available from the Intersalt Study, which included only subjects of 20 years and over. Marked variation in population mean blood pressures was observed in the 15-19 year age-group, both for systolic pressure (range 105.4 to 134.3 mmHg for males, 107.4 to 125.4 mmHg for females) and for diastolic pressure (range 60.9 to 82.5 mmHg for males, 61.4 to 80.5 mmHg for females). The relationships between population blood pressure levels at 15-19 years and 50-59 years are summarized in Figure 2.5 and Table 2.7A. Blood pressure levels at 15-19 years are strongly related to levels at 50-59 years, particularly for systolic pressure, although the regression coefficients are smaller than those for 20-29 years. The validity of the relationship between population blood pressures at 15-19 and 50-59 years can be examined in the same way as was done for the 20-29 year age-group. First, when the position of independently classified 'high blood pressure populations' and 'low blood pressure populations' on the regression slopes are considered (Figure 2.5), the 'high blood pressure populations' tend to occupy the right upper quadrant of the scatter plot while 'low blood pressure populations' tend to occupy the lower left quadrant. The mean systolic pressures of 15-19 year-old males are markedly lower in 'low blood pressure populations' than in 'high blood pressure populations' (mean difference 7.8 mmHg, s.e. 2.5, df 21, p = 0.006) while there is a small, non-significant difference in diastolic pressure (mean difference 1.9 mmHg, s.e. 2.1mmHg, df 21, p = 0.38). A similar pattern is seen for girls, but in view of the small number of observations in the low blood pressure populations (N =4) results are not formally presented.

Examining the relationships between population blood pressure levels at 15-19 and subsequent blood pressure change between 20-29 and 50-59 years (Table 2.7B), it is apparent that systolic blood pressure levels at 15-19 years are positively related to subsequent systolic blood pressure change, although no relationship is observed for diastolic pressure. As in the 20-29 year age-group, these findings provide additional support for the view that the population differences in blood pressure at 15-19 years and their relationships with those at 50-59 years are not merely due to measurement bias.

(iii) <u>Population blood pressure levels in younger children</u>

Tracing the development of population differences in blood pressure becomes increasingly difficult at younger ages because, while there have been many studies of blood pressure in childhood in populations in which hypertension is prevalent in adult life, few studies of blood pressure in childhood have been carried out in population groups with little or no hypertension in adults. Blood pressure in childhood has been studied in two unacculturated populations. Oliver and his colleagues (Oliver WJ et al, 1975) studied the blood pressure levels of the unacculturated Yanomamo Indian tribe in Brazil, a population in whom blood pressure in adult life showed no tendency to rise with age, and presented mean blood pressure levels for children aged 0-9 years and 10-19 years. The values for 0-9 years are difficult to interpret without additional information, because they are critically dependent on the precise age composition of the study sample. For the 10-19 year age-group data are standardized to the mean age (15 years) and can therefore be compared with data from other sources. Using for comparison the most recent American Task Force population, based on blood pressure surveys in the United States and the United Kingdom (Task Force on Blood Pressure Control in Children, 1987), mean systolic blood pressures at 15 years are lower in the Yanomamo Indians (mean systolic difference 4.1 mmHg in boys, 2.8 mmHg in girls) while diastolic pressures show little difference. A more detailed source of information about blood pressure in childhood in unacculturated communities is the Tokelau Island Migrant Study. Tokelau is an isolated Pacific Atholl, whose inhabitants live on a subsistence diet, predominantly of fish and fruit. After the island was struck by a hurricane in 1966, many inhabitants migrated to New Zealand, a country with a high prevalence of hypertension-related disease. The Tokelau Island Migrant Study examined blood pressure patterns in Tokelauans before migration began and subsequently re-examined blood pressure patterns in migrants and non-migrants (Prior IAM et al, 1974; Beaglehole

R et al, 1978 and 1979; Joseph JG et al, 1983). Considerable attention was given to standardization of blood pressure measurement between Tokelau and New Zealand, with the use of the same observers and measurement techniques in the two locations. Both systolic and diastolic blood pressure levels in adult Tokelauans on Tokelau were considerably lower than those of British or American subjects, although they did show some tendency to rise with age; systolic patterns are shown in Figure 2.6. The validity of the lower mean blood pressures observed in Tokelauan adults on Tokelau was supported by the observation that the blood pressures in Tokelauan adults who had migrated to New Zealand were markedly higher than those who had remained on Tokelau (Joseph JG et al, 1983), and were comparable with those of the British and American groups (Figure 2.6). Moreover, a comparison of pre-migration blood pressures in the migrant and non-migrant groups provided no evidence of any selection effect (Joseph JG et al, 1983).

The systolic blood pressures of children on Tokelau are compared with those of children in the United States (Task Force on Blood Pressure Control in Children, 1987) in Figure 2.7. Mean blood pressure levels in childhood were markedly lower on Tokelau than those in the United States from 6-8 years onwards. These differences must be interpreted with caution because systematic differences in blood pressure measurement between the two settings (for example, the use of a single blood pressure reading in the Task Force and two readings in the Tokelau study) may have contributed to the differences. However, support for their validity is provided by the observation that systolic blood pressure levels in Tokelauan children measured after migration to New Zealand were higher than those in children remaining on Tokelau between 4 and 14 years (Beaglehole R et al, 1978 and 1979) and were comparable with those of children in the United States (Figure 2.7). However, differences in diastolic pressure in children (not presented) were not marked. As in adults, a comparison of premigration blood pressures in migrant and non-migrant children provided no evidence of a blood pressure selection effect on migration.

2.2.4.4 Commentary

Previous reviews have not systematically examined the variation in population blood pressure levels in groups with widely differing blood pressure levels in middle age. The findings of the current review suggest that population differences in blood pressure corresponding to those seen in middle age may be apparent in early adult life (20-29 years) and in adolescence (15-19 years). While these observations may be influenced by measurement bias, the observations that blood pressures at 15-19 years and 20-29 years are related both to independent measures of the extent of high blood pressure in a population and to the extent of change in blood pressure with age in older age-groups, particularly for systolic pressure, provides additional support for their validity. Data relating adult blood pressure patterns to younger age-groups is sparse, but the findings of the Tokelau Island Migrant Study provide some support for the possibility that blood pressure levels may be lower in unacculturated populations than in Western ones during the first decade of life, a conclusion which is supported by the observation that blood pressures in Tokelauan children were higher after migration to a Westernized setting. However, the contribution of confounding factors (particularly environmental temperature, which may well have been lower in New Zealand) to these findings is difficult to assess.

Another reason for treating these findings with caution is that the studies on which they are based were all cross-sectional rather than longitudinal in design. However, this would only present a major difficulty if strong cohort effects in the development of blood pressure patterns were expected. No consistent evidence for such effects has yet been established (see section 2.4). Furthermore, the analyses presented have not examined the contribution of factors (for example environmental temperature, body build, sodium and/or potassium intake) which may confound the associations between blood pressure in childhood or early adult life and blood pressure in middle-age. While the exclusion of studies in specific ethnic groups, particularly blacks or Asians, makes no difference to the analyses, information on the other variables was not consistently presented in the studies reviewed, making detailed examination impossible.

The possibility that population differences in blood pressure emerge at some stage during childhood and are established in early adult life does however receive additional support from other sources, particularly studies investigating the influence of environmental factors (especially dietary) on blood pressure in infancy, childhood and early adult life. Khaw and Thom conducted a randomized double-blind crossover trial of potassium supplementation in 20 healthy men aged 22-35 years, which showed a statistically significant reduction in diastolic pressure (though not in systolic) after the two week intervention period (Khaw KT and Thom S, 1982). Grobbee and his colleagues conducted a trial of similar design to examine the effect of sodium restriction with and without potassium supplementation on blood pressure in forty subjects aged 18-28 years with mildly raised blood pressure. A statistically significant fall in systolic blood pressure was observed after six weeks of combined sodium restriction and potassium supplementation, but not after sodium restriction alone (Grobbee DE et al, 1987). In an observational study of 233 children, aged 5-17 years at entry and followed for an average of seven years, potassium excretion was inversely related to rate of blood pressure change with age (Geleijnse JM et al, 1990). Finally, in a randomized double-blind controlled trial of sodium restriction in neonates, Hofman and his colleagues observed lower systolic blood pressures in the intervention group from two months to the end of the six month intervention period (Hofman et al, 1983a). These observations are therefore consistent with the possibility that environmental factors may influence blood pressure in the first decades of life. However, they do not exclude the possibility that factors related to blood pressure in adults (for example, weight gain and alcohol intake) may modify the initial blood pressure patterns, a point which is discussed further in sections 5.4.4 and 7.2.1.

2.3 <u>FACTORS AFFECTING BLOOD PRESSURE LEVEL IN THE FIRST DECADE OF LIFE</u>

The purpose of this section is to examine the most important determinants of blood pressure level in the first decade of life. The review will concentrate on the findings of three of the most important epidemiological studies of blood pressure, referring to others where appropriate. The three studies considered in detail are the Bogalusa

Heart Study, the Minneapolis Children's Blood Pressure Study, (both conducted in the United States) and the Brompton Study (conducted in southern England).

(i) The Bogalusa Heart Study (Voors AW et al, 1976; Voors AW et al, 1978) included two cross-sectional surveys, one of 3524 children aged between 5 and 14 years and the second of 714 children aged 2.5 to 5.5 years. Both studies, carried out between 1973 and 1974, were based on a whole population sample of one ward in Washington, Louisiana (including the town of Bogalusa). In the study of 5-14 year-olds, carried out in schools, high response rates were observed both for black children (97%) and for whites (91%). Three seated blood pressure measurements were made in each child after voiding, by three different observers in random order, two using a mercury sphygmomanometer, the third using a Physiometrics blood pressure recorder. Each observer made three blood pressure measurements; a cuff with a bladder sufficiently long to encircle the subject's arm was used throughout. All observers underwent tape training before entry to the study and were tested using double-headed stethoscopes. Other physical measurements made in the study included height, weight, indices of sexual maturation and triceps skinfold thickness. Blood samples were taken for measurement of serum lipids and haemoglobin. In the study of younger children, the overall response rate was slightly lower (80%). The instruments used for blood pressure measurement were the mercury sphygmomanometer, the Infrasonde and the Arteriosonde, which again were used in a randomly ordered sequence. The cuff used for measurements was the largest which would comfortably fit the subject's arm.

(ii) The Minneapolis Children's Blood Pressure Study (Prineas RJ et al, 1980a, 1980b) was a cross-sectional study of 9977 Minneapolis children aged between 6-9 years, conducted during the winter and spring of 1978. Children were recruited through the public school system and an exceptionally high response rate (99%) was obtained. Survey measurements were carried out in schools throughout. After a period of rest two supine blood pressure measurements were recorded by 27 technician observers in five teams using Hawksley random zero sphygmomanometers; the mean of the two readings was used in subsequent analyses. Cuff sizes were chosen to ensure that cuff width corresponded to 120% of arm diameter (which corresponded to a cuff width: arm circumference ratio of 40%) and that cuff length corresponded to at least 90% of arm circumference. All observers underwent tape training and testing before entry to the study and their performances were monitored throughout fieldwork. Other physical measurements made in the study included height, weight and triceps skinfold thickness.

(iii) The Brompton Study (de Swiet M et al, 1976, 1980a, 1980b, 1984) was a longitudinal study based on 2000 consecutive births at Farnborough Hospital in Kent between May 1975 and June 1977. Once neonatal deaths and refusals were taken into account and 105 infants born before 38 weeks' gestation were excluded, 1797 infants were available for study in the first instance. Children were measured at 4 days, 6 weeks, 6 months, 1 year and then annually up to 5 years. However, during the follow-up period a number of children moved or were withdrawn by their parents, so that only 1307 children (73%) could be measured at either 4 or 5 years (de Swiet M et al, 1984). Measurements were generally carried out at home until the age of five years, at which point most were made in schools. Blood pressure was measured after a five minute rest period by one of four trained research nurses, using the Parks Doppler ultrasound system and the Hawksley random zero sphygmomanometer. A single cuff bladder size (8 cm x 15cm) was used in the older children. Three seated measurements were made on each occasion in the older children; the mean of the three formed the basis for analyses. Other physical measurements in this study included weight and, in older age-groups, height.

2.3.1 FACTORS RELATED TO BLOOD PRESSURE MEASUREMENT

2.3.1.1 Observer and instrument

The influence of the observer on blood pressure measurement, particularly using the mercury sphygmomanometer, has long been recognized (Rose GA et al, 1982). Observers may differ both in their technique of measurement, including particularly the interpretation of Korotkow sounds, and in their interaction with the subject being measured. Observer prejudice is another important potential source of bias. Several measures have been advocated to overcome these problems. These include the use of training procedures, particularly tape training and testing (Rose G, 1965), to standardize the interpretation of Korotkow sounds. Modified instruments have been developed to blind the observer to the true blood pressure level and thereby minimize the influence of observer prejudice and digit preference. These include the random-zero sphygmomanometer (Garrow JS, 1963; Wright BM and Dore CF, 1970) and the London School of Hygiene sphygmomanometer (Rose GA et al, 1964). More recently, automated blood pressure devices have been developed, which offer the possibility for keeping the influence of observers on blood pressure measurement to a minimum. However, many early devices were found to be inaccurate and unreliable (Labarthe DR et al, 1973). The need for critical evaluation of newer automated instruments continues to receive emphasis (O'Brien ET et al, 1987).

Have the use of training procedures and automated instruments abolished the influence of observer on blood pressure measurement? In adults, Bruce has shown that observer differences in blood pressure measurement may persist despite tape training (Bruce NG et al, 1988). In children, Prineas observed considerable variation between observers in the Minneapolis Study, despite extensive training; observer means varied by over 8 mmHg for both systolic and diastolic pressure (Prineas RJ et al, 1980a). These observations suggest that it is not necessarily possible to eliminate observer differences simply by means of observer training. Moreover, it is by no means certain that the use of automated instruments will eliminate observer differences in blood pressure measurement. In the Bogalusa Study, marked differences in blood pressures were recorded by different observers using the Physiometrics automated blood pressure recorder (Voors AW et al, 1976). Differences in blood pressure measurement between observers using an automated blood pressure recorder has also been described in adults (Bruce NG et al, 1990b). These observations suggest that neither training nor the use of automated instruments can completely eliminate the influence of observer on blood pressure measurement, a conclusion which has important consequences for the design of epidemiological studies of blood pressure.

2.3.1.2 Cuff size

The influence of cuff size on blood pressure measurement has been recognized for many years (von Recklinghausen H, 1903). Particular emphasis has been placed on the tendency for the small cuff to produce inappropriately high blood pressure readings (Frohlich ED et al, 1988), which has been noted both in adults (Maxwell MH et al, 1982) and in children (Moss AJ and Adams FH, 1962). The optimal cuff size for children has been a matter of debate. Recommendations have included the use of the largest cuff to fit the arm (Petrie JC et al, 1986; Task Force on Blood Pressure Control in Children, 1987), while the American Heart Association have recommended a cuff which provides a cuff width/arm circumference ratio of 40-50% (Frohlich ED, 1988). However, other authorities have recommended that the American Heart Association criteria should be extended to ensure that the length of the cuff bladder is sufficient to encircle at least 90% of arm circumference (Prineas RJ et al, 1980a). The influence of cuff size on blood pressure measurement in children is considered in more detail in Appendix I.

2.3.1.3 Circumstances of measurement

(i) Ambient temperature and season An inverse relationship between ambient temperature and blood pressure and blood pressure has been observed in adults (Heller RF et al, 1978; Brennan PJ et al, 1982). In children, an inverse relationship between room temperature (measured hourly) and systolic blood pressure was described in the large Minneapolis Children's Blood Pressure Study (Prineas RJ et al, 1980a), with a fall of approximately one mmHg in systolic blood pressure being associated with a rise of 10°C, While this association was highly statistically significant, diastolic blood pressure showed an opposite relationship, tending to rise with increasing room temperature. Strong inverse relationships between outdoor temperature and blood pressure were described in an Australian study of 1037 children, with falls in blood pressure of 4-6 mmHg (systolic) and 5-8 mmHg (diastolic) being observed for a 10°C rise in temperature (Jenner DA et al, 1987). An inverse trend between ambient temperature and systolic blood pressure was observed in the Brompton Study, but did not achieve statistical significance (de Swiet M et al, 1984). Relationships between season and blood pressure have also been described in children. In both the Minneapolis Study (Prineas RJ et al, 1980a) and the Brompton Study (de Swiet M et al, 1984) the highest mean blood pressures were observed in the winter months; in the large Minneapolis Study the effect of season appeared to be independent of room temperature.

(ii) Time of day: relation to meals A slight rise in systolic blood pressure during the day was observed in the Minneapolis study, with mean pressures being approximately 2 mmHg higher in the afternoon (Prineas RJ et al, 1980). A similar, but statistically non-significant, trend was observed in the Brompton Study (de Swiet M et al, 1984). The possibility that the time since the previous meal might be importantly related to blood pressure was raised by the observation that blood pressures were particularly low in subjects after an overnight fast (Orchard TJ et al, 1982). However, in the Brompton Study no relationship between the timing of the last meal and blood pressure was observed over an interval of greater than five hours (de Swiet M et al, 1984).

(iii) Other factors

Several other factors influence the measurement of blood pressure, which need to be taken into account in designing or comparing studies. Acute physical exercise and mental arousal are responsible for a marked rise in blood pressure (Millar Craig MW et al, 1978); accordingly in most studies measurements are carried out after a period of rest. The observation that blood pressure measurements conducted before venepuncture are higher than those conducted afterwards may well be related to anxiety (Fixler DE et al, 1980). The posture, both of the trunk and of the arm may influence may influence blood pressure (Frohlich ED et al, 1988). While it has been suggested that supine blood pressure measurements are easiest to standardize (Prineas RJ et al, 1980a), most authorities consider that seated measurements offer the best prospect for universal standardization of measurement (World Health Organization, 1985). The place of blood pressure measurement in children (school or home) has little or no influence on blood pressure in childhood (de Swiet M et al, 1984).

2.3.2 INDIVIDUAL DETERMINANTS OF BLOOD PRESSURE LEVEL

2.3.2.1 Age and sex

Virtually all studies of blood pressure in childhood have shown a rise in blood pressure with age (Szklo M, 1979; Kotchen JM et al, 1982; Brotons C et al, 1989). The average rise in blood pressure between birth and 20 years is steeper for systolic pressure (1.0 to 2.0 mmHg per year) than for diastolic pressure (0.5 to 1.0 mmHg per year). However, this rise is not uniform. In the Brompton study it was observed that blood pressure rose steeply between the first and sixth weeks of life, but then changed little until the sixth year (de Swiet M et al, 1984). This observation was consistent with the findings of the Bogalusa Heart Study, in which blood pressure did not change between 2.5 and 5.5 years (Voors AW et al, 1978). From this point blood pressure begins to rise again with age, the rise being particularly steep during adolescence, until it levels off in the late teens.

Blood pressure patterns differ between sexes at certain stages of life. While blood pressures in early life show little difference between sexes (Levine RS et al, 1978; de Swiet M et al, 1980b), at the end of the first decade pressures are slightly higher in females (Weiss NS et al, 1973). During the second decade blood pressure rises more steeply in males (Roberts J and Maurer K, 1977), so that by the age of 20 years blood pressures, particularly systolic pressures, are markedly higher in males (Szklo M, 1979). The sex difference remains until middle-age, when blood pressures in females again begin to exceed those in males.

The universal occurrence of a rise in blood pressure with age in childhood populations implies that the phenomenon is likely to be physiological, although the reasons for the differences in rates of rise at different ages, and the sex differences at different ages, remain to be established. However, despite the universal occurrence of the rise in blood pressure with age in childhood, there may be differences in the extent of rise and in attained blood pressure levels in different populations (see section 2.2) which require further investigation.

2.3.2.2 Body build

Strong relationships between blood pressure and various measures of body build, including weight, height and skinfold thickness, have been established in many studies (for review see Szklo M, 1979; World Health Organization, 1985). Of these measures, the associations between weight and blood pressure (Prineas RJ et al, 1980b) and height and blood pressure (Voors AW et al, 1977) are particularly strong. Once account is taken of weight and height, the effect of skinfold thickness is of little importance (Prineas RJ et al, 1980b). In order to relate degree of fatness to blood pressure, several investigators have explored the relationship of weight/height indices to blood pressure in childhood. However, different indices have been used in different studies. In the Bogalusa Heart Study (5-14 year-olds) an index of weight/height3 was chosen because it was closely related to fatness in adults (Voors AW et al, 1976). In the Brompton Study, an index of weight/height1.7 was chosen because it was independent of age in the study population (de Swiet M et al, 1984). Both of these indices were strongly related to blood pressure. Recently Ballew and her colleagues have examined the relationships between three indices - weight/height2, weight/height3 and weight/height^{p} (the weight-for-height index which is independent of height in a particular population) - and blood pressure in 3601 Chicago schoolchildren aged 5-10 years from different racial backgrounds (Ballew C et al, 1990). The three indices produced very similar regression models with blood pressure, leading to the conclusion that there was little to choose between these three indices.

Changes in body build during childhood are closely related to age in childhood, raising the question of whether age related changes can be accounted for by changes in body build. In the 5-14 year age-group of the Bogalusa Heart Study, adjustment for height or body mass index removed the relationship between age and blood pressure (Voors AW et al, 1977). Similar results were observed in the Minneapolis study of 6-9 year-olds (Prineas RJ et al, 1980b). However, as de Swiet has pointed out (de Swiet M et al, 1984) the timing of increases in weight and height do not coincide with the time course of increases in blood pressure in the first years of life. This implies that growth rate and attained body size are not the only factors which are important in the changes in blood pressure patterns observed during childhood.

The relationship between body build at birth, of which birthweight is the most accessible measure, and blood pressure, both in the neonatal period and later in childhood has been examined by several investigators. While blood pressure soon after birth has shown either a positive relationship to birthweight (Kitterman JA et al, 1969; Lee YH et al, 1976; de Swiet M et al, 1980b) or no relationship (Schachter J et al, 1979), inverse associations between birthweight and blood pressure in later childhood have been described by several authors (Simpson A et al, 1981; Cater J and Gill M, 1984; Ounsted MK et al, 1985; Barker DJP et al, 1989). The importance of these associations will be considered further in chapter 6.

2.3.2.3 <u>Social factors</u>

In adults, consistent relationships between social class (whether measured by occupation or by length of education) have been described both in Britain (Marmot MG et al, 1978; Pocock SJ et al, 1986) and in the United States (Syme SL et al, 1974; Dyer J et al, 1976). In all these studies less extensive education or manual occupation was associated with higher blood pressure levels. In the United States a similar pattern of social differences in blood pressure has been observed in younger subjects. In the Health Examination Survey a 2 millimetre gradient in both systolic and diastolic blood pressures across parental education groups was observed in 6-11 year-olds (Weiss NS et al, 1973) while in the Health and Nutrition Survey, a two millimetre gradient in systolic pressures was observed both in 12-17 and 7-11 year-olds (Roberts J and Maurer K, 1977). Consistent findings were also observed in other studies of both white and black adolescents (Langford HG et al, 1968; Miller RA and Shekelle RB, 1976). Less information is available on the relationship between social class and blood pressure in British children. In a study of 357 15-16 year-old schoolchildren in North West London, a marked difference in average blood pressures was observed between two schools, the school with higher blood pressure levels having a higher incidence of unemployment and single parent families (Khaw KT and Marmot MG, 1983). However, the relationships between social factors and blood pressure in individuals were not described. Support for the presence of social class differences in younger children (5-8 years) was provided by a study of 491 Harrow children (Beresford SA and Holland WW, 1973). In that study, a statistically significant four millimetre gradient in systolic blood pressure across the social groups (classified on the basis of occupation) was observed, with higher pressures being observed in children from manual households, a pattern similar to that observed in adults. However, further confirmation of this finding, based on a relatively small study population, has yet to be provided.

2.3.2.4 Racial factors

The pattern of racial differences in blood pressure in Britain remains uncertain and contradictory. Black-white patterns of blood pressure have been extensively studied in the United States, where the blood pressures of adult blacks have been consistently observed to be higher than those of whites, both in the nationwide Health and Nutrition Survey (Roberts J and Maurer K, 1977) and in two census-based surveys in Georgia (Comstock GW, 1957; McDonough JR et al, 1964). Similar patterns have been observed in adolescents (Kotchen JM et al, 1974; Miller RA and Shekelle RB, 1976) although in one study the differences were largely accounted for by social class (Harburg E et al, 1973). In younger age-groups, most studies found little ethnic difference in blood pressure levels (Levinson S et al, 1985). In Britain, mortality rates from hypertension and stroke are higher in West Indian and African migrants than in the native born (Marmot MG et al, 1981). Mean blood pressures levels in blacks were higher than those in whites in the Northwick Park Heart Study (Meade TW et al, 1978). However, in the larger Birmingham Factory Study, no consistent differences between the blood pressures of blacks and whites were observed (Cruickshank JK et al, 1983). A study of 357 15-16 year-olds in North West London schools observed markedly higher mean blood pressures in whites than in blacks (Khaw KT and Marmot MG, 1983), while no important black-white differences were observed in a study of Birmingham adolescents of similar age (De Giovanni JV et al, 1983). The results of studies carried out to date in Britain therefore provide little evidence that blood pressures in children vary between blacks and whites. There is little data on blood pressure patterns in Asian children in Britain, although adult blood pressures may be lower in at least some Asian groups than those in whites (McKeigue PM et al, 1988).

2.3.2.5 Familial factors

It is well established that there are familial relationships in blood pressure, both between the blood pressures of siblings and between the blood pressures of parents and their offspring. Twin studies have demonstrated higher correlations of blood pressure in monozygotic twins than those observed in dizygotic twins and non-twin siblings (Feinlieb M et al, 1975; McIlhaney ML et al, 1975). Consistent relationships have been established between parental and offspring blood pressures (Londe S, 1966; Zinner SH et al, 1971; Beresford SA and Holland WW, 1973), while studies of adopted and biological children have observed that the correlation between the blood pressure of the parent and the natural child is considerably greater than that between the foster parent and adopted child (Biron P and Mongeau JG, 1978; Annest JL et al, 1979a and 1979b). These studies have suggested that genetic factors make an important contribution to the variation in blood pressure level within populations. The age at which familial aggregation is first established has been studied by several investigators. Beresford and Holland, in their study of 455 families, were able to demonstrate highly significant associations between the blood pressures of 5-8 year-old children and their parents (Beresford SA and Holland WW, 1973). Zinner and his colleagues were able to demonstrate maternal-offspring and sib clustering in 721 children aged 2-14 years (Zinner SH et al, 1971). More recently studies have investigated familial aggregation in infants and newborns. Although associations between the blood pressures of twins were observed in a study of infants aged 6 months to 1 year (Levine RS et al, 1982), familial aggregation in younger subjects has been inconsistent. In one study, a weak association was demonstrated between the diastolic (but not systolic) blood pressures of 257 neonates and their mothers (Lee YH et al, 1976) while in another study of 392 neonates the only association which could be demonstrated was between the diastolic pressures of the neonates and the systolic pressures of their mothers (Schachter J et al, 1979). However, in a larger study of 500 neonates no correlation between offspring and parental blood pressures was observed either at 4-6 days or at 5-7 weeks (de Swiet M and Shinebourne EA, 1977). Sibling aggregation between newborns and their siblings (mean age 5.8 years) has been described at two days for systolic but not for diastolic pressure (Hennekens CH et al, 1976). These observations suggest that, while the influence of familial factors on blood pressure level may begin to develop during the first year, the relationships are weak and inconsistent until later in childhood.

2.3.2.6 Sodium intake and blood pressure

(i) Relationship in adults The relationship between sodium intake and blood pressure in adults has been extensively examined, both by observational and experimental studies. The demonstration of ecological relationships between sodium intake and blood pressure (Dahl LK, 1972; Gleibermann L, 1973) stimulated many investigators to conduct studies of the relationship between urinary sodium excretion and blood pressure within single populations. However, such studies are difficult because of the limited range of sodium excretions within populations and the marked within-subject variability of sodium excretion and blood pressure (Liu K et al, 1979). Many of the earlier studies were too small to detect the expected magnitude of relationships between sodium intake and blood pressure with adequate power (Watt GCM and Foy CJW, 1982). Several of the more recent observational studies have been sufficiently large to overcome these problems; these include the Intersalt Study, which included 10,079 subjects in 52 different population groups (Intersalt Co-operative Research Group, 1988), the Scottish Heart Health Study, which included 7,354 subjects in Scotland (Smith WCS et al, 1988) and a study of 9,321 men in the Belgian Army (Kesteloot H and Geboers J, 1982). Both the Intersalt Study and the Scottish Heart Health Study observed positive associations between sodium intake and blood pressure, although the estimated regression slopes were small (a change of 0.02 mmHg in systolic pressure for a 1 mmol change in sodium intake being estimated in Intersalt), while the Belgian study reported no association. However, a more recent review of within-population data on sodium intake and blood pressure in earlier published reports, has suggested that the estimates from Intersalt may underestimate the true relationship by a factor of two (Frost CD et al, 1991). Moreover, two overviews combining the results of trials examining the effect of sodium restriction on blood pressure have also suggested that the within-population relationship between sodium and blood pressure may be stronger than that estimated by Intersalt (Grobbee DE and Hofman A, 1986; Law MR et al, 1991b).

(ii) <u>Relationship in children</u> No consistent relationship between sodium intake and blood pressure has been demonstrated in childhood. Between-population studies include the study by Knuiman referred to earlier, involving 887 boys aged 8-9 years from 19 centres in 13 European countries (Knuiman JT et al, 1988). No relationship between urinary sodium excretion (estimated from a single 24 hour collection) and blood pressure was observed either on an ecological or an individual basis. Several studies have examined the relationship between drinking water sodium and blood pressure in childhood. One study observed higher mean blood pressure levels in an area of higher drinking water sodium concentration, but did not measure urinary sodium output in that group (Calabrese EJ and Tuthill RW, 1977). Two other studies, while observing slightly higher mean blood pressure levels in high sodium areas, were unable to demonstrate that higher levels of sodium in drinking water had any marked effect on urinary sodium excretion (Hofman A et al, 1980; Hallenbeck WH et al, 1981). Among the most powerful within-population studies was that by Cooper and his colleagues, in which 73 11-14 year-olds were asked to produce 7 repeat 24-hour urine samples each in oder to overcome the problem of within-subject variability in urinary sodium excretion. A weak positive association between sodium excretion and blood pressure was observed (Cooper R et al, 1980), but the finding could not be substantiated in a further observational study (Cooper R et al, 1983), nor in an experimental study of sodium restriction (Cooper R et al, 1984). The strongest evidence for a relationship between sodium intake and blood pressure comes from a randomized controlled trial of sodium restriction in 476 neonates, in which the sodium content of formula milk and solid feeds were reduced for a six month period from birth (Hofman A et al, 1983), producing a substantial reduction in urinary sodium excretion. Mean systolic blood pressure was at least 1 mmHg lower in the intervention group than in the control group from 17 weeks to the end of the intervention at 25 weeks, with the difference at that point (2.0 mmHg) achieving statistical significance at $p = 0.1$. These results, if valid, give rise to a paradox. In both the Intersalt Study (Elliot P et al, 1989) and in the two trial reviews referred to earlier (Grobbee DE and Hofman A, 1986; Law MR et al, 1991b) the relationship between sodium intake and blood pressure appeared to become stronger with age. However, the findings of Hofman's study raise the possibility, which requires further substantiation, that there is also a period of sodium sensitivity early in life.

(iii) Sodium sensitivity The possibility that sensitivity to sodium varies between individuals, either as a result of genetic or acquired influences, has been examined in studies of children and young people. Skrabal and colleagues tested the hypothesis of genetic sensitivity by examining the effect of sodium restriction in ten students (21-25 years) with and ten without a family history of hypertension (Skrabal F et al, 1981). Although there appeared to be a difference in the blood pressure response to sodium in the two groups, the study had little statistical power. Watt and his colleagues compared the effect of four week periods of differing sodium intakes in 66 offspring whose parents were in the top and bottom thirds of a local population blood pressure distribution (Watt GCM et al, 1985). In this larger study, no difference in the blood pressure response to dietary sodium intake was observed between the two groups. Evidence against acquired susceptibility is provided by the study by Grobbee and colleagues, who examined the effect of sodium restriction in 80 young adult subjects selected from the upper part of the blood pressure distribution in an original group of 1600 subjects (Grobbee DE et al, 1987). A six-week period of sodium restriction had no discernible effect on blood pressure level in these subjects. The results of these studies have therefore provided no strong evidence of sodium sensitivity in individuals, either genetic or acquired. Age-related change in response to sodium (see above) is the only form of sodium sensitivity which seems to be a possibility at present.

2.3.2.7 Potassium intake and blood pressure

Inverse associations between potassium intake and blood pressure have been demonstrated by two large observational studies in adults (Smith WCS et al, 1988; Intersalt Co-operative Research Group, 1988). Studies of the relationships between potassium intake and blood pressure within populations have provided some support for an inverse relationship in young adults and children. One randomized double blind crossover study of potassium supplementation in young males suggested that an increase in potassium consumption was associated with a small increase in diastolic blood pressure (Khaw KT and Thom S, 1982). The results of a longitudinal study of 233 Dutch children (between 5 and 17 years at entry), who had multiple 24 hour urine collections and blood pressure measurements over a seven year period, has suggested that potassium intake may be related to the rate of change of blood pressure in childhood and adolescence (Geleijnse JM et al, 1990).

The relationship between sodium intake, potassium intake and blood pressure in childhood is complex and not fully resolved. The possibility that sodium and potassium intake are interdependent has been emphasized by the demonstration of consistent relationships between the sodium:potassium ratio and blood pressure both in the Intersalt Study (Intersalt Co-operative Research Group, 1988) and the Scottish Heart Health Study (Smith WCS et al, 1988). An association between sodium: potassium ratio and rate of blood pressure change has also been observed in childhood (Geleijnse JM et al, 1990). The observation that potassium may be related to the rate of blood pressure change in childhood provides some support for the view advanced by Lever and his colleagues (based on their observation that the relationships between exchangeable sodium, exchangeable potassium and blood pressure vary at different ages) that potassium may be particularly important in the early stages of development of high blood pressure (Lever AF et al, 1981).

2.3.2.8 <u>Other dietary factors</u>

Observational studies have observed a relationship between dietary calcium and blood pressure in adults (Kesteloot H and Geboers J, 1982). The effect of calcium supplementation has been examined in two small experimental studies in young adult subjects. Belizan and his colleagues observed a small but statistically significant fall in diastolic blood pressure with dietary calcium supplementation in 57 subjects aged 18-35 years (Belizan JM et al, 1983). In a second study of 90 mildly hypertensive subjects aged 16-29 years, a fall in diastolic pressure of marginal statistical significance was observed (Grobbee DE and Hofman A, 1987). The observation by these authors that the effects were more marked in subjects with high levels of parathyroid hormone is based on a subgroup analysis and requires further substantiation. The influence calcium intake and of other dietary factors, including most interestingly the hypotensive effect of a vegetarian diet (Rouse IL et al, 1983), have yet to be firmly established in childhood.

2.3.2.9 Physical activity and fitness

Studies have suggested that physical activity and, in particular, physical fitness may influence blood pressure levels in children. Dwyer and his colleagues observed a fall in diastolic pressure in 10 year-olds after a programme of intensive physical activity (Dwyer T et al, 1983). However, no adjustment was made for the effect of changes in body build or pulse rate. Hofman and Walter observed a strong relationship between physical fitness and systolic blood pressure in a cross-sectional survey of 633 children at 9 years and documented an inverse relationship between change in physical fitness and change in blood pressure during a five year follow-up period (Hofman A and Walter H, 1989). These findings were independent of body build and pulse rate.

2.3.3 CONCLUSIONS

Blood pressure measurement in childhood is affected by many factors including the observer, the instrument (including cuff size) and the circumstances in which measurements are carried out. Age and body build are strongly related to blood pressure in childhood. While the influence of familial factors on blood pressure is apparent very early in life, the effects of race and social circumstances on blood pressure in the first decade of life are less clearly established. Dietary sodium may be related to blood pressure in neonates, while relationships between potassium intake and blood pressure change may be important in older children. Physical fitness shows a marked inverse association with blood pressure by the end of the first decade.

2.4 DEVELOPMENT OF THE STUDY HYPOTHESIS

The study described in the following chapters of this thesis set out to examine whether population differences in blood pressure of the adult pattern are apparent in the first decade. The setting for this investigation was the geographic variation in adult blood pressure levels observed in the British Regional Heart Study, described in section 1.5.1. The selection of the age-group for study was based on the review in section 2.2. While this provided strong evidence for the presence of population differences in blood pressure at 15-19 years, other studies, particularly the Tokelau Island Migrant Study (Beaglehole R et al, 1978 and 1979) and the study of sodium restriction in neonates (Hofman A et al, 1983) raised the possibility that population differences in blood pressure might be apparent in the first decade of life. The results of these studies suggested that it would be reasonable to postulate population differences of some 2-4 mmHg in blood pressure (particularly systolic pressure) in the first decade, between population groups with widely differing mean pressures in middle age. While it would be possible to argue that the differences which might occur within Great Britain might be smaller than those observed in the studies referred to above, it was considered that a difference of 2-4 mmHg in systolic pressure between groups would represent an effect of potential public health importance, with the demonstration that relatively small changes in the mean level of cardiovascular risk factors can make a marked difference to population risk (Rose G, 1981). Differences smaller than 2-4 mmHg would be difficult to detect and their public health importance less certain.

The use of a cross-sectional study design (i.e. examining children in different geographic locations at approximately the same time as the study in adults) presented the only reasonably practical method of investigating this hypothesis. However, the use of such a method is only appropriate if blood pressure is reasonably free from important influences between generations (i.e. cohort effects). There is to date little evidence to suggest the presence of marked cohort effects on blood pressure, either in developed or less developed communities. In developed communities, the most likely reason for a cohort effect on blood pressure would be the widespread use of antihypertensive drugs in adults. However, in the United States, a comparison of the results of the Health and Nutrition Survey of adults aged 6-74 years (measured between 1971 and 1974) with earlier population-based surveys provided no evidence for such an effect; indeed, the results suggested that blood pressure levels might be falling with time in children rather than in adults (Roberts J and Maurer K, 1977). While the possibility of cohort effects in less developed populations has not been studied in detail, the observation that the pattern of blood pressure changes on migration from Tokelau to New Zealand was observed in all age-groups between infancy (Beaglehole R et al, 1978 and 1979) and middle-age (Joseph JG et al, 1983) provides no support for the possibility that the effects of environmental change on blood pressure occur only in specific age-groups. Within Great Britain, the absence of marked changes in the geographic distribution of mortality from cardiovascular disease during the last 70 years (Office of Population, Censuses and Surveys, 1990a) argues against the presence of a strong cohort effect on blood pressure on a geographic basis within Britain. The validity of the decision to use a cross-sectional study design is further supported by the fact that the studies on which the hypothesis is based (section 2.2.4) are without exception cross-sectional in design.

In a study of geographic differences in childhood blood pressure levels within Britain, several of the factors discussed above as determinants of blood pressure in childhood (section 2.3) needed to be taken into account. The standardization of blood pressure measurement, to take observer, instrument, cuff size and circumstances of measurement into account was of considerable importance. Age and body build, strongly related to blood pressure in childhood, needed to be measured. The relationship between social factors and blood pressure, described both in adults and children, needed to be quantified. Racial factors needed to be considered, although their importance would depend on the extent to which children in ethnic minority groups were included in the study. While the influence of familial and genetic factors on blood pressure in childhood was considered important, practical considerations rendered the measurement of parental blood pressures in the study impossible, although all parents could be asked about a history of high blood pressure. While sodium and potassium intakes were considered important, it was considered impracticable to collect 24 hour urine samples from the 5-7 year-old study population in the present study and an investigation of these factors was deferred until the geographic patterns of blood pressure in childhood had been explored.

TABLE 2.1 SYSTOLIC BLOOD PRESSURE RANK IN 13 YEAR-OLD CHILDREN IN 15 COUNTRIES

	BOYS	GIRLS
HIGH	Finland	Finland
	France	Greece
	Greece	Netherlands
	Japan	France
	Netherlands	Italy
	West Germany	Japan
	U.S.A.	West Germany
	Kuwait	U.S.A.
	Taiwan	Kuwait
	Italy	Norway
	Kenya	Thailand
	Norway	Kenya
	Nigeria	Nigeria
	Thailand	Yugoslavia
LOW	Yugoslavia	Taiwan

Countries are ranked by the mean systolic blood pressure level for each sex separately.

(Adapted from Wynder EL, Williams CL, Laakso K et al, 1981)

TABLE 2.2 MEAN SYSTOLIC AND DIASTOLIC BLOOD PRESSURES IN 8-9 YEAR-OLD BOYS IN 19 EUROPEAN CENTRES.

		BLOOD PRESSURE (mm Hg)			
CENTRE	N	SYSTOLIC		DIASTOLIC	
		Mean	(s.e.)	Mean	(s.e.)
Rome	45	105	(1.3)	63	(1.2)
Lund	40	103	(1.3)	63	(0.9)
Wageningen	43	102	(1.1)	66	(1.2)
Warsaw	60	101	(1.0)	60	(0.9)
Santiago	57	101	(1.1)	63	(1.1)
Madrid	57	101	(1.1)	65	(1.1)
Ghent	38	100	(1.3)	66	(1.1)
Budapest (I)	46	100	(1.3)	53	(1.5)
Berlin	44	99	(1.2)	51	(1.7)
Sofia	58	99	(1.2)	63	(1.1)
Heidelberg	40	98	(1.1)	59	(1.1)
Vienna	43	98	(1.5)	61	(1.4)
Freiburg	46	97	(1.3)	65	(0.9)
Athens	50	97	(1.0)	58	(1.3)
Milano	48	97	(1.3)	61	(1.3)
Turku	48	96	(1.7)	58	(1.4)
Budapest (II)	27	96	(1.7)	53	(1.3)
Catania	45	95	(1.6)	54	(2.2)
Lisbon	52	91	(1.1)	55	(1.0)

Centres are ranked by mean systolic pressure.

(Data from Knuiman JT, Hautvast JGAJ, Zwiauer KFM et al, 1988)

TABLE 2.3A RELATION BETWEEN CHILDHOOD BLOOD PRESSURE (<10 YEARS) AND BLOOD PRESSURE SLOPE BETWEEN CHILDHOOD AND OLD AGE IN DIFFERENT POPULATION GROUPS (MALES).

AGE SLOPE	CHILDHOOD SYSTOLIC BLOOD PRESSURE LEVEL (mmHg) 105-115	115-125	125-135
0	Caracas Indians Thailand Ethiopia Bushmen-Africa Uganda nomads	Vietnam India-rural India-urban Kenyan Africans Uganda semi-nomads	New Guinea Gilbertese Ugandan Africans
1	Ceylon	Colombia Fiji India W. Africa	Rural Zulu
2	Mundurucus Indians Javanese Formosa (mainland) Liberia	Bahamas (whites) Fiji	St Kitts (blacks)
3	Atiu-Mitiaro Formosa (Taiwanese) India (Wilson)	Tecumseh, Michigan Jamaica (rural) Jamaica (urban) Rarotonga Japan (Nagasaki) Japan (Hiroshima)	
4	Georgia (whites) Chile Fiji (Indians) Atlas Jews Zulus (urban) Uganda (villagers) London Wales Bergen II	Georgia (blacks) Bahamas (blacks) Bergen I	Georgia (blacks)

Change in blood pressure between 10 and 70 years represented by age-slopes are as follows:- 0 = 0-10 mmHg; 1 = 10-20 mmHg; 2 = 20-30 mmHg; 3 = 30-40 mmHg; 4 = 40-50 mmHg

(After Epstein FH and Eckoff RD, 1967)

TABLE 2.3B RELATION BETWEEN CHILDHOOD BLOOD PRESSURE (<10 YEARS) AND BLOOD PRESSURE SLOPE BETWEEN CHILDHOOD AND OLD AGE IN DIFFERENT POPULATION GROUPS (FEMALES).

AGE SLOPE	CHILDHOOD SYSTOLIC BLOOD PRESSURE LEVEL (mmHg) 105-115	115-125	125-135
0	Mundurucus & Caracas Indians Thailand Ethiopia Africa (bushmen)	Gilbertese Vietnam	New Guinea (coast)
1	India (rural) Ceylonese	Colombia	New Guinea (highlands)
2	Formosa (mainland) Zulus (rural)	Fiji Javanese	
3	Formosa (Taiwanese) India	Bahamas (whites) Fiji Atiu-Mitiaro Japan (Nagasaki)	Bahamas (blacks)
4	Georgia (whites) Chile Japan (Hiroshima) Zulu (urban) Uganda (villagers) W. Africa London Wales Bergen II	Georgia (blacks) Tecumseh, Michigan Jamaica (urban) Jamaica (rural) St Kitts (blacks) Fiji (Indians) Rarotonga Atlas Jews	Georgia (blacks) Bergen I

Change in blood pressure between 10 and 70 years represented by age-slopes are as follows:- 0 = 0-10 mmHg; 1 = 10-20 mmHg; 2 = 20-30 mmHg; 3 = 30-40 mmHg; 4 = 40-50 mmHg

(After Epstein FH and Eckoff RD, 1967)

TABLE 2.4 YOUNGEST AND OLDEST AGE-GROUPS IN PUBLISHED STUDIES REFERRED TO BY EPSTEIN AND ECKOFF (1967).

AUTHOR/YEAR		COUNTRY	YOUNGEST AGE-GROUP	OLDEST AGE-GROUP
Abrahams	1960	W Africa	20-29 years	60 years +
Bailey	1963	Java	17-19 years	60 years +
Bibile	1949	Ceylon	10-11 years	41-50 years
Boe	1957	Norway	15-19 years	75 years +
Comstock	1957	United States	8-14 years	65 years +
Donnison	1929	Kenya	15-19 years	60 years +
Dreyfuss	1961	Israel	<30 years	70 years +
Hamilton	1954	England	10-14 years	80-84 years
Hunter	1962	Polynesia	5-9 years	70 years +
Johnson	1965	United States	0-2 years	80 years +
Johnson	1961	Bahamas	6-9 years	60 years +
Kaminer	1960	Kalahari	2-17 years	60 years +
Lin	1959	China	15-19 years	65 years +
Loewenstein	1961	Brazil	16-20 years	51-60 years
Lovell	1960	Fiji	10-19 years	70 years +
Maddocks	1961	Pacific Islands	20-29 years	70 years +
McDonough	1964	United States	15-24 years	65-74 years
Miall	1962	Jamaica	15-19 years	70 years +
Miall	1963	Wales	5-9 years	80 years +
Moser	1962	Liberia	10-19 years	60 years +
Padmavati	1959	India	10-19 years	60-69 years
Schneckloth	1962	W. Indies	20-29 years	50-59 years
Scotch	1963	S. Africa	15-20 years	70 years +
Shaper	1964	E. Africa	10-14 years	75 years +
Switzer	1963	Japan	13-19 years	70 years +
Whyte	1958	New Guinea	10-19 years	60 years +
Williams	1941	E. Africa	16-20 years	51 years +
Wilson	1958	India	10-14 years	70-74 years

TABLE 2.5 MEAN BLOOD PRESSURE LEVELS IN POPULATION STUDIES AT 20-29 YEARS AND 50-59 YEARS: UNSTANDARDIZED STUDIES AND INTERSALT STUDY

	UNSTANDARDIZED		INTERSALT	
	MALE	FEMALE	MALE	FEMALE
SYSTOLIC (mmHg)				
Number of study populations	62	54	52	52
20-29 YEARS				
Mean	121.9	116.4	117.5	108.4
Minimum	104.5	97.0	99.4	93.3
Maximum	135.6	129.5	126.6	118.3
Standard deviation	7.3	6.4	6.0	5.3
50-59 YEARS				
Mean	130.4	139.2	127.3	126.2
Minimum	100.0	103.9	101.2	87.0
Maximum	158.6	172.3	154.0	156.3
Standard deviation	14.1	17.2	8.6	10.7
DIASTOLIC (mmHg)				
Number of study populations	62	53	52	52
20-29 YEARS				
Mean	75.0	72.6	69.4	65.1
Minimum	60.8	56.7	59.5	54.8
Maximum	85.3	81.5	78.0	73.2
Standard deviation	5.2	5.1	4.9	4.3
50-59 YEARS				
Mean	80.9	83.3	79.2	75.9
Minimum	61.1	58.9	64.1	57.4
Maximum	96.1	105.1	88.2	87.1
Standard deviation	7.8	9.8	5.2	6.1

TABLE 2.6A RELATIONSHIP BETWEEN BLOOD PRESSURE LEVELS AT 20-29 YEARS AND 50-59 YEARS: UNSTANDARDIZED STUDIES AND INTERSALT STUDY.

	UNSTANDARDIZED				INTERSALT			
	No. of centres	Slope	s.e.	p	No. of centres	Slope	s.e.	p
SYSTOLIC								
Males	62	1.51	0.16	<0.0001	52	0.77	0.17	<0.0001
Females	54	1.96	0.25	<0.0001	52	1.28	0.22	<0.0001
DIASTOLIC								
Males	62	0.95	0.15	<0.0001	52	0.55	0.13	0.0001
Females	53	1.32	0.20	<0.0001	52	0.94	0.15	<0.0001

Slopes refer to regression coefficients representing change in blood pressure at 50-59 years (mmHg) for each 1 mmHg change in blood pressure at age 20-29 years.

TABLE 2.6B RELATIONSHIP BETWEEN BLOOD PRESSURE LEVELS AT 20-29 YEARS AND CHANGE IN BLOOD PRESSURE BETWEEN 30-39 AND 50-59 YEARS: UNSTANDARDIZED STUDIES AND INTERSALT STUDY.

	UNSTANDARDIZED				INTERSALT			
	No. of centres	Slope	s.e.	p	No. of centres	Slope	s.e.	p
SYSTOLIC								
Males	62	0.44	0.13	0.002	52	-0.12	0.13	0.36
Females	54	0.80	0.21	0.0003	52	0.36	0.19	0.08
DIASTOLIC								
Males	62	0.00	0.12	0.98	52	-0.26	0.09	0.004
Females	53	0.22	0.14	0.11	52	0.16	0.14	0.26

Slopes refer to regression coefficients representing change in blood pressure difference between 30-39 years and 50-59 years (mmHg) for each 1 mmHg change in blood pressure at age 20-29 years.

TABLE 2.7A RELATIONSHIP BETWEEN BLOOD PRESSURE LEVELS AT 15-19 YEARS AND 50-59 YEARS: UNSTANDARDIZED STUDY GROUP ONLY.

	No. of centres	Slope	s.e.	p
SYSTOLIC				
Males	35	1.26	0.22	<0.0001
Females	28	1.55	0.35	0.0001
DIASTOLIC				
Males	35	0.46	0.19	0.02
Females	28	0.51	0.22	0.03

Slopes refer to regression coefficients representing change in blood pressure at 50-59 years (mmHg) for each 1 mmHg change in blood pressure at age 15-19 years.

TABLE 2.7B RELATIONSHIP BETWEEN BLOOD PRESSURE LEVELS AT 15-19 YEARS AND CHANGE IN BLOOD PRESSURE BETWEEN 20-29 AND 50-59 YEARS: UNSTANDARDIZED STUDY GROUP ONLY.

	No. of centres	Slope	s.e.	p
SYSTOLIC				
Males	35	0.37	0.18	0.05
Females	28	0.78	0.33	0.025
DIASTOLIC				
Males	35	-0.36	0.15	0.02
Females	28	-0.15	0.20	0.46

Slopes refer to regression coefficients representing change in blood pressure difference between 20-29 years and 50-59 years (mmHg) for each 1 mmHg change in blood pressure at age 15-19 years.

Figure 2.1 RELATIONSHIPS BETWEEN POPULATION BLOOD PRESSURE LEVELS AT 20-29 YEARS AND 50-59 YEARS FOR EACH SEX SEPARATELY: UNSTANDARDIZED STUDIES.

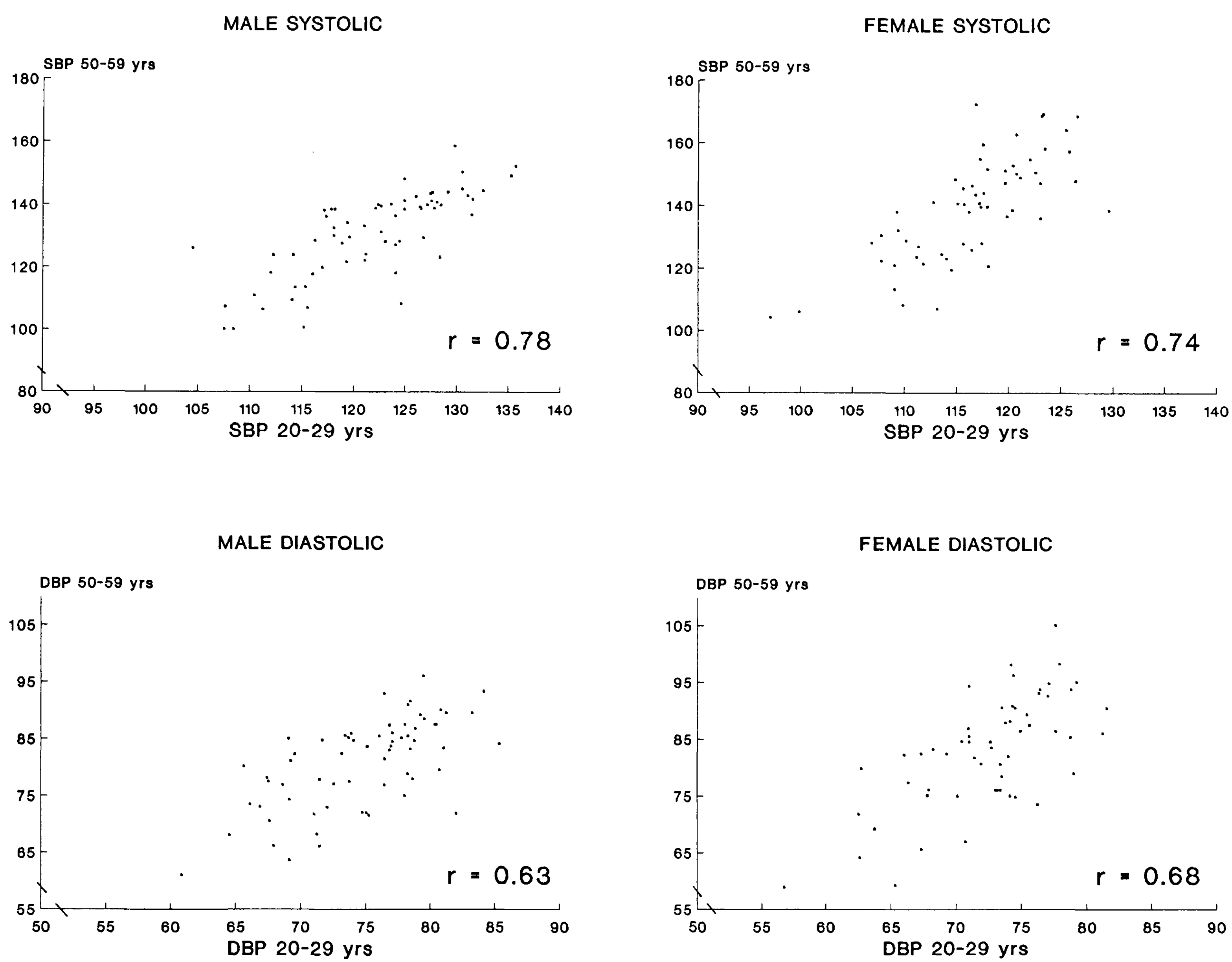


Figure 2.2 RELATIONSHIPS BETWEEN POPULATION BLOOD PRESSURE LEVELS AT 20-29 YEARS AND 50-59 YEARS FOR EACH SEX SEPARATELY: INTERSALT STUDY.

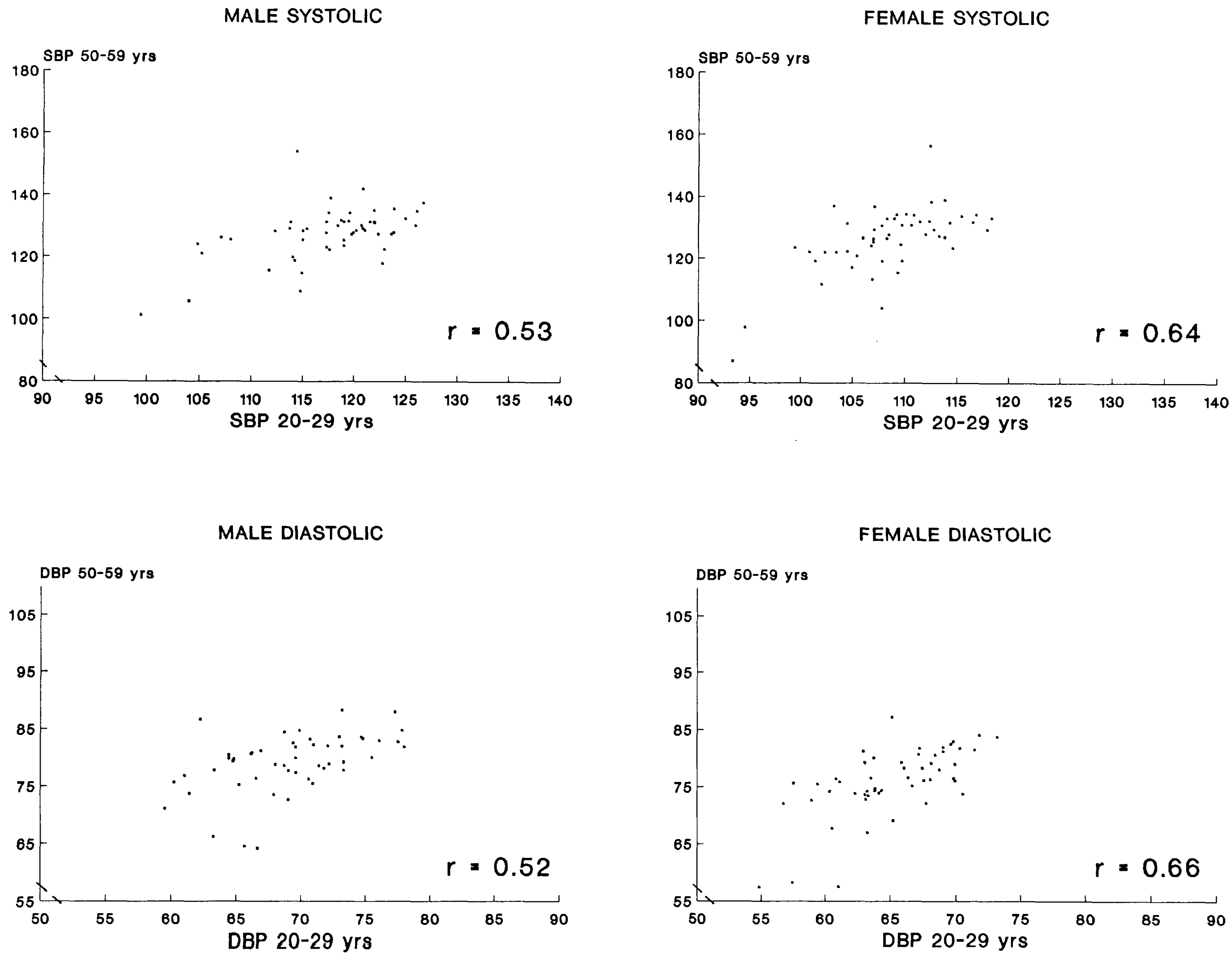


Figure 2.3 RELATIONSHIPS BETWEEN POPULATION SYSTOLIC BLOOD PRESSURE LEVELS AT 20-29 YEARS AND 50-59 YEARS: UNSTANDARDIZED STUDIES AND INTERSALT STUDY. POPULATIONS CLASSIFIED ACCORDING TO INDEPENDENT ESTIMATE OF PREVALENCE OF HYPERTENSION (see text).

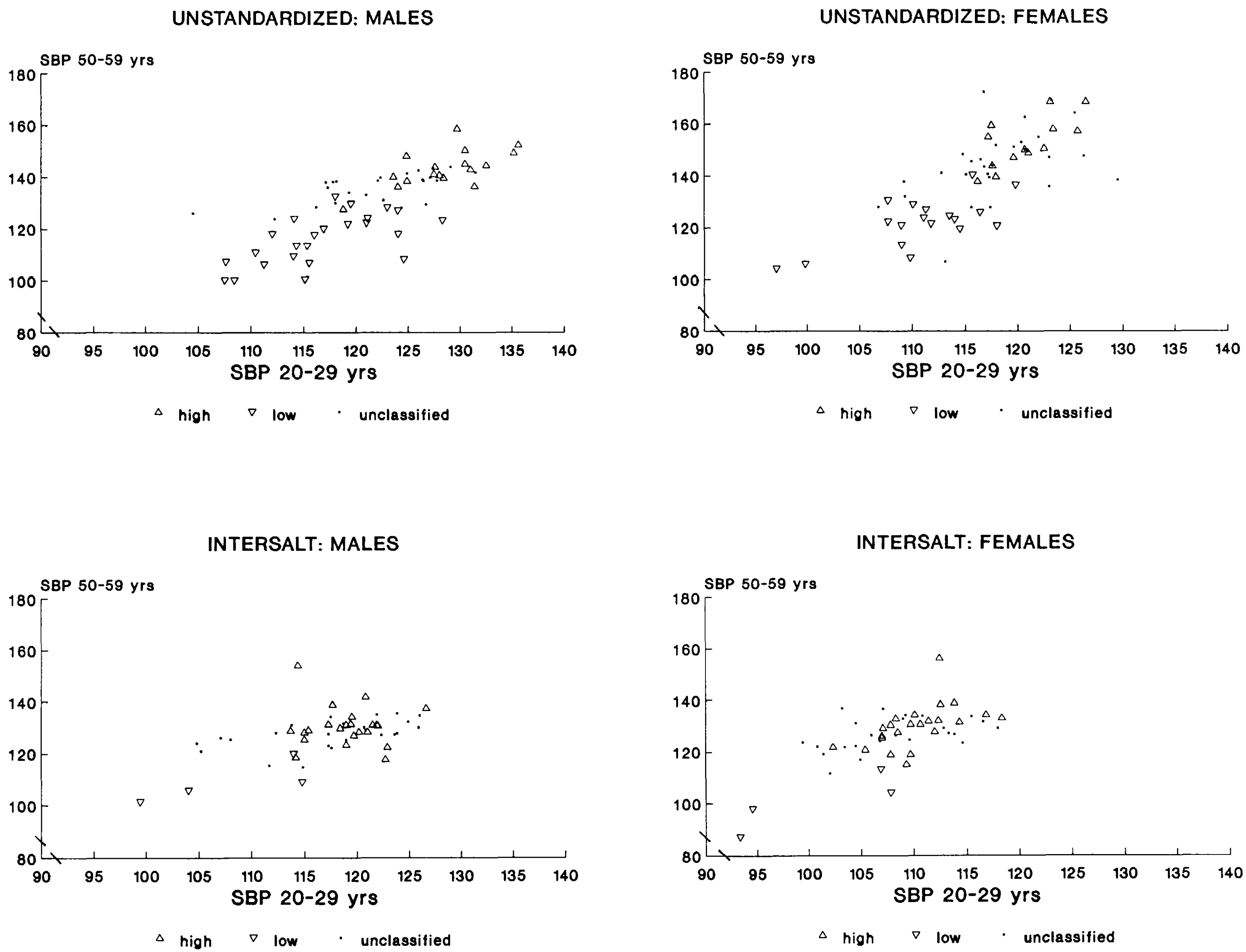


Figure 2.4 RELATIONSHIPS BETWEEN POPULATION SYSTOLIC BLOOD PRESSURE LEVELS AT 20-29 YEARS AND CHANGE IN SYSTOLIC BLOOD PRESSURE BETWEEN 30-39 AND 50-59 YEARS: UNSTANDARDIZED STUDIES AND INTERSALT STUDY.

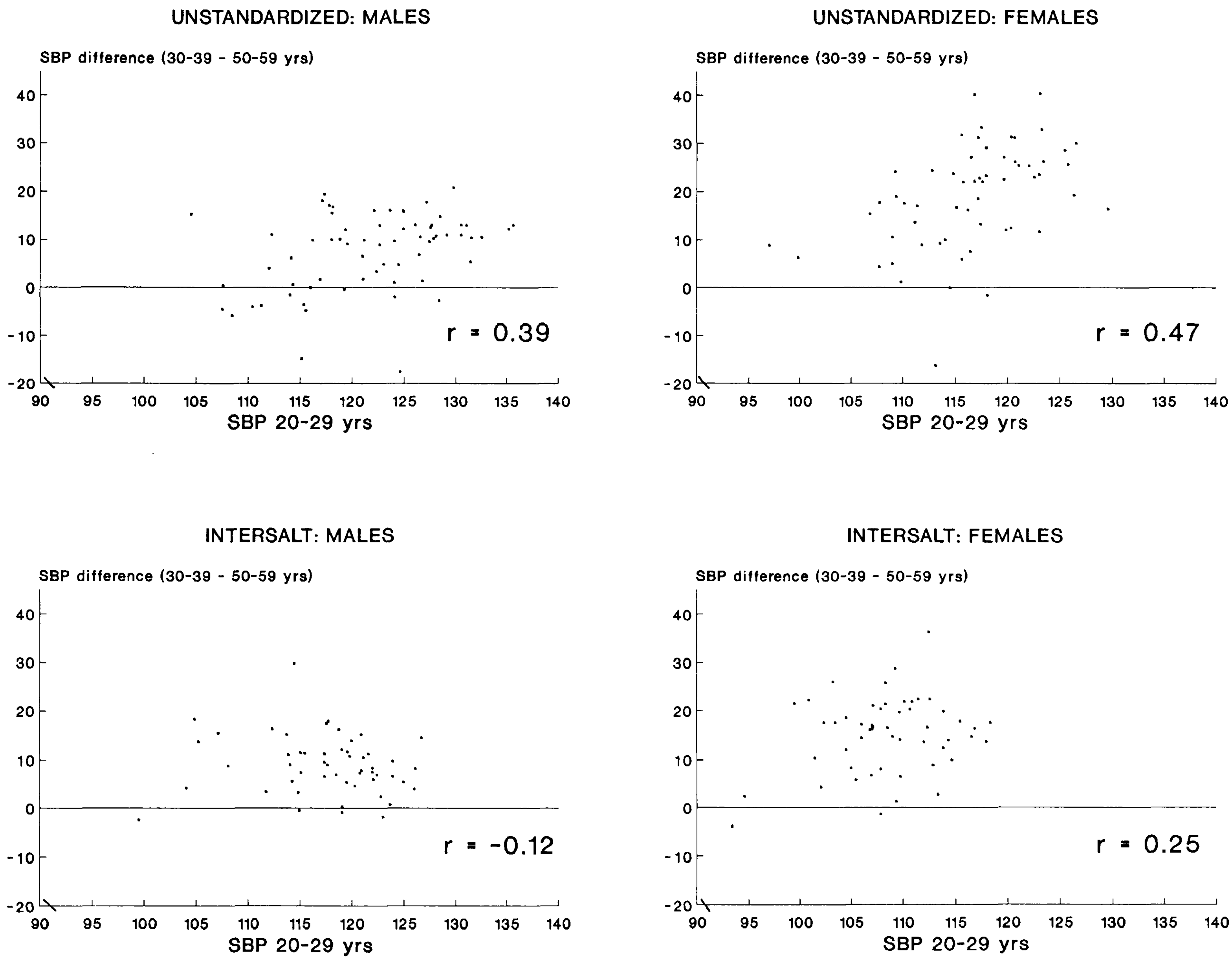


Figure 2.5 RELATIONSHIPS BETWEEN POPULATION BLOOD PRESSURE LEVELS AT 15-19 YEARS AND 50-59 YEARS: UNSTANDARDIZED STUDIES. POPULATIONS CLASSIFIED ACCORDING TO INDEPENDENT ESTIMATE OF PREVALENCE OF HYPERTENSION (see text).

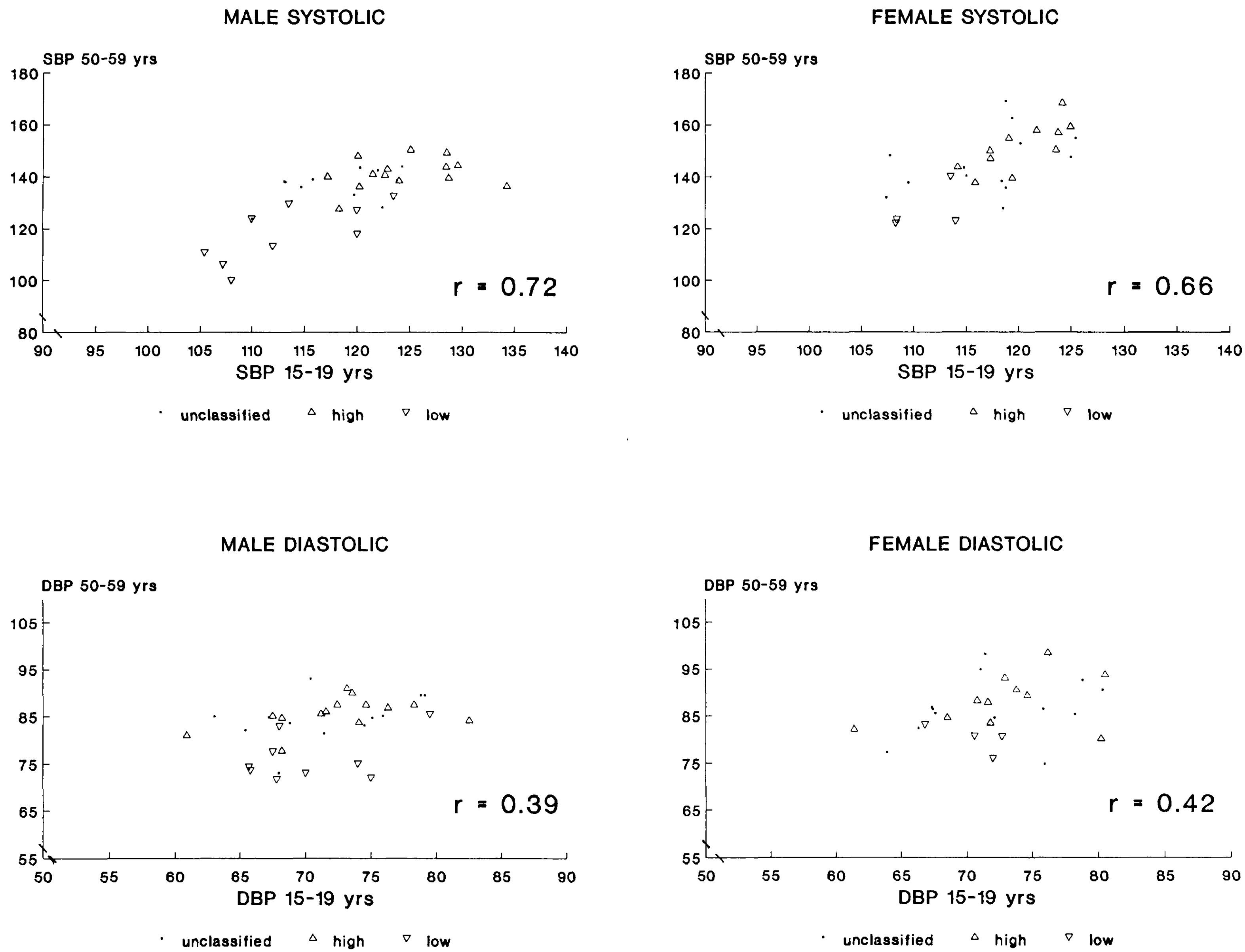
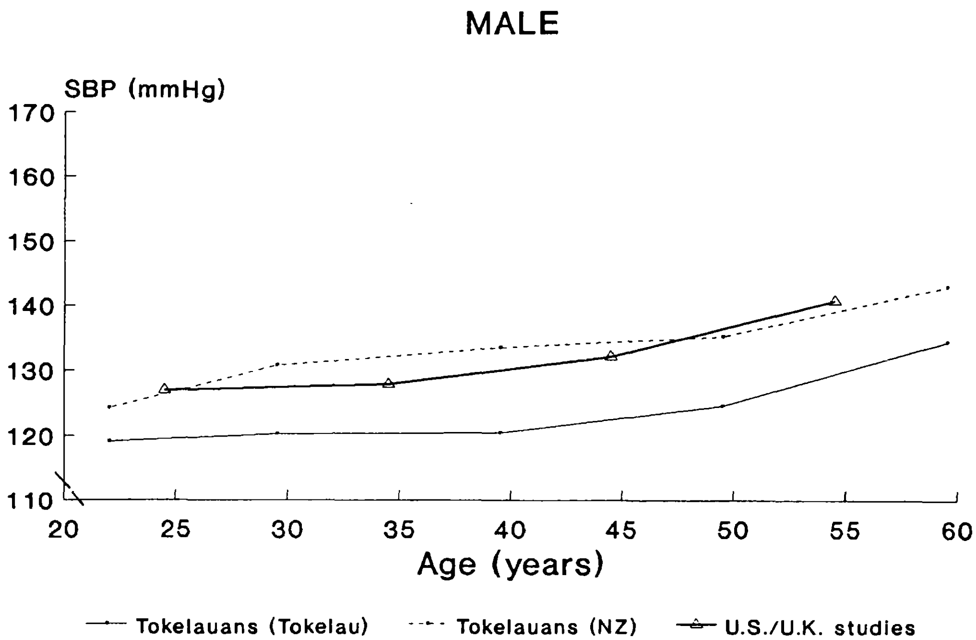
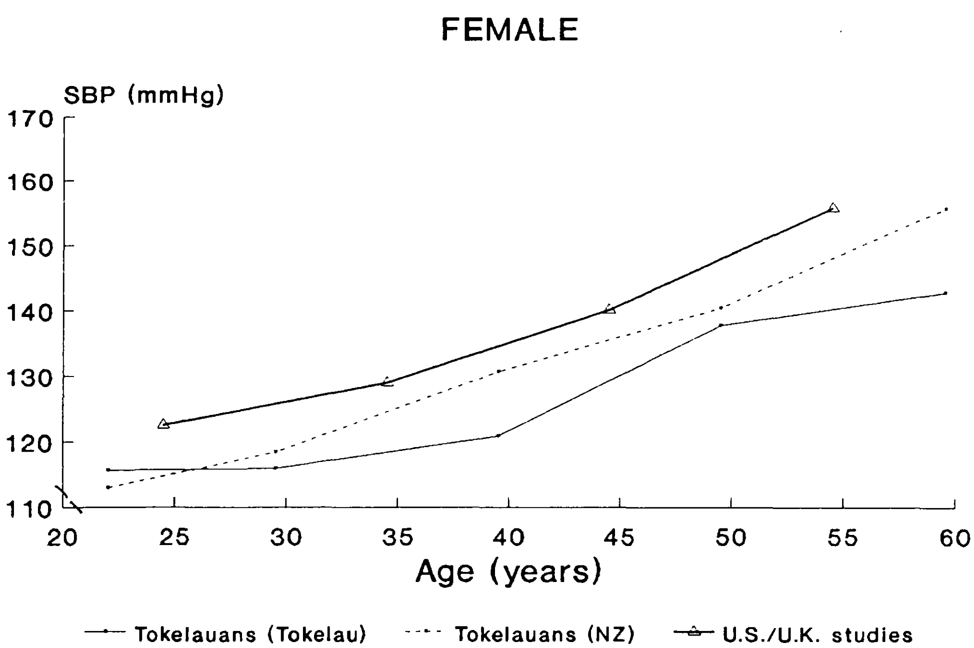


Figure 2.6 COMPARISON OF ADULT BLOOD PRESSURE LEVELS ON TOKELAU WITH ADULT BLOOD PRESSURE LEVELS IN THE UNITED STATES AND THE UNITED KINGDOM.

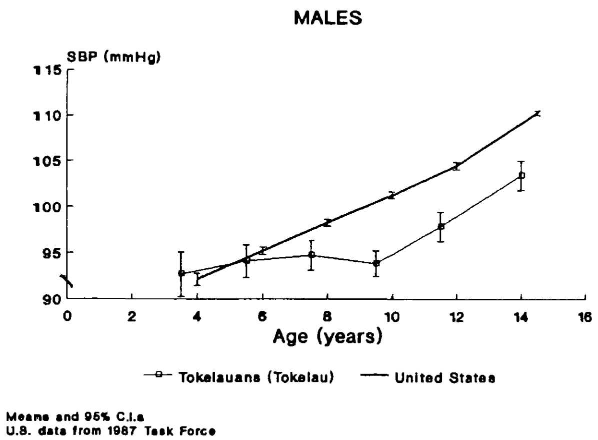


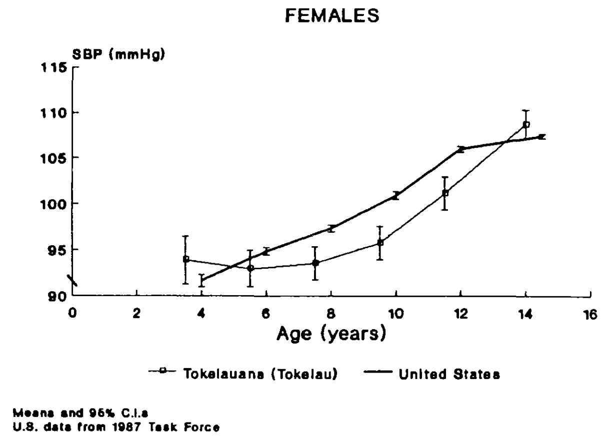


(U.S./U.K. studies include Comstock, 1957; Johnson, 1965; Hamilton, 1954; Miall 1958)

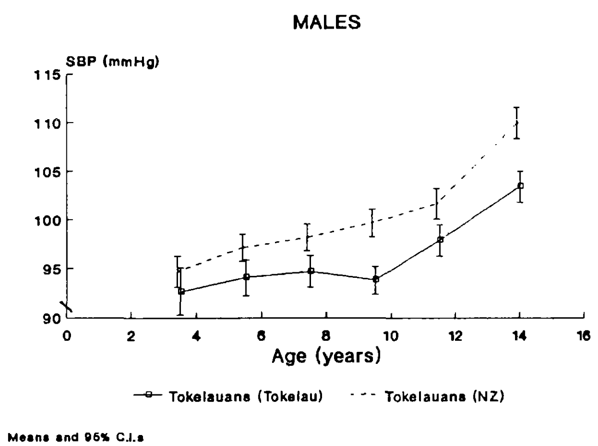
Figure 2.7 COMPARISON OF CHILDHOOD SYSTOLIC BLOOD PRESSURES OF TOKELAUAN CHILDREN ON TOKEKAU WITH (UPPER) AMERICAN CHILDREN AND (LOWER) TOKELAUAN CHILDREN ON NEW ZEALAND.

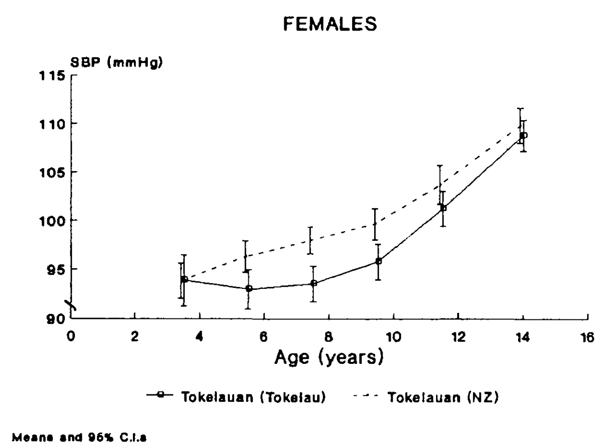
TOKELAU-UNITED STATES COMPARISON





TOKELAU-NEW ZEALAND MIGRANTS COMPARISON





CHAPTER 3

DESIGN AND METHODOLOGY OF THE NINE TOWNS STUDY OF BLOOD PRESSURE IN CHILDREN

3.1 INTRODUCTION

This chapter will describe the main features of the design of the Nine Towns Study of Blood Pressure in Children. The first section (3.2) deals with the aims and objectives of the study, the second (3.3) with the selection and invitation of participants, the third (3.4) with the survey measurement procedures and the fourth (3.5) with the analyses proposed at the outset. A full discussion of the rationale for the procedures used is provided in Appendix I.

3.2 AIMS AND OBJECTIVES OF THE STUDY

3.2.1 AIMS

3.2.1.1 To determine whether the striking pattern of between-town differences in mean blood pressures observed in middle-aged men in the British Regional Heart Study is already established in children 5-7 years of age.

3.2.1.2 To examine the contribution of personal factors (e.g. height, weight, skinfold thickness), environmental factors (e.g. ambient temperature) and markers of early life experience (e.g. birthweight) to individual and between-town differences in blood pressure in childhood.

3.2.1.3 To establish the basis for in-depth studies which will permit exploration of the reasons why blood pressure rises with age at different rates in different population groups.

3.2.2 SPECIFIC OBJECTIVES

3.2.2.1 Estimation of town mean blood pressures

To permit the estimation of town mean systolic pressures with a standard error of 0.5 mmHg (for both sexes combined) and 2 mmHg (sex-specific), assuming a between-subject standard deviation of 10 mm Hg for systolic blood pressure.

3.2.2.2 Detection of differences in blood pressure between individual towns

To permit the detection of a true difference of 2 mmHg difference in the average blood pressure of children (both sexes) between any two towns at the 0.02 level with a power of 80%.

3.2.2.3 Detection of differences in blood pressure between town groups

To permit the detection of a mean difference in systolic pressure of 2.5 mmHg between towns with high and low adult town mean blood pressures at the 5% level with a power of 80%, assuming a standard deviation of 1 mmHg for the mean blood pressures of towns within the groups with high and low levels of adult blood pressure.

3.3 SELECTION AND INVITATION OF PARTICIPANTS

3.3.1 SAMPLE SIZE CONSIDERATIONS

The aims of the study called for both the precise estimation of the blood pressure level in each town and the demonstration of a consistent relationship between town mean blood pressure levels in children and adults. These aims required a balance between the number of subjects within each town and the number of towns in the study. The decision to include nine towns with four hundred subjects in each town was based on the calculations described below.

3.3.1.1 Number of towns required A sample of 3 low and 3 high blood pressure towns would permit a true difference of 2.5 mmHg in systolic pressure between high and low towns to be detected at the 5% level with a power of 80%. (This assumed a standard deviation of 1 mmHg for the town mean blood pressures of the towns with high adult blood pressure levels and low adult blood pressure levels). Such an analysis aimed to generalize the statement that towns with higher (or lower) adult blood pressure levels had higher (or lower) blood pressure levels in children from the study towns to all such towns in Britain. The inclusion of towns with intermediate adult pressures was favoured because it would allow correlations between child and adult blood pressures to be examined using a full range of town adult mean pressures.

3.3.1.2 Number of children in each town It was calculated that the measurement of 400 subjects (200 boys, 200 girls) in each town would permit the estimation of town mean systolic pressures with a standard error of 0.50 mmHg, assuming a between-subject standard deviation of 10 mm Hg. This sample size would also permit the estimation of sex-specific means with a standard error of 2 mmHg and would enable town mean systolic blood pressure differences of 2 mmHg to be detected between pairs of towns with a power of 80% at $p = 0.02$. Assuming a response rate of 80%, the invitation of some 500 children in each town would be required.

3.3.2 SELECTION OF TOWNS

Nine towns were selected from the original 24 towns of the British Regional Heart Study in order to provide a full range of mean adult blood pressure levels. In order to take both systolic and diastolic blood pressure into account, mean arterial pressure (diastolic pressure + 1/3 systolic pressure minus diastolic pressure) was used as a basis for selection. The three towns with the highest mean arterial pressure (Dunfermline, Carlisle and Merthyr Tydfil) and three of the four towns with the lowest mean arterial pressure (Guildford, Exeter and Scunthorpe) were included. Shrewsbury was excluded from the selection of low towns in the earlier Nine Towns Study (Adults), because no single General Practice of sufficient size and with a practice population representative of that in the study town could be identified. Shrewsbury was also excluded from the study in children, to ensure comparability with the Nine Towns Study (Adults). Three towns with intermediate levels of mean arterial pressure (100-105 mmHg), stratified geographically to include one town in South Eastern England (Maidstone), one town in Northern England (Southport) and one town in Scotland (Ayr), were also included. The geographical distribution of the towns selected is shown in Figure 3.1.

3.3.3 SELECTION OF SCHOOLS AND CHILDREN

The aim of the selection procedure was to obtain a sample of between 500 and 550 children aged between 5.0 and 7.5 years who would be representative of the children in the particular town from which the sample was drawn. A two-stage sampling procedure was used, with a stratified random sampling of schools being followed by random sampling of classes within the selected schools. The stages in the sampling procedure were as follows:-

3.3.3.1 Obtaining data for school selection

A list of all primary schools in the town, with details of the number of subjects aged five and six years in each school, was obtained from the relevant Local Authority. From this information the proportion of children attending schools of each religious denomination could be determined, as could the proportion of children attending non-denominational schools of various sizes.

3.3.3.2 Sampling of denominational schools

The proportion of children attending schools of each denominational type was examined. If a particular denomination accounted for less than 5% of all children, no schools of that denomination were included in the sample. If the proportion was 5% or more, denominational schools were included so that the proportion of children attending these schools was matched as closely as possible to the proportion of schools overall. Thus, if the proportion of children attending schools of a particular denomination was 5-14%, one school was selected; if the proportion was between 15 and 24% two schools were selected and so on. The selection of denominational schools was carried out randomly from the list of schools, but excluding those with less than 50 children in the five and six year age-groups combined.

3.3.3.3 Selection of non-denominational (i.e. county primary) schools

Once denominational school sampling was completed all county primary schools in the town were classified on the basis of their size into three categories on the basis of the numbers of pupils aged five and six - small (less than 100 pupils); intermediate (100-150 pupils); large (more than 150 pupils). The proportion of subjects attending each size of school was calculated and used to determine the allocation of schools of different sizes in the county primary sample. The sites of all county primary schools were then plotted on a town map and the town divided into four concentric zones, each containing as close to a quarter of the county primary population as possible, given the constraints imposed by variable school sizes. A minimization method (Pocock SJ, 1983) was used to select large, then intermediate and finally small schools in each quadrant in such a way that selection of schools of various sizes was balanced as evenly as possible between the four quadrants. Schools with less than 50 children in the five and six year age-groups combined were again excluded from the sample.

3.3.3.4 Special circumstances

Exceptions to this sampling procedure were made for schools which were very large. Any school attended by 15% or more of the total school population of five and six year-olds in a particular town was allocated two (or more as appropriate) of the ten school-day visits.

3.3.3.5 Sampling within each school

Within each school selected, a random sample of two classes, one of five year-olds and one of six year-olds, was selected to provide fifty-five to sixty children who were invited for examination.

3.3.3.6 Procedure for replacing schools not taking part in the study

If any school selected was unable to take part it was replaced by the school matching most closely in its characteristics. The replacement school was selected to be in the same denominational group. In the case of county primary schools, the replacement school was also matched on location and size, location being considered the more important factor.

3.3.4 APPROACH TO PARTICIPANTS

The approval and co-operation of each local Education Authority was obtained by writing to the Chief Education Officer. The Authority was asked to provide a list of Primary Schools with numbers of five and six year-old children in each school to enable sampling to be carried out. A standard letter was sent to the Head Teachers of all schools selected to seek their co-operation. A standard invitation letter, signed by the Head Teacher, was sent to the parents of all children in the classes selected two weeks before the survey, seeking written consent to the participation of their child. The invitation letter provided full details of the study proceedings and specified the week of the survey team's visit. Parents were not routinely invited to attend but those making specific enquiries were assured that they were welcome to do so. A reminder letter was sent to all parents not replying to the initial invitation after one week.

3.4 SURVEY PROCEDURES

3.4.1 TIMING AND ORDER OF TOWN SURVEYS

The pilot survey was carried out in March 1987 and the main field survey between May 1987 and February 1988. Towns were examined consecutively in three sets, each set containing one town with intermediate, one with high and one with low adult pressure surveyed in that order (Table 3.1). The survey of each town was carried out over a two week period (i.e. ten working days), with each of the ten schools normally being visited for one day. After a two-week interval the visit to the next town was carried out. The examination of each set of towns was carried out over a total of ten weeks, to minimize possible changes in measurement or climate within the group.

3.4.2 OBSERVERS

All measurements were made by two trained nurses. In each measurement session (morning or afternoon) one nurse made all anthropometric measurements while the other carried out blood pressure measurements. Duties were alternated for each session so that each nurse carried out approximately half the anthropometric measurements and half the blood pressure measurements in each school. Both nurses received detailed training in all techniques of measurement before the field studies commenced. In the event of illness, the surviving observer was to carry out blood pressure measurements, with a substitute carrying out anthropometric measurements.

3.4.3 SCHOOL SURVEY

Working procedures were standardized as far as possible in all schools visited. Measurements were carried out in the Medical Room or similar accommodation between 0900 and 1215 hours and between 1315 and 1530 hours. The temperature of the examination room was maintained close to 20^{o}C by the use of an electric heater or fan. The noise level in the room was strictly controlled. Children were called in groups of four and were examined in underclothes without shoes after resting for approximately five minutes. Measurements were made in the following order:-

3.4.3.1 Height was measured to the nearest millimetre with a Holtain electronic stadiometer, using the supported stretch technique (Tanner JM et al, 1965).

3.4.3.2 Weight was measured to the nearest 0.1 kg with a Soehnle digital electronic weighing scale.

3.4.3.3 Arm circumference (right side) was measured to the last complete millimetre at the midpoint between the acromial process and the olecranon with the arm pendant. Determination of the midpoint was carried out with the arm flexed.

3.4.3.4 Skinfold thickness (left side) Two measurements of triceps and subscapular skinfold thickness measurements were made using a Holtain skinfold caliper, with a pressure of 10 gm/mm^2, according to the method of Tanner and Whitehouse (Tanner JM and Whitehouse RH, 1962).

3.4.3.5 Blood Pressure The Dinamap 1846SX automated oscillometric blood pressure recorder was used to record three blood pressure measurements at one minute intervals, with the child seated and the arm supported at chest level. A full explanation of the procedure was given to the child at the time of application of the blood pressure cuff. Cuff size was selected in accordance with the modified American Heart Association criteria recommended by Prineas and colleagues (Prineas 1980a). These were designed to ensure not only that cuff bladder width was at least 40% of arm circumference (as specified by the American Heart Association) but also that cuff bladder length was sufficient to encircle 90% of the arm circumference. However, these criteria were relaxed slightly, with the adult cuff being used up to arm circumferences of 25 cm, in order to avoid the introduction of an extra cuff size for a very small number of subjects. The Dinamap cuff sizes used at different arm circumferences are summarized in Table 3.2.

3.4.3.6 Resting pulse rate This was provided automatically at the time of blood pressure measurement by the Dinamap machine.

3.4.3.7 Time of day The time at which the first blood pressure measurement was taken were documented for each subject.

3.4.3.8 Temperature Indoor temperature, measured to the nearest $0.1^{\circ}C$

with an RS digital thermocouple, was recorded at the time of blood pressure measurement for each subject. Hourly outdoor temperature data were available from local meterological stations for seven of the nine study towns.

3.4.3.9 Other factors recorded At the time of blood pressure measurement the observers noted the child's ethnic origin (based on appearance), whether or not a parent was present, whether or not the child talked during measurement and whether or not the child appeared anxious or distressed by the measurements.

3.4.3.10 Questionnaire (Appendix III) A self administered questionnaire was given out to the parents of all children participating in the measurement survey to take home to their parents. A reminder letter, together with a second questionnaire, was sent out two weeks later to all parents who had not returned the original. Information on the subjects listed below was sought, using previously validated questions from the Census or the General Household Survey wherever possible.

(i) Demographic including date and place of birth, family size, and history of recent migration.

(ii) Personal history of child, including birthweight, feeding pattern in infancy, previous serious illnesses and current medications.

(iii) Parental medical history with particular reference to measurement of blood pressure and reported findings.

(iv) Socioeconomic factors including details of parental employment, educational level, car ownership and housing tenure.

3.4.4 MONITORING OF INSTRUMENT PERFORMANCE DURING THE STUDY

3.4.4.1 Blood pressure measurement

(i) Internal monitoring The Dinamap blood pressure recorder was checked and calibrated daily throughout the study using the procedures laid down in the instrument manual (Critikon, 1986). These included checks on the electricity supply and the performance of electronic components. In addition, the performance of the pressure transducer was monitored using a standard mercury column.

(ii) External monitoring During the course of the main study three comparisons of blood pressure measurement by the study Dinamap 1846SX instrument were conducted, using a single Hawksley random zero sphygmomanometer as a reference instrument. Children aged between five and seven years and attending three primary schools (separate from those of the main study) were invited to take part in this investigation. A total of 152 subjects (response rate 82%) took part. The first comparison was conducted before the survey of the first study town, the second after the fifth town and the third after the ninth and final town - a period of ten months in total. All measurements were made by the two study observers, each of whom made approximately half of the paired blood pressure measurements on each occasion. Training and testing in auscultatory blood pressure measurement was carried out using standard training tapes (Rose G, 1965) less than a week before the beginning of each stage of the investigation. All measurements were made on the right arm with the subject seated after 5 minutes' rest. Two consecutive blood pressure measurements were taken one minute apart on each participant, one with a Dinamap 1846 SX and one with a Hawksley random-zero sphygmomanometer. Both instruments were different from those used in the adult study. The order in which the instruments were used was determined randomly and balanced for each session. The Hawksley random zero instrument was fitted with a 20 mmHg cam, enabling the use of the same initial inflation pressure with both instruments (170 mmHg). Diastolic pressure was recorded at the point of muffling of Korotkow sounds (Phase IV) because of the difficulty in recording Phase V pressures accurately in children (Frohlich ED et al, 1988). The criteria described above (Prineas RJ et al, 1980a) were used to select appropriate cuff sizes with both instruments (Table 3.2).

3.4.4.2 Height, weight and skinfold thickness measurements The stadiometer was calibrated against a standard meter rule daily. The 'zero' of the electronic scales was checked daily and the instrument checked against a series of standard weights between 1 and 20 kg between each set of three towns. The skinfold calipers were checked against a standard measure between each set of three towns.

3.4.4.3 Temperature measurements The RS digital thermometer was checked daily against a standard alcohol thermometer. The mean differences between instruments were monitored for evidence of drift in measurement.

3.4.5 REPORTING OF ABNORMAL BLOOD PRESSURE LEVELS

Liaison was established with the school health service in each town before the visit of the survey team, and a protocol for communicating abnormally high blood pressure results established. At the end of each measurement session all blood pressure measurements were reviewed. Details of subjects with blood pressure levels considered to require immediate action (normally a sustained systolic pressure $\geq$ 150 mmHg and/or a sustained diastolic pressure $\geq$ 100 mmHg) were notified to the school health service within 24 hours. Subjects with blood pressures in the top two percentiles of the blood pressure distribution for each six month age-group were made available to the school health service at the end of the field survey visit to each town.

3.4.6 ETHICAL APPROVAL: CONFIDENTIALITY

The study design conformed to the ethical guidelines established by the Medical Research Council (Medical Research Council, 1985). Ethical approval was obtained from the British Paediatric Association and from the Medical Ethical Committee of each study town.

3.4.7 PILOT STUDY

All examination procedures and the study questionnaire were tested formally with 400 subjects in one town. This took place in Ipswich six weeks before the beginning of the main study so that any modifications needed could be made to the protocol for the main study.

3.5 <u>MAIN ANALYSES PROPOSED AT OUTSET</u>

3.5.1 To determine whether there are marked between-town differences in the average blood pressure of 5-7 year-olds.

3.5.2 To establish whether between-town differences in childhood blood pressure are related to the between-town differences previously described in adult mean blood pressure level, and to between-town differences in adult cardiovascular mortality rates.

3.5.3 To assess the contribution of the personal and environmental variables measured to the explanation of individual variability of blood pressure, using univariate and multivariate analysis.

3.5.4 To assess the contribution of those explanatory variables which contribute towards individual variability to the explanation of between-town differences in blood pressure.

3.6 PARTICIPATION IN THE STUDY

A full account of the participation of schools and children is given in Appendix I. Of 88 schools invited, ten declined and were replaced by schools matching closely in denomination, size and location. Of 4877 individual subjects invited, 4056 (83%) participated in the measurement survey and had complete triplicate blood pressure measurements made. Parental questionnaires were returned for 3693 subjects (76%), although not all were completed in full. A summary of the numbers of subjects on which analyses of the main variables are based is presented in Table 3.3.

3.7 VALIDATION OF STUDY METHODOLOGY

A detailed account of the rationale and validation of important aspects of the study methodology is given in Appendix I.

TABLE 3.1 NINE TOWNS STUDY OF BLOOD PRESSURE IN CHILDREN: ORDER OF EXAMINATION OF STUDY TOWNS

ORDER	MONTH	YEAR	TOWN	ADULT BP STATUS
-	March	1987	Ipswich	(Pilot)
1	May	1987	Maidstone	Intermediate
2	June	1987	Dunfermline	High
3	July	1987	Guildford	Low
4	September	1987	Ayr	Intermediate
5	October	1987	Carlisle	High
6	November	1987	Exeter	Low
7	December	1987	Southport	Intermediate
8	January	1988	Merthyr Tydfil	High
9	February	1988	Scunthorpe	Low

TABLE 3.2 PROTOCOL FOR SELECTION OF APPROPRIATE CUFF SIZE FOR DINAMAP AND HAWKSLEY INSTRUMENTS, BASED ON MEASUREMENT OF RIGHT ARM CIRCUMFERENCE.

DINAMAP 1846SX OSCILLOMETRIC RECORDER

ARM CIRCUMFERENCE (cm)		CUFF SIZE	
Lower	Upper	Bladder dimensions (cm)	Type
11.6	12.7	12 x 7	Infant
12.8	16.6	15 x 9	Child
16.7	25.0	22 x 12	Adult

HAWKSLEY RANDOM ZERO SPHYGMOMANOMETER

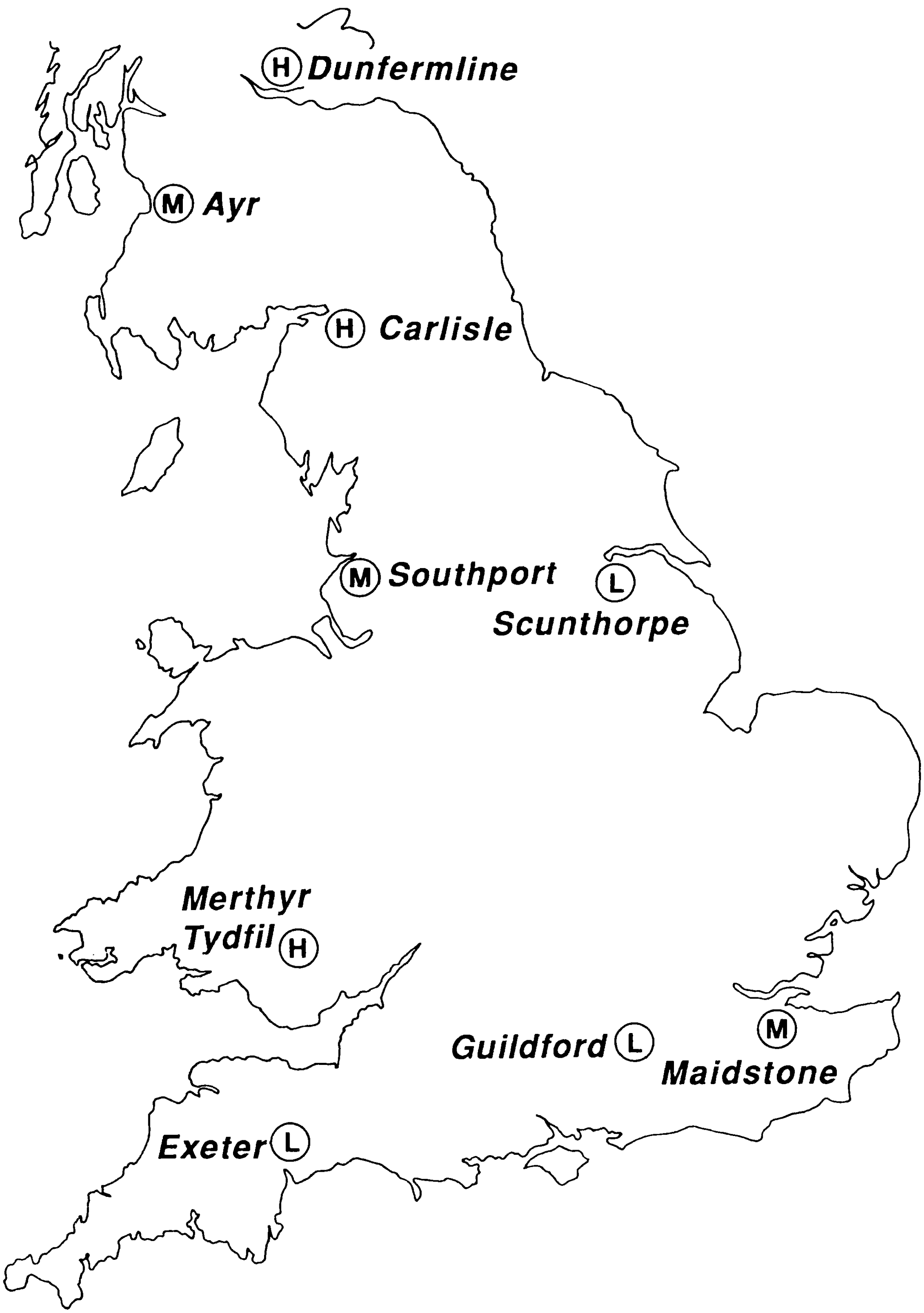
ARM CIRCUMFERENCE (cm)		CUFF SIZE	
Lower	Upper	Bladder dimensions (cm)	Type
10.0	12.7	12 x 6	Infant
12.8	18.3	18 x 9	Child
18.4	26.0	23 x 12	Adult

TABLE 3.3 NUMBERS OF PARTICIPANTS AND RESPONSE RATES IN THE NINE TOWNS STUDY OF BLOOD PRESSURE IN CHILDREN

	N	(%)
INVITED	4877	(100)
MEASUREMENT SURVEY		
Blood pressure and pulse rate	4056	(83)
Body build (height, weight, arm circumference, skinfold measurements)	4056	(83)
Circumstances of blood pressure measurement (child state and presence/absence of parent)	4048	(83)
PARENTAL QUESTIONNAIRES RETURNED	3693	(76)
Information supplied on the following variables:-		
SOCIAL FACTORS (chapter 4)		
Housing tenure	3602	(74)
Age full-time education of head of household completed	3599	(74)
Longest-held occupation of head of household	3472	(71)
(grouped into Registrar General classes I-V)	3355	(69)
Current employment status of head of household	3397	(70)
(grouped into employed and unemployed categories)	3135	(64)
EARLY INFLUENCES (chapter 6)		
Birthweight	3591	(74)
Number of older and younger sibs	3559	(73)
Maternal age	3542	(73)

(All data are based on the age-group 5.00 to 7.50 years)

Figure 3.1 NINE TOWNS STUDY OF BLOOD PRESSURE IN CHILDREN: GEOGRAPHIC DISTRIBUTION OF TOWNS



Towns are classified on the basis of observed adult male blood pressures as high (H) medium (M) and low (L)

CHAPTER 4

BLOOD PRESSURE AND ITS CORRELATES IN INDIVIDUALS

4.0 SUMMARY

In this chapter, the factors related to blood pressure levels in individuals are examined. Strong relationships between age, body build (particularly weight and height) and blood pressure are described. Of several weight-for-height indices examined, weight/height^2 (body mass index) appeared most useful. Pulse rate and a parental history of high blood pressure are also related to blood pressure in childhood, while social factors show little or no association. Circumstances of measurement, particularly time of day and the presence of anxiety in the child, are related to blood pressure level. The methods used to standardize blood pressure for age, sex and body build in subsequent analyses are discussed.

4.1 INTRODUCTION

This chapter will describe the overall patterns of blood pressure and its correlates in individuals. Personal factors examined include age, sex, body build measures and pulse rate. The influence of social factors and a parental history of high blood pressure on blood pressure in childhood will also be examined. Finally, the influence of circumstances of measurement (including the day and time of measurement, the state of the child at examination and the presence or absence of a parent) on blood pressure will be explored.

Some individual correlates of blood pressure are not considered in this chapter because they can be more appropriately be dealt with elsewhere. In particular, a group of factors which may be related to blood pressure in individuals but whose relations may date from an early age (including birthweight, birth order, maternal age and infant feeding patterns) are considered in chapter 6. One factor which may be related to blood pressure measurement, environmental temperature, is of particular importance in the context of between-town differences in blood pressure and is therefore considered in chapter 5.

4.2 SUBJECTS, METHODS AND PRESENTATION OF RESULTS

4.2.1 SUBJECTS

Relationships between personal factors and blood pressure are based on 4056 subjects, 2027 girls and 2029 boys, aged between 5.00 and 7.50 years (83% of those invited) in whom triplicate blood pressure measurements were recorded. Seventeen children were noted to be of Asian origin (thirteen of these in Scunthorpe), with no representation from other ethnic minority groups; blood pressures in this group were not markedly different from those of other subjects and have been included in all analyses. The analyses of social factors and a parental history of high blood pressure are based on 3693 subjects (76% of those invited) for whom parental questionnaires were returned. However, analyses of particular social variables are based on the slightly smaller numbers of subjects for whom responses to particular questions were recorded (Table 3.3). Analyses of parental history of blood pressure are restricted to 3524 mothers and 2633 fathers who actually reported having had a blood pressure measurement made.

4.2.2 METHODS

Social class The longest-held occupation of both parents was classified into the Registrar General's six social classes using the 1980 Office of Population Censuses and Surveys manual. The head of household was determined by the standard method used for the Childhood Decennial Supplement (Office of Population, Censuses and Surveys, 1988); the head of household was male in 89% using this classification.

4.2.3 DATA PRESENTATION

All subjects included in the analyses had three complete blood pressure readings, recorded at one minute intervals. A systematic fall in average blood pressure between the first and third readings was observed for both systolic and diastolic pressure (Figure 4.1). All results presented in this and the following chapters are based on the mean of the three readings. The distribution of systolic and diastolic blood pressures is normal, with minimal skew to the right. Mean values are therefore used as a summary measure of blood pressures throughout. Blood pressure readings are standardized for the effect of cuff bladder size, using the procedure described in Appendix I, which makes all measurements comparable with those made by the child cuff. Standardization of measurements for other factors, including age, sex and body build is discussed in section 4.5.

4.3 RESULTS

4.3.1 PERSONAL FACTORS AND BLOOD PRESSURE

4.3.1.1 Age, sex and blood pressure

Overall mean systolic and diastolic blood pressure levels in the study population are presented in Table 4.1. No important difference in systolic pressure level is observed between the sexes. However, mean diastolic pressure level is 0.7 mmHg higher in girls than in boys, a small but statistically highly significant sex difference. The relationships between age and blood pressure are reasonably linear over the study age-range (Figure 4.2). The corresponding regression coefficients (Table 4.1) suggest that systolic blood pressure rises by 2.43 mmHg/year and diastolic pressure by 1.18 mmHg/year. Rates of blood pressure rise with age are essentially similar in both sexes; although estimates of slopes are slightly larger in girls, the differences are small and do not approach conventional levels of statistical significance.

4.3.1.2 Body build and blood pressure

Weight, height and both triceps and subscapular skinfold measurements all show reasonably linear univariate relationships with blood pressure; those for weight and blood pressure are shown in Figure 4.3. The linear regression coefficients for these relationships, both in the univariate form and when standardized for age (a procedure which has little effect on the findings) are presented in Table 4.2. In order to compare the relative strength of the relationships for height, weight and skinfold measurements, standardized regression coefficients (representing the change in blood pressure for a one standard deviation in the measure of body build) have been calculated. These coefficients, presented at the foot of Table 4.2, emphasize that the relationships between weight and blood pressure and between height and blood pressure are considerably stronger than those of the skinfold thickness measures.

The four measures of body build examined are strongly related to one another and also to age (Table 4.3A). An assessment of the independent contribution of each factor is therefore necessary. This process has been carried out in two stages; first, to establish the best summary measures of weight and height and, second, to establish whether triceps and subscapular skinfold thickness are related to blood pressure once height and weight are considered. Finally, it is important to consider whether age is independently related to blood pressure once the effects of body build are taken into account.

(i) Establishing the best summary measure of weight and height Height and weight are both independently related to blood pressure, although the associations are reduced in magnitude in both cases by taking the other factor into account (Table 4.2). However, the use of two strongly interrelated measures of body build is unsatisfactory. In order to define the independent components of these variables, the best approach appeared to be the use of height, together with a weight-for-height index independent of height, as used in earlier studies (Voors AW et al, 1977). The criteria for an acceptable weight-for-height index have been summarized elsewhere (Billewicz WZ et al, 1962; Roland-Cachera MF et al, 1982). Apart from independence of height, the criteria include a high positive correlation with weight and a high positive correlation with direct measures of fatness, such as skinfold measures. Four possible weight-for-height indices - weight/height, weight/height^2, weight/height^3 and weight/height^p - have been examined. Weight/height^p is the weight/height index which achieves the greatest independence of height in a particular population, and is determined by regressing the logarithm of weight on the logarithm of height for all subjects and taking the exponential of the regression coefficient. The value of p in this study population as a whole is 2.41; a small but highly statistically significant difference in p between sexes (2.47 for girls, 2.34 for boys; p = 0.02) is taken into account in the analyses presented. The results in Table 4.3B summarize the characteristics of the weight-for-height indices in the study population. While weight/height^p is effectively independent of height, the correlations between weight/height^2, weight/height^3 and height are not strong. Predictably, the index which is most strongly related to weight is weight/height. Examining the relationships of these indices with two independent measures of obesity, triceps skinfold and subscapular skinfold, correlations are highest for weight/height^2 and for weight/height^p. Overall, it appears that weight/height^p and weight/height^2 comply most closely with the criteria for a weight-for-height index specified above. Neither of these indices is strongly related to age in this study population. An examination of the proportion of variance in blood pressure accounted for by each of these indices in combination with height gave virtually identical values for each one (12.3% for systolic pressure, 4.4% for diastolic pressure). In this study weight/height^2 (body mass index, BMI) has been selected as the weight-for-height index for use in further analyses because it fulfils the criteria outlined above reasonably well, is conceptually simple and is already widely used. Its general applicability is an advantage over the weight/height^p index, which varies between different study populations.

(ii) Independence of skinfold thickness measurements The relationships between triceps and subscapular skinfold measurements and blood pressure, standardized for body mass index and for body mass index and height, are presented in Table 4.4. The inclusion of body mass index results in attenuation of these relationships, with only that between triceps skinfold and diastolic pressure remaining statistically significant. The inclusion of both height and body mass index effectively removes all association between skinfold measures and blood pressure level. More detailed analyses (not presented) provide no evidence for an independent effect of skinfold thickness at different levels of body mass index, particularly in the top fifth of the body mass index distribution.

(iii) Body build, age and blood pressure Age and body build (particularly weight and height) are closely related in children in this study population (Table 4.3A). It has already been demonstrated (Table 4.2) that the relationships of height and weight to blood pressure are virtually independent of age. To what extent do changes in body build account for the relationship between age and blood pressure in this study population? This question is addressed at the foot of Table 4.4. It is apparent that adjustment for height and body mass index together, or even for height alone, completely removes the relationship between age and blood pressure. Body mass index per se has little effect. These findings suggest that changes in body build, particularly in height, could account for the rise in blood pressure with age in the 5-7 year age-group. The findings also have important implications for the standardization of blood pressure measurement in this population, considered in the next section.

4.3.1.3 Pulse rate and blood pressure

Pulse rate shows smooth linear univariate relationships with both systolic and diastolic blood pressure (Figure 4.4). The corresponding linear regression coefficients (Table 4.5A) suggest that a rise in pulse rate of five beats/minute is associated with a rise of 1.1 mmHg in systolic pressure and of 0.85 mmHg in diastolic pressure. However, pulse rate tends to fall with increasing age (by -2.17 min^{-1} per year) and, independently of age, with increasing height (by -0.27 min^{-1} per cm). Pulse rate also shows a weak inverse relationship with body mass index. It is therefore not surprising that adjustment for the effect of age, or, more particularly, height, increases the strength of the relationships between pulse and blood pressure (Table 4.5A). Conversely, adjustment for the effect of pulse rate results in an increase of the strengths of the relationships between height and blood pressure and, marginally, those between body mass index and blood pressure (Table 4.5B).

4.3.2 SOCIAL FACTORS AND BLOOD PRESSURE

Four measures of social position and blood pressure have been examined in these analyses. Three of these measures are based on characteristics of the child's head of household, defined using standard OPCS definitions (Office of Population, Censuses and Surveys, 1988), which in this study population refer to the father in 89% of cases. These measures are parental social class (based on longest held occupation), parental education (based on the age at which full-time education was completed) and parental employment status (based on the current work position). The fourth measure is housing tenure, included because it is a powerful predictor of morbidity and mortality in other studies (Office of

Population, Censuses and Surveys, 1990b). The relationships between these factors and blood pressure are presented in Table 4.6. For social class, although average blood pressures appear to increase slightly between social classes I and V, the differences are small. There is no strong evidence either of heterogeneity or of a trend between the social class groups, either for systolic or diastolic pressure. Although the analysis based on parental education shows slightly lower average blood pressures in the group whose parent completed education at 25 years or more, the differences are very small and are likely to be explained by chance. However, for employment status and housing tenure, differences in blood pressure between categories are apparent. Mean blood pressure levels are significantly lower in subjects whose parents are unemployed and in those living in rented accommodation.

In considering the relationships between social measures and blood pressure, the influence of other factors may need to be taken into account. Town of residence is potentially important, being related both to social class (Table AI.2B) and to blood pressure (Table 5.1). However, adjustment for town does not affect the relationships between social measures and blood pressure described. Body build also needs to be taken into consideration, being strongly related to blood pressure (section 4.3.1.2) and to the social factors examined. The relationships between body build and social factors are presented in detail in Table 4.7. Mean heights vary between social groups, being greater in children from households in which the head of household's longest-held occupation is non-manual, in which the head of household is in full-time employment and in which accommodation is owned rather than rented. Mean height is also greater when parental education was completed after 16 years, although there is little evidence of a trend above this age. In contrast to the findings for height, body mass index shows little tendency to vary between social groups. Pulse rate, another potential confounding factor, also shows little relation to social factors (Table 4.7).

In view of the differences in height between the social groups, it was considered important to examine the effect of height standardization on the relationships between social factors and blood pressure. Even after standardizing for height, social class and parental education show no relationship with either systolic or diastolic blood pressure. Adjustment for height produces marked attenuation of the differences in blood pressure between housing tenure groups, although they remain statistically significant (adjusted systolic difference 0.8 mmHg, p = 0.006; adjusted diastolic difference 0.6 mmHg, p = 0.004). In the case of employment status, adjustment for height renders the blood pressure differences non-significant (adjusted systolic difference 0.5 mmHg, p = 0.20; adjusted diastolic difference 0.5 mmHg, p = 0.06).

4.3.3 PARENTAL HISTORY OF HIGH BLOOD PRESSURE

The mean systolic and diastolic blood pressures of those subjects whose mothers or fathers reported a history of high blood pressure are compared with subjects in which no such history was obtained in Table 4.8A. Children in whom either parent reported a history of high blood pressure had systolic blood pressures on average at least 1.0 mm higher and diastolic pressures on average 0.7 mmHg or more than those who did not. These differences, which were similar in boys and girls, achieved conventional levels of statistical significance for both paternal and maternal analyses. The presence of a history of high blood pressure in both parents (n = 101) was not associated with a marked difference in pressures from the presence of a history in one parent. Children with either a positive maternal or a paternal history of high blood pressure had a higher mean body mass index than those who did not, while there was no consistent pattern of differences in height (Table 4.8A). However, adjustment for differences in body mass index and height produced only a slight reduction in the differences in blood pressure level between those with and those without a parental history (Table 4.8B). The circumstances under which maternal blood pressure was high - in pregnancy (n = 1145), at other times (n = 58), or both (n = 206) appeared to have no important effect on blood pressure level (results not presented).

4.3.4 CIRCUMSTANCES OF MEASUREMENT AND BLOOD PRESSURE

Although every effort was made to standardize the circumstances of measurement in the study, certain factors could not be controlled. These included the day of the week, the time of day, indoor and outdoor temperature, the state of the child on examination (whether talking or silent, whether perceived to be anxious or not), and the presence or absence of a parent. With the exception of temperature (discussed separately in section 5.4.1.3), the influence of these factors on blood pressure measurement are discussed below.

4.3.4.1 Day of week and time of day

No consistent relationship between the day of week and blood pressure was observed (Figure 4.5). The relationship between hour of day and blood pressure is presented in Figure 4.6. Mean systolic blood pressure levels were higher in the afternoon session than in the morning (mean difference 1.5 mmHg, s.e. 0.3 mmHg, $p < 0.0001$). A small but non-significant difference in the same direction was observed for diastolic pressure (mean difference 0.2 mmHg, s.e. 0.2 mmHg, $p = 0.24$).

4.3.4.2 Child and parental factors

The relationships between the circumstances of measurement and blood pressure are presented in Table 4.9A. Whether or not the child was talking during measurement did not apparently influence systolic pressure, although mean diastolic pressures and pulse rates were significantly higher in children who talked. Children who were identified as anxious by the nurse observer had markedly higher mean systolic and diastolic pressures and pulse rates than those who did not. Children who were accompanied by a parent had on average lower mean blood pressure and pulse rates than those who were not. However, only the difference in systolic pressure achieved statistical significance. The effect of adjustment for differences in pulse rates between the groups is presented in Table 4.9B. While the differences are reduced in size, all remain statistically significant, suggesting that pulse rate can only explain a part of the differences in blood pressure. Adjustment for height and body mass index had no important effect on the results described.

4.4 COMMENTARY

4.4.1 BLOOD PRESSURE LEVELS

In order to compare the blood pressure levels observed in the present study with those of other studies, a correction must be made for the systematic overestimation of systolic pressure by the Dinamap 1846SX (Appendix I). The mean blood pressures after correction (92.7 mmHg systolic, 58.9 mmHg diastolic at age 6.24 years) are similar to those in the most recent American Task Force (Task Force on Blood Pressure Control in Children, 1987). This is not surprising, given the earlier demonstration of the similarity of blood pressures in British and American children between the earlier American Task Force (Task Force on Blood Pressure Control in Children, 1977) and the Brompton Study (de Swiet M et al, 1984). However, the systolic values are several millimetres lower than those reported in a review of recent European studies (de Man SA et al, 1991). The reasons for this discrepancy, which reflects a difference between the systolic pressures recorded in American and European studies, have yet to be resolved.

4.4.2 AGE AND BLOOD PRESSURE

A marked rise in both systolic and diastolic blood pressure with age was observed over the five to seven year age-group studied. Although this observation is based on cross-sectional data, it is consistent with earlier reports, including those based on longitudinal studies. While blood pressure shows little tendency to rise between six weeks and five years (Voors AW et al 1978; de Swiet M et al, 1984), a progressive rise in blood pressure from five years through to adolescence has been documented in many studies (Task Force on Blood Pressure Control in Children, 1987) and appears to be characteristic of virtually all populations in childhood (Brotons C et al, 1989). The rises in blood pressure described in the present study, 2.43 mmHg/year for systolic pressure and 1.18 mmHg/year for diastolic pressure, are comparable with those of the American Task Force (Task Force on Blood Pressure Control in Children, 1987).

4.4.3 SEX AND BLOOD PRESSURE

In the present study no important sex difference was observed in systolic pressure. However, girls had slightly but significantly higher diastolic pressures than boys. These findings are consistent with those of earlier studies, which have reported no marked sex differences in blood pressure between two and five years (Voors AW et al, 1978), while between six and eleven years blood pressures appear to be slightly higher in girls (Weiss NS et al, 1973), for reasons which are not understood.

4.4.4 BODY BUILD AND BLOOD PRESSURE

All measures of body build examined (weight, height, triceps skinfold and subscapular skinfold) show strong positive associations with blood pressure. These associations are particularly strong for height and weight, which are however strongly intercorrelated. In identifying an appropriate weight-for-height index, it was apparent that there was little to choose between the different indices studied, and particularly between weight/height^2 and weight/height^p. These observations were consistent with those of Ballew and her colleagues, who found little difference between weight/height2, weight/height3 and weight/height^b in a study of 3601 Chicago children from several ethnic backgrounds (Ballew C et al, 1990). The decision to use body mass index (weight/height2) in the present study was strongly influenced by its simplicity and ease of comparability between studies. While other studies of blood pressure in childhood have used different weight-for-height indices, their criteria for selecting an appropriate index varied. The use of a weight/height3 index for 5-14 year-olds in the Bogalusa Heart Study was justified on the grounds that this index was closely related to body fatness in adults (Voors AW et al, 1976). The use of a weight/height1.7 index in four to five year-olds in the Brompton Study was justified on the grounds that the index was independent of age (de Swiet M et al, 1984). If there is to be general agreement on the use of weight-for-height indices in blood pressure studies in childhood, agreement on the criteria for selecting a suitable index must be the first step.

In the present study, adjustment for the effect of height and body mass index removed the influence of skinfold measurements on blood pressure. Adjustment for the effect of height removed the effect of age. The observations on skinfold thickness are consistent with the findings of the large Minneapolis Children's Blood Pressure Study, which found no independent relationship between triceps skinfold and blood pressure once height and weight were in the model (Prineas RJ et al, 1980b). However, the findings did not confirm Prineas' suggestion that skinfold thickness is independently related to blood pressure in the top fifth of the body mass index distribution (Prineas RJ et al, 1980b). The observation that the relationship between age and blood pressure can be completely accounted for by taking height into account is also consistent with the findings of earlier studies (Prineas RJ et al, 1980a; de Swiet M et al, 1984). The observation that height and blood pressure are more strongly associated than age and blood pressure supports earlier suggestions that height-standardization is a more useful procedure in childhood than age-standardization (Andre JL et al, 1980; de Swiet M and Dillon MJ, 1989). However, as de Swiet has pointed out, the independence of the timing of weight gain and blood pressure rise in childhood suggests that growth is not the only factor responsible for the rise in blood pressure observed during childhood (de Swiet M et al, 1984).

4.4.5 PULSE RATE AND BLOOD PRESSURE

The positive association between pulse rate and blood pressure observed here is consistent with reports from earlier studies (Hofman A et al, 1981). The association is independent of body build. While sympathetic arousal probably accounts for at least part of the association, the contribution of physical fitness, which may be a determinant both of pulse rate and blood pressure in childhood (Hofman A and Walter H, 1989), has still to be established.

4.4.6 SOCIAL FACTORS AND BLOOD PRESSURE

In the present study, no relationship was observed between childhood blood pressure and either parental social class or parental education. Mean blood pressures were marginally lower in subjects whose head of household was unemployed or who lived in rented rather than owned accommodation, but these differences were attenuated after adjustment for body build. The findings do not support the earlier observation by Beresford and Holland in 472 Harrow children that systolic blood pressures at 5-8 years may be approximately four millimetres higher in unskilled manual occupational groups than in professional groups (Beresford SA and Holland WW, 1973). The present study, based on a considerably larger number of subjects, is able to exclude an effect of that magnitude with considerable confidence. Moreover, the use of several social indices suggests that the absence of social differences is not simply an artefact arising from the use of parental social class alone (MacIntyre S and West P, 1991). Earlier studies have suggested that a social class gradient in blood pressure has been present in adults in Great Britain during the past two decades (Marmot MG et al, 1978; Pocock SJ et al, 1986). The present results could be explained either by the fact that social class differences do not develop until later in childhood, or by the fact that they will not appear in this cohort. Recent studies in British adolescents have been conflicting. A study in London described differences in the average blood pressure of 15-16 year-olds attending two schools with different social characteristics, but presented no information on the relations between social factors and blood pressure in individuals (Khaw KT and Marmot MG, 1983). In a study of 1009 15 year-olds from the West of Scotland, no consistent relationship between a variety of social factors (including the social class of both parents, parental education and housing tenure) and blood pressure was observed (MacIntyre S and West P, 1991). Further studies, particularly longitudinal studies, may help in resolving whether or not social differences in blood pressure are still emerging.

4.4.7 PARENTAL HISTORY OF HIGH BLOOD PRESSURE AND BLOOD PRESSURE IN CHILDHOOD

In this study population a history of high blood pressure in either parent is associated with higher levels of blood pressure in childhood; relationships for maternal and paternal history appear to be of similar magnitude. Self-reported parental blood pressure status is a very indirect measure of parental blood pressure and it is likely that the strength of the familial relationship is being underestimated. However, the finding is qualitatively consistent with earlier studies which have measured parental blood pressures and have demonstrated associations between the blood pressures of parents and offspring in this age-group (Zinner SH et al, 1971; Beresford SA and Holland WW, 1973). The results of the present study suggest that while differences in body build, particularly body mass index, between children with and without a parental history of high blood pressure may contribute to the differences observed, they are unlikely to be wholly responsible. It has been noted earlier that familial blood pressure associations may be apparent very early in life (section 2.3.2.5). The relationship between parental history of blood pressure and other early influences on blood pressure, particularly birthweight, birth order and maternal age, may therefore be of particular interest; this issue is examined in chapter 6.

4.4.8 CIRCUMSTANCES OF BLOOD PRESSURE MEASUREMENT

Of the circumstances of measurement examined, the factors most strongly related to blood pressure are the time of day, anxiety in the child apparent to the observer, and the presence of a parent at examination. The time of day effect, with higher blood pressure readings in the afternoon session, is consistent with the observations of other investigators (Prineas RJ et al, 1980a; de Swiet M et al, 1984). The differences in blood pressure between those children identified as anxious and those not so identified are marked. However, the proportion of children identified as being markedly anxious was very small (2.4%) and the exclusion of this small number of children from the analyses described in the following chapters makes no important difference to the findings. Similarly, the proportion of children accompanied by a parent (0.9%) was very small and the exclusion of these children had no important influence on the main study results. The absence of a relationship between the day of the week and blood pressure in children is of interest because an association between day of week and blood pressure has been described in middle-aged British men, with blood pressures being highest at the beginning of the week (Wannamethee G and Shaper AG, 1991). The absence of an association in children would be consistent with the explanation put forward in adults, namely that the differences reflect variation in alcohol intake between different days of the week.

4.5 A NOTE ON THE STANDARDIZATION OF BLOOD PRESSURE MEASUREMENT

The most important factors for which standardization of blood pressure measurement is required are age, sex and body build. Standardization for the effect of cuff bladder size (which is performed throughout) is discussed in detail in Appendix I.

4.5.1 STANDARDIZATION FOR AGE AND SEX

4.5.1.1 Age On the basis of the age-blood pressure relationships described in Table 4.1, standardization has been carried out using linear modelling techniques and assuming that age-blood pressure slopes are identical in boys and girls. All estimates have been standardized to the mean age of the study population, 6.24 years.

4.5.1.2 Sex The majority of analyses presented have examined determinants of blood pressure in boys and girls combined, subsequently fitting an interaction term to test for sex differences in relationships. Combining blood pressure values for boys and girls presents no difficulties for systolic blood pressure, for which mean values are almost identical for the two sexes (Table 4.1). However, in view of the small but highly statistically significant difference in diastolic pressure between sexes, sex standardization has been carried out for all diastolic analyses by fitting a -1/+1 term for sex in all analyses; the analyses therefore provide estimates for a 1:1 ratio of boys to girls.

4.5.2 STANDARDIZATION FOR BODY BUILD

The analyses described in section 4.3.1.2 demonstrate that both height and a component of weight which is independent of height are separately related to blood pressure. Where standardization for body build is needed, height and body mass index have been used together. No allowance has been made for measures of skinfold thickness, since these are not related to blood pressure once the effects of height and body mass index are taken into account. Since age is unrelated to blood pressure once height and body mass index are included in regression analyses (Table 4.4), this model provides standardization for age in its own right. Although the inclusion of pulse rate in models relating body build and blood pressure appears to increase the influence of height on blood pressure (Table 4.5), this probably reflects two different facets of the relationship between body build and blood pressure, one a positive relationship, the other an inverse relationship acting through pulse rate, reflecting the tendency for pulse rate to fall as size increases. Because adjustment for pulse rate may create an artificial distinction in the components of the relationship between body build and blood pressure, no such adjustment has been made. However, where it has been considered important to establish whether differences in blood pressure could be accounted for by differences in pulse rate, adjustment for this factor (usually in combination with age and sex) has been made in linear regression analyses.

TABLE 4.1 AGE, SEX AND BLOOD PRESSURE

	FEMALE	MALE	ALL	
Number of subjects	2027	2029	4056	
MEAN VALUES	Mean (s.e)	Mean (s.e.)	Mean (s.e.)	p (no sex difference)
Age (years)	6.24 (0.01)	6.24 (0.01)	6.24 (0.01)	0.99
SBP (mmHg)	100.7 (0.2)	100.8 (0.2)	100.8 (0.1)	0.83
DBP (mmHg)	59.2 (0.1)	58.5 (0.1)	58.9 (0.1)	0.001

AGE SLOPES	Slope (s.e.)	Slope (s.e.)	Slope (s.e.)	p (no sex difference)
SBP (mmHg/year)	2.46 (0.33)	2.41 (0.32)	2.43 (0.23)	0.90
DBP (mmHg/year)	1.15 (0.23)	1.21 (0.22)	1.18 (0.16)	0.85

TABLE 4.2 BODY BUILD AND BLOOD PRESSURE: RELATIONSHIPS FOR FOUR FACTORS

	BLOOD PRESSURE (mmHg)					
	SYSTOLIC			DIASTOLIC		
	Regression coefficient	(s.e.)	p	Regression coefficient	(s.e.)	p
WEIGHT (kg)						
Adjustment						
None	0.89	(0.03)	<0.0001	0.38	(0.03)	<0.0001
Age	0.86	(0.04)	<0.0001	0.33	(0.03)	<0.0001
Height	0.76	(0.06)	<0.0001	0.25	(0.04)	<0.0001
HEIGHT (cm)						
Adjustment						
None	0.43	(0.02)	<0.0001	0.20	(0.02)	<0.0001
Age	0.44	(0.03)	<0.0001	0.19	(0.02)	<0.0001
Weight	0.10	(0.03)	0.004	0.09	(0.02)	<0.0001
TRICEPS SKINFOLD (mm)						
Adjustment						
None	0.52	(0.05)	<0.0001	0.23	(0.03)	<0.0001
Age	0.51	(0.05)	<0.0001	0.23	(0.03)	<0.0001
SUBSCAPULAR SKINFOLD (mm)						
Adjustment						
None	0.74	(0.06)	<0.0001	0.30	(0.04)	<0.0001
Age	0.73	(0.06)	<0.0001	0.28	(0.04)	<0.0001

(Regression coefficients refer to regression of blood pressure on variables specified in the left-hand column.)

STANDARDIZED REGRESSION COEFFICIENTS RELATING FOUR MEASURES OF BODY BUILD TO BLOOD PRESSURE

		STANDARDIZED REGRESSION COEFFICIENT (mmHg/1S.D.)	
Measure	Standard deviation	Systolic	Diastolic
Weight (kg)	3.47 kg	3.09 mmHg	1.32 mmHg
Height (cm)	6.06 cm	2.61 mmHg	1.21 mmHg
Triceps skinfold (mm)	2.87 mm	1.49 mmHg	0.66 mmHg
Subscapular skinfold (mm)	2.18 mm	1.61 mmHg	0.65 mmHg

TABLE 4.3A INTERRELATIONSHIPS OF FOUR BODY BUILD MEASURES AND AGE

	AGE	WEIGHT	HEIGHT	TRICEPS SKINFOLD	SUBSCAPULAR SKINFOLD
AGE	-	0.41***	0.58***	-0.03	-0.00
WEIGHT	-	-	0.78***	0.56***	0.50***
HEIGHT	-	-	-	0.14***	0.13***
TRICEPS SKINFOLD	-	-	-	-	0.74***

Figures are Pearson correlation coefficients. *** $p < 0.0001$

TABLE 4.3B PROPERTIES OF FOUR WEIGHT-FOR-HEIGHT INDICES

	WEIGHT-FOR-HEIGHT INDEX			
VARIABLE CORRELATED	WEIGHT/HEIGHT	WEIGHT/HEIGHT^2	WEIGHT/HEIGHT^3	WEIGHT/HEIGHT^p
HEIGHT	0.60	0.22	-0.29	0.009
WEIGHT	0.97	0.78	0.37	0.63
TRICEPS SKINFOLD	0.59	0.64	0.55	0.62
SUBSCAPULAR SKINFOLD	0.66	0.72	0.63	0.71
AGE	0.30	0.07	-0.23	-0.05

Figures are Pearson correlation coefficients. All correlations are standardized for sex.

TABLE 4.4 BODY BUILD, AGE AND BLOOD PRESSURE: ADJUSTMENT FOR THE EFFECT OF BODY MASS INDEX AND HEIGHT.

	BLOOD PRESSURE (mmHg)					
	SYSTOLIC			DIASTOLIC		
	Regression coefficient	(s.e.)	p	Regression coefficient	(s.e.)	p
HEIGHT (cm)						
Adjustment						
None	0.43	(0.02)	<0.0001	0.20	(0.02)	<0.0001
Body mass index	0.37	(0.02)	<0.0001	0.18	(0.02)	<0.0001
BODY MASS INDEX (kg/m^2)						
Adjustment						
None	1.34	(0.08)	<0.0001	0.46	(0.06)	<0.0001
Height	1.08	(0.08)	<0.0001	0.34	(0.06)	<0.0001
TRICEPS SKINFOLD (mm)						
Adjustment						
None	0.52	(0.05)	<0.0001	0.23	(0.03)	<0.0001
Body mass index	0.04	(0.06)	0.50	0.09	(0.04)	0.02
Body mass index and height	-0.03	(0.05)	0.54	0.01	(0.04)	0.85
SUBSCAPULAR SKINFOLD (mm)						
Adjustment						
None	0.74	(0.06)	<0.0001	0.30	(0.04)	<0.0001
Body mass index	0.03	(0.09)	0.75	0.07	(0.06)	0.25
Body mass index and height	-0.10	(0.07)	0.17	-0.07	(0.05)	0.18
AGE (years)						
Adjustment						
None	2.43	(0.23)	<0.0001	1.18	(0.16)	<0.0001
Body mass index	2.19	(0.23)	<0.0001	1.09	(0.16)	<0.0001
Height	-0.18	(0.27)	0.51	0.03	(0.20)	0.87
Body mass index and height	0.08	(0.27)	0.78	0.11	(0.19)	0.57

(Regression coefficients refer to regression of blood pressure on variables specified in the left-hand column).

TABLE 4.5A PULSE RATE AND BLOOD PRESSURE

	BLOOD PRESSURE (mmHg)					
	SYSTOLIC			DIASTOLIC		
	Regression coefficient	(s.e.)	p	Regression coefficient	(s.e.)	p
PULSE RATE						
Adjustment						
None	0.22	(0.01)	<0.0001	0.17	(0.01)	<0.0001
Age	0.24	(0.01)	<0.0001	0.18	(0.01)	<0.0001
Height	0.26	(0.01)	<0.0001	0.19	(0.01)	<0.0001
Body mass index	0.23	(0.01)	<0.0001	0.17	(0.01)	<0.0001
Height and body mass index	0.27	(0.01)	<0.0001	0.19	(0.01)	<0.0001

(Regression coefficients refer to regression of blood pressure on variables specified in the left-hand column).

TABLE 4.5B PULSE RATE, BODY BUILD AND BLOOD PRESSURE

	BLOOD PRESSURE (mmHg)					
	SYSTOLIC			DIASTOLIC		
	Regression coefficient	(s.e.)	p	Regression coefficient	(s.e.)	p
HEIGHT (cm)						
Adjustment						
Body mass index	0.37	(0.02)	<0.0001	0.18	(0.02)	<0.0001
Body mass index and pulse	0.45	(0.02)	<0.0001	0.23	(0.02)	<0.0001
BODY MASS INDEX (kg/m2)						
Adjustment						
Height	1.08	(0.08)	<0.0001	0.34	(0.06)	<0.0001
Height + pulse	1.09	(0.08)	<0.0001	0.35	(0.06)	<0.0001

(Regression coefficients refer to regression of blood pressure on variables specified in the left-hand column).

TABLE 4.6 SOCIAL FACTORS AND BLOOD PRESSURE

		BLOOD PRESSURE (mmHg)			
		SYSTOLIC		DIASTOLIC	
SOCIAL CLASS	N	Mean	(s.e.)	Mean	(s.e.)
I	208	100.9	(0.6)	59.1	(0.4)
II	846	100.6	(0.3)	58.8	(0.2)
IIIN	497	101.3	(0.5)	59.3	(0.3)
IIIM	1282	101.1	(0.2)	59.0	(0.2)
IV	434	100.4	(0.5)	58.8	(0.3)
V	88	101.5	(1.0)	59.8	(0.7)
Test for heterogeneity		$p = 0.54$		$p = 0.89$	
Test for trend		$p = 0.96$		$p = 0.81$	
PARENTAL EDUCATION COMPLETED	N	Mean	(s.e.)	Mean	(s.e.)
≤ 16 years	2475	100.9	(0.2)	59.0	(0.1)
17-19 years	626	101.0	(0.4)	59.1	(0.3)
20-25 years	449	100.6	(0.4)	58.9	(0.3)
> 25 years	49	99.8	(1.3)	57.3	(0.9)
Test for heterogeneity		$p = 0.88$		$p = 0.46$	
Test for trend		$p = 0.50$		$p = 0.43$	
EMPLOYMENT STATUS	N	Mean	(s.e.)	Mean	(s.e.)
Employed	2843	100.9	(0.2)	59.0	(0.1)
Unemployed	292	99.8	(0.5)	58.2	(0.4)
Test for difference		$p = 0.04$		$p = 0.06$	
HOUSING TENURE	N	Mean	(s.e.)	Mean	(s.e.)
Owner occupier	2471	101.2	(0.2)	59.2	(0.1)
Renting	1131	100.0	(0.3)	58.3	(0.2)
Test for difference		$p = 0.001$		$p < 0.0001$	

Figures presented are means (standard errors). All figures are adjusted for age and (diastolic pressure only) for sex. Social class, employment status and parental education refer to the head of the household.

TABLE 4.7 SOCIAL FACTORS, BODY BUILD AND PULSE RATE

		HEIGHT (cm)		BODY MASS INDEX (kg/m2)		PULSE RATE (min^{-1})	
SOCIAL CLASS	N	Mean	(s.e.)	Mean	(s.e.)	Mean	(s.e.)
I	208	118.0	(0.3)	15.50	(0.11)	92.1	(0.8)
II	846	117.7	(0.2)	15.61	(0.05)	92.5	(0.4)
IIIN	497	117.5	(0.3)	15.51	(0.07)	92.9	(0.5)
IIIM	1282	116.7	(0.1)	15.56	(0.04)	93.1	(0.3)
IV	434	116.4	(0.3)	15.53	(0.08)	92.9	(0.5)
V	88	116.0	(0.6)	15.71	(0.17)	93.8	(1.2)
Test for heterogeneity		$p < 0.0001$		$p = 0.76$		$p = 0.74$	
Test for trend		$p < 0.0001$		$p = 0.99$		$p = 0.14$	
PARENTAL EDUCATION COMPLETED	N	Mean	(s.e.)	Mean	(s.e.)	Mean	(s.e.)
≤ 16 years	2475	116.6	(0.1)	15.60	(0.03)	92.9	(0.2)
17-19 years	626	117.8	(0.2)	15.56	(0.06)	92.3	(0.4)
20-25 years	449	117.5	(0.2)	15.40	(0.07)	92.9	(0.5)
> 25 years	49	117.7	(0.7)	15.75	(0.22)	91.2	(1.6)
Test for heterogeneity		$p < 0.0001$		$p = 0.08$		$p = 0.51$	
Test for trend		$p < 0.0001$		$p = 0.06$		$p = 0.48$	
EMPLOYMENT STATUS	N	Mean	(s.e.)	Mean	(s.e.)	Mean	(s.e.)
Employed	2843	117.1	(0.1)	15.56	(0.03)	92.8	(0.2)
Unemployed	292	116.2	(0.2)	15.55	(0.07)	92.9	(0.5)
Test for difference		$p < 0.0001$		$p = 0.94$		$p = 0.88$	
HOUSING TENURE	N	Mean	(s.e.)	Mean	(s.e.)	Mean	(s.e.)
Owner occupier	2471	117.3	(0.1)	15.56	(0.03)	92.9	(0.2)
Renting	1131	116.1	(0.1)	15.59	(0.05)	92.4	(0.3)
Test for difference		$p < 0.0001$		$p = 0.60$		$p = 0.17$	

Figures presented are means (standard errors). All figures are adjusted for age and sex. Social class, employment status and parental education refer to the head of the household.

TABLE 4.8A PARENTAL HISTORY OF HIGH BLOOD PRESSURE AND BLOOD PRESSURE IN CHILDHOOD

MATERNAL HISTORY	YES (N = 1409)		NO (N = 2115)		
	Mean	(s.e.)	Mean	(s.e.)	p (no diff.)
Systolic B.P. (mmHg)	101.6	(0.2)	100.3	(0.2)	<0.0001
Diastolic B.P. (mmHg)	59.3	(0.2)	58.6	(0.1)	0.002
Height (cm)	117.1	(0.1)	116.8	(0.1)	0.04
Body Mass Index (kg/m^2)	15.65	(0.04)	15.52	(0.03)	0.01

PATERNAL HISTORY	YES (N = 257)		NO (N = 2376)		
	Mean	(s.e.)	Mean	(s.e.)	p (no diff.)
Systolic B.P. (mmHg)	101.8	(0.5)	100.7	(0.2)	0.04
Diastolic B.P. (mmHg)	60.1	(0.4)	58.9	(0.1)	0.004
Height (cm)	116.4	(0.3)	117.0	(0.1)	0.06
Body Mass Index (kg/m^2)	15.78	(0.10)	15.53	(0.03)	0.02

TABLE 4.8B DIFFERENCES IN BLOOD PRESSURE BETWEEN THOSE WITH AND WITHOUT A PARENTAL HISTORY OF HIGH BLOOD PRESSURE: ADJUSTMENT FOR BODY BUILD.

	BLOOD PRESSURE DIFFERENCE (mmHg)					
	SYSTOLIC			DIASTOLIC		
MATERNAL HISTORY	Mean	(s.e.)	p	Mean	(s.e.)	p
Adjustment						
Age (sex)	1.2	(0.3)	<0.0001	0.6	(0.2)	0.002
Height and body mass index	0.9	(0.3)	0.0009	0.5	(0.2)	0.007
PATERNAL HISTORY						
Adjustment						
Age (sex)	1.1	(0.5)	0.04	1.2	(0.4)	0.004
Height and body mass index	0.9	(0.5)	0.08	1.2	(0.4)	0.004

Figures presented are means (standard errors). All figures are adjusted for age and (diastolic pressure only) for sex.

TABLE 4.9A CIRCUMSTANCES OF MEASUREMENT AND BLOOD PRESSURE IN CHILDREN.

CHILD TALKING	YES (N = 1132)		NO (N = 2916)		
	Mean	(s.e.)	Mean	(s.e.)	p (no diff.)
Systolic B.P.(mmHg)	100.8	(0.3)	100.7	(0.2)	0.90
Diastolic B.P.(mmHg)	59.4	(0.2)	58.7	(0.1)	0.002
Pulse (min^{-1})	93.6	(0.3)	92.5	(0.2)	0.002

CHILD ANXIOUS	YES (N = 96)		NO (N = 3952)		
	Mean	(s.e.)	Mean	(s.e.)	p (no diff.)
Systolic B.P.(mmHg)	108.1	(0.9)	100.6	(0.1)	<0.0001
Diastolic B.P.(mmHg)	62.6	(0.6)	58.8	(0.1)	<0.0001
Pulse (min^{-1})	99.6	(1.1)	92.6	(0.2)	<0.0001

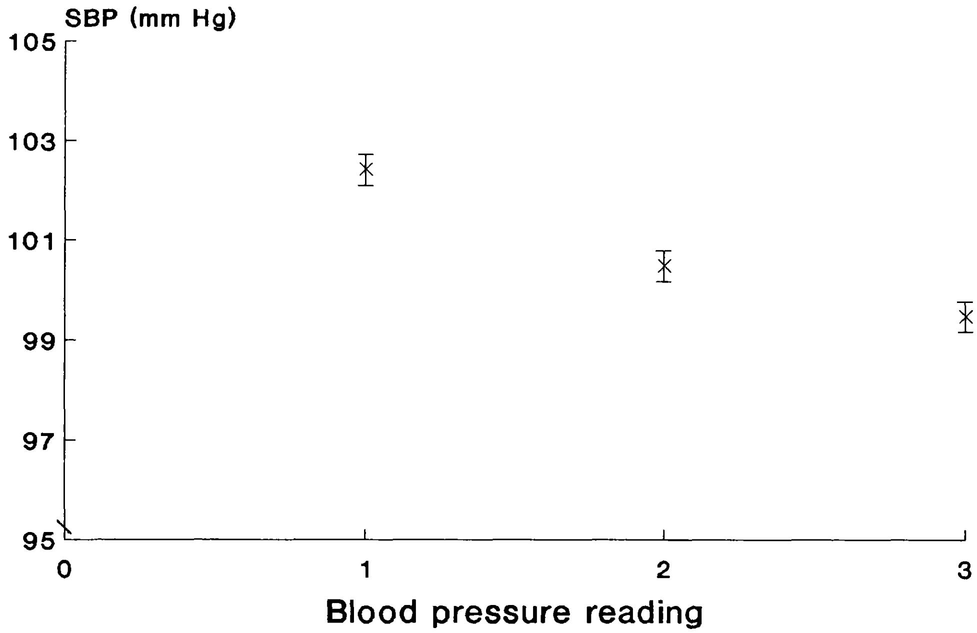
PARENT PRESENT	YES (N = 36)		NO (N = 4012)		
	Mean	(s.e.)	Mean	(s.e.)	p (no diff.)
Systolic B.P.(mmHg)	97.0	(1.4)	100.8	(0.1)	0.008
Diastolic B.P.(mmHg)	58.4	(1.0)	58.9	(0.1)	0.65
Pulse (min^{-1})	91.3	(1.9)	92.8	(0.2)	0.42

TABLE 4.9B DIFFERENCES IN BLOOD PRESSURE BY CIRCUMSTANCES OF MEASUREMENT, WITH AND WITHOUT ADJUSTMENT FOR PULSE RATE

	SYSTOLIC			DIASTOLIC		
TALKING/NOT TALKING	Mean	(s.e.)	p value	Mean	(s.e.)	p value
Adjustment						
None	0.1	(0.3)	0.80	0.7	(0.2)	0.002
Pulse	-0.2	(0.3)	0.51	0.4	(0.2)	0.04
ANXIOUS/NOT ANXIOUS						
Adjustment						
None	7.5	(0.9)	<0.0001	3.8	(0.6)	<0.0001
Pulse	5.9	(0.9)	<0.0001	2.5	(0.6)	<0.0001
PARENT PRESENT/ABSENT						
Adjustment						
None	3.8	(1.4)	0.007	0.5	(1.0)	0.61
Pulse	3.6	(1.4)	0.01	0.5	(1.0)	0.60

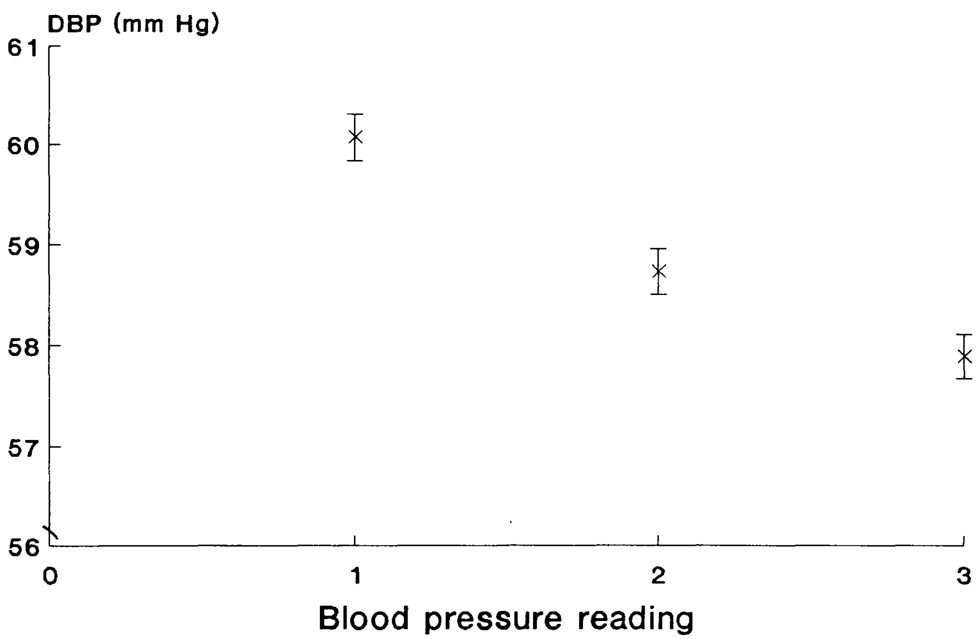
Figure 4.1 BLOOD PRESSURE AT FIRST, SECOND, THIRD READINGS

SYSTOLIC



Means and 95% C.I.s

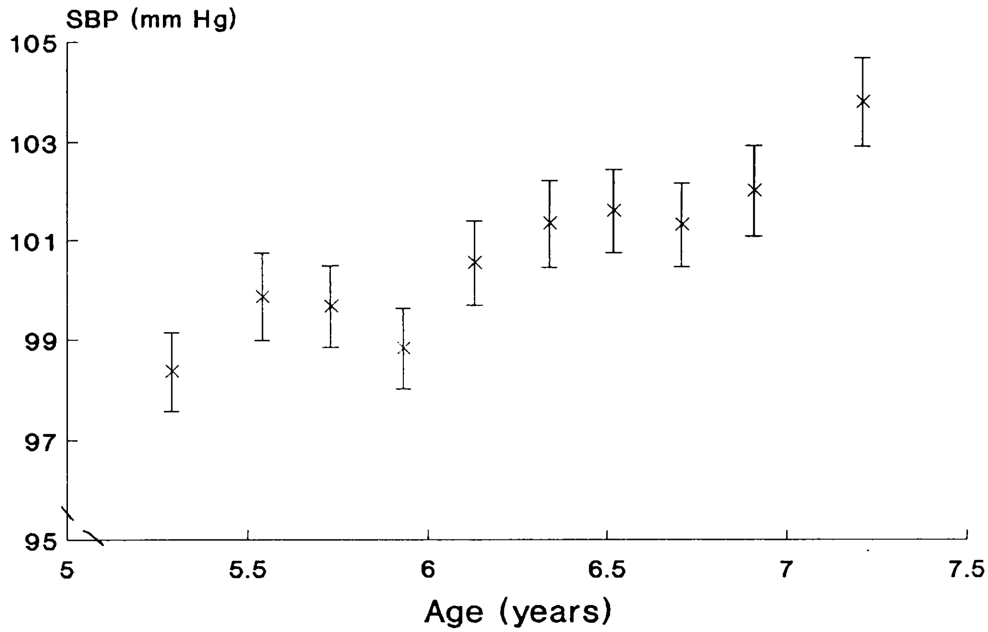
DIASTOLIC



Means and 95% C.I.s

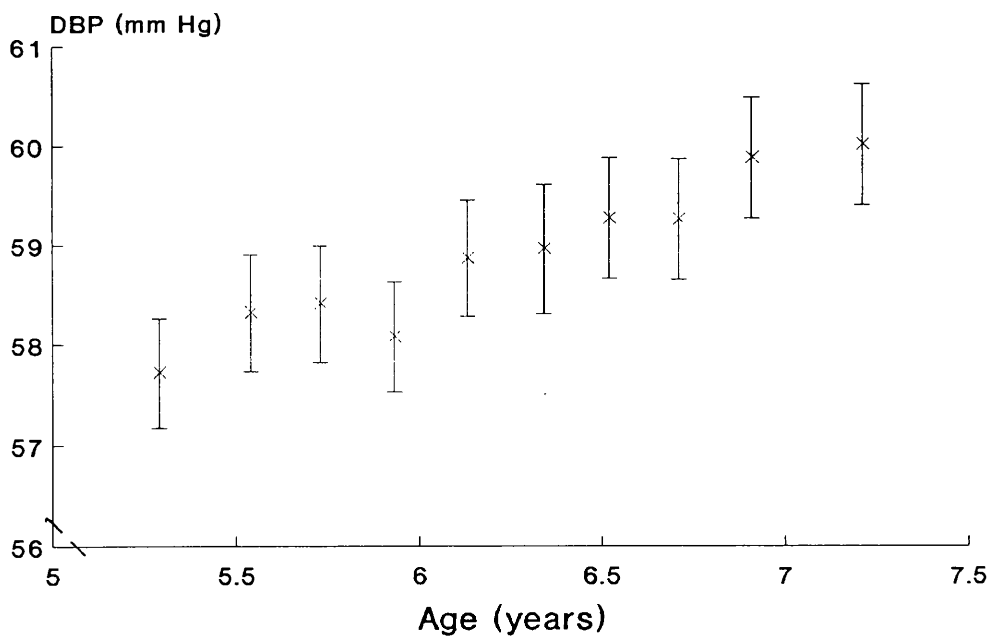
Figure 4.2 AGE AND BLOOD PRESSURE

SYSTOLIC



Means and 95% C.I.s

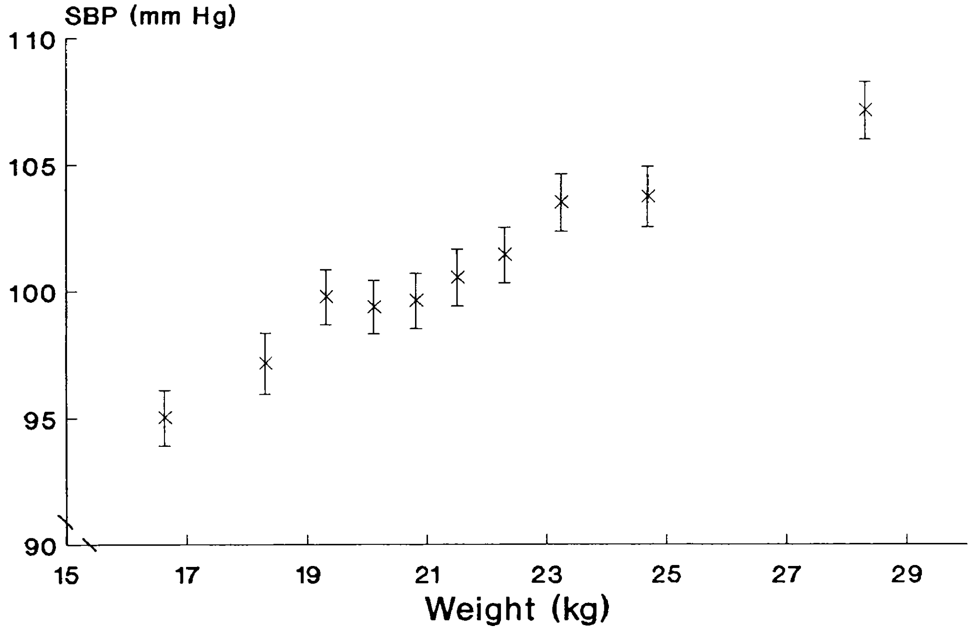
DIASTOLIC



Means and 95% C.I.s

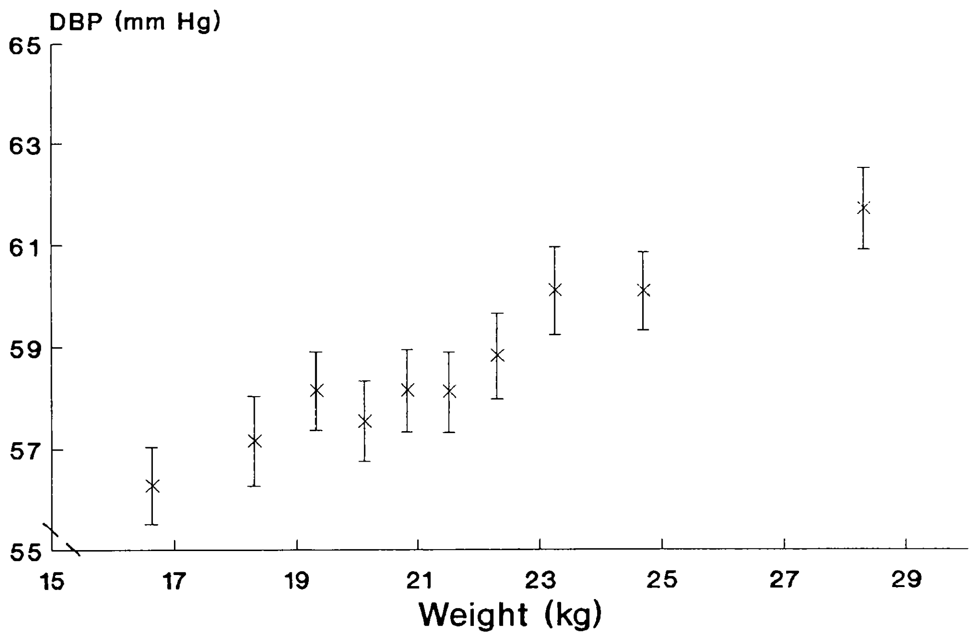
Figure 4.3 WEIGHT AND BLOOD PRESSURE

SYSTOLIC



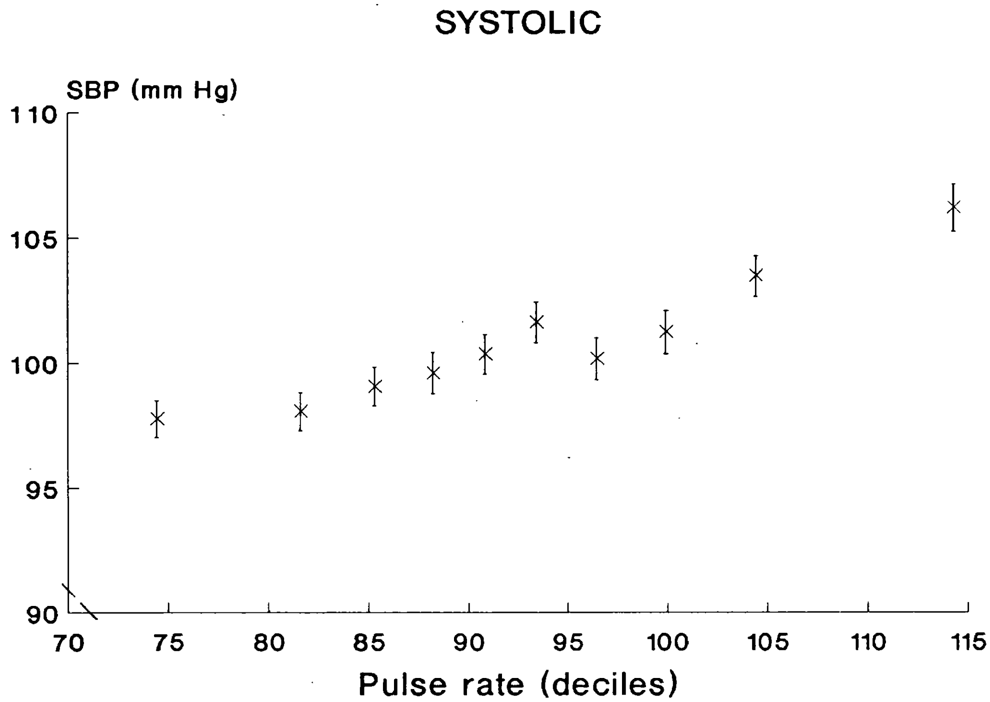
Means and 95% C.I.s

DIASTOLIC

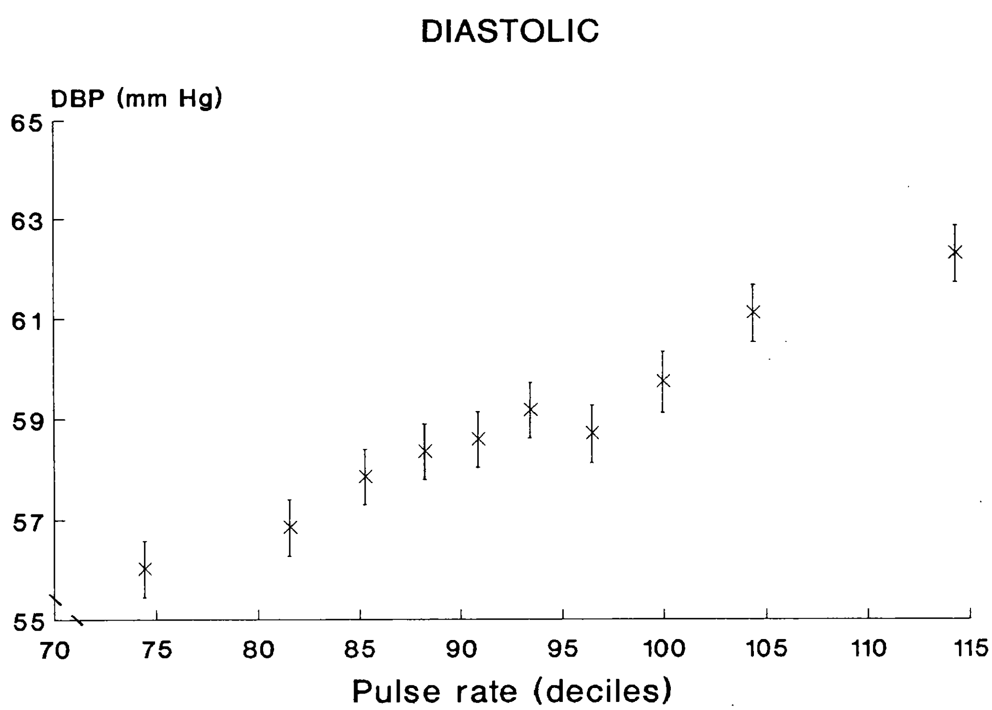


Means and 95% C.I.s

Figure 4.4 PULSE RATE AND BLOOD PRESSURE



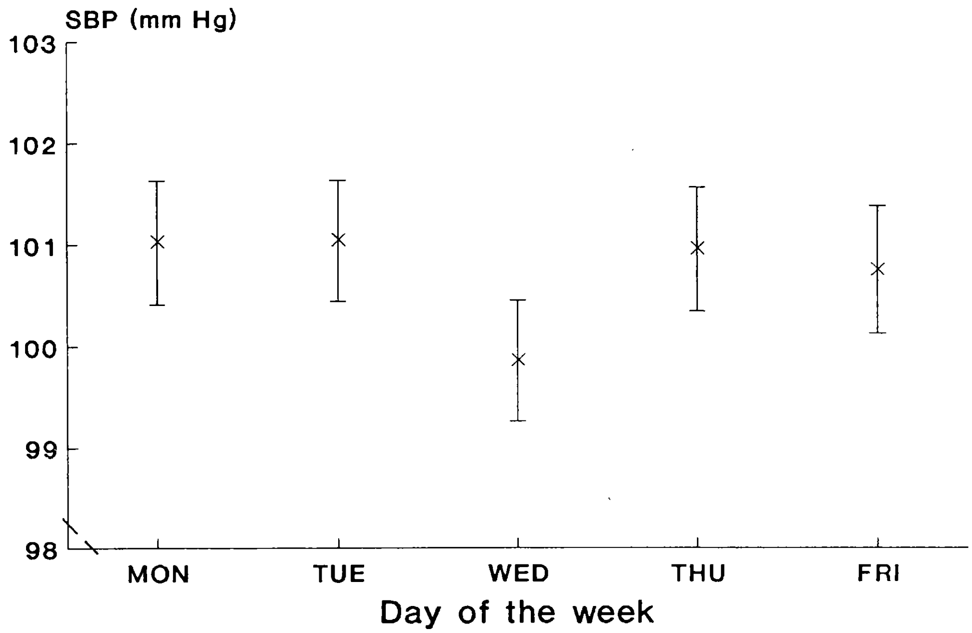
Means and 95% C.I.s



Means and 95% C.I.s

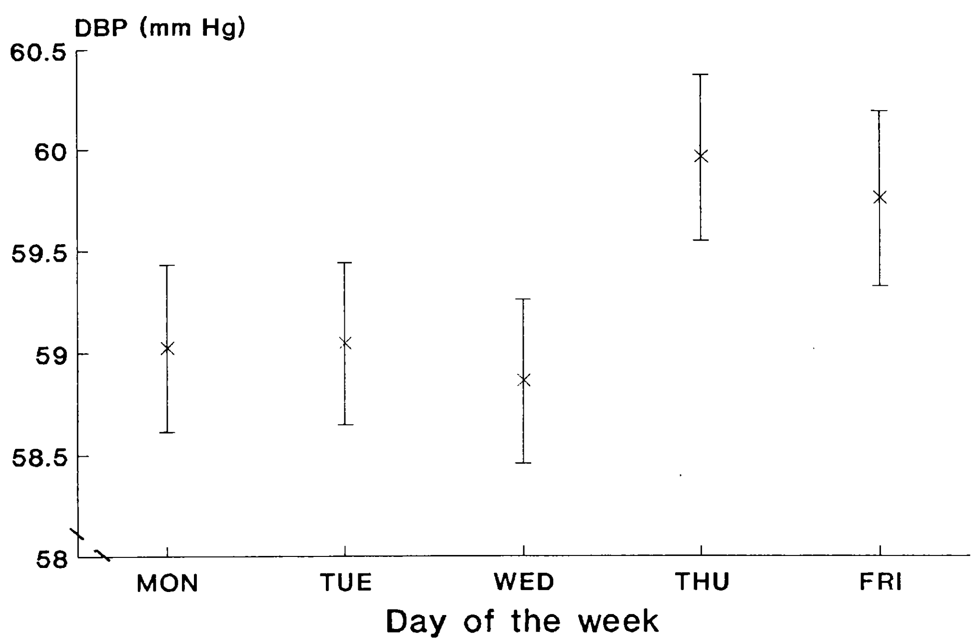
Figure 4.5 DAY OF WEEK AND BLOOD PRESSURE

SYSTOLIC



Means and 95% C.I.s

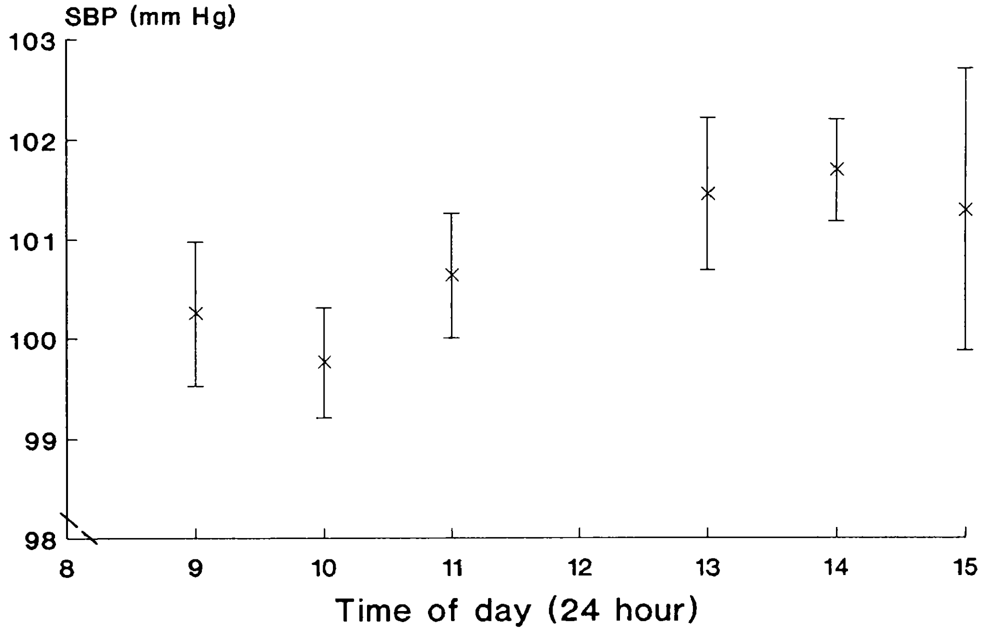
DIASTOLIC



Means and 95% C.I.s

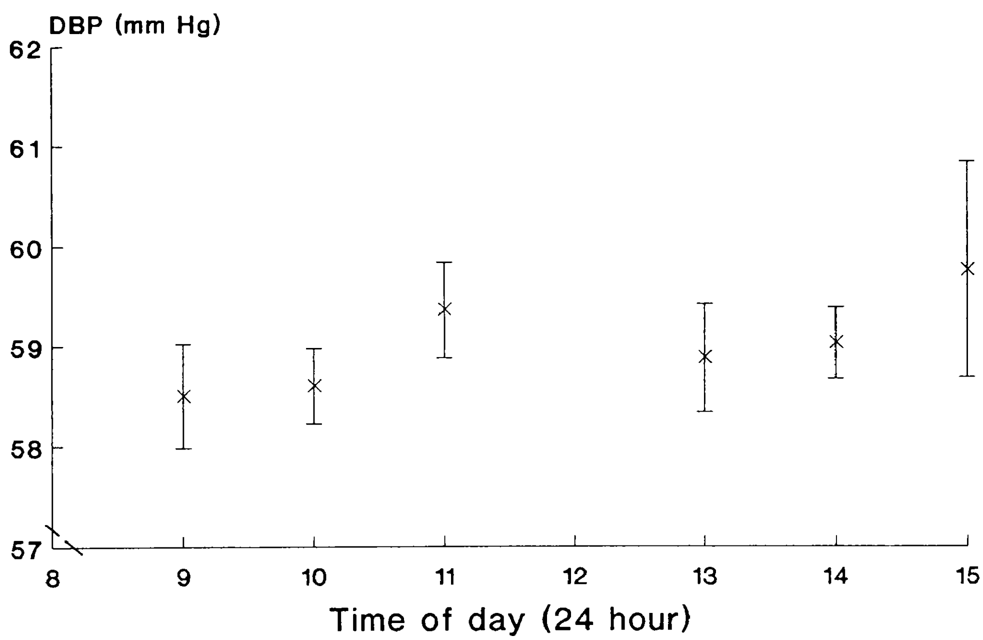
Figure 4.6 HOUR OF DAY AND BLOOD PRESSURE

SYSTOLIC



Means and 95% C.I.s

DIASTOLIC



Means and 95% C.I.s

CHAPTER 5

GEOGRAPHIC DIFFERENCES IN BLOOD PRESSURE IN CHILDREN

5.0 SUMMARY

In this chapter the marked geographic differences observed in the mean blood pressure levels of children in different towns are described. The differences in blood pressure are related to adult mean blood pressure levels and adult cardiovascular mortality rates. Although bias and confounding factors do not appear to explain the patterns observed, the findings are strongly dependent on the observations made in Guildford, a town with exceptionally low blood pressure levels both in children and in adults. The results require substantiation, but suggest that the pattern of geographic differences in blood pressure observed in middle-aged British men may have its origins early in life.

5.1 INTRODUCTION

In this Chapter the principal geographical hypotheses of the Nine Towns Study of Blood Pressure in Children are explored. The questions addressed are, first, whether average blood pressure levels of children differ between British towns and, second, whether variation in childhood blood pressure levels between towns is related to the variation in adult blood pressure levels previously described in the British Regional Heart Study. The ecological relationship between childhood blood pressure levels and adult cardiovascular mortality rates on a town basis is also examined. The presentation of results is followed by a commentary which examines the validity of the findings in detail. The potential importance of the findings is considered in more detail in chapter 7.

5.2 SUBJECTS AND DATA PRESENTATION

Analyses are presented here on 4056 children aged between 5.00 and 7.50 years (mean 6.24 years) in whom complete triplicate blood pressure measurements were made. Adjustment for the effect of cuff size on blood pressure measurement has been carried out as described in Appendix I. However, because the number of subjects examined with the different cuff sizes varies little between towns, this adjustment makes little difference to the results presented. All results are standardized for age. In view of the small but highly significant difference in diastolic blood pressure between sexes (section 4.3.1.1) all diastolic results have been standardized for the effect of sex.

5.3 RESULTS

5.3.1 MEAN BLOOD PRESSURES IN STUDY TOWNS

Age-standardized town mean blood pressures, derived from an analysis of covariance in which blood pressure have been regressed on age fitted as a continuous variable and town fitted as a factor with 9 levels, are presented in Table 5.1. In this table, and in the following tables, towns are ranked by their mean systolic pressures. Town mean systolic pressures vary between 102.4 mmHg in Carlisle and 96.7 mmHg in Guildford, a range of 5.7 mmHg. Town diastolic pressures vary between 60.3 mmHg in Southport and 55.9 mmHg in Guildford, a range of 4.4 mmHg. In an analysis of covariance including age and, in the case of diastolic pressure, sex, the variation in town means is highly statistically significant both for systolic pressure ($F = 62749$, df 8,4046, $p < 0.0001$) and for diastolic pressure ($F = 44520$, df 8,4045, $p < 0.0001$). However, one study town, Guildford, is an obvious outlier, with both systolic and diastolic pressures markedly below those in the other towns. When the analyses are repeated with Guildford excluded, the differences remain highly statistically significant, although the associated F values are markedly reduced both for systolic pressure ($F = 5.01$, df 7,3599, $p < 0.0001$) and for diastolic ($F = 5.38$, df 7,3598, $p < 0.0001$). This suggests that the variation between towns is unlikely to be explained by chance, even with the outlying Guildford values excluded.

The analyses presented so far assume that the variability of blood pressure within towns is based entirely on between-individual variation. However, it is possible that <u>systematic</u> variation occurs between groups of individuals <u>within</u> each town. If this is the case, an analysis of covariance of the kind described above, fitting only town and individuals, would constitute an insufficiently conservative test of between-town variation in blood pressure. The most important possible source of systematic blood pressure variation within towns lies in variation between the school-day sessions which form the primary sampling units in each town. Figure 5.1 shows the extent of variation in mean systolic and diastolic pressures between these school-day units in each town (the two day survey in one Merthyr school is counted as two school-day sessions). The ranges in mean systolic pressure for school-day units within towns vary between 4.8 mmHg in Maidstone and 11.0 mmHg in Dunfermline, those for diastolic between 2.9 mmHg in Southport and 7.1 mmHg in Dunfermline. The results of analyses of variance confirm that these variations between school-day sessions within towns are highly statistically significant both for systolic pressure ($F = 3.26$, df 80,3966, $p < 0.0001$) and for diastolic pressure ($F = 3.53$, df 80,3965, $p < 0.0001$), a conclusion which was unaffected by the inclusion of height and body mass index in the analysis.

While it is impossible to separate the 'day' and 'school' components of variation in the present study, school-day variation in blood pressure is clearly an important source of blood pressure variation within towns, which needs to be taken into account when examining the statistical significance of between-town variation in blood pressure. This can be achieved by comparing the extent of between-town variation with the extent of school-day variation within each town, in an analysis of covariance including age and (in the case of diastolic pressure) sex. In this analysis, between-town variation remains statistically significant both for systolic pressure ($F = 5.92$, df 8,79, $p < 0.005$) and for diastolic pressure ($F = 6.80$, df 8,78, $p < 0.001$). However, if the outlying town, Guildford, is excluded from this analysis, between-town variation is markedly attenuated, becoming non-significant for systolic pressure ($F = 1.98$, df = 7,70, $p = 0.1$) although it remains significant for diastolic pressure ($F = 2.26$; df = 7,69; $p < 0.05$). These analyses further emphasize that the finding of statistically significant variation in between-town blood pressure levels depends heavily on the Guildford observation.

5.3.2 RELATIONSHIP BETWEEN TOWN BLOOD PRESSURE LEVELS IN CHILDHOOD AND TOWN BLOOD PRESSURE LEVELS IN ADULTHOOD

The relationship between town blood pressures in children and adults can be examined in two ways. It will be recalled that the nine towns studied were examined in three sets, each set containing one town with high, one with medium and one with low adult pressure levels. The relationship between blood pressure levels in childhood and adulthood can be examined either taking the set of examination into account, or ignoring it to fit an overall regression of childhood blood pressure levels on adult blood pressure levels. An assessment taking the set of examination into account is of particular value in minimizing the influence of measurement drift between the sets of towns on childhood blood pressure levels. Conversely, an assessment of the relationship between childhood and adulthood blood pressures ignoring the set of examination, potentially the most powerful method for relating child and adult pressures, would be weakened by the presence of measurement drift. Results are presented both within sets and across sets. However, in the absence of strong evidence of measurement drift (Appendix I) detailed analyses are presented only across sets and not within sets.

5.3.2.1 Results within each set of towns

The age-standardized blood pressures of the towns in each of the three sets examined during the study are shown in Figure 5.2. Within each set the systolic pressure of the town with high adult pressure is greater than that in which adult pressure is low, with the intermediate town occupying an intermediate position in two of the three sets. However, the pattern for diastolic pressure is less striking. Mean town diastolic pressures are higher in the towns with high adult pressures than in those with low adult pressures in only two of the three sets and the position of the intermediate towns is also less consistent. When the results from the three sets are combined the overall mean difference in systolic pressure between children in high towns and those in low towns is 2.5 mmHg (95% confidence limits 1.8, 3.2); that for diastolic pressure is 1.6 mmHg (95% confidence limits 1.1, 2.1). However, these confidence limits, based on the variability of subjects within these high and low blood pressure towns, apply only to these particular towns and cannot form the basis for generalizations which might apply to all towns with high or low levels of adult blood pressure. In order to generalize the hypothesis that town mean blood pressures in childhood are related to those in adults to <u>all</u> such towns, an analysis based on the town rather than the individual is required. Such an analysis is described in the next section.

5.3.2.2 Results and analysis across all towns

When town set is ignored the relationship between mean town blood pressure levels in children and adults can be examined using standard regression and correlation techniques. The relationships for both systolic and diastolic pressure are presented in Figure 5.3. There appear to be positive associations between mean town blood pressure level in childhood and mean town blood pressure in adulthood, both for systolic and diastolic pressure. If the assumption is made that these relations are linear, the unweighted regression coefficient for the systolic relationship is 0.21 mmHg/mmHg (95% confidence limits -0.01 to 0.40), implying a difference of approximately 0.2 mmHg in town mean systolic pressure for each 1 mmHg difference in town mean adult systolic pressure. The corresponding figure for diastolic pressure is 0.15 (95% confidence limits -0.13 to 0.43). The correlation coefficients for these relationships are 0.65 (systolic) and 0.49 (diastolic). A test for the significance of these unweighted correlation coefficients constitutes a test of the null hypothesis that there is no relationship between town mean blood pressures in adults and children, a hypothesis which can be generalized to all similar towns in Britain. The test for the statistical significance of the systolic correlation co-efficient ($t = 2.24$, $df = 7$, $p = 0.058$) is of borderline statistical significance; that for diastolic pressure does not approach statistical significance ($t = 1.49$, $df = 7$, $p = 0.18$). However, in both cases these relationships are heavily dependent on Guildford (co-ordinate arrowed in Figure 5.3), an outlying town with extremely low mean blood pressure levels in both adults and children. This dependence is emphasized by the fall in the strength of the correlation if non-parametric Spearman correlation coefficients are calculated; these are 0.60 for systolic pressure ($p = 0.09$) and 0.41 for diastolic pressure ($p = 0.27$).

5.3.3 CHILDHOOD BLOOD PRESSURE LEVELS AND ADULT CARDIOVASCULAR MORTALITY

For the analyses described here Standardized Mortality Ratios (SMRs) for heart disease between 1979 and 1983 have been determined by comparing the observed number of deaths from all cardiovascular disease in subjects of both sexes aged 35 to 64 years from all cardiovascular disease (except rheumatic heart disease) in each town with the number expected, calculated by applying the age-sex-specific rates for England, Wales and Scotland combined to the town populations. Ten year age-stratification has been used.

The scatter diagrams in Figure 5.4 describe the relationship between mean town blood pressures in childhood (systolic and diastolic) and the standardized mortality ratio (SMR) for cardiovascular disease. There is a positive association between childhood mean systolic pressure and cardiovascular mortality ($r = 0.67$), which attains conventional levels of statistical significance ($t = 2.41$, $df = 7$, $p = 0.047$). However, this relationship is again heavily dependent on the lowest town, Guildford. Diastolic pressure also shows a positive association with cardiovascular mortality, although the correlation is weaker ($r = 0.39$) and not statistically significant ($t = 1.11$, $df = 7$, $p = 0.30$).

5.4 COMMENTARY

The report of the analyses described above (Whincup PH et al, 1988) was the first to suggest that there are systematic geographic differences in the average blood pressure levels of children within Great Britain in children aged 5-7 years, and that these average blood pressure levels may be related both to adult blood pressure levels and adult cardiovascular mortality rates. Several previous investigators have measured blood pressure patterns in children and adolescents in specific locations within Great Britain (Hamilton M et al, 1954; Miall WE and Oldham PD, 1958; Orchard TJ et al, 1982; Dornall MC, 1984). While the results of these studies have provided no strong support for a systematic geographic blood pressure pattern (Table 5.2), methods were not standardized and numbers of subjects were small in most of these studies. Geographic patterns in systolic blood pressure in 9921 ten year-old subjects from the 1970 Birth Cohort were examined indirectly in a recent report, which examined childhood blood pressure levels in districts of England and Wales grouped into five categories on the basis of adult cardiovascular mortality (Barker DJP et al, 1989a). No consistent relationship between childhood blood pressure levels and cardiovascular mortality was observed. However, a lack of standardization of blood pressure measurement and the rounding of blood pressure measurements to the nearest 10 mmHg is likely to have limited the power of the study to detect geographic differences, despite the large number of participants.

5.4.1 VALIDITY OF BETWEEN-TOWN DIFFERENCES IN CHILDHOOD BLOOD PRESSURE LEVELS

In order to address the validity of between-town differences in childhood blood pressure levels, the possibility of biases in sampling and response and in blood pressure measurement (including the circumstances of measurement, particularly ambient temperature) must be considered. The influence of confounding factors (especially body build and pulse rate) also needs to be addressed. These factors are considered in turn below.

5.4.1.1 Sampling and response rates: influence on between-town blood pressure differences

The variations in sampling characteristics and response rates between towns are summarized in Table 5.3. The figures presented include the proportion of children in the town attending independent schools (who are therefore excluded from sampling), the proportion of subjects from manual households in the sample, the relationship of occupation in the sample to that in the census and the response rate for each town. The order in which the towns are ranked again reflects their childhood mean systolic blood pressure level. There is some suggestion that the towns in which average blood pressures are lower (i.e. at the foot of the table) have a lower proportion of respondents from non-manual households (column 3). Moreover, towns in which average blood pressures are lower tend to have a higher proportion of children attending independent schools (column 1). However, these differences are unlikely to account for the observations in blood pressure observed. In towns in which the proportion of children attending independent schools is high, it might be expected that children from non-manual, particularly professional, households would be <u>under-</u>

represented in the study sample and manual households might be over-represented. There is no evidence from the sample-census comparison presented in Table 5.3 (column 3) that marked over-representation of subjects from manual households has occurred in the towns in which a high proportion of children attend independent schools, particularly in Guildford, the town with the highest proportion of independent school attendance. Moreover, the absence of any important relationship between social class and blood pressure in these children (section 4.3.2) implies that neither differences in the proportion of children attending independent schools nor differences in the proportion of children from manual households are likely to be important in the explanation of between-town differences in blood pressure. Finally, response rates in the towns, which vary between 86% in Dunfermline and Merthyr and 77% in Scunthorpe (Table 5.3, column 4), show no relationship with the ranking of town mean blood pressure levels.

5.4.1.2 Blood pressure measurement: influence on between-town differences in blood pressure

The performance of the study instrument and the observers require detailed examination in this context. Changes in performance of the blood pressure instrument, particularly drift in blood pressure measurement over time, is an important possible explanation of between-town blood pressure differences. However, the studies carried out to examine instrument performance over time (Appendix I) provided no evidence that a serious degree of measurement drift had occurred. Moreover, given the intermediate-high-low sequence in which the towns were examined (Table 3.3), measurement drift could not account for the pattern of between town differences observed, particularly for systolic pressure. Two particular types of observer error require consideration. First, it is possible that the two observers recorded systematically different blood pressure levels and that there were marked differences in the proportion of subjects measured by the two observers in different towns. Second, it is possible that there were marked differences in the behaviour of the two observers between individual towns. The first possibility is unlikely, first because there were no overall differences in blood pressure measurement between observers (Appendix I) and second because the variation in the proportion of measurements made by the two observers in different towns shows no relationship to the ranking of town mean systolic pressure (Table 5.4). Moreover, although the differences in blood pressure measurement by the two observers vary between towns this variation shows no relationship with the blood pressure rank of different towns (Table 5.4).

5.4.1.3 Ambient temperature: influence on between-town differences in blood pressure

The mean outdoor and indoor temperatures in each town at the time of examination are displayed in Table 5.5. Mean outdoor temperatures (available for seven towns only) showed considerable variation between towns, with a range of 15.3°C between the coldest town (Southport) and the warmest (Guildford). By contrast, mean indoor temperatures in eight of the nine towns lay within a 1°C range. The exception, Guildford, had an mean indoor temperature of 24.2°C, almost 2°C higher than that in any other town. Since previous studies have suggested that ambient temperature may be inversely related to blood pressure both in adults (Brennan PJ et al, 1978) and in children (Prineas RJ et al, 1980a; de Swiet M et al, 1984; Jenner DA et al, 1987), the potential contribution of ambient temperature to between-town differences in blood pressure, and particularly to the low value observed in Guildford, requires careful examination.

An assessment of the unadjusted relationships between temperature and blood pressure on an individual basis is presented in Figure 5.5 (for indoor temperature) and Figure 5.6 (for outdoor temperature). These figures both demonstrate inverse relationships between temperature and blood pressure consistent with those of the earlier reports. The regression coefficients for these unadjusted relationships are presented in Table 5.6. However, these coefficients are highly dependent on the values for the top tenth of the temperature distribution in each case (marked on Figures 5.5 and 5.6 with arrows), which consist entirely of subjects from Guildford, a town with exceptionally low mean blood pressure levels. When Guildford subjects are removed from this analysis, the relationships between temperature and blood pressure are markedly attenuated, and in the case of systolic pressure become non-significant (Table 5.6). This observation implies that the relationships between temperature and blood pressure are being confounded by town and need to be examined on a within-town basis.

The relationships between temperature and blood pressure <u>within</u> each town are presented in Table 5.7. In the case of outdoor temperature, two of seven towns showed negative relationships for systolic pressure and four of seven for diastolic pressure. One positive relationship and one negative relationship achieved statistical significance for both systolic and diastolic pressure at the 5% level. In the case of indoor temperature, four of nine towns showed negative relationships for systolic pressure and seven of nine for diastolic pressure. Two of the negative and one of the positive relationships achieved statistical significance for both systolic and diastolic pressure. It is of particular note that the temperature-blood pressure relationships in Guildford (the town with exceptionally high mean temperatures), are not strikingly negative and do not approach statistical significance. Tests of heterogeneity, examining the statistical significance of the differences in temperature-blood pressure slopes between towns (Table 5.7) are, not surprisingly, significant for both indoor and outdoor temperature and for systolic and diastolic pressure. This heterogeneity in temperature-blood pressure relationships is biologically extremely implausible and argues against an overall causal relationship between temperature and blood pressure in this study population. Further support for this view is provided by the overall estimates of the within-town relationship between temperature and town, derived by pooling within-town estimates, in an analysis which ignores the possibility of heterogeneity of slopes. The regression coefficients for these overall within-town relationships (presented in Table 5.6) are extremely weak, with only that between indoor temperature and diastolic pressure achieving conventional levels of statistical significance. Adjustment for the effect of indoor temperature reduces the range of town mean blood pressures only slightly, from 5.7 to 5.5 mmHg (systolic) and from 4.4 to 3.9 mmHg (diastolic). Thus, despite the markedly higher ambient temperatures observed in Guildford, the temperature-blood pressure relationships do not appear sufficient to account for the between-town variation in blood pressure, particularly that observed between Guildford and the other towns.

5.4.1.4 Confounding factors and between-town differences in blood pressure

Can the differences in blood pressure level observed between towns be accounted for by the presence of confounding factors? Differences in the mean age and sex distributions of children in different towns were minimal and were taken into account in the initial analyses. However, other factors which are strongly related to blood pressure in individuals, particularly body build and pulse rate, need to be considered. Social class is another potentially important factor, particularly as there is marked variation in the social class composition of the different towns (Table A1.2B). However, the absence of any consistent relationship between social class and blood pressure (section 4.3.2) suggests that this factor is not important in this context.

The mean heights, body mass indices and pulse rates of children in each study town, and their correlations with town mean blood pressure levels, are presented in Table 5.8. There are differences between the mean heights, body mass indices and pulse rates of the various towns, which are highly statistically significant. While there is little relationship between town mean heights and town mean blood pressures, town mean body mass indices and pulse rates both show strong positive correlations with town mean blood pressures, although those for body mass index in particular are heavily weighted by Guildford, which has both strikingly low mean body mass index and low mean blood pressure. However, adjustment for these factors has little effect on town mean differences in blood pressure (Figure 5.7).

5.4.2 VALIDITY OF ASSOCIATION BETWEEN TOWN BLOOD PRESSURE LEVELS IN ADULTHOOD AND CHILDHOOD

How valid are the relationships between blood pressure levels in childhood and those in adulthood? Although the systolic relationship is unlikely to be explained by chance, both systolic and diastolic relationships are heavily dependent on the findings in Guildford. The validity of the observation that mean blood pressures in Guildford are low in middle-aged men, made in the British Regional Heart Study (Shaper AG et al, 1981) received further support from the findings of a further study in adults (Bruce NG et al, 1990a), in which low mean blood pressure levels were observed in Guildford both in middle-aged men and women. The observation of low blood pressures in children was consistent both for boys and girls and for all six month age-groups, suggesting that the findings are not restricted to particular subgroups. However, the dependence of the findings on the Guildford results emphasizes that the consistency of the association between blood pressure patterns in adulthood and childhood is not as great as had been anticipated at the outset of the study, a point which is considered in section 5.4.4 below.

The possibility that bias or the presence of confounding factors might explain the association between adult and childhood blood pressures requires careful consideration. However, sampling procedures, seasons and temperatures of examination were quite different in the two surveys and are therefore unlikely to provide an explanation. Moreover, the timing of the surveys and the age-distribution of the participants minimized the number of first-degree relatives in the two studies, making familial association an unlikely explanation for the observations. One important potential source of bias is that blood pressure measurement in the study of children may have been affected by knowledge of the earlier investigation in adults. However, although the observers were aware of the general nature of the hypothesis under test, they were not aware of the precise ordering of adult blood pressures which would be used to test the hypothesis. Moreover, the fully automated nature of the blood pressure instrument used in the study should have minimized the potential for expression of observer prejudice in blood pressure measurement.

5.4.3 OTHER APPROACHES TO THE VALIDITY OF GEOGRAPHIC OBSERVATIONS

The validity of the between-town differences in childhood blood pressure and their relationships with adult blood pressure and cardiovascular mortality, and in particular the contribution of biases and confounding factors, have been examined in detail. Can the results be corroborated in any other way within the existing study? Two approaches could, in theory, be used. The first depends on the assumption that the differences in blood pressure between towns have developed since birth. If the differences in blood pressure between towns are continuing to widen in the study age-group, it might be expected that the rates of blood pressure rise with age would vary between towns, being lowest in the towns with the lowest blood pressure levels. However, such an analysis, based on a cross-sectional rather than a longitudinal analysis and with a limited age-range for study participants of only 2.5 years, has very limited power for the detection of differences in the relationship between age and blood pressure between towns. The rates of blood pressure change with age in the different towns are presented with their standard errors in Table 5.9. Although the lowest rate of rise of systolic blood pressure on age is observed for Guildford, the town with the lowest mean blood pressure level, this observation is not repeated for diastolic pressure. Moreover, there is little evidence of heterogeneity of the town slopes, nor of any overall trend relating age slopes to blood pressure level (Table 5.9). A second approach to the validity of between-town differences in blood pressure could be based on the observation that the blood pressure distribution in a hypertensive population tends to display a rightward (positive) skew (Rose G, 1985b). If the differences in blood pressure observed between towns signify the beginnings of the emergence of hypertensive populations one might expect that the extent of skewness in the blood pressure distribution would be greater in the towns with higher mean blood pressure levels. However, the age-adjusted coefficients of skewness show no evidence of marked rightward skew in any of the towns, with no relationship apparent between the extent of skewness and blood pressure level (data not presented). The examination of age-blood pressure relationships and skewness of the blood pressure distribution of different towns therefore provides no strong evidence to substantiate the differences in blood pressure observed between the study towns further.

5.4.4 INTERPRETATION OF THE GEOGRAPHIC OBSERVATIONS

5.4.4.1 Associations with adult blood pressure

The results of the study described above imply that there may be important differences in blood pressure in childhood between different

British towns which are related to adult blood pressure levels and cardiovascular mortality. The findings, although not apparently explained by confounding factors, are critically dependent on the observations of one town with remarkably low blood pressure levels. It is therefore apparent that the hypotheses examined here require further study, probably in a new setting; ways in which this could be done are considered in detail in chapter 7. The justification for following up the observations is that, if substantiated, they imply that population differences in blood pressure may be present in childhood. Such a finding would have implications both for the study of aetiological factors and for the timing of preventive measures. Moreover, the size of the differences in blood pressure described between population groups in Guildford and Carlisle are sufficiently large to be of public health importance (Rose G, 1981), despite being too small to be of clinical importance. The findings would be consistent with the evidence presented in chapter 2, suggesting that blood pressure differences between populations begin to develop before adult life and, in particular, with the studies of migration in childhood (Beaglehole R et al, 1978 and 1979) and sodium restriction in infancy (Hofman A et al, 1983) which raised the possibility that population differences in blood pressure might be present in the first decade.

Despite the precision with which childhood blood pressure levels were estimated in each town, the consistency of the relation between childhood and blood pressure patterns is weaker than had been anticipated. This may reflect the superimposed influence of factors affecting blood pressure levels in adult life. Important factors in this context are likely to include body build and alcohol intake, both of which vary between the towns studied (Shaper AG et al, 1981; Cummins R et al, 1982). The influence of factors acting in adult life may be responsible for the weak associations between town childhood and adult blood pressure levels. In particular, high adult alcohol intakes in the Scottish towns (Cummins R et al, 1982) may explain the observation that in both Ayr and Dunfermline childhood blood pressure levels are slightly lower than might be expected on the basis of adult blood pressure levels (Figure 5.8). The possibility that childhood influences on blood pressure can be subsequently modified by factors acting in adult life has received further support from the study of the determinants of blood pressure in migrant men in the British Regional Heart Study. In these men, the relative contribution of place of birth and place of adult residence on blood pressure in middle-age was examined (Elford J et al, 1990). The results suggested that place of residence was more important than place of birth in determining adult blood pressure level. The results imply that influences on blood pressure in childhood are likely to be obscured by influences acting later in life, and are consistent with the possibility that blood pressure patterns in childhood may be modifiable by preventive measures.

5.4.4.2 Associations with adult cardiovascular mortality

The importance of the association observed between childhood blood pressure level and adult cardiovascular mortality requires cautious interpretation. Barker and his colleagues have suggested that cardiovascular disease may have its origins in utero or in infancy (Barker DJP et al, 1989b; Barker DJP, 1991). In particular, they have suggested that differences in early life experience may explain the geographic variations in cardiovascular disease within Britain (Barker DJP et al, 1986 and 1987) and that blood pressure may be an important factor linking early life experience with later cardiovascular disease (Barker DJP et al, 1989a). Does the observation that childhood blood pressure levels may be related to adult cardiovascular mortality rates on a geographic basis provide support for the hypothesis? While at first sight the observation would appear to be consistent with the hypothesis, it must be remembered that adult blood pressure levels are also related to adult cardiovascular mortality on a town basis (Shaper AG et al, 1981), as well as to childhood blood pressure levels (Figure 5.3). Thus blood pressure in adult life is a potential confounding factor for the relationship between childhood blood pressure and adult cardiovascular mortality. The relative contribution of childhood and adulthood influences, both on the incidence of cardiovascular disease and on blood pressure, has been studied in subjects who migrate between areas of Great Britain where mean blood pressure and cardiovascular mortality are low and those where they are high (Elford J et al, 1989; Elford J et al, 1990). The results inply that both mean blood pressure level and risk of cardiovascular disease are related to the region in which subjects spent their adult life rather than the region in which they spent their childhood. These findings suggest that the relationship between childhood blood pressure level and adult cardiovascular mortality is an indirect one, in which adult blood pressure may well play a central role.

TABLE 5.1 AGE-STANDARDISED TOWN MEAN BLOOD PRESSURES IN CHILDREN AGED BETWEEN 5.00 AND 7.50 YEARS

		BLOOD PRESSURE (mmHg)			
		SYSTOLIC		DIASTOLIC	
TOWN	N	Mean	(S.D.)	Mean	(S.D.)
Carlisle	469	102.4	(8.6)	60.1	(6.0)
Merthyr Tydfil	488	102.3	(8.6)	59.4	(6.0)
Southport	483	102.1	(8.6)	60.3	(6.0)
Scunthorpe	412	101.4	(8.6)	59.6	(6.0)
Ayr	438	101.0	(8.7)	57.8	(6.0)
Maidstone	429	100.1	(8.6)	59.4	(5.9)
Dunfermline	451	100.7	(8.6)	58.9	(6.0)
Exeter	438	99.9	(8.6)	58.4	(6.0)
Guildford	448	96.7	(8.6)	55.9	(6.0)

Values shown are means and standard deviations. Towns are ranked by their mean systolic blood pressure level. Analyses are standardized for age and, in the case of diastolic pressure, for sex.

TABLE 5.2 MEAN BLOOD PRESSURE LEVELS IN ADOLESCENTS IN FOUR LOCATIONS IN GREAT BRITAIN

MALES

			BLOOD PRESSURE mmHg			
			10-14 years		15-19 years	
AUTHOR	LOCATION	N	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC
Hamilton (1954)	London	46	105.0	61.3	117.2	68.2
Miall (1958)	S Wales	27	111.2	71.8	131.4	80.4
Orchard (1982)	Nottingham	319	113.3*	61.7*	123.2+	60.7+
Donmall (1984)	Hebrides	195	98	62	111	67

FEMALES

			BLOOD PRESSURE mmHg			
			10-14 years		15-19 years	
AUTHOR	LOCATION	N	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC
Hamilton (1954)	London	73	111.1	65.0	117.3	70.8
Miall (1958)	S Wales	19	111.4	70.5	123.3	76.7
Orchard (1982)	Nottingham	306	114.4*	63.7*	113.8+	65.0+
Donmall (1984)	Hebrides	202	99	63	105	65

N values are based on the number of subjects aged 10-19 years

* subjects aged 13 years + age-group 15-18 years

TABLE 5.3 SAMPLING CHARACTERISTICS AND RESPONSE RATES IN THE STUDY TOWNS

TOWN	INDEPENDENT SCHOOL ATTENDANCE RATE (%)	REPRESENTATION OF MANUAL HOUSEHOLDS IN SAMPLE (compared with 1981 census) (%)	MANUAL HOUSEHOLDS IN SAMPLE (%)	RESPONSE RATE (%)
Carlisle	1.5	+3	59	81
Merthyr Tydfil	0.6	-7	67	86
Southport	2.1	-8	42	85
Scunthorpe	2.9	-4	70	77
Ayr	0.4	-10	46	82
Maidstone	5.2	+5	49	82
Dunfermline	0.5	-12	53	86
Exeter	5.1	+4	54	83
Guildford	18.5	+1	45	85

Towns are ranked by their mean systolic blood pressure level.

TABLE 5.4 OBSERVERS AND BLOOD PRESSURE MEASUREMENT IN THE STUDY TOWNS

TOWN	N	PROPORTION OF MEASUREMENTS MADE BY OBSERVER 1 (%)	DIFFERENCE IN BLOOD PRESSURE MEASUREMENT BETWEEN OBSERVERS (OBSERVER 1 - OBSERVER 2) (mmHg) SYSTOLIC Mean	(s.e.)	DIASTOLIC Mean	(s.e.)
Carlisle	469	53	-0.6	(0.8)	-0.1	(0.5)
Merthyr Tydfil	488	46	+1.3	(0.8)	-0.2	(0.6)
Southport	483	48	-0.6	(0.8)	-1.2	(0.6)
Scunthorpe	412	12	-1.4	(1.1)	-0.3	(0.9)
Ayr	438	51	-1.8	(0.8)	-0.6	(0.6)
Maidstone	429	45	+2.7	(0.8)	+1.3	(0.6)
Dunfermline	451	49	+0.8	(0.8)	+0.9	(0.6)
Exeter	438	54	-0.8	(0.8)	+0.7	(0.6)
Guildford	448	51	+0.7	(0.7)	+0.9	(0.5)

Values shown are means (standard errors). Towns are ranked by their mean systolic blood pressure level. Analyses are standardized for age and, in the case of diastolic pressure, for sex.

TABLE 5.5 MEAN INDOOR AND OUTDOOR TEMPERATURES IN THE STUDY TOWNS

		INDOOR TEMPERATURE (°C)		OUTDOOR TEMPERATURE (°C)	
	N	Mean	(s.e.)	Mean	(s.e.)
Carlisle	469	22.1	(0.1)	10.3	(0.1)
Merthyr Tydfil	488	21.4	(0.1)	--	--
Southport	483	21.4	(0.1)	5.7	(0.1)
Scunthorpe	412	21.8	(0.1)	6.4	(0.1)
Ayr	438	22.4	(0.1)	14.0	(0.1)
Maidstone	429	21.7	(0.1)	--	--
Dunfermline	451	21.9	(0.1)	11.9	(0.1)
Exeter	438	21.4	(0.1)	9.6	(0.1)
Guildford	448	24.2	(0.1)	21.0	(0.1)

Values shown are means (standard errors). Towns are ranked by their mean systolic blood pressure level.

TABLE 5.6 RELATIONSHIPS BETWEEN TEMPERATURE (OUTDOOR AND INDOOR) AND BLOOD PRESSURE

	BLOOD PRESSURE (mmHg)					
	SYSTOLIC			DIASTOLIC		
OUTDOOR TEMPERATURE (°C)	Regression coefficient	(s.e.)	p	Regression coefficient	(s.e.)	p
<u>Adjustment</u>						
None	−0.24	(0.03)	<0.0001	−0.23	(0.02)	<0.0001
Removal of Guildford	−0.01	(0.05)	0.91	−0.12	(0.03)	<0.0001
Town	0.05	(0.07)	0.49	−0.04	(0.05)	0.42

	SYSTOLIC			DIASTOLIC		
INDOOR TEMPERATURE (°C)	Regression coefficient	(s.e.)	p	Regression coefficient	(s.e.)	p
<u>Adjustment</u>						
None	−0.39	(0.08)	<0.0001	−0.44	(0.04)	<0.0001
Removal of Guildford	−0.03	(0.10)	0.76	−0.22	(0.07)	0.002
Town	−0.02	(0.09)	0.80	−0.19	(0.06)	0.002

Regression coefficients refer to regression of blood pressure on temperature (mmHg/°C), adjusted as specified in the left-hand column. Analyses are standardized for age and, in the case of diastolic pressure, for sex.

TABLE 5.7 RELATIONSHIPS BETWEEN TEMPERATURE AND BLOOD PRESSURE (OUTDOOR AND INDOOR) WITHIN EACH STUDY TOWN

OUTDOOR TEMPERATURE

TOWN	SYSTOLIC Regression coefficient	SYSTOLIC (s.e.)	DIASTOLIC Regression coefficient	DIASTOLIC (s.e.)
Carlisle	-0.30	(0.20)	-0.25	(0.14)
Merthyr Tydfil	--	--	--	--
Southport	0.19	(0.29)	-0.08	(0.20)
Scunthorpe	0.35	(0.15) *	0.20	(0.10) *
Ayr	0.06	(0.46)	0.17	(0.31)
Maidstone	--	--	--	--
Dunfermline	0.18	(0.18)	0.05	(0.13)
Exeter	-0.47	(0.21) *	-0.35	(0.15) *
Guildford	0.08	(0.14)	-0.22	(0.13)
Test for heterogeneity of slopes	p = 0.025		p = 0.02	

INDOOR TEMPERATURE

TOWN	SYSTOLIC Regression coefficient	SYSTOLIC (s.e.)	DIASTOLIC Regression coefficient	DIASTOLIC (s.e.)
Carlisle	0.84	(0.29) **	0.41	(0.20) *
Merthyr Tydfil	0.27	(0.31)	0.10	(0.21)
Southport	0.10	(0.24)	-0.04	(0.17)
Scunthorpe	0.41	(0.25)	-0.03	(0.17)
Ayr	-0.87	(0.27) **	-0.76	(0.18) ***
Maidstone	0.09	(0.25)	-0.14	(0.17)
Dunfermline	-0.67	(0.27) *	-0.78	(0.19) ***
Exeter	-0.16	(0.26)	-0.15	(0.18)
Guildford	-0.14	(0.19)	-0.22	(0.14)
Test for heterogeneity of slopes	p < 0.001		p < 0.001	

Regression coefficients refer to regression of blood pressure on temperature (mmHg/^{o}C) within each town. Towns are ranked by their mean systolic blood pressure level. Analyses are standardized for age and, in the case of diastolic pressure, for sex.

p values for coefficients: * < 0.05 ** < 0.01 *** < 0.001

TABLE 5.8 MEAN HEIGHT, BODY MASS INDEX AND PULSE RATE BY TOWN

		HEIGHT (cm)		BODY MASS INDEX (kg/m^2)		PULSE RATE (min^{-1})	
	N	Mean	(s.e.)	Mean	(s.e.)	Mean	(s.e.)
Carlisle	469	117.4	(0.2)	15.63	(0.07)	92.8	(0.5)
Merthyr	488	115.7	(0.2)	15.80	(0.08)	95.1	(0.5)
Southport	483	117.1	(0.2)	15.57	(0.07)	94.4	(0.5)
Ayr	438	117.6	(0.3)	15.48	(0.07)	92.8	(0.5)
Scunthorpe	412	116.8	(0.3)	15.53	(0.07)	91.4	(0.5)
Maidstone	429	117.0	(0.2)	15.62	(0.08)	92.0	(0.5)
Dunfermline	451	117.1	(0.2)	15.38	(0.07)	92.0	(0.5)
Exeter	438	117.1	(0.2)	15.64	(0.08)	93.5	(0.5)
Guildford	448	116.9	(0.2)	15.28	(0.07)	91.0	(0.5)
p (no difference between towns)		<0.0001		<0.0001		<0.0001	
Correlation with town mean blood pressure level							
r (systolic)		-0.08		0.72		0.65	
r (diastolic)		0.15		0.61		0.64	

Towns are ranked by their mean systolic blood pressure level. All analyses are standardized for age and sex.

TABLE 5.9 RATE OF CHANGE OF BLOOD PRESSURE WITH AGE IN EACH STUDY TOWN

	SYSTOLIC		DIASTOLIC	
	Regression coefficient	(s.e.)	Regression coefficient	(s.e.)
TOWN				
Carlisle	2.70	(0.61)	1.24	(0.42)
Merthyr	1.65	(0.71)	0.86	(0.47)
Southport	2.48	(0.68)	1.68	(0.48)
Scunthorpe	1.73	(0.69)	0.89	(0.47)
Ayr	3.24	(0.73)	1.80	(0.49)
Maidstone	2.97	(0.65)	1.22	(0.46)
Dunfermline	1.67	(0.79)	1.04	(0.56)
Exeter	3.97	(0.79)	1.88	(0.53)
Guildford	0.97	(0.72)	1.11	(0.51)
Test for heterogeneity of slopes	p = 0.11		p = 0.75	

Figures are regression coefficients for blood pressure on age (mm Hg/year) and standard errors. Towns are ranked by their mean systolic blood pressure level.

Figure 5.1 MEAN BLOOD PRESSURES BY SCHOOL-DAY SESSION

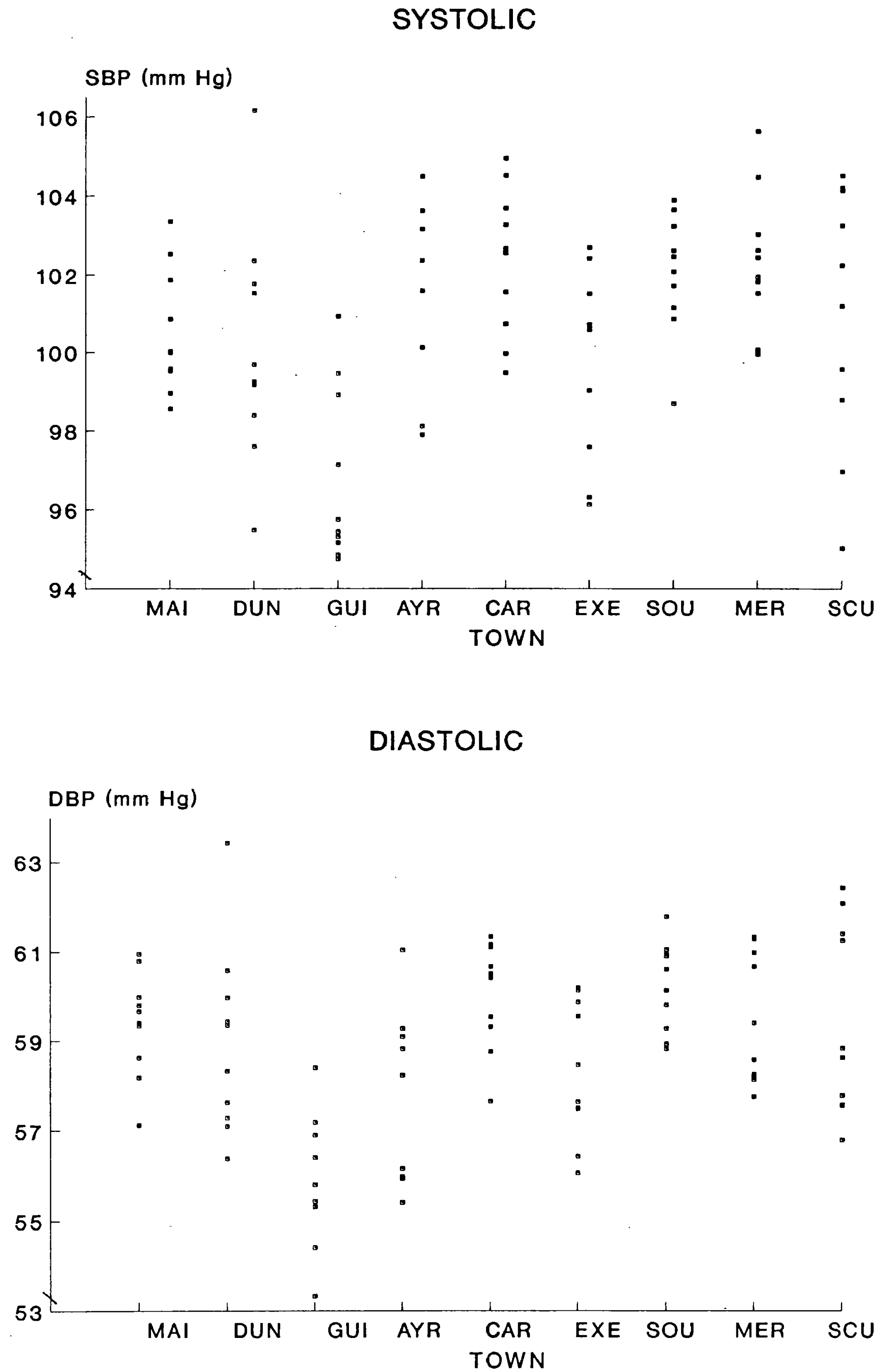


Figure 5.2 MEAN BLOOD PRESSURES IN EACH SET OF TOWNS

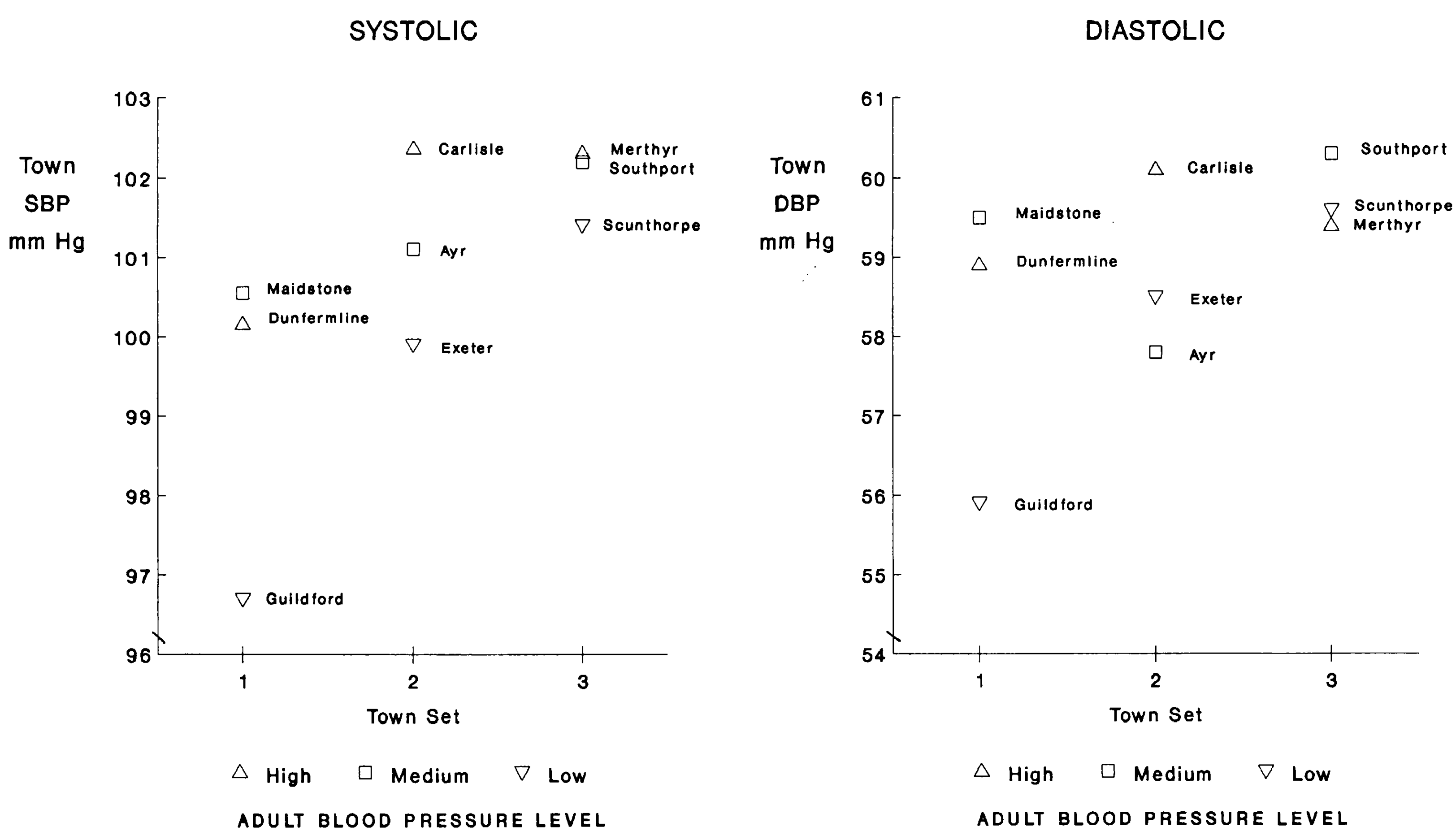
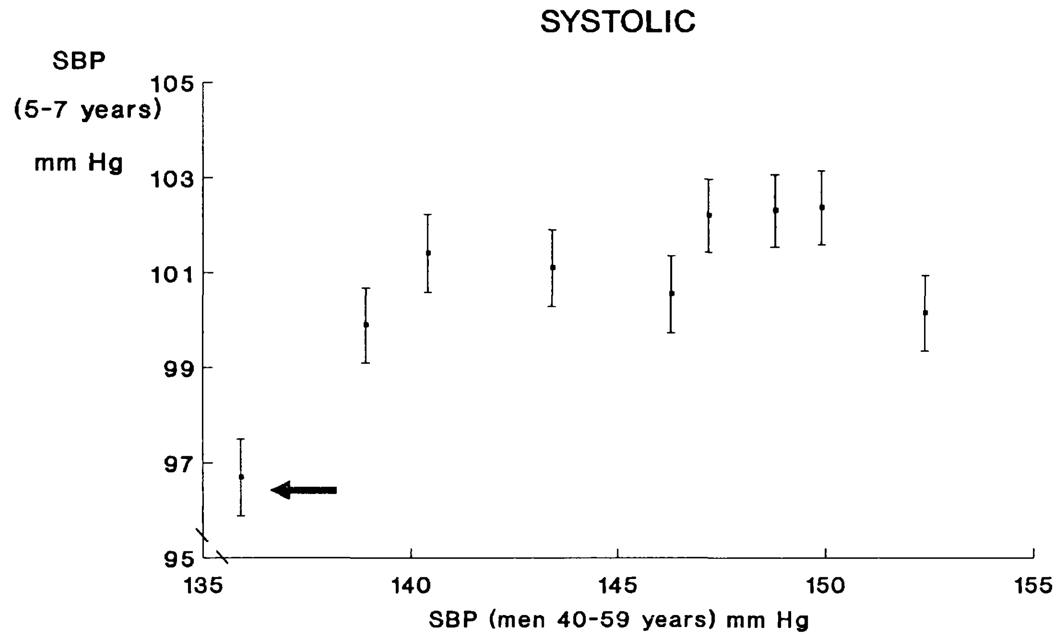
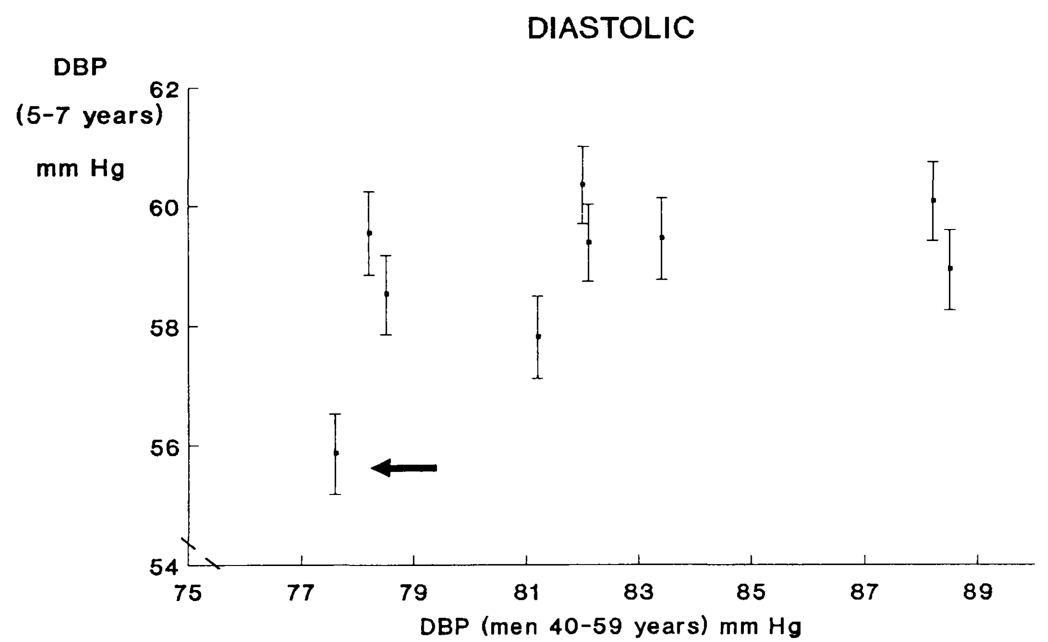


Figure 5.3 ADULT AND CHILD TOWN MEAN BLOOD PRESSURES



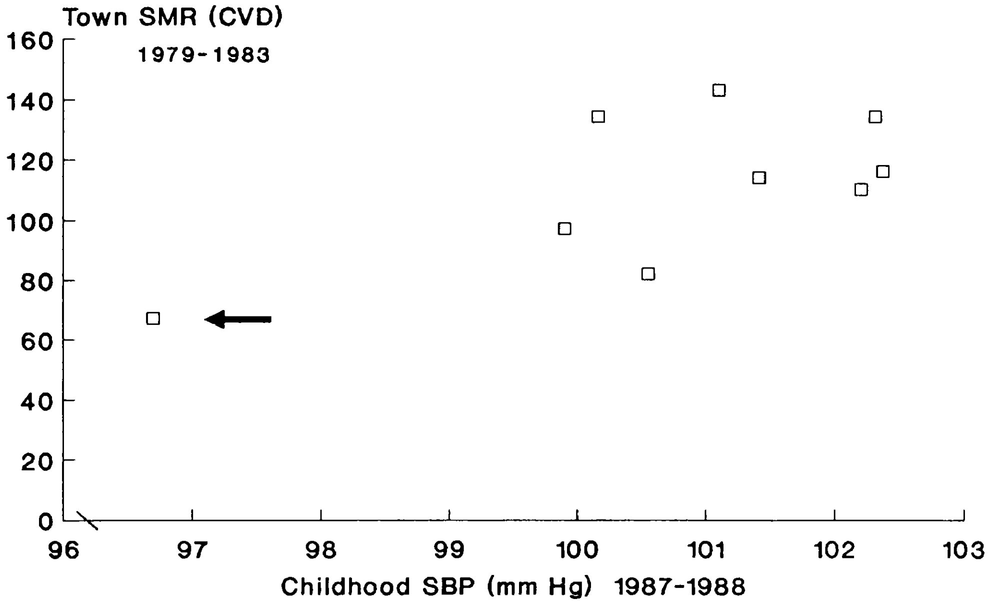
Means and 95% C.I.s (children)
Guildford coordinate arrowed



Means and 95% C.I.s (children)
Guildford coordinate arrowed

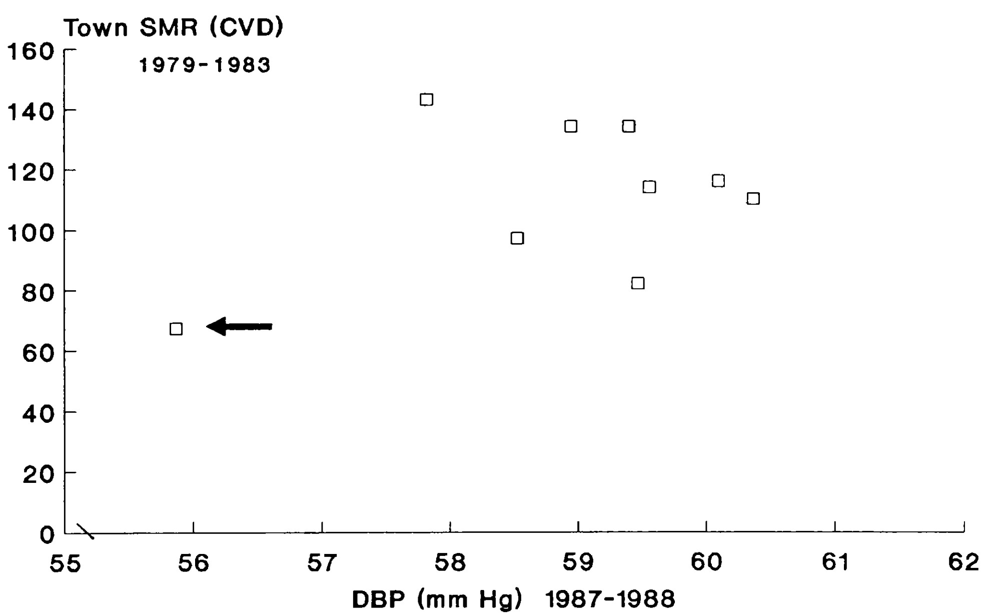
Figure 5.4 CHILDHOOD BLOOD PRESSURE AND ADULT CARDIOVASCULAR MORTALITY: BY TOWN

SYSTOLIC



Guildford coordinate arrowed

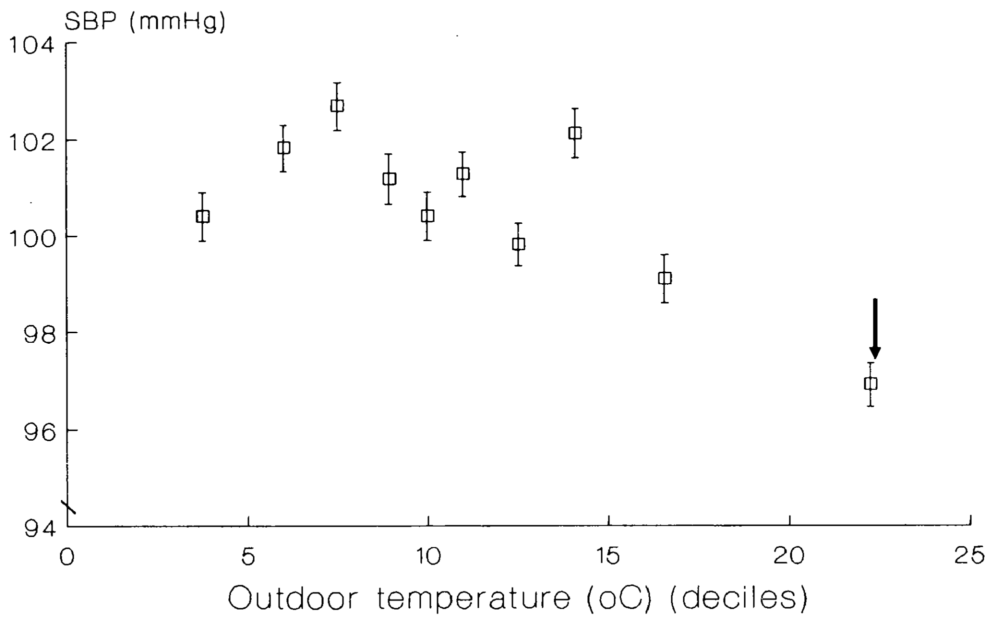
DIASTOLIC



Guildford coordinate arrowed

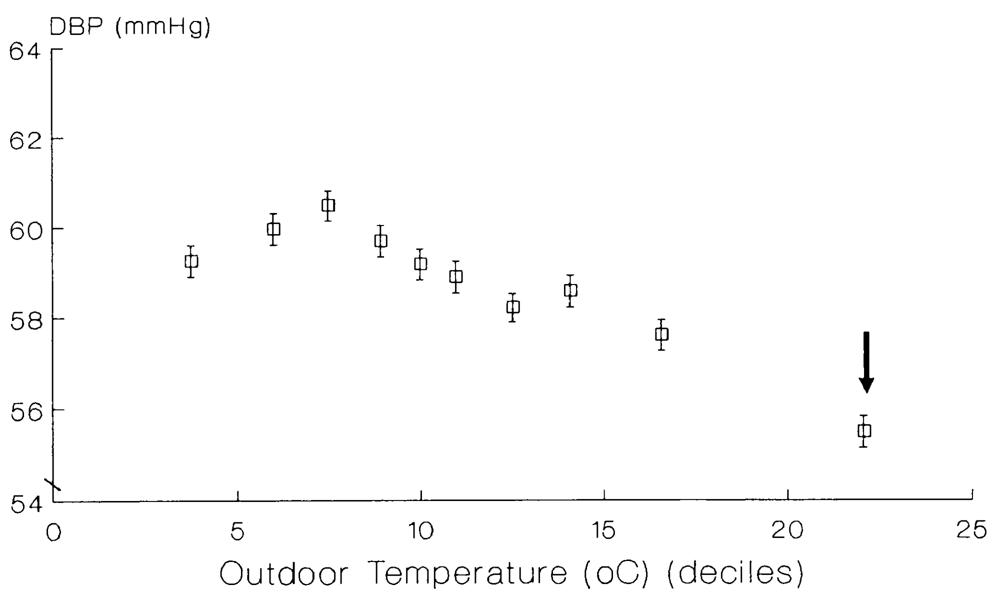
Figure 5.5 OUTDOOR TEMPERATURE AND BLOOD PRESSURE

SYSTOLIC



Means and 95% C.I.s
Top decile arrowed (see text)

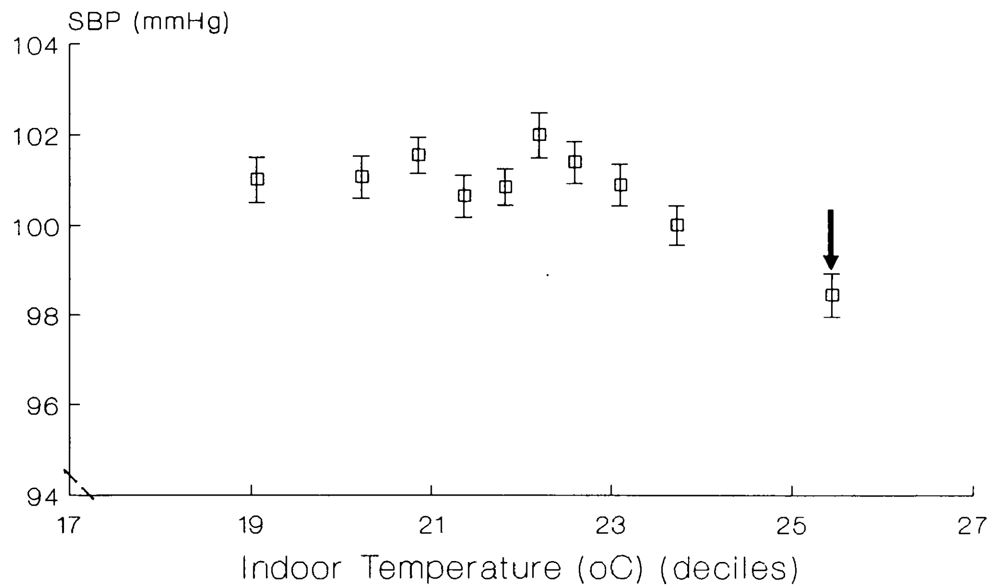
DIASTOLIC



Means and 95% C.I.s
Top decile arrowed (see text)

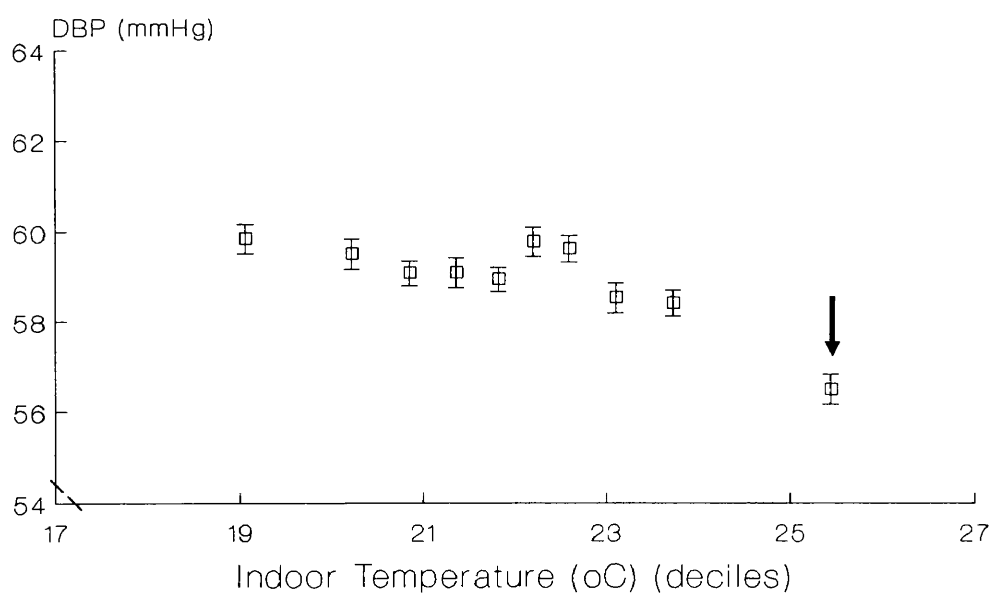
Figure 5.6 INDOOR TEMPERATURE AND BLOOD PRESSURE

SYSTOLIC



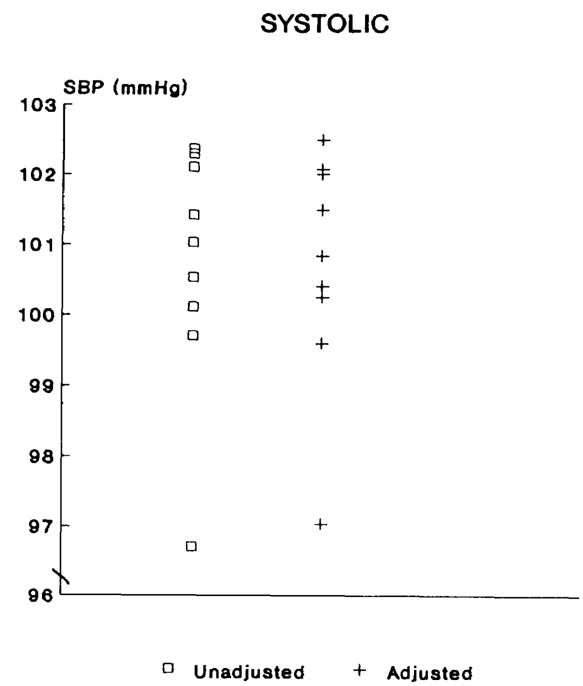
Means and 95% C.I.s
Top decile arrowed (see text)

DIASTOLIC



Means and 95% C.I.s
Top decile arrowed (see text)

Figure 5.7 TOWN MEAN BLOOD PRESSURE LEVELS: EFFECT OF ADJUSTMENT FOR HEIGHT, BODY MASS INDEX AND PULSE RATE



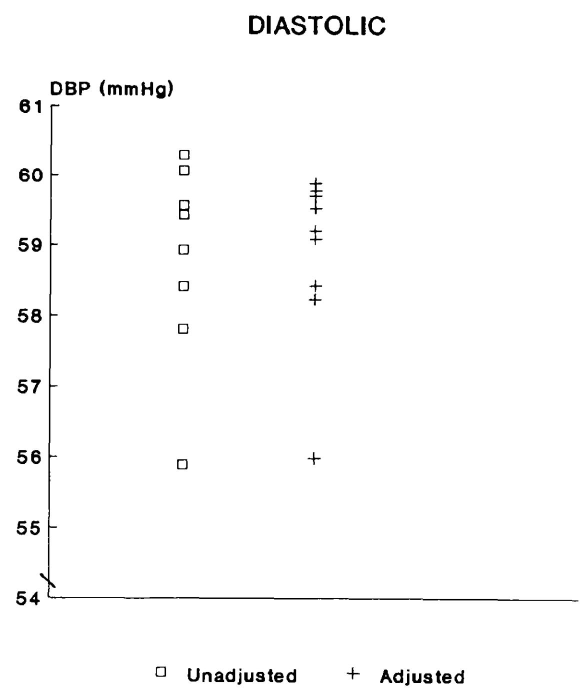
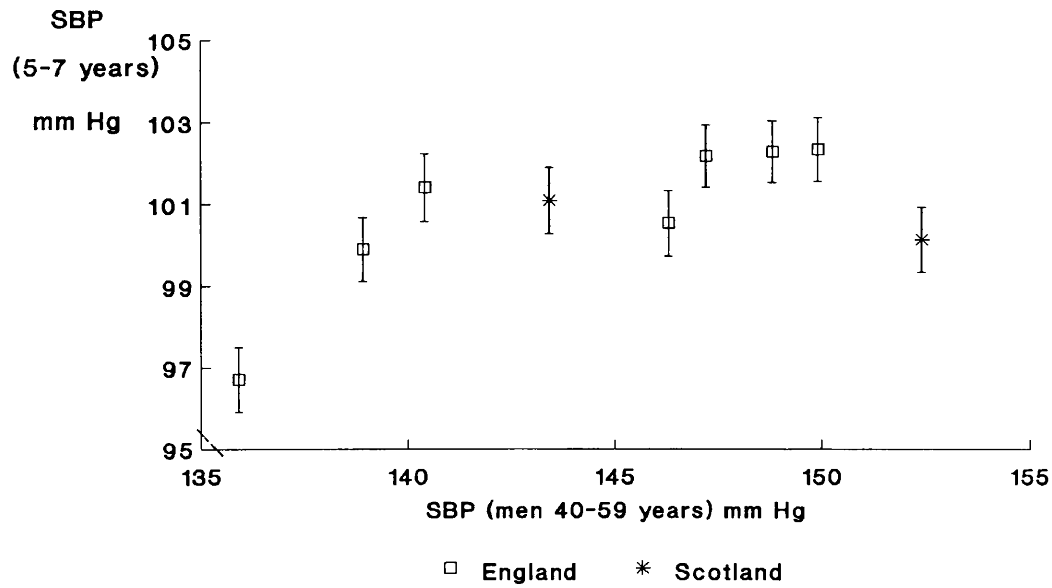


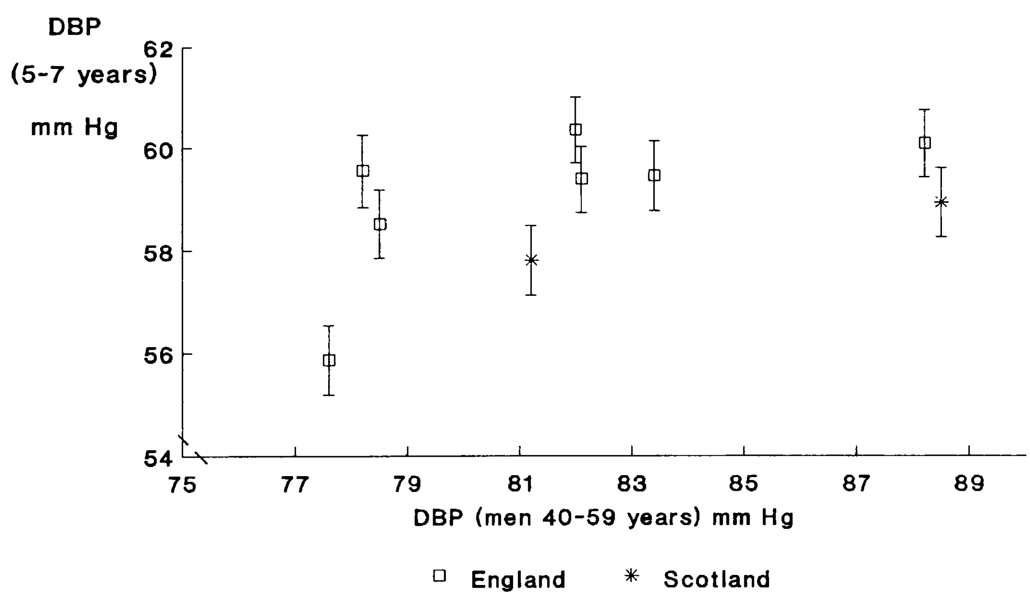
Figure 5.8 RELATION BETWEEN ADULT AND CHILDHOOD MEAN BLOOD PRESSURES: ENGLISH AND SCOTTISH CENTRES

SYSTOLIC



Means and 95% C.I.s (children)

DIASTOLIC



Means and 95% C.I.s (children)

CHAPTER 6

EARLY INFLUENCES ON BLOOD PRESSURE IN CHILDHOOD

6.0 SUMMARY

In this chapter relationships between birthweight, birth order, maternal age, infant feeding and blood pressure in childhood are examined. Birthweight is inversely related to both systolic and diastolic pressure once the effect of current body build is taken into account. Maternal age is positively related and birth order inversely related to blood pressure in childhood. The effects described are largely independent of one another and of age and social class. The relation for birth order is, however, closely related to that between the total number of sibs and blood pressure. The relation between birthweight and blood pressure may reflect the rate of weight gain in infancy; the reasons for relations with birth order and maternal age are so far unknown. The relationships described do not appear to explain the geographic differences in childhood blood pressure described earlier.

6.1 INTRODUCTION

In this chapter the relationships between several factors which may represent influences acting early in life and blood pressure in childhood are examined. The factors studied include birthweight, birth order, maternal age and infant feeding pattern. Parental history of hypertension, already referred to in chapter 5, is also included in these analyses because familial associations in blood pressure are established by the 5-7 year age-group (Zinner SH et al, 1971; Beresford SAA and Holland WW, 1973; Levine RS et al, 1982). Current body build, pulse rate and social factors are considered as possible confounding factors in the analyses.

Associations between these factors and blood pressure are of potential interest for two reasons. First, if population differences in blood pressure level have emerged by the age of 5-7 years, a possibility considered in the last chapter, then the determinants of blood pressure in that age-group are of considerable potential importance. Second, it has been hypothesized that early life experience is directly related to the risk of cardiovascular disease in adult life (Barker DJP, 1991) and that blood pressure may be important in linking early life experience, particularly intrauterine experience, to adult cardiovascular risk (Barker DJP et al, 1989a and 1990). An examination of the determinants of blood pressure in early childhood may provide further information on this question, although it cannot provide a definitive test of the hypothesis.

6.2 SUBJECTS, METHODS, ANALYSIS AND PRESENTATION OF RESULTS

6.2.1 SUBJECTS

The analyses presented here are based on 3693 subjects aged between 5.00 and 7.50 years, 1845 boys and 1848 girls, who attended for examination and for whom parental questionnaires were returned (76% of those invited). However, the numbers of subjects vary slightly between analyses because a small number of questionnaires were only partially completed. Analyses of birthweight are based on 3591 subjects, birth order on 3559 subjects and maternal age on 3542 subjects. Analyses based on birthweight are not restricted to singleton births; however, the exclusion of multiple births makes no difference to the results. Analyses including parental history of blood pressure are restricted to those subjects whose parents reported having a blood pressure measurement at some time (3524 for maternal history and 2633 for paternal history).

6.2.2 METHODS

Information on birthweight, birth order, number of younger siblings, maternal age, infant feeding and parental history of hypertension were obtained from a self-administered questionnaire sent to the parents of all participating children (Appendix III).

Birthweight Mothers were asked to record the child's birthweight, as accurately as possible. The reliability of maternal recall after a 5-7 year interval has previously been demonstrated (Eaton-Evans J and Dugdale AE, 1986).

Birth order The number of living siblings older than the child in question aged upto and including 16 years has been used to provide a measure of birth order. Firstborns are assigned a value of 1, secondborn children a value of 2 and so on. (The results of a supplementary study have indicated that the 16 year restriction makes little or no difference to estimates of the number of older sibs in this age-group).

Younger siblings refers to the number of living siblings who were younger than the child in question.

Maternal age is defined as the mother's age at the time of birth of the child examined.

Feeding in infancy Mothers were asked to specify the method of feeding used in the first three months of the child's life as breast feeding only, bottle feeding only or both. The duration of breast feeding in months (where applicable) was also recorded.

Maternal history of high blood pressure Mothers were asked whether they had ever had their blood pressure measured and, if so, whether it had been high at any time. Mothers replying in the affirmative were asked to specify whether this had been in pregnancy, at other times or both.

Paternal history of high blood pressure Fathers were asked whether they had ever had their blood pressure measured and, if so, whether it had been high at any time.

Social class Social class is based on the longest-held occupation of the head of the household, as described in section 4.3.2.

6.2.3 ANALYSIS AND PRESENTATION OF RESULTS

Birthweight and maternal age have been treated as continuous variables in analysis. Univariate associations between these variables and blood pressure have been examined before accepting the use of linear regression models to examine the relationships between these factors and blood pressure. Parental history of high blood pressure has been treated as a 0/1 variable; birth order and number of younger sibs have been treated as class variables. Standardization for age and, in the case of diastolic pressure, for sex has been carried out as described earlier (section 4.5). Where appropriate, data have been standardized for the effect of current body build by including height and body mass index in the model, a procedure which also provides standardization for the effect of age (section 4.3.1.2). Standardization for differences in blood pressure between the study towns has no important effect on the results observed and has not been carried out routinely.

6.3 RESULTS

6.3.1 VALIDATION OF BIRTHWEIGHT DATA

In order to examine the validity of birthweight data obtained by maternal recall, the data were examined to determine whether they displayed well-established patterns observed in earlier studies. This indirect method of internal validation was used because a study of direct validation, which would require access to maternal obstetric records, would have been difficult to conduct in the present study. Birthweight characteristics are presented in Table 6.1A. Mean birthweights are higher in boys, higher with increasing birth order and in non-manual social classes. All these patterns are consistent with those described in children in the two national birth cohorts of 1958 and 1970, in which birthweight information was recorded directly (Fredrick J and Adelstein P, 1978; Peters TJ et al, 1983). These observations provide support for the validity of the maternal recall method used to obtain birthweight data in the present study.

6.3.2 BIRTHWEIGHT AND BLOOD PRESSURE

The univariate relationships between tenths of birthweight and systolic blood pressure are presented in Figure 6.1, for boys and girls separately. The corresponding linear regression coefficients (for both systolic and diastolic pressure) are presented in Table 6.2. No association between birthweight and blood pressure is apparent for either sex. Standardization for age (which shows no systematic relationship with birthweight when the age range is as narrow as that in the current study) predictably has no effect on this result (Table 6.2). However, a more important potential confounding factor in this context is current body build. Birthweight is independently correlated both with height ($r = 0.23$, $df = 3589$, $p < 0.0001$) and with body mass index ($r = 0.21$, $df = 3589$, $p < 0.0001$). Adjustment for the effect of height and body mass index, which are both strongly related to blood pressure (section 4.3.1.2) is therefore important. When these factors are taken into account a strong negative association between birthweight and both systolic and diastolic blood pressure is apparent for both sexes (Table 6.2). The relationship is of a similar magnitude for boys and girls, with no strong evidence of a sex difference in the relationship either for systolic pressure ($p = 0.36$) or for diastolic pressure ($p = 0.83$). Subsequent results are therefore presented for both sexes combined.

In order to examine whether the relationship between birthweight and blood pressure varies at different levels of current body build, birthweight-blood pressure relationships have been examined within each fifth of the distributions of height and body mass index. The relationships for fifths of height are presented in Table 6.3 for both systolic and diastolic pressure. The corresponding regression slopes for each fifth of the height distribution are presented in Figure 6.2. The inverse relationship between birthweight and blood pressure is apparent in all five height groups, but there is no indication either that the relationships between birthweight and blood pressure differ in any particular group, an impression supported by formal tests for heterogeneity of slopes (systolic $p = 0.46$; diastolic $p = 0.96$), or that a trend occurs across the height groups. Similarly, there is no apparent difference in birthweight-blood pressure relationships at different levels of body mass index (data not presented). Pulse rate shows no relationship with birthweight, even after standardization for current height ($r = 0.00$, df 3589, $p = 0.89$), and has no effect on the birthweight-blood pressure relationships described.

The possibility that the association between birthweight and blood pressure is the result of confounding factors requires consideration. Social class, while strongly related to birthweight (Table 6.1A), shows no consistent relationship with blood pressure (section 4.3.2). It is therefore not surprising that adjustment for social class makes no difference to the birthweight-blood pressure relationship (data not presented). Birth order is strongly related to birthweight (Table 6.1A) and must therefore be considered as a potential confounder. Maternal age is also related, both to birth order (Table 6.1B) and, in a more complex way, to birthweight (Table 6.1A). Birth order rises progressively with increasing maternal age. Birthweight is lowest in the youngest maternal age-group, rises in the subsequent age-groups and then falls in the oldest age-group. Because birth order and maternal age are related to birthweight, it is important to establish whether they are also related to blood pressure and, if so, whether they could account for the birthweight-blood pressure relationship. These questions are addressed in the following sections.

6.3.3 BIRTH ORDER AND BLOOD PRESSURE

The relationships between birth order and blood pressure (systolic and diastolic) are presented in Table 6.4A. A stepwise fall in both systolic and diastolic blood pressures is observed with increasing birth order, with a mean difference of 2.3 mmHg systolic and 1.9 mmHg diastolic between birth order 1 (i.e firstborns) and birth order 4+. These differences, which are similar in both sexes, are highly statistically significant and remain so if height and body mass index are included in the model (section 6.3.7).

The finding of an association between birth order and blood pressure calls for further examination to distinguish between possible explanations. In particular, 'birth order' as defined in this study reflects not only birth order, but also the number of older siblings in the family. It is therefore possible that the association reflects the total number of siblings rather than birth order per se. In an attempt to distinguish between these possibilities, an analyses is presented in order to establish whether the number of younger sibs is related to blood pressure in childhood, independent of the number of older sibs. The results of this analysis are presented in Table 6.5 for both systolic and diastolic pressure. By following the rows of the table it can be seen that the inverse association between birth order and blood pressure already described is present for each number of younger siblings. By following the columns it can be seen that an increasing number of younger siblings is associated with a fall in mean blood pressure (both systolic and diastolic) even after the effect of birth order has been taken into account. The younger sibs effect is highly statistically significant for systolic pressure ($p < 0.0001$) but just fails to reach conventional levels of statistical significance for diastolic pressure ($p = 0.063$). These results therefore provide some support for the view that the total number of siblings, rather than birth order, may be the important factor related to blood pressure in this context.

6.3.4 MATERNAL AGE AND BLOOD PRESSURE

The univariate relationships between maternal age and blood pressure are presented in Table 6.4B. With increasing maternal age there is a progressive rise in both systolic and diastolic pressure. The regression coefficients for blood pressure on maternal age controlling for age are 0.11 mmHg/year for systolic pressure (s.e. 0.02, $p < 0.0001$) and 0.06 mmHg/year for diastolic pressure (s.e. 0.02, $p < 0.0001$). These figures imply a rise of 1.1 mmHg in systolic and 0.6 mmHg in diastolic pressure for each 10 year increase in maternal age.

The results presented above provide evidence that both birth order and maternal age are related to blood pressure. It is therefore important to consider whether these factors could account for the birthweight-blood pressure relationship described in Section 6.3.2. This question is addressed in the multiple regression analyses presented in Section 6.3.7. However, before moving to these multiple regression models, two other potential early influences on blood pressure level, infant feeding method and parental history of high blood pressure, are considered.

6.3.5 INFANT FEEDING METHOD AND BLOOD PRESSURE

The blood pressures of children who had been fed exclusively on either breast or bottle milk have been compared. Both systolic and diastolic blood pressures are identical in the two groups (100.8 mmHg systolic; 58.9 mmHg diastolic). The 95% confidence intervals for the differences are small, extending from -0.62 mmHg to 0.62 mmHg for systolic pressure and from -0.25 mmHg to 0.25 mmHg for diastolic pressure.

6.3.6 MATERNAL AND PATERNAL HISTORY OF HIGH BLOOD PRESSURE

The differences in mean systolic and diastolic blood pressures associated with the presence or absence of a parental history of high blood pressure have already been examined in section 4.3.3. The inclusion of parental history of high blood pressure in multiple regression analyses examining the relations between early life influences and blood pressure is justified, by the observation in earlier studies that parental history is associated with differences in blood pressure in early childhood (Zinner SH et al, 1971; Beresford SAA and Holland WW, 1973; Levine RS et al, 1982). In addition, earlier reports have suggested that parental history of high blood pressure may be related to factors already referred to in this chapter, particularly birthweight (Gennser G et al, 1988). However, the results of the present study provide little support for this possibility. The relationships between a maternal and paternal history of high blood pressure and birthweight, birth order and maternal age are presented in Table 6.6. Mean birthweights are slightly but not significantly lower in those children with either a maternal or paternal history of high blood pressure. Neither maternal nor paternal history is strongly related to maternal age or birth order.

6.3.7 INTERRELATIONS OF FACTORS

The independent contributions of the principal factors discussed above which are related to blood pressure - birthweight, birth order, maternal age and parental history of high blood pressure - have been examined in a multiple regression analysis taking all these variables together with height and body mass index (which standardize for age in this population) into account. The principal analyses have been conducted with maternal history of hypertension rather than paternal history for two reasons. The reasons for this are, first, that an analysis based on maternal history can be based on larger numbers of subjects and, second, that maternal history may be more important than paternal history in the context of analyses including birthweight, birth order and maternal age. Infant feeding method, which shows no relationship with blood pressure, has not been included. The results of the regression analyses are presented in Table 6.7, for both systolic and diastolic pressure. In the left-hand column of each table regression coefficients are given for the relationship between each variable and blood pressure adjusted for height and body mass index alone; in the right-hand column adjustment is made for height, body mass index and for all other factors in the table in a simultaneous regression model. The effects of height, body mass index, birthweight, maternal age, birth order and maternal history of high blood pressure all remain highly significant in the multiple regression models both for systolic and diastolic pressure and are little affected by the addition of the other factors. The strengths of relations between maternal age and blood pressure and between birth order and blood pressure are increased by taking the other factors into account; this results from the association between maternal age and birth order (Table 6.1B), two factors which have opposing effects on blood pressure. The results of these analyses are not markedly affected by the use of paternal history rather than maternal history, nor by the inclusion of number of younger sibs. The addition of town and social class to the model similarly has little effect.

6.3.8 CONTRIBUTION OF BIRTHWEIGHT, BIRTH ORDER AND MATERNAL AGE TO BETWEEN-TOWN DIFFERENCES IN BLOOD PRESSURE

The mean birthweight, birth order and maternal age for each of the study towns are presented in Table 6.8. Mean birthweight varies between 3.24 kg in Scunthorpe and 3.40 kg in Ayr. However, there is no evidence that differences in town mean birthweight are strongly related to town mean blood pressure levels; correlation coefficients between birthweight and blood pressure by town are both weakly positive. Both town mean birth order and maternal age show modest inverse correlations with town mean blood pressure, none of which achieve statistical significance. However, the directions of the relationships between birthweight and blood pressure and between maternal age and blood pressure are opposite to those described earlier in individuals. This implies that differences in these variables between towns cannot account for between-town differences in blood pressure. While the inverse relationship between birth order and blood pressure is in the same direction both within and between towns, the associations are very weak and adjustment for the effect of birth order has no important effect on between-town differences in blood pressure, and particularly on the low mean blood pressures observed in Guildford.

6.4 COMMENTARY

The data examined in this report have two important strengths. First, they are based on a socially representative sample of children from nine British towns, which has ensured the inclusion of a wide range of birthweights, maternal ages and birth orders for study. Second, blood pressure measurement procedures in the study have been standardized in detail. The main potential weakness is the retrospective nature of data collection on early life influences and the relatively low response rates for data on these variables. However, error in parental recall in this context is likely to be predominantly random, leading to underestimation rather than overestimation of the strength of associations with blood pressure. Moreover, even for birthweight, an item for which parental recall might be expected to be weak, well established relationships (particularly with parity and social class) can be clearly documented in the study population.

6.4.1 BIRTHWEIGHT AND BLOOD PRESSURE

In this study population an inverse association between birthweight and blood pressure is observed once the effect of current body build is taken into account. The results of several previous studies which have examined the relationships between birthweight and blood pressure in childhood, adolescence and adults are reviewed briefly below.

6.4.1.1 Birthweight and blood pressure in childhood

Four studies have reported on the association between birthweight and blood pressure in childhood, two in 7 year-olds (in Dunedin and Oxford), two in 10 year-olds (in Aberdeen and in Great Britain as a whole). Simpson and colleagues (Simpson A et al, 1981) examined 692 children 7 years of age, 67% of a cohort of births at a hospital in Dunedin, New Zealand. In a comparison of the characteristics of children with relatively high blood pressure levels (SBP $\geq$ 114 mmHg and/or DBP $\geq$ 74 mmHg with children in an intermediate blood pressure group (SBP $\geq$ 96 mmHg and or DBP $\geq$ 54 mmHg, mean birthweight was observed to be lower in the high group (mean 3240 gm) than in the intermediate group (mean 3400 gm). In a multiple regression analysis including all subjects and examining the relationships between birthweight, birth length and gestational age, a significant negative association between birthweight and systolic blood pressure was observed. Ounsted and colleagues in Oxford (Ounsted MK et al, 1985) measured supine blood pressures in 216 children aged 7.5 years who had been born to mothers with hypertension of pregnancy. Weak negative correlations were observed between birthweight and blood pressure; only that for systolic pressure in males was statistically significant. No estimate of the magnitude of the relationship was provided. Cater and Gill reported on a study of 282 10 year-old children in Aberdeen followed from birth (Cater J and Gill M, 1984). Of these children, 143 had been of low birthweight (<2500 gm), while 139 were included as normal birthweight controls. Procedures of blood pressure measurement were not described in detail. Mean blood pressures were markedly higher in the low birthweight group than in controls, by approximately 5 mmHg systolic and 3 mmHg diastolic. Barker and colleagues (Barker DJP et al, 1989a) examined the relationship between birthweight and blood pressure in a cohort of 9921 10 year-olds born in Great Britain during one week during 1970 (the British Birth Survey). Blood pressure measurements were made by many different school medical officers in locations across the country and measurements were rounded to the nearest 10 mmHg, two potential sources of error which may have led to underestimation of associations. An inverse relationship between birthweight was observed for systolic blood pressure was observed, with systolic ranges of 0.38mmHg for boys and 1.32 mmHg for girls across the birthweight groups. However, no association was described for diastolic pressure.

<u>Comparison of present and previous studies</u> The relationships described in the present study were of a similar order of magnitude to those described in 10 year-olds by Cater and Gill but larger than those described by Barker. However, the circumstances of blood pressure measurement in the British Birth Survey, a large number of observers making rounded measurements, are likely to have reduced the magnitude of the effects observed. In the younger children in the present study, the relationship is only observed when the effect of current body build is taken into account. This presumably reflects the strong association between birthweight and current body build in the early years of life, which becomes increasingly attenuated with age. This attenuation is confirmed in the present data set, in which the correlation coefficient relating birthweight and current weight falls from 0.36 at age 5.0-5.5 years to 0.22 at age 7.0-7.5 years. The magnitude of the association therefore appears to be small. A one standard deviation change in birthweight is associated with an estimated change in systolic blood pressure of -0.98 mmHg, compared with 3.09 mmHg for a one standard

deviation change in current weight. However, a relationship between birthweight (an important marker of intrauterine experience, closely related to perinatal and infant mortality) and blood pressure would be of considerable interest - if the association persists beyond childhood and into adult life, when the importance of blood pressure as a determinant of cardiovascular risk is well established, and if the association is causal. These two issues are addressed in the next sections.

6.4.1.2 Birthweight-blood pressure relationships in older age-groups

(i) Studies in adolescence Two studies have examined the relationship between birthweight and blood pressure in adolescence. In 4500 subjects aged 0 to 20 years examined in a community survey in Tecumseh, Michigan no association between birthweight and blood pressure was observed (Higgins M et al, 1980). However, the effect of adjustment for current body size was not reported in that study. More recently, the report of a study of 32,580 17 year-olds examined on entry to the Israeli army described weak positive associations between birthweight and blood pressure in univariate analyses, which were statistically significant (Seidman DS et al, 1991). Adjustment for the effect of current body build had little influence on the relations described. Although the large numbers of observers and an apparent lack of standardization in blood pressure measurement might have reduced the power of the study to detect associations, these factors would be unlikely to alter the direction of the associations observed.

(ii) Studies in adult life

Three studies have examined the relationships between birthweight and blood pressure in adults. In the National Survey of Health and Development, a cohort of 5362 subjects born in Great Britain in 1946, blood pressure measurements were carried out in 3259 subjects (61% of the original group) at the age of 36 years by a team of survey nurses. A weak negative association between birthweight and systolic, but not diastolic, blood pressure was observed in univariate analysis (Wadsworth MEJ et al, 1985). After standardization for the effect of current weight, differences of between 2 and 3 mmHg were observed between the upper and lower thirds of the birthweight distribution. However, very much stronger associations between birthweight and blood pressure in adult life were described in a more recent study which also took placental weight into account (Barker DJP et al, 1990). During 1935-43 detailed birth records (including birthweights, head circumferences and placental weights) had been recorded on 1298 subjects born at a Preston hospital, of whom 1122 (86%) could be traced in 1989. Five hundred and three subjects were still living in Lancashire, of whom 449 were studied. An inverse relationship was observed between birthweight and systolic blood pressure, with a difference of approximately 5 mmHg between the highest and lowest birthweight groups. However, once the effect of placental weight was taken into account the relationship was considerably stronger, with differences of 10 mmHg or more in systolic pressure between the highest and lowest birthweight groups. This association did not appear to be accounted for either by adult social class or by differences in alcohol intake. Finally, in a study of 77 Swedish army conscripts aged 28 years (Gennser G et al, 1988), it was observed that the 25 subjects with diastolic blood pressure of 90 mmHg or more had a higher proportion of subjects with low birthweight than the 52 with diastolic pressures below 90 mmHg. However, no estimate of the magnitude of the birthweight-blood pressure relationship was provided in that study.

6.4.1.3 <u>Birthweight and blood pressure: association or causation?</u>
In a review of the characteristics of an association which suggested causality, the strength of the association, independence of confounding factors, consistency and biological plausibility were identified as important factors (Hill AB, 1965). Each of these factors will be considered in turn for the birthweight-blood pressure relationship.

(i) <u>Strength of association</u> In all the studies reporting associations in children these were weak, while two large studies in adolescence failed to find any inverse association. The Israeli study, despite its apparent lack of blood pressure measurement standardization, should have had considerable power to do so, particularly with a narrowly defined age-group. The apparent lack of measurement standardization in that study, while limiting its power, is not likely to account for a reversal of the direction of the association. While all three adult studies reported an inverse association between birthweight and blood pressure, the magnitude of the effect in the largest and most representative study, the National Study of Health and Development, was small. The very large effect described in the smaller Preston study requires further confirmation. First, the study was based on a small proportion (35%) of the original cohort of hospital deliveries, a group which (as the authors point out) would have been atypical in an age when most deliveries occurred at home. Second, the strong association was dependent on standardization for placental weight. While the authors' suggestion that this is a valid procedure, providing an estimate of mismatch in foetal and placental size, may be valid, this has yet to be firmly established.

(ii) Confounding factors While the associations between birthweight and blood pressure have for the most part been weak, the relationships have not so far been accounted for by confounding factors. In the present study, the effects of social class, birth order, maternal age and a parental history of high blood pressure did not confound the association. The strong associations between birthweight, placental weight and blood pressure in adult life described in the Preston study were not confounded by adult social class and alcohol intake (Barker DJP et al, 1990). The influence of parental smoking on the relationship has yet to be examined, although this variable is likely to be strongly related to parental social class.

(iii) Consistency The consistency of relationships between birthweight and blood pressure over time and in different countries have yet to be examined in detail. However, it is apparent that many of the communities which have low rates of blood pressure rise and little or no hypertension tend to be relatively unacculturated, often living on subsistence diets. Although little information has been documented about the perinatal experience of such communities, it seems likely that average birthweights would be low rather than high. In contrast, the societies in which birthweights are high, the developed Western Countries, tend to have higher mean blood pressures than the unacculturated communities. Moreover, within developed countries it has yet to be established that secular trends in birthweight are matched by changes in blood pressure patterns (Strachan DP and Tudor-Hart J, 1990). If the birthweight-blood pressure relationships observed within societies are not consistent with secular trends and international patterns this will raise important reservations about the causality of the birthweight-blood pressure relationship.

(iv) Biological plausibility: mechanisms

The mechanism of the association between low birthweight and blood pressure remains unknown. The observations presented above suggest that the effect is independent of the effects of birth order, maternal age and a maternal history of high blood pressure. Barker and his colleagues observed that the relationship between birthweight and blood pressure was independent of gestational age and went on to suggest that a retarded intrauterine growth rate, associated with an adverse intrauterine environment, might be a critical factor in the relationship (Barker DJP et al, 1989a). A second possible explanation of the birthweight-blood pressure relationship is that low birthweight is associated with postnatal events which are responsible for the relationship between birthweight and blood pressure (Ounsted MK et al, 1985). An important possibility here is the rapid gain in weight experienced during the first year of life by most babies of low birthweight - 'catch-up growth' - (Thomson J, 1955; Cruise MO, 1973), which would constitute one possible mechanism for this effect. This explanation may be particularly attractive in that it may be dependent on adequate nutrition, and may therefore offer a reason why the birthweight-blood pressure association has been described within developed countries, but may not be apparent between countries.

How can the intrauterine and postnatal explanations for the birthweight-blood pressure association be distinguished? In the current study no information on early postnatal weight gain is available, so that this issue cannot be addressed directly. However, if intrauterine factors are responsible for the birthweight-blood pressure relationship, it might be expected that the association would be apparent at birth. If, on the other hand, postnatal factors are responsible, the relationship would be expected to appear at a later stage, probably in early childhood. The results of studies which have examined birthweight and blood pressure at birth are presented in Table 6.9, classified according to whether the infants included were full-term, pre-term or specifically of low birthweight. Although several of the studies provide little information on the magnitude of birthweight-blood pressure relationships and the potential extent of error, none observed an inverse birthweight-blood pressure association at birth and the majority observed positive associations. This implies that the relationship between birthweight and blood pressure is likely to become apparent in infancy or early childhood rather than in utero. This observation would therefore be most consistent with a postnatal explanation for the development of the birthweight-blood pressure relationship. Although this does not exclude an intrauterine basis for the association, it does imply that the intra-uterine mechanism proposed would have to be modified to account for the delay in appearance of the relationship until after the causal factor was removed.

6.4.2 MATERNAL AGE, BIRTH ORDER AND BLOOD PRESSURE

The relationships between maternal age, birth order and blood pressure were originally examined to determine whether they might confound the birthweight-blood pressure relationship. It became apparent that both these factors are related to blood pressure independently of birthweight. The relationships of maternal age and birth order are in opposing directions; by taking both factors into account the strengths of the individual associations with blood pressure are increased. The magnitude of the effects are smaller but of the same order of magnitude as birthweight; the change in systolic blood pressure for a one standard deviation change in maternal age is 0.51 mmHg, compared with -0.98 mmHg for birthweight. A positive relationship between maternal age and blood pressure has been described in one study, of 4500 subjects aged 0 to 20 years in Tecumseh, Michigan (Higgins M et al, 1980). The reason for this association is unknown and its persistence into adult life has yet to be described. No earlier report of a relationship between birth order and blood pressure has been identified. While the basis of this association is also unknown, the observation that the number of younger sibs is related to blood pressure, particularly systolic pressure, independently of birth order suggests that the association may well have a postnatal basis and that the total number of sibs may be the most important factor. Again, the importance of the association depends on its persistence into adult life; in this context a report from the United States, suggesting that the absence of siblings may be associated with a higher prevalence of hypertension in adults (Trevisan M et al, 1991), may be of interest.

6.4.3 INFANT FEEDING METHOD AND BLOOD PRESSURE

The relationship of feeding method to blood pressure has long been of interest because of the differing sodium content of breast and bottle milks. For many years the sodium content of bottled preparations has been higher than that of breast milk in Great Britain (Paul AA and Southgate DAT, 1978), although the differences are now diminishing (Department of Health and Social Security, 1988). In the present study, the feeding methods employed in the first months of life did not appear to influence blood pressure at age 5-7 years. This remains the case even when the slightly greater average current weight of breast fed children, consistent with earlier findings (Marmot MG et al, 1980), is taken into account. The results are consistent with the findings of other observational studies (summarized in Table 6.10) which with one exception found no relationship between blood pressure in infancy or childhood and previous feeding methods. However, at first sight, these results do not agree with the findings of the one randomized controlled trial of sodium restriction in neonates carried out to date (Hofman A et al, 1983). In that study, mean systolic blood pressure levels in the intervention group were lower than those in the control group by 2 mmHg at the end of the six month intervention period. However, the differences observed in that study took nine weeks to become apparent, and remained less than 1 mmHg in size until 17 weeks. Moreover, there was little difference between the blood pressures of the two groups at one year, six months after the end of intervention (Hofman A, 1989). The results of this study must be interpreted with caution, because the confidence intervals on blood pressure differences between groups during the intervention are wide. However, if the results are accepted, they suggest that the effect of differences in sodium intake on blood pressure in early life requires at least two months to become apparent, and that the effect is reversible. Of the studies presented in Table 6.10, the first four would have measured blood pressure too soon after the introduction of different feeding methods to detect an effect, while studies 6 to 8 would have carried out measurements too long after the end of the infant feeding period to detect an effect. This leaves only the fifth study (Schachter et al, 1979). However, in Schachter's study a large proportion of those mothers who did breastfeed had weaned their babies at 2-3 months, a point at which blood pressure differences might well be small. This study would therefore have had a limited ability to detect a difference between breast-fed and bottle-fed babies at six months, even if it was sufficiently large to do so.

For the reasons discussed, none of the observational studies described could have provided an adequate test of the hypothesis that differences in sodium intake as a result of differences in infant feeding method are related to short-term differences in blood pressure level in infancy or early childhood. However, the results of the observational studies imply consistently that differences in infant feeding method have no important long-term effect on blood pressure. If a short-term effect does occur, as Hofman's observations suggest may be the case, it is likely to disappear once differences in infant feeding practice are discontinued, and to be overshadowed by other, more powerful, influences on blood pressure, among which weight gain may be particularly important.

6.4.4 PARENTAL HISTORY OF HIGH BLOOD PRESSURE: INFLUENCE ON OTHER FACTORS

The association between parental and child blood pressure levels is well established. Of particular interest in the present context is the question of whether the association between parental history and blood pressure in childhood, which appears to develop very early in life, can be accounted for by the effects of birthweight, maternal age or birth order. In particular, it has been suggested that low birthweight might be an important corollary of hypertension of pregnancy (Gennser G et al, 1988). However, average birthweights are not markedly different in subjects with and without a maternal history of high blood pressure

(Table 6.6) and adjustment for birthweight has little effect on the magnitude of the maternal history effect (Table 6.7). Moreover, further analyses, not presented here, have shown that the relationship between birthweight and blood pressure is very similar in subjects with and without a parental history of high blood pressure. These observations imply that the relations of parental history of high blood pressure and of birthweight to childhood blood pressure are largely independent of one another.

6.4.5 BETWEEN-TOWN DIFFERENCES IN BIRTHWEIGHT, BIRTH ORDER AND MATERNAL AGE

The small differences in birthweight, birth order and maternal age between towns do not appear to account for the geographic differences in blood pressure described. The absence of any consistent geographic relationship between birthweight and childhood blood pressure, or indeed between birthweight and adult cardiovascular mortality rate ($r = 0.13$) is of particular interest in the light of Barker's earlier suggestion that intrauterine factors are related to cardiovascular risk on a geographic basis (Barker DJP et al, 1987 and 1989a). While this observation does not exclude an association between intrauterine factors and cardiovascular risk in an earlier generation, it provides no support for the possibility that intrauterine factors are likely to be important in sustaining the present pattern of geographic differences in cardiovascular risk in the present cohort.

TABLE 6.1A BIRTHWEIGHT AND ITS CORRELATES

BIRTHWEIGHT (kg)

SEX	N	Mean	(s.e.)		
Female	1802	3.25	(0.01)	p (no sex	
Male	1789	3.39	(0.01)	difference)	<0.0001

BIRTH ORDER	N	Mean	(s.e.)		
1	1653	3.28	(0.01)		
2	1390	3.37	(0.01)		
3	424	3.44	(0.03)	p (test	
4+	92	3.43	(0.06)	for trend)	<0.0001

SOCIAL CLASS	N	Mean	(s.e.)		
I	208	3.38	(0.04)		
II	846	3.39	(0.02)		
IIIN	497	3.32	(0.02)		
IIIM	1283	3.30	(0.01)		
IV	434	3.27	(0.03)	p (test	
V	88	3.35	(0.06)	for trend)	<0.001

MATERNAL AGE (yrs)

Fifth	Mean	N	Mean	(s.e.)		
1	20.3	787	3.25	(0.02)		
2	24.1	720	3.37	(0.02)		
3	26.5	567	3.31	(0.02)		
4	29.0	679	3.36	(0.02)	p (test for	
5	33.8	789	3.32	(0.02)	heterogeneity)	<0.0001

TABLE 6.1B BIRTH ORDER AND MATERNAL AGE

MATERNAL AGE (yrs)

BIRTH ORDER	N	Mean	(s.e.)		
1	1647	25.2	(0.1)		
2	1386	27.6	(0.1)		
3	420	29.1	(0.2)	p (test	
4+	89	30.1	(0.6)	for trend)	<0.0001

All results are standardized for sex.

TABLE 6.2 BIRTHWEIGHT AND BLOOD PRESSURE: UNADJUSTED, AGE-ADJUSTED AND BODY BUILD-ADJUSTED RELATIONSHIPS.

BOYS (N = 1789)

	SYSTOLIC			DIASTOLIC		
Adjustment	Regression coefficient	(s.e.)	p	Regression coefficient	(s.e.)	p
None	0.33	(0.39)	0.40	-0.04	(0.27)	0.89
Age	0.37	(0.38)	0.33	-0.01	(0.27)	0.95
Height and body mass index	-1.66	(0.38)	<0.0001	-0.88	(0.27)	0.0024

GIRLS (N = 1802)

	SYSTOLIC			DIASTOLIC		
Adjustment	Regression coefficient	(s.e.)	p	Regression coefficient	(s.e.)	p
None	-0.58	(0.39)	0.13	-0.31	(0.27)	0.24
Age	-0.56	(0.38)	0.12	-0.32	(0.27)	0.23
Height and body mass index	-2.15	(0.37)	<0.0001	-0.96	(0.27)	<0.0001

Regression coefficients refer to regression of blood pressure on birthweight (mmHg/kg), adjusted as specified in the left-hand column. Analyses of diastolic pressure are standardized for sex.

TABLE 6.3 BIRTHWEIGHT AND BLOOD PRESSURE BY FIFTHS OF HEIGHT.

SYSTOLIC

BIRTH WEIGHT (kg)	HEIGHT (cm) 98.6-111.7	111.8-115.1	115.2-118.3	118.4-122.0	122.1-138.9	ALL
1.05-2.89	97.2	100.2	102.9	103.6	105.7	100.6
2.90-3.22	97.6	99.3	99.5	101.9	106.4	101.1
3.23-3.44	95.8	99.3	100.3	102.2	105.0	100.6
3.45-3.74	97.8	99.3	100.4	102.3	104.1	101.1
3.75-5.47	97.0	98.9	99.6	100.9	103.8	100.7
ALL	96.7	99.4	100.3	102.2	105.3	

DIASTOLIC

BIRTH WEIGHT (kg)	HEIGHT (cm) 98.6-111.7	111.8-115.1	115.2-118.3	118.4-122.0	122.1-138.9	ALL
1.05-2.89	57.4	58.9	59.2	59.8	61.0	58.8
2.90-3.22	57.6	57.8	58.8	60.2	61.9	59.0
3.23-3.44	56.4	57.9	58.5	60.0	61.0	58.8
3.45-3.74	57.5	58.2	58.5	59.8	60.7	59.1
3.75-5.47	56.7	57.5	58.3	58.6	60.0	58.5
ALL	57.5	58.1	58.6	59.4	60.7	

Birthweight (kg) and height (cm) are presented in fifths of their distribution. Analyses are presented for both sexes combined (1789 boys + 1802 girls); results for diastolic pressure are standardized for sex.

TABLE 6.4A BIRTH ORDER AND BLOOD PRESSURE

BIRTH ORDER	N	BLOOD PRESSURE (mmHg) SYSTOLIC		DIASTOLIC	
		Mean	(s.e.)	Mean	(s.e.)
1	1653	101.4	(0.2)	59.4	(0.2)
2	1390	100.4	(0.2)	58.5	(0.2)
3	424	100.0	(0.4)	58.3	(0.3)
4+	92	99.1	(0.9)	57.5	(0.6)

TABLE 6.4B MATERNAL AGE AND BLOOD PRESSURE

MATERNAL AGE (yrs)	N	BLOOD PRESSURE (mmHg) SYSTOLIC		DIASTOLIC	
		Mean	(s.e.)	Mean	(s.e.)
15.0-22.4	787	99.8	(0.3)	58.2	(0.2)
22.5-25.4	720	100.7	(0.3)	58.9	(0.2)
25.5-27.4	567	100.5	(0.4)	58.9	(0.2)
27.5-30.4	679	101.1	(0.3)	59.1	(0.2)
30.5 and above	789	101.8	(0.3)	59.3	(0.2)

Analyses are standardized for age and, in the case of diastolic pressure, for sex.

TABLE 6.5 BIRTH ORDER, NUMBER OF YOUNGER SIBLINGS AND BLOOD PRESSURE

SYSTOLIC

YOUNGER SIBLINGS	BIRTH ORDER 1	2	3	4+
0	102.1 (0.4) 450	100.9 (0.3) 969	100.3 (0.5) 328	99.4 (1.2) 47
1	101.3 (0.3) 944	99.2 (0.5) 347	99.0 (1.0) 83	98.1 (1.3) 45
2+	100.4 (0.5) 259	99.2 (1.0) 74	-	-

DIASTOLIC

YOUNGER SIBLINGS	BIRTH ORDER 1	2	3	4+
0	59.5 (0.3) 450	58.7 (0.2) 969	58.5 (0.3) 328	58.1 (0.9) 47
1	59.4 (0.2) 944	57.9 (0.3) 347	57.5 (0.6) 83	56.9 (0.8) 45
2+	59.0 (0.4) 259	57.6 (0.7) 74	-	-

Analyses are standardized for age and, in the case of diastolic pressure, for sex. Figures presented are means (standard errors) and numbers of subjects for each cell. Cells based on less than 25 subjects have been excluded.

TABLE 6.6 BIRTHWEIGHT, BIRTH ORDER AND MATERNAL AGE IN SUBJECTS WITH AND WITHOUT A MATERNAL OR PATERNAL HISTORY OF HIGH BLOOD PRESSURE

MATERNAL HISTORY	YES		NO		
	(N = 1409)		(N = 2115)		
	Mean	(s.e.)	Mean	(s.e.)	p (no diff.)
Birthweight (kg)	3.31	(0.01)	3.33	(0.01)	0.16
Maternal age (yrs)	26.8	(0.1)	26.8	(0.1)	0.95
Birth order	1.71	(0.02)	1.70	(0.02)	0.72

PATERNAL HISTORY	YES		NO		
	(N = 257)		(N = 2376)		
	Mean	(s.e.)	Mean	(s.e.)	p (no diff.)
Birthweight (kg)	3.27	(0.04)	3.33	(0.01)	0.15
Maternal age (yrs)	27.7	(0.3)	27.3	(0.1)	0.20
Birth order	1.79	(0.05)	1.72	(0.02)	0.19

TABLE 6.7 REGRESSIONS OF BLOOD PRESSURE ON HEIGHT, BODY MASS INDEX, BIRTHWEIGHT, MATERNAL AGE, BIRTH ORDER AND A MATERNAL HISTORY OF HIGH BLOOD PRESSURE.

SYSTOLIC

		Adjusted for height and body mass index			Adjusted for all factors in the table		
		Regression coefficient	(s.e.)	p	Regression coefficient	(s.e.)	p
Height		0.37	(0.02)	<0.0001	0.40	(0.02)	<0.0001
Body mass index		1.08	(0.08)	<0.0001	1.08	(0.09)	<0.0001
Birthweight		-1.94	(0.26)	<0.0001	-1.79	(0.27)	<0.0001
Maternal age		0.09	(0.03)	0.0007	0.12	(0.03)	<0.0001
Birth order	1	0.00	-		0.00	-	
	2	-0.82	(0.29)		-1.09	(0.33)	
	3	-1.09	(0.44)		-1.43	(0.48)	
	4+	-2.38	(0.88)	0.0008	-2.71	(0.90)	0.0003
Maternal	No	0.00	-		0.00	-	
history	Yes	+0.94	(0.28)	0.0009	+0.92	(0.28)	0.001

DIASTOLIC

		Adjusted for height and body mass index			Adjusted for all factors in the table		
		Regression coefficient	(s.e.)	p	Regression coefficient	(s.e.)	p
Height		0.18	(0.02	<0.0001	0.19	(0.02)	<0.0001
Body mass index		0.34	(0.06	<0.0001	0.32	(0.06)	<0.0001
Birthweight		-0.97	(0.19	<0.0001	-0.86	(0.19)	<0.0001
Maternal age		0.05	0.02	0.02	0.08	(0.02)	0.0002
Birth order	1	0.00	-		0.00	-	
	2	-0.85	(0.21)		-0.97	(0.24)	
	3	-0.84	(0.32)		-1.03	(0.35)	
	4+	-1.72	(0.63)	<0.0001	-1.94	(0.65)	<0.0001
Maternal	No	0.00	-		0.00	-	
history	Yes	+0.55	(0.20)	0.006	+0.54	(0.20)	0.013
Sex	M	0.00	-		0.00	-	
	F	+0.82	(0.19)	<0.0001	+0.78	(0.20)	<0.0001

Units of regression coefficients are as follows:- height mmHg/cm; body mass index mmHg/kg m^{-2}; birthweight mmHg/kg; maternal age mmHg/year.

TABLE 6.8 BIRTHWEIGHT, MATERNAL AGE AND BIRTH ORDER BY TOWN

TOWN	BIRTHWEIGHT (kg)		BIRTH ORDER		MATERNAL AGE (yrs)	
	Mean	(s.e.)	Mean	(s.e.)	Mean	(s.e.)
Carlisle	3.37	(0.03)	1.63	(0.03)	26.1	(0.2)
Merthyr	3.26	(0.03)	1.57	(0.03)	26.2	(0.3)
Southport	3.37	(0.03)	1.61	(0.03)	27.5	(0.2)
Scunthorpe	3.24	(0.03)	1.61	(0.04)	26.5	(0.3)
Ayr	3.40	(0.03)	1.58	(0.03)	27.0	(0.3)
Maidstone	3.35	(0.03)	1.75	(0.03)	27.4	(0.2)
Dunfermline	3.31	(0.03)	1.66	(0.03)	26.7	(0.3)
Exeter	3.31	(0.03)	1.62	(0.03)	26.1	(0.3)
Guildford	3.29	(0.03)	1.67	(0.03)	27.1	(0.3)

Towns are ranked by mean systolic blood pressure.

CORRELATIONS WITH TOWN MEAN BLOOD PRESSURES

	BIRTHWEIGHT (kg)	BIRTH ORDER	MATERNAL AGE (yrs)
SYSTOLIC	0.20	-0.44	-0.25
DIASTOLIC	0.11	-0.12	-0.14

TABLE 6.9 STUDIES EXAMINING ASSOCIATIONS BETWEEN BIRTHWEIGHT AND BLOOD PRESSURE AT BIRTH

FULL TERM INFANTS

Author	Year	No of subjects	Association
Moss	1963	74	Positive
Kitterman	1969	45	Positive
Lee	1976	257	Positive
Schachter	1979	392	None
de Swiet	1980	1740	Positive

PRETERM INFANTS

Author	Year	No of subjects	Association
Holland	1956	15	Positive
Goodman	1962	28	Positive
Moss	1963	26	Positive
Levison	1966	21	Positive

LOW BIRTHWEIGHT INFANTS

Author	Year	No of subjects	Association
Versmold	1981	16	Positive

(Studies included in this list measured blood pressures within seven days of birth)

TABLE 6.10 STUDIES RELATING INFANT FEEDING METHOD AND BLOOD PRESSURE IN CHILDHOOD.

OBSERVATIONAL STUDIES

STUDY		YEAR	COMPARISON	N	AGE AT ASSESSMENT	EFFECT
1	Schachter	1979	Breast/bottle	392	3 days	None
2	Lee	1976	Breast/bottle	257	2-4 days	None
3	de Swiet	1977	Breast/bottle	500	6 days	None
4	de Swiet	1977	Breast/bottle	500	6 weeks	None
5	Schachter	1979	Breast/bottle	318	6 months	None
6	Lucas	1987	Varying Na in nasogastric feed	347	18 months	None
7	Whincup	1989	Breast/bottle	3591	5-7 years	None
8	Ellison	1978	Breast/bottle	**	7 years	DBP lower in breast fed

RANDOMIZED CONTROLLED TRIALS

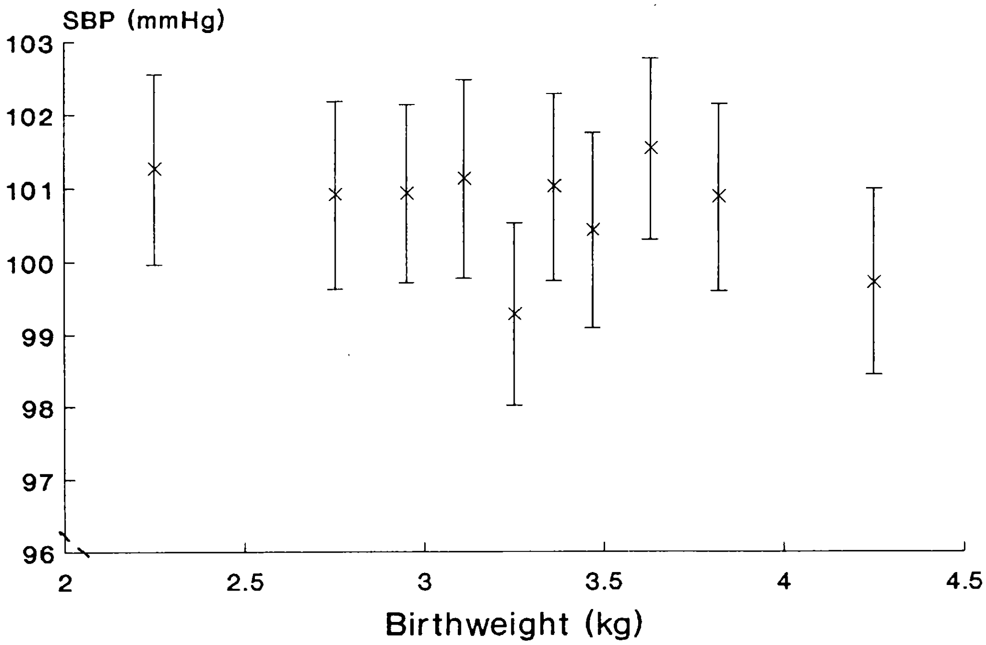
STUDY		YEAR	COMPARISON	N	AGE AT ASSESSMENT	EFFECT
9	Hofman	1983	Varying Na in supplement feeds	476	6 months	SBP lower in low Na group

Observational studies are ranked by the age of assessment (i.e. the age at which blood pressure measurements were made).

** Data not published

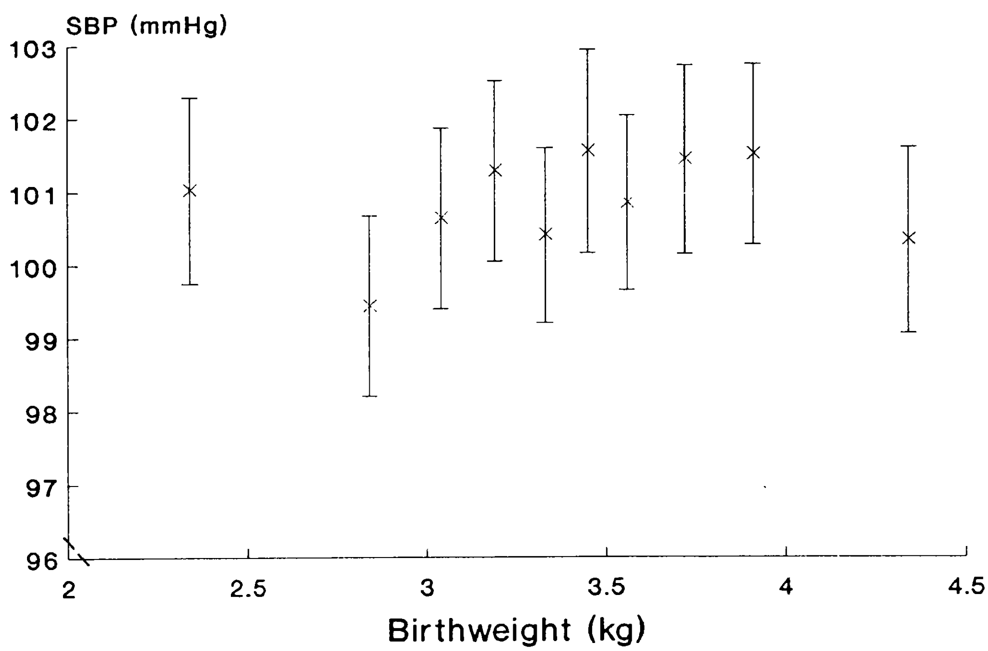
Figure 6.1 BIRTHWEIGHT AND SYSTOLIC BLOOD PRESSURE

GIRLS



Means and 95% C.I.s

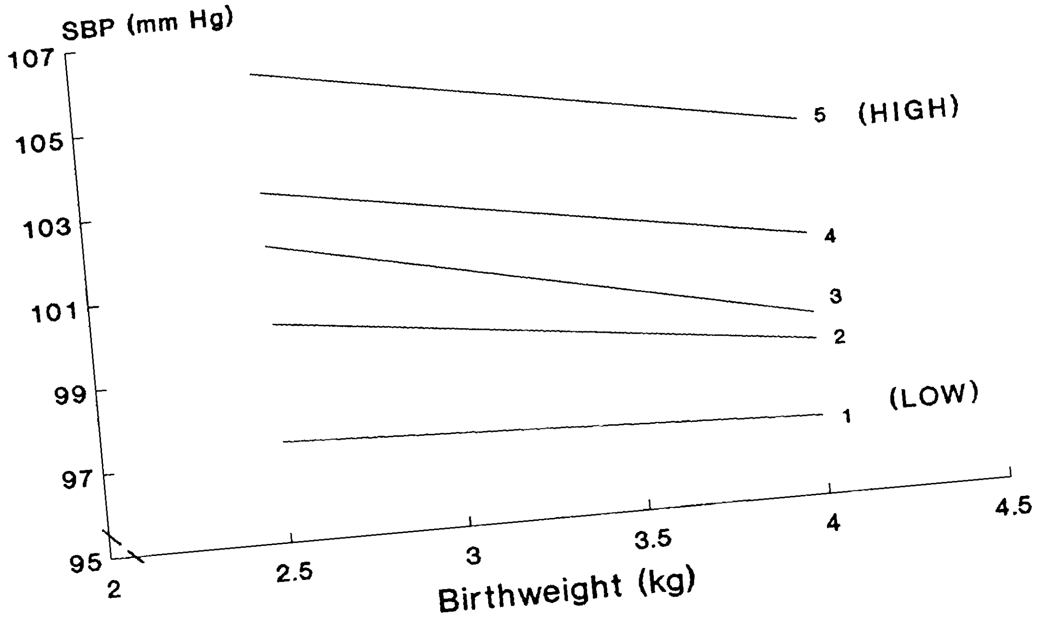
BOYS



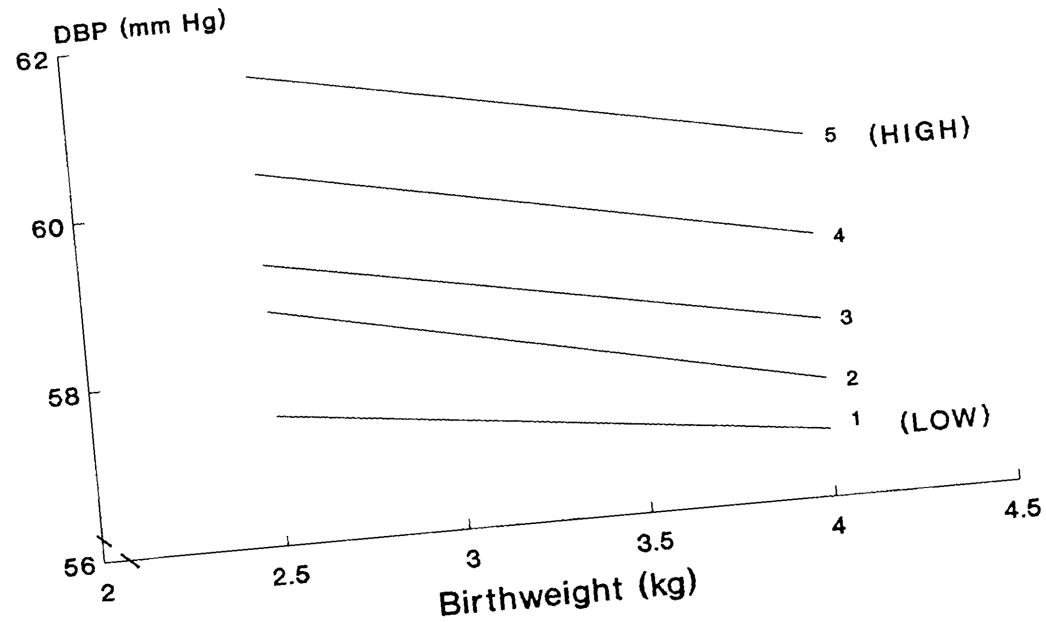
Means and 95% C.I.s

Figure 6.2 BIRTHWEIGHT AND BLOOD PRESSURE BY HEIGHT (FIFTHS)

SYSTOLIC



DIASTOLIC



CHAPTER 7

CONCLUSIONS AND RECOMMENDATIONS FOR FURTHER RESEARCH

7.0 SUMMARY

The implications of the Nine Towns Study of Blood Pressure in Children for public health and for further research are reviewed. The observations considered of greatest potential public health importance are (i) the finding that childhood blood pressure levels vary between towns, and are related to adult blood pressure levels and cardiovascular mortality rates, (ii) the strong relationship between body build and blood pressure and (iii) the association between birthweight and blood pressure. Factors which may contribute to the development of between-town differences in blood pressure (including body build, electrolyte intake and, in adults, alcohol intake) are discussed. The design of further studies to explore the geographic aspects of blood pressure in childhood and the birthweight-blood pressure association are outlined.

7.1 INTRODUCTION

The previous chapters have examined the determinants of blood pressure in childhood in a study carried out in nine British towns. The strongest individual determinants of blood pressure described were age and body build, particularly height and body mass index. Marked variations in blood pressure levels were observed between the towns studied; the variation in childhood blood pressure levels was related both to adult blood pressure levels and to adult cardiovascular mortality rates. However, this relationship was strongly influenced by the exceptionally low mean blood pressure levels observed in Guildford. In an exploration of the relation between early life influences and blood pressure, an inverse relationship between birthweight and blood pressure was observed once the effect of current body size had been taken into account. Increasing maternal age was positively related and an increasing number of sibs negatively related to blood pressure level. These observations were independent of the relationship between a parental history of hypertension and blood pressure level. Method of feeding in the first three months was unrelated to blood pressure at five to seven years.

In this chapter the implications of the study findings are considered in more detail. The first section (7.2) examines the potential public health importance of the findings. Aspects which receive particular attention in this context are the differences in mean childhood blood pressures observed between the study towns and the relationships described at the individual level, particularly those between current body build and blood pressure and those between birthweight and blood pressure. The second section (7.3) considers the implications of the study for further research. The principal issues discussed are ways in which the geographic variations in childhood blood pressure (chapter 5) and the relationships between birthweight, other 'early life influences' and blood pressure (chapter 6) can be further elucidated.

7.2 PUBLIC HEALTH IMPORTANCE OF THE FINDINGS

7.2.1 BLOOD PRESSURE DIFFERENCES BETWEEN TOWNS

The differences in childhood blood pressure levels between the study towns and their relationships to adult blood pressure levels and cardiovascular mortality are of considerable potential public health importance if they can be further substantiated. The finding suggests that at least some of the factors responsible for geographic differences in blood pressure in adult life are acting from an early age. However, the observations on migrants in the British Regional Heart Study, suggesting that place of examination rather than place of birth is important in determining blood pressure in middle-age (Elford J et al, 1990) complicate the picture, because they suggest that the patterns of blood pressure established in childhood are likely to be modifiable. In particular, they suggest that influences on blood pressure in adult life (for example, alcohol intake and overweight), are likely to modify the patterns of blood pressure first seen in childhood. Thus, a model more complicated than that postulated in Figure 1.5 is required, in which differences in blood pressure developing in childhood are modified by more powerful influences in adult life (Figure 7.1). However, the adult influences themselves may also be modifiable in some degree; an example is the influence of alcohol on blood pressure, which is likely to be reversible on withdrawal (Potter JF and Beevers DG, 1984).

The observation that population differences in blood pressure in a geographic setting may emerge during childhood raises the possibility that primary prevention of blood pressure should begin in childhood and continue into adult life. The detailed components of such a strategy depend on the aetiological factors which are important at different stages. While the precise nature of the factors responsible for the geographic differences in blood pressure considered here are unknown, some preliminary observations are made in the following section.

7.2.1.1 Potential determinants of geographic blood pressure differences

(i) Adults In the British Regional Heart Study, alcohol intake was positively related to blood pressure levels both on an individual basis (Shaper AG et al, 1988b) and on a geographic basis (Shaper AG et al, 1981). While body build, particularly body mass index, was strongly related to blood pressure in individuals, there was little relationship between body mass index and blood pressure on a geographic basis (for systolic pressure $r = 0.13$; $df = 22$; $p = 0.55$), suggesting that differences in body build do not make an important contribution to between-town differences. The relationship between sodium and potassium intake and blood pressure was explored in the Nine Towns Study using spot urine samples (Bruce NG et al, submitted for publication). Marked differences in adult urinary sodium excretion and urinary sodium:potassium ratios were observed between the towns, with town urinary sodium concentrations varying between 99 mmol/l and 125 mmol/l and sodium:potassium ratios between 1.7 and 2.1. Strong ecological relationships between town urinary sodium excretion, sodium:potassium ratio and blood pressure were observed. Similar, but weaker, associations were observed at the individual level. However, even after correction for regression dilution bias the individual relationships between electrolyte intake and blood pressure could not account for more than a small part of the ecological relationships. Thus, while these dietary factors may contribute to the explanation of blood pressure differences between the study towns, it is unlikely that they are completely responsible.

(ii) Children Among the factors measured in the Nine Towns Study of

Blood Pressure in Children, body build (particularly body mass index) and pulse rate were the only ones to show a consistent relationship with blood pressure both at within-town and between-town levels. However, adjustment for these factors had little effect on the geographic blood pressure differences observed. Birthweight, maternal age and birth order were related to blood pressure in individuals but of these factors only birth order showed a consistent pattern in individual and between-town relationships. However, this factor again did not account for the between-town differences in blood pressure. Sodium and potassium intakes were not examined in the Nine Towns Study of Blood Pressure in Children and no comment can be made on their importance in the present setting. However, sodium:potassium ratios in the Nine Towns Study (Adults) were lowest in Guildford and highest in Merthyr, suggesting that hypotheses relating electrolyte intake and blood pressure may be worth exploring in this context. Earlier studies have suggested that potassium in particular may be particularly important in the early development of blood pressure patterns (Lever AF et al, 1981; Geleijnse JM et al, 1990).

7.2.2 DETERMINANTS OF BLOOD PRESSURE LEVEL IN INDIVIDUALS

Several factors have been identified which are strongly related to blood pressure in individuals in the present study. Among these, the strong relationships between body build and blood pressure in childhood may be of particular importance for prevention. The association between birthweight (an important indicator of health in early life) and blood pressure may also be important. The relationships between maternal age, birth order and blood pressure are of interest, although not yet well established.

7.2.2.1 Body build

Strong relationships were observed in this study between measures of body build and blood pressure, which were consistent with those of earlier studies. From a public health viewpoint it is necessary to separate two components of body build, height and body mass index (or other measures of obesity), which have different relationships with blood pressure in childhood and adulthood. Height is strongly related to blood pressure in childhood, but this association is not apparent in adults in Great

Britain. In adult life, height shows a weak inverse association with blood pressure level, and with mortality, both from cardiovascular and non-cardiovascular causes (Marmot MG et al, 1984; Walker M et al, 1989). In contrast, positive relationships between body mass index (and other measures of obesity) are apparent not only in childhood but also in adult life (Dyer AR and Elliott P, 1989). Moreover, it has been observed that weight in childhood is related to subsequent blood pressure rise (Hofman A and Valkenburg HA, 1983) and that weight gain between childhood and adult life is related to adult blood pressure level (Lauer RM and Clarke WR, 1984). In adults, there is evidence that a reduction in calorie intake leading to weight loss is associated with reduction in blood pressure (Reisin E et al, 1978).

These observations make it likely that the prevention of obesity in childhood would play a part in the prevention of high blood pressure in the community. This issue may be particularly important in the context of the increase in the prevalence of childhood obesity which has been occurring in Great Britain (Peckham CS et al, 1983). This emphasizes the need for experimental studies examining the influence of a reduction in weight on blood pressure level and change in childhood, and the development of strategies for the prevention of obesity in childhood on a population-wide basis. Such strategies are likely to include not only measures directed to the reduction of calorie intake, but also to an increase in levels of physical activity and physical fitness, both of which may be associated with reductions in blood pressure in their own right (Dwyer T et al, 1983; Hofman A and Walter H, 1989).

7.2.2.2 <u>Birthweight</u> The inverse association between birthweight and blood pressure described in this study is reasonably consistent with the findings of several reports in older children, both in Great Britain (Cater J et al, 1984; Ounsted MK et al, 1985; Barker DJP et al, 1989a) and in New Zealand (Simpson A et al, 1981). While the association has not been confirmed in two large studies in adolescents in the United States (Higgins M et al, 1980) and Israel (Seidman D et al, 1991), inverse associations in adult life have been described in Great Britain (Barker DJP et al, 1989a and 1990) and in Sweden (Gennser G et al, 1988).

Estimates of the strength of the relationship in adult life vary between a difference of approximately 2mmHg in systolic pressure across the range of birthweight (Barker DJP et al, 1989a) to 10 mmHg or more once the effect of placental weight is taken into account (Barker DJP et al, 1990). Further clarification of the causal relationships underlying this association is needed. If birthweight is causally related to blood pressure in adult life, this would be of considerable potential public health importance. If the consequences of low birthweight on blood pressure could be reversed, even a small fall in blood pressure levels in the population might produce an important effect on cardiovascular complications (Rose G, 1985a).

While the most obvious approach to reducing the incidence of low birthweight would be to reduce the major determinants of low birthweight, particularly cigarette smoking in pregnancy and other factors related to social class (Peters TJ et al, 1983), an alternative public health approach has been proposed, based on observations made in a cohort of 5654 Hertfordshire men, born between 1911 and 1930, for whom detailed records of birth and infancy had been retained (Barker DJP et al, 1989b). In these subjects, breast fed from birth, it was observed that low birthweight was associated with a high mortality rate for ischaemic heart disease, and that the relationship was particularly strong in those subjects who were both of low birthweight and were also underweight at one year. Barker and his colleagues suggested that the association between birthweight and blood pressure might be the mechanism by which the effect was mediated and concluded by recommending that intensive feeding to ensure rapid weight gain in the first year of life in low birthweight babies might have particular benefits for low birthweight babies. However, this recommendation can be questioned on several grounds. First, it implies that a low rate of weight gain in the first year of life is causally, and reversibly, related to ischaemic heart disease in subjects with low birthweight. Second, it does not take into account the possibility that stimulating rapid weight gain in low birthweight infants might actually be harmful. The possibility, first raised by Ounsted (Ounsted MK et al, 1985), that the relationship between low birthweight and higher blood pressure level is actually the consequence of rapid postnatal weight gain, rather than of low birthweight per se, has already been discussed (section 6.4.1.3). The stimulation of rapid weight gain in low birthweight babies would be an intervention whose long term effects had not been properly assessed, and one which would not directly address the determinants of low birthweight.

7.3 IMPLICATIONS FOR FURTHER RESEARCH

The results of the study pose several questions for further exploration. The areas selected for most detailed consideration here are the geographic differences in blood pressure levels in childhood and the relationship between birthweight and blood pressure. Both of these are of potential public health importance and may offer opportunities for strategies directed at the prevention of high blood pressure in the early years of life.

7.3.1 GEOGRAPHY OF BLOOD PRESSURE IN CHILDHOOD

The finding of a strong positive relationship between childhood blood pressure level and adult cardiovascular mortality would imply that differences in blood pressure between population groups were being established before the age of five years, offering particular opportunities for the study of determinants of blood pressure patterns in early childhood. However, the findings in the present study were strongly influenced by the observation of exceptionally low levels of childhood blood pressure in Guildford, a town with low mean adult blood pressure and cardiovascular mortality rate. The results of this study therefore require further substantiation, which might be carried out in a number of ways.

One approach would be to repeat the study or a part of it, particularly to re-examine blood pressure levels in Guildford and compare them with those in other towns in which higher mean blood pressure levels were observed (for example, Carlisle or Merthyr Tydfil). This would provide specific additional information on mean blood pressure levels in towns already studied. However, it would provide little additional information on the validity of the main geographic hypotheses, that town mean blood pressures in childhood are related to adult blood pressures and adult cardiovascular mortality rates. Even if all the nine towns originally studied were included in a further investigation, this would replicate two weaknesses in the design of the present study. First, the towns in the present study include only one, Guildford, which has an exceptionally low adult blood pressure and SMR for cardiovascular disease. The absence of any other town with an adult blood pressure level and cardiovascular mortality pattern comparable with that of Guildford makes the interpretation of the exceptional Guildford observations more difficult. Second, the relationships between childhood and adult blood pressures in the study were weaker than had been anticipated at the outset, limiting the power of a study based on nine towns equally divided in their selection between high, intermediate and low adult mean pressures. The design of a new study taking these issues into consideration is outlined below.

7.3.1.1 Defining the study hypothesis

In order to formulate a new hypothesis, three issues must be addressed. First, should the selection of new centres for study of childhood blood pressure levels be based on adult blood pressures or on adult cardiovascular mortality rates? Second, should a new study take place in Great Britain, or be restricted to England and Wales? Third, is it acceptable to base a new study on towns of 50,000 to 100,000 people as in the earlier study, or is a different population base required?

(i) Adult blood pressure or cardiovascular mortality rate?

In the earlier study, two geographic hypotheses concerning childhood blood pressure levels were examined. The original hypothesis specified a relationship between childhood blood pressure level and adult blood pressure level; a secondary hypothesis specified a relationship between childhood blood pressure level and adult cardiovascular mortality rate. These hypotheses are closely related, because in both the British Regional Heart Study and the Nine Towns Study there was a strong relationship between adult blood pressure level and adult cardiovascular mortality rate on a geographic basis (Shaper AG et al, 1981; Bruce NG et al, 1990a). However, they have quite different implications for the design of a new study. Although the Scottish Heart Health Study has recently provided information about blood pressure patterns in Scottish districts (Tunstall-Pedoe H et al, 1989), the British Regional Heart Study remains the most important standardized source of information about blood pressure differences across Great Britain as a whole. If a new hypothesis is based on adult blood pressure levels, the study would therefore need to take place within the British Regional Heart Study town network, unless a new survey of adult blood pressure levels were to be carried out. This would be a serious disadvantage because those towns in the network with the most extreme average adult blood pressure levels were already examined in the earlier study. The power of a new study excluding those towns would therefore be limited. In contrast, the selection of new towns, either in Great Britain or in England and Wales, on the basis of their adult cardiovascular mortality rate would permit towns with an exceptionally wide range of cardiovascular mortality rates to be included. This would be an important advantage of the use of cardiovascular mortality rate as a basis for town selection, which must however be set against one disadvantage. If no relationship were demonstrated between childhood blood pressure and adult cardiovascular mortality, the fact that the blood pressure levels of the towns studied had not been measured directly would make the interpretation of the findings difficult, particularly for the original hypothesis relating childhood and adulthood blood pressures.

(ii) Great Britain or England and Wales?

The earlier study included towns from England, Wales and Scotland and was based on the assumption that the relationships between childhood blood pressure and adult blood pressure and cardiovascular mortality were similar in all parts of Britain. However, the results raised the possibility that average childhood blood pressure levels in Scotland were lower than might have been expected on the basis of adult blood pressure levels and cardiovascular mortality rates (Figure 5.8). This post hoc observation raised the possibility that the relationships were different in Scotland from those in England and Wales, possibly because of the greater alcohol intakes prevalent among Scottish adults (Cummins R et al, 1982). There would therefore be potential advantages in restricting a new study to towns in England and Wales, in which the relationship between childhood blood pressure and adult cardiovascular mortality appeared to be particularly strong (r = 0.86 for systolic pressure in the earlier study). However, this restriction, although having little effect on the range of cardiovascular mortality rates available for study, would limit the extent to which the results could be generalized.

(iii) Selection of population centres

The use of towns with populations of 50,000 to 100,000 (consistent with those of the earlier British Regional Heart Study) in a new study would have the advantage of permitting the use of a sampling method validated in the original study without modification; an increase in the size of population centes would almost certainly complicate sampling procedures further. However, the inclusion of inner city areas among the centres with high cardiovascular mortality rates would tend to make the results of the study more generally representative.

7.3.1.2 Sample size considerations in a new study

Since the comparison of towns would form the main test of the study hypothesis, the number of towns included would be the most important issue. The restriction of towns to include only those with exceptionally high or exceptionally low cardiovascular mortality rates (excluding an intermediate group) would provide the most efficient test of the study hypothesis, although it would remove the possibility of detecting a continuous, dose-response relationship. In order to establish the number of towns needed, estimates of the mean difference in childhood blood pressure levels between high and low mortality towns, and the standard deviation of the high and low mortality town groups, are required.

(i) Mean difference in childhood blood pressure level expected between high and low mortality groups The regression model relating childhood blood pressure level and adult cardiovascular mortality in England and Wales in the earlier study can be used to calculate that a change in childhood mean systolic blood pressure of 2.51 mmHg is associated with a change in cardiovascular mortality rate (35-64 years: men and women combined) of approximately 1.0 death/thousand. (Such a calculation requires conversion of SMRs to mortality rates by multiplying them by the appropriate cardiovascular mortality rates). If the new study were to be based on a group of 'low mortality' towns with an SMR for cardiovascular disease of 75 or less (maximum death rate 2.15 per thousand population) and a group of 'high mortality' towns with an SMR for cardiovascular disease of 130 or more (minimum death rate 3.73 per thousand population), a mean systolic difference of 3.9 mmHg or more would be expected between the high and low mortality towns. However, the regression co-efficient, like the results of the earlier study, is strongly influenced by the outlying value of Guildford. A more conservative assessment of the strength of the association, excluding the Guildford co-ordinate, would suggest that a mean systolic difference of 2.2 mmHg would be expected between childhood blood pressures in the high and low mortality town groups.

(ii) Standard deviation of blood pressure levels within high and low mortality town groups If the towns in the earlier study are arbitrarily regrouped on the basis of their cardiovascular SMR into those with high rates of cardiovascular mortality (i.e. SMR 100 or above) and those with low cardiovascular mortality (SMR less than 100), the pooled estimate of the within-group standard deviation for systolic blood pressure is 1.36 mmHg, larger than the value of 1.0 mmHg estimated at the outset of the study. The precision with which this standard deviation is estimated is limited by the small numbers of towns on which it is based. Moreover, the figure is strongly influenced (and enlarged by) the Guildford observation.

(iii) Number of towns required Based on the estimates of the relationship between adult cardiovascular mortality rate and childhood blood pressure and on the estimates of the standard deviation of mean systolic blood pressure levels in the high and low mortality town groups, the power of studies including different numbers of high and low mortality towns are shown in Table 7.1A. A study based on five high mortality and five low mortality towns would be sufficient to detect a mean systolic difference of 2.4 mmHg at $p = 0.05$ with a power of 80%, while a mean systolic difference of 2.8 mmHg would be detected with 90% power. A study of this size would therefore have considerable power to detect the systolic blood pressure difference between high and low mortality towns of 3.9 mmHg predicted by the earlier study, although its power to detect the more conservative estimate of 2.2 mmHg would be more limited.

(iv) Numbers of children and schools While the measurement of 400 children in each town in the earlier study provided very precise estimates of mean blood pressure level in each town, it might be possible to reduce the numbers of children examined in each town without producing an appreciable increase in the standard deviation of high and low mortality town groups; this would be a particular advantage if it permitted an increase in the number of towns studied. Estimates of the most efficient balance of schools and individual children within a particular town has been obtained using data from the Nine Towns Study of Blood Pressure in Children (Table 7.1B). The results suggest that, for a given number of children, the smallest standard error (and therefore the greatest precision of measurement) would be obtained from sampling the maximum possible number of schools, rather than increasing the number of children examined within a particular school.

7.3.1.3 Other aspects of study design

A new study would need to include measurement of factors related to blood pressure in childhood. The findings of the earlier study imply that age, height, body mass index and pulse rate would be particularly important. The measurement of levels of physical activity and physical fitness would be desirable. Despite the absence of an unequivocal relationship between ambient temperature and blood pressure in the earlier study, it would be unwise to exclude measurement of this factor. In order to reduce the possibility of exceptional mean temperature levels in a particular town (as observed in Guildford in the earlier study) a case could be made for carrying out each town survey in two stages, ideally separated by visits to one or more other towns. Measurements of urinary sodium and potassium intakes (using conventional urinary excretion methods) would permit exploration of the relationship between electrolyte intakes and blood pressure in a setting in which marked geographic variations in sodium and potassium intake are likely. Further assessment of the relationship between early life influences (including birthweight, gestational age, maternal age and birth order) and blood pressure would enable the individual relationships described in the earlier study to be substantiated and extended, although there is no evidence at present that these factors contribute to geographic differences in blood pressure in childhood.

7.3.2 EARLY INFLUENCES ON BLOOD PRESSURE IN CHILDHOOD

The results of the present study have corroborated earlier findings of an inverse association between birthweight and blood pressure in childhood and described associations between maternal age, birth order and blood pressure. Ways in which these relationships might be investigated further are described below.

7.3.2.1 Explanation of the birthweight-blood pressure relationship

Graded inverse relationships between birthweight and blood pressure have been described within several developed, 'Western' countries both in childhood and in adulthood. However, several important questions remain. Is the birthweight-blood pressure relationship between countries consistent with that observed within countries? Has the marked rise in mean birthweight which appears to have occurred in developed countries such as Britain been followed by a corresponding fall in stroke and other blood pressure-related conditions, occurring in a way which is related to a time-of-birth effect? The answers to these questions will help to throw further light on the consistency and hence the potential causality of the birthweight-blood pressure relationship.

Studies in individuals may also help to elucidate the relationship between birthweight and blood pressure further. As discussed in chapter 6, two possible explanations for the birthweight-blood pressure relationship have been proposed. The first possibility is that low birthweight is the consequence of an adverse intrauterine environment, resulting in retardation of intrauterine growth (Gennser G et al, 1988; Barker DJP et al, 1989a). The second possibility is that the rapid postnatal weight gain characteristic of low birthweight infants, or another postnatal correlate of low birthweight, is the factor directly responsible (Ounsted MK et al, 1985). Individual studies may help to resolve this issue in two ways. First, studies which can examine the relation between birthweight and blood pressure taking gestational age into account will be able to establish whether the birthweight-blood pressure relationship is observed in low birthweight infants with and without retardation of intrauterine growth. If the association is limited to small-for-dates infants (i.e. those with intrauterine growth retardation) this will strengthen the case for the importance of growth retardation in utero. If, on the other hand, the effect is specific to preterm infants (i.e. those born prematurely without marked growth retardation), this will suggest that another process, specifically affecting premature infants, is responsible. If the association is seen in both these low birthweight categories, one associated with retarded intrauterine growth and the other with prematurity, this will suggest that factors other than the intrauterine environment are important in the development of the association. Longitudinal studies of blood pressure including repeated measurements of body size in the early years of life may also help to resolve this issue. Such studies, if sufficiently large, will be able to examine the relative importance of weight gain in infancy and birthweight in determining childhood blood pressure independently of one another.

7.3.2.2 Maternal age, birth order and blood pressure

The results of the Nine Towns Study of Blood Pressure in Children have suggested that maternal age and birth order are related to blood pressure in childhood. Although one study has previously reported a relationship between maternal age and blood pressure (Higgins M et al, 1980) this study appears to have provided the first documentation of a relationship between birth order and blood pressure. Both these relationships require confirmation in other study populations; in particular, the extent to which they are observed in adult life will be particularly important in assessing their potential public health importance. A recent report, suggesting that blood pressures are higher in adults with no siblings (Trevisan M et al, 1991) raises the possibility that this may be the case for birth order, although evidence is still lacking for maternal age. Studying the emergence of the associations may provide clues to the underlying causal relationships. While the association between birth order and blood pressure is likely to have a postnatal basis (section 6.4.2), raising the possibility that dietary or psychosocial factors acting in early childhood may be important, the point at which the association between maternal age and blood pressure becomes apparent has yet to be resolved.

TABLE 7.1A SAMPLE SIZE CALCULATIONS FOR A NEW GEOGRAPHIC STUDY OF BLOOD PRESSURE IN CHILDHOOD

NUMBER OF TOWNS IN EACH GROUP	SIZE OF SYSTOLIC DIFFERENCE (mmHg) BETWEEN HIGH AND LOW MORTALITY TOWNS				
	2.0	2.5	3.0	3.5	4.0
3	0.44	0.61	0.77	0.88	0.95
4	0.55	0.74	0.88	0.95	0.99
5	0.64	0.83	0.94	0.98	0.99
6	0.72	0.89	0.97	0.99	0.99
7	0.79	0.93	0.98	0.99	0.99

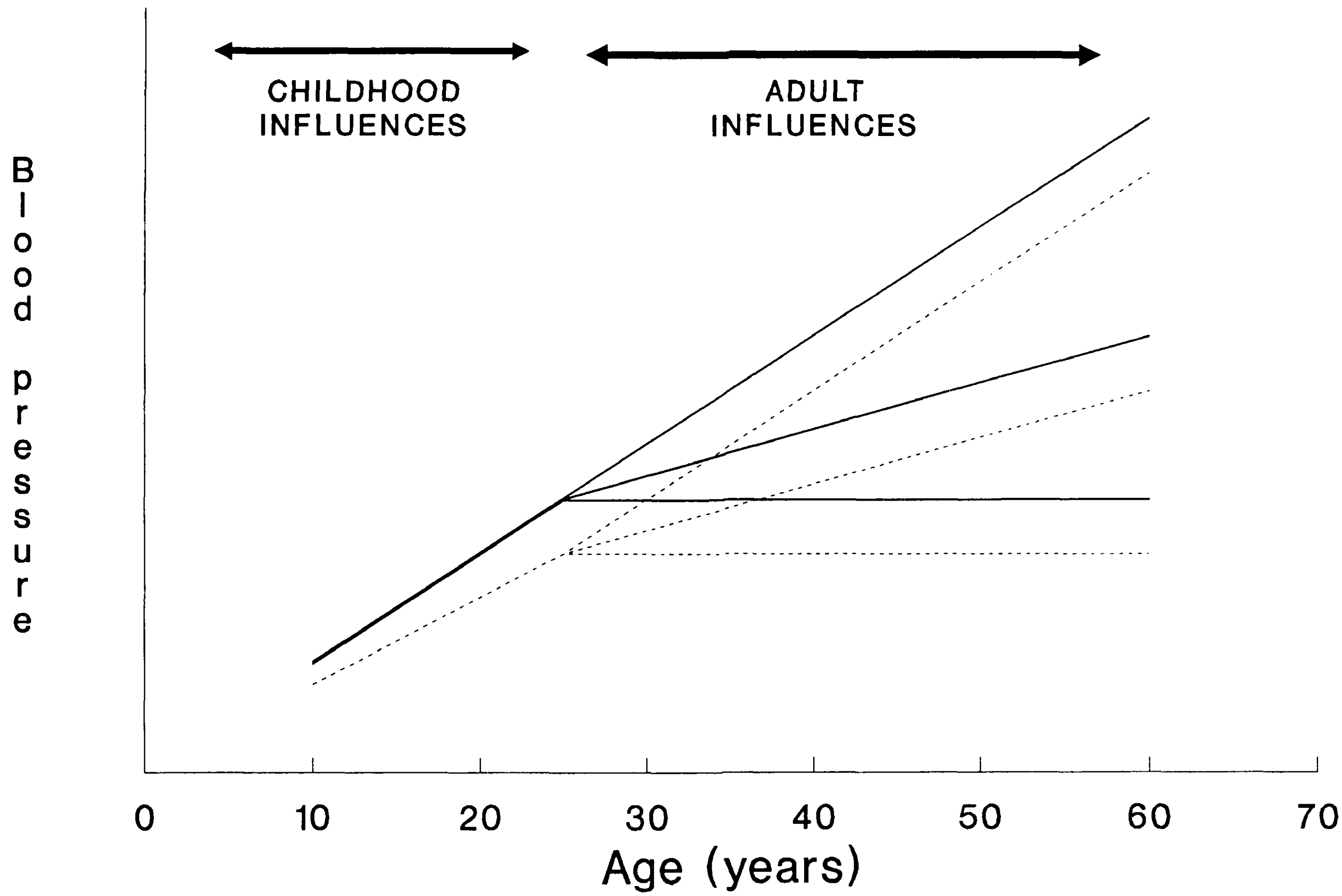
The figures represent the probability of detecting a specified systolic difference with each number of towns in the two groups, assuming a standard deviation within each group of 1.36 mmHg (see text).

TABLE 7.1B PRECISION OF TOWN SAMPLING IN RELATION TO NUMBER OF SCHOOLS AND INDIVIDUALS WITHIN EACH SCHOOL

NUMBER OF CHILDREN PER SCHOOL	NUMBER OF SCHOOLS		
	5	10	20
23	1.15 (115)	0.81 (230)	0.57 (460)
46	1.00 (230)	0.71 (460)	0.50 (920)
92	0.91 (460)	0.65 (920)	0.46 (1840)

Figures are standard errors of town mean systolic blood pressure associated with use of a particular sampling strategy and (number of subjects studied). Data are based on the Nine Towns Study of Blood Pressure in Children. A smaller standard error, for a similar number of subjects studied, implies a greater sampling precision.

Figure 7.1 MODEL OF DEVELOPMENT OF POPULATION DIFFERENCES IN BLOOD PRESSURE



APPENDIX I

METHODOLOGICAL ISSUES AND RESULTS IN THE NINE TOWNS STUDY OF BLOOD PRESSURE IN CHILDREN

AI.0 SUMMARY

In this Appendix the reasons for the sampling and measurement procedures used are discussed and their validity examined. A comparison of the social class characteristics of the pilot study sample with 1981 Census data suggested that the sampling procedure provided a socially representative group of subjects. However, the lower response rates in the main study were associated with slight under-representation of subjects from manual households. The performance of the Dinamap 1846SX instrument appeared to be consistent throughout the study, although measurements of systolic pressure by this instrument were consistently higher than those of a reference Hawksley random zero sphygmomanometer. No consistent observer effects on blood pressure measurement were observed. Cuff bladder size was strongly related to blood pressure measurement and correction factors were developed to take this into account.

AI.1 INTRODUCTION

While there have been many previous surveys of blood pressure in childhood, certain aspects of the design and methodology of the Nine Towns Study of Blood Pressure in Children were novel. These included particularly the sampling methods used in each town and the use of an automated instrument for making blood pressure measurements. The reasons for the particular designs and methodologies used are discussed and, where appropriate, methodological results are presented which throw light on the strengths and weaknesses of the methodologies used. In the first part (sections AI.2 to AI.4) sampling methods, invitation, response rates and the representativeness of the study sample are considered. In the second part (AI.5), the methodology of blood pressure measurement, the performance of the automated blood pressure instrument and the influence of observer and cuff size on blood pressure measurement are addressed.

AI.2 SAMPLING METHODS

AI.2.1 CONSIDERATIONS IN STUDY DESIGN

AI.2.1.1 Aim of sampling procedure: possible sampling frames

In order to conduct a valid comparison of childhood blood pressure levels between different towns, it was important that the sampling method used would select a group of children for invitation who were representative of all children in that town as far as possible. Several ways in which this could be done were considered. In theory the ideal method would be the construction of a sampling frame including all individual children of appropriate age in a particular town, and selecting the required number of children by random sampling. Such a method, while likely to provide the most representative sample, was dismissed for two reasons. First, no list of the children in a particular town was available, so that a full register would have had to be formulated by contacting a large number of individual schools or general practices. Second, surveying a sample of individual children with no clustering would have been practically difficult and statistically inefficient. Two alternative methods suggested themselves, with sampling based either on general practices or on schools.

Sampling based on general practices had been used successfully in the British Regional Heart Study, which identified one general practice in each town with a practice population which was socially representative of the town as a whole (Shaper AG et al, 1981); in that practice the age-sex register provided a sampling frame for selecting individuals in the required age-group. This procedure could be modified to provide samples of children. However, despite the availability of general practices in the study towns through the British Regional Heart Study's general practice network, school based sampling was preferred, for three main reasons. First, it offered an opportunity to sample more widely within the town than would have been possible using a single general practice. Second, because the blood pressure results of the study were to be related to the results of a previous study of adults based in general practice, the use of a school-based sampling frame in the study of children, quite different from that in adults, would strengthen the interpretation of any differences in blood pressure observed against an explanation of sampling artefact. Third, the method could be easily linked to school-based surveys, which would be considerably more convenient for both children and parents than a survey carried out through general practices.

AI.2.1.2 Possible sampling methods

Having decided on a school-based survey method, a decision was required as to the best method of sampling schools to obtain a representative sample of children in each town. Sampling methods used by previous investigators conducting school-based surveys in children on a geographic basis were examined. Of particular interest were a geographic study of respiratory symptoms in childhood (Colley JRT and Reid DD, 1970) and the National Study of Health and Growth (Altman DG and Cook J, 1973). Colley and Reid examined samples of 500 children in several large towns and cities. In some towns, regarded as socially homogeneous (Bristol and Reading), a simple random sample of primary schools was used, whereas in others, regarded as socially heterogeneous (Bolton and Newcastle), samples of primary schools stratified by district were identified. In the National Study of Health and Growth, 22 employment exchange districts were selected in England and six in Scotland, with a bias towards socially deprived areas. Within each of these districts a random sample of primary schools provided the basis for the selection of children. However, neither of these procedures appeared ideally suited to the aims of the present investigation. In the first of these studies the procedure varied between the centres studied, while the second was designed to provide a sample of children from deprived social circumstances rather than one which was representative of a particular location. It was therefore necessary to develop a sampling procedure and devise a method to test its validity.

Practical constraints were posed by the requirement to examine a minimum of 400 children in each town; examining 40 children per day, ten days' fieldwork in each town would be required. Because it was practically impossible for the survey team to work in more than one school on a single day, the maximum number of schools which could be visited in one town was ten. At the other extreme, by restricting the survey to the largest schools and examining a large number of children in each the study could be restricted to five schools or fewer. It was considered that, since children from particular social backgrounds were likely to be clustered in particular schools, there would be advantages in visiting as many schools as possible. A decision was make to examine the greatest number practicable, ten schools per town.

How should the ten schools to be surveyed be selected? Enquiries to Local Authority Education Departments suggested that the location of school, their size and religious denomination all affected the social mix of the children, although in a way which might differ from town to town (for example, Roman Catholic schools have a distinct social mix of children, but this would vary between Surrey and Merseyside). Accordingly, a random sample of Local Authority schools stratified by religious denomination and, in the case of county primary schools, school size and location, was selected in each town. Independent schools were excluded from the survey because the proportion of children attending these schools in each town were extremely small, with the exception of Guildford (Table AI.1A). The effect of excluding children from independent schools specifically in a 'low blood pressure' town was considered. From existing evidence on the relationship between social class and blood pressure in childhood (Beresford SAA and Holland WW, 1973) the bias introduced by the omission of children of non-manual parents would tend to produce a higher town mean blood pressure level, thereby diminishing rather than increasing the possibility of finding between-town blood pressure differences in the expected direction. Within each school selected, a random sample of two classes (55-60 children) were invited to participate. The use of whole classes facilitated both the explanation of the study to parents and the conduct of the survey within each school, keeping disruption to a minimum.

AI.2.2 VALIDATION OF SAMPLING METHODOLOGY

A comparison of the social class of the parents of the study population with the social class of adults in the town as a whole seemed to offer the best possibility for validation of the method. The detailed information on a 10% sample of all households collected in the 1981

Census could be used to provide information on the social class mix of the town population. However, parental social class in the study population could only be established for children whose parents returned the study questionnaire. The comparison would therefore be prone to bias unless return of parental questionnaires was complete or almost complete. Moreover, the comparison could also be biased if marked differences in family size between social class groups occurred, which would produce an imbalance in representation of children in the sample.

Because of the need for a high questionnaire return rate, this comparison was carried out using data from Ipswich, the pilot study town, in which the questionnaire response rate was exceptionally high (81% of all subjects invited). A comparison of the social class balance of the survey sample and the Census 10% sample for the town is presented in Table AI.1B. The findings show extremely close agreement between the social class balance of the study sample and the Census sample, suggesting that the sampling method is likely to be producing a group of children who are socially representative of the town. The validity of the sampling method is more difficult to examine in the other study towns, where lower response rates are likely to bias social class comparisons between the questionnaire and the census; this question is considered further in section AI.4.2. However, the sampling method used in the other towns was precisely the same as that in Ipswich; the one town where the validity of the sampling method might be a particular concern would be Guildford, with its high proportion of independent school attenders (Table AI.1A). The total numbers of children reported in manual and non-manual households showed very little difference, suggesting that differences in numbers of children between social class groups were unlikely to be an important source of bias.

AI.3 <u>INVITATIONS AND PARTICIPATION IN THE STUDY: SCHOOLS</u>

AI.3.1 CONSIDERATIONS IN STUDY DESIGN

Several features of the study design were included to facilitate the participation of schools in the study. The involvement of the Local Authority Education Department and the School Health Service were essential steps in organization; wherever possible preliminary contact and encouragement to the schools from these agencies was arranged. Attention was given to ensuring that administrative and clerical work involved was conducted by the Study Department rather than imposed on participating schools. In addition, attempts were made to interest the schools in the study, encouraging them to exploit educational opportunities provided by the survey team visit.

AI.3.2 RESPONSE AND REPRESENTATIVENESS OF PARTICIPATING SCHOOLS

Eighty-eight schools were invited to take part in the study. Ten schools were sampled in all towns except Ayr (in which a local holiday event limited the survey visit to nine days) and Merthyr, which had one exceptionally large school requiring a two day visit. Ten schools declined; two in Maidstone, two in Guildford, one in Carlisle, one in Exeter, two in Merthyr and two in Scunthorpe. Reasons given for non-participation included inadequate space (two), inadequate staffing (two), excessive workload (three) and concern about parental reaction to the study (one). No reason was given for refusal in two schools. In an attempt to ascertain whether the non-participating schools were in particularly socially deprived areas, the proportion of children receiving free school meals in participating and non-participating schools in the five towns with non-participant schools were compared. The average proportion of children receiving free school meals was 20% in participating schools and 16% in non-participating schools. These results did not provide strong evidence that schools in socially deprived areas were being systematically excluded from the study.

AI.4 <u>PARTICIPATION IN THE STUDY: INDIVIDUAL CHILDREN</u>

AI.4.1 CONSIDERATIONS IN STUDY DESIGN

Several features of the study were specifically designed to maximize response rates for the measurement survey. The school-based survey method avoided the need for a special journey for the child and rendered the presence of parents unnecessary, although it was emphasized that parents could attend if they wished. The invitation of whole classes of children was used to minimize worries of parents and children about individual participation. The signing of a master-copy of both invitation and reminder letters to parents by the Head Teacher of each school was used throughout, so that the approach to parents came from a person already known to them. Finally, it was decided that the study questionnaire should be handed out after the measurement survey, so that parents were not discouraged from participation at this stage by the need to complete the questionnaire first. The fact that the parents received the questionnaire when their child had already participated appeared to increase parental motivation to complete and return the questionnaire. The omission of names and addresses from the questionnaire and the use of reply-paid envelopes to return questionnaires to the research centre rather than the school were used to emphasize the research team's concern about confidentiality. A reminder was sent to parents two weeks after the study to maximize the questionnaire response rates.

AI.4.2 RESPONSE AND REPRESENTATIVENESS OF PARTICIPATING SUBJECTS

AI.4.2.1 Response rates

In the pilot study a total of 501 children aged between 5.00 and 7.50 years were invited to take part, of whom 447 (89%) participated in the measurement survey; completed questionnaires were returned for 404 children (81% of those initially invited). The corresponding figures for the main study (overall and for each town separately) are presented in Table AI.2A. Overall, 4877 children aged between 5.00 and 7.50 years were invited to participate, of whom 4056 subjects participated and had complete triplicate blood pressure measurements made. Response rates for the measurement survey varied between 86% (Dunfermline and Merthyr) and 77% (Scunthorpe). Of the 821 subjects who did not complete in the measurement survey, 443 (54%) were absent, 263 (32%) refused to take part (includes both parent and child refusals) and 115 (14%) were no longer attending the school through which the invitation had been made. Completed questionnaires were returned for 3693 children (76% of those initially invited; 91% of those measured). Response rates for questionnaire return varied between 78% (Dunfermline, Exeter, Southport) and 70% (Scunthorpe).

AI.4.2.2 Representativeness of study population

Examining the characteristics of responders is complicated by the fact that two stages of response were possible, and that information on parental social class and related factors is only available on subjects who participated in the measurement survey and returned the study questionnaire. It was considered unreasonable to re-approach subjects who had already refused to give informed consent to study participation, or to attempt to obtain confidential information about them from their school. However, the possibility of bias in the characteristics of responders can be examined in two ways.

First, the social class pattern of participants in a particular town can be compared with the estimate of the pattern of the town as a whole which is provided by the 10% sample of subjects by the 1981 Census in the town. Table AI.2B summarizes the results of this comparison, presented as the proportion of heads of households in manual occupations in the study sample and the 1981 Census sample in each town. There is considerable variation in the agreement between survey and Census samples in the different towns. Maidstone, for example, has a 6% excess of manual households in the sample, and Dunfermline a 12% deficit. Overall, there is a small deficit (3%) in the proportion of subjects with heads of households in manual occupations in the study sample, which suggests that the sample as a whole may have under-represented children with parents in manual occupations.

A second approach to assessment of the characteristics of non-responders is to compare the characteristics of children attending the measurement survey for whom questionnaires were or were not returned. The results of such a comparison, based on the 4056 subjects with complete blood pressure measurements, is presented in Table AI.3. The average age and sex ratios were almost identical in both groups. Mean heights and body mass indices were lower in the subjects for whom questionnaires were not returned. However, mean systolic and diastolic blood pressures were similar in both groups. An examination of the relationship between social class and body build in the study population showed that mean heights were greatest in children whose head of household was in a professional occupation and shortest in those children whose head of household was is an unskilled manual occupation. This suggests that the rate of non-return of questionnaires is likely to be higher in subjects from manual rather than non-manual households. These results are consistent with the findings of the overall comparison between the study samples and Census samples for the study towns, suggesting that children from manual households are under-represented in the subjects for whom both measurement and questionnaire data was collected. However, the results suggest that non-response, at least at the questionnaire stage, has little relation to blood pressure levels - a finding which is broadly consistent with that of an investigation of responders and non-responders to blood pressure screening in adults (Silman AJ and Locke C, 1982).

AI.5 BLOOD PRESSURE MEASUREMENT

AI.5.1 CONSIDERATIONS IN STUDY DESIGN

A most important priority in study design was the need to avoid systematic error in blood pressure measurement, particularly between the different study towns. Potential sources of error recognized were the blood pressure instrument, the observer or observers, and the circumstances of measurement. Several steps were taken to reduce the possibility of systematic error in blood pressure measurement and to minimize the consequences of any such error on the study results, which are discussed and examined in detail in the following sections. These included, first, the use of a blood pressure instrument selected for its validity and reliability, with a standard protocol for cuff size selection, second, detailed training and systematic allocation of blood pressure observers and, third, the ordering of towns in such a way as to minimize the consequences of drift in blood pressure measurement should it occur. Finally, detailed recording was made of those aspects of the circumstances of blood pressure measurement which could not be completely controlled (for example the ambient temperature, anxiety level of the child, presence or absence of parent). Analyses of these factors are described in chapters 4 and 5.

AI.5.2 SELECTION OF BLOOD PRESSURE INSTRUMENT

Three categories of instrument were considered for use in the study. These included, first, the standard mercury sphygmomanometer and, second, the modified sphygmomanometers developed to reduce observer prejudice in blood pressure measurement, including the random-zero sphygmomanometer

(Garrow JS, 1963; Wright BM and Dore CF, 1970) and the London School of Hygiene Sphygmomanometer (Rose GA et al, 1964). The third possibility was the use of an automated or semi-automated blood pressure recorder. While the use of a sphygmomanometer would have offered the advantage of comparability with earlier studies and the use of a modified instrument would have offered the possibility of reducing observer bias and digit preference, the use of a sphygmomanometer had several potential disadvantages in this setting. Differences in observer performance in blood pressure measurement with the sphygmomanometer may persist despite observer training and may vary over time (Bruce NG et al, 1988). Moreover, not even the modified sphygmomanometers described above eliminate the possibility of observer prejudice on blood pressure measurement. The use of an automated blood pressure recorder, which would have standardized the technical aspects of blood pressure measurement and recording, offered distinct theoretical advantages over the sphygmomanometer in a study of this kind. In particular, drift in blood pressure measurement over time, observer differences and observer prejudice could theoretically be reduced or eliminated by such an instrument. However, questions have been raised about the reliability and validity of many automated instruments (Labarthe DR et al, 1973; O'Brien ET et al, 1987). Previous reports on the performance of several instruments were reviewed. The Dinamap oscillometric blood pressure recorder (Critikon Inc) had been extensively validated both in comparison with the sphygmomanometer (Silas JH et al, 1980; Ellison RC et al, 1984; Pessenhofer H, 1986; Linden W and Wright JM, 1986; Jenner DA et al, 1988; Ornstein S et al, 1988) and with direct intra-arterial measurement (Ramsey M et al, 1979; Yelderman M and Ream AK, 1979; Friesen RH and Lichtor JL, 1981; Kimble KJ et al, 1981; Borow KM and Newburger JW, 1982; Pellegrini-Caliumi G et al, 1982; Colan S et al, 1983; Hutton P et al, 1984; Johnson CJH and Kerr JH, 1985; Rutten AJ et al, 1986; Park MK and Menard SM, 1987). One of these previous validation studies had also monitored the performance of the Dinamap during a population-based study, and had reported favourably on its performance (Ellison RC et al, 1984). Other particular advantages of the Dinamap over the other automated instruments considered were the availability of a full range of cuff sizes for the instrument and the facility for the observer to carry out regular checks on the performance of the electronic components and the pressure transducer of the instrument. A decision was made to use a recent Dinamap model, because it offered the possibility of direct linkage to a printer; the instrument was however reported by the manufacturers to be similar in all important respects to the earlier 845 and 847 models.

AI.5.3 VALIDATION OF DINAMAP 1846SX INSTRUMENT DURING THE STUDY

Considerable importance was attached to the monitoring of the performance of the Dinamap instrument during the study. The presence of measurement drift would be important both for the analysis and interpretation of the present study and in assessment of whether the Dinamap was an appropriate instrument for use in future epidemiological studies. Two methods of monitoring the performance of the blood pressure instrument were available within the study design. First, the results of the daily calibration checks on electronic function and the pressure transducer could be monitored. Second, the level of blood pressure measurement in the study could be monitored over time. However, it was considered that these checks by themselves were inadequate. In particular, calibration checks offered a very limited view of instrument performance while the level of blood pressure over time would be affected by several factors beside measurement drift; neither method was adequate for examining drift in blood pressure measurement. It was therefore considered important to provide external validation of blood pressure measurement in this investigation, by comparing blood pressure measurement with the study instrument with that of a reference instrument at intervals during the study. A random zero sphygmomanometer (Hawksley, UK) was chosen as the standard reference device. Three comparisons of blood pressure measurement between the study and reference instruments were conducted at intervals throughout the study involving approximately 40 subjects on each occasion. It was estimated that within-subject comparisons based on 40 subjects would provide estimates of systolic differences in Dinamap-Hawksley measurement with a standard error of approximately 1 mm Hg, assuming a within-subject standard deviation for consecutive systolic blood pressure measurements of 6 mmHg, as demonstrated in the pilot study. The first comparison was carried out immediately before the beginning of the main study (39 subjects), the second after the fifth town (55 subjects) and the third after the ninth town (58 subjects). Full details of the protocol of this investigation are provided elsewhere (section 3.4.4.1).

AI.5.4 ASSESSMENT OF THE DINAMAP 1846SX WITHIN THE MAIN FIELD STUDY

AI.5.4.1 Performance

The instrument performed reliably throughout the pilot and main studies and through the supplementary studies described during the course of this Thesis. In the main study blood pressure measurements were obtained successfully in all 4056 subjects but in 7 subjects (0.17%) one of the three readings made in each subject was not recorded by the instrument (usually as a result of the child moving) and required remeasurement. To place this proportion in context, in a study of blood pressure measurement in 400 subjects using the Hawksley random zero sphygmomanometer under identical circumstances, 2.5% of subjects could not be measured at the first attempt.

AI.5.4.2 Consistency of Dinamap blood pressure measurement: assessment within the study

The results of calibration of the study instrument were recorded daily throughout the study period and showed no systematic variation either in the function of electronic components or of the instrument's pressure transducer (results not presented). The measurement of blood pressure over time in the main study has been examined by plotting the average systolic and diastolic blood pressures of the towns by the order in which they were surveyed (Figure AI.1). The results show no clear evidence of a systematic trend in blood pressure measurement between study towns. However, with particularly low levels of blood pressure being observed in the third town (Guildford) and higher levels in subsequent towns, the results raise the possibility of a progressive rise in blood pressure level after the third town. This possibility is reflected in highly statistically significant evidence for an overall trend in blood pressure measurement between towns, both for systolic pressure ($F = 39.1$, $df = 1,7$, $p < 0.0001$) and for diastolic pressure ($F = 22.7$, $df = 1,7$, $p < 0.0001$). However, if this trend is the result of progressive drift in blood pressure measurement it should be observed <u>within</u> towns as well as between towns. A test for trend in blood pressure measurement during the study period conducted within towns provided no evidence for a trend, either for systolic pressure (p = 0.80) or for diastolic pressure (p = 0.40).

AI.5.5 EXTERNAL ASSESSMENT OF DINAMAP BLOOD PRESSURE MEASUREMENT

The results of the three serial comparisons between the study Dinamap instrument and the reference Hawksley random zero sphygmomanometer are presented below. Differences in blood pressure measurement between instruments, based on within-subject comparisons, are presented as Dinamap measurement minus Hawksley measurement throughout. The results have been adjusted for the order in which the machines were used for each subject because blood pressure tends to fall with successive measurements. Standardization for age, sex and observer made no difference to the results and has not been carried out. A systematic difference in blood pressure measurement was observed between different cuff sizes (see section AI.5.7); measurements with each instrument were therefore adjusted to the child cuff. However, this adjustment did not have a marked effect on the results. The blood pressure level for each subject has been calculated as the mean of the two readings for each subject, one of which was made using the Dinamap and the other the Hawksley.

AI.5.5.1 <u>Agreement between instruments: consistency over time</u>

The differences in blood pressure measurement between the Dinamap and Hawksley instrument in the three successive comparisons are presented in Figure AI.2. Systolic blood pressure measurements made by the Dinamap instrument appeared to be systematically greater than those with the Hawksley instrument in all three sessions, while those for diastolic pressure showed little overall difference. While differences in measurement varied between sessions, particularly for systolic pressure, there was no strong evidence either of variation in systolic measurement between sessions (F = 1.99, df = 2,148, p = 0.14) or of a trend between sessions (F = 0.89, df = 1,149, p = 0.50). The minor variation in diastolic measurement between sessions was very likely to be due to chance ($F = 0.38$, $df = 2,148$, $p = 0.69$). When the results from all three sessions were pooled, the overall difference between systolic measurements made with the Dinamap and Hawksley instruments was 8.3 mmHg (95% confidence interval 6.9 to 9.7 mmHg, $p < 0.0001$). Pooling of diastolic results confirmed the close overall agreement between Dinamap and Hawksley instruments for diastolic pressure measurement, with a mean diastolic difference of -0.2 mmHg (95% confidence interval -1.8 to 1.4 mmHg, $p = 0.96$).

AI.5.5.2 Blood pressure level and agreement between instruments

In order to determine whether agreement in blood pressure measurement with the two instruments is related to blood pressure level, the relationships between blood pressure level and blood pressure differences between instruments were examined (Figure AI.3). Systolic differences in blood pressure measurement between instruments show no important relationship to blood pressure level. The regression coefficient, representing the change in systolic blood pressure difference between instruments (mmHg) for each mmHg change in systolic blood pressure level, is 0.013 (95% confidence interval -0.131 to 0.157, $p = 0.85$). For diastolic pressure, despite the close overall agreement in measurement between instruments, there is an inverse relationship between instrument agreement and blood pressure level; at low blood pressure levels Dinamap readings are higher than Hawksley readings whereas at high pressure levels the reverse is true. The regression co-efficient for this relationship is -0.324 (95% confidence interval -0.12 to -0.528, $p = 0.002$), indicating that a 10 mmHg rise in diastolic blood pressure level is accompanied by a fall in Dinamap-Hawksley differences of 3.1 mmHg, an effect of potential practical importance. A similar inverse association between blood pressure level and instrument agreement has also been demonstrated in an independent study comparing the Dinamap 1846SX and the Hawksley random zero sphygmomanometer in adults (Whincup PH et al, 1991). However, in that study, close overall agreement was observed in diastolic blood pressure measurement between the Dinamap and Hawksley instruments (Figure AI.4), in a population with a higher mean diastolic blood pressure level. The relationship between blood pressure level and instrument differences is therefore not consistent between the study in children and the study in adults, suggesting that a factor other than blood pressure level itself may be responsible for the relationship.

AI.5.5.3 Consistency of findings with previous studies: interpretation

The results described above imply that measurements made by the Dinamap were consistent over the study period. This is in agreement with one earlier report, which described the consistency of Dinamap performance over a six month period during which two instruments were used to make measurements in 6000 subjects (Ellison RC et al, 1984). The overall differences between the Dinamap and Hawksley instruments described in the present study are compared with the results of other studies comparing Dinamap models with mercury sphygmomanometers in Figure AI.4. The Dinamap model and the sphygmomanometer used in each study are specified. It can be seen that the difference in systolic measurement reported in the present study agrees closely with the findings of two independent studies of the Dinamap 1846SX instrument in adults (Maheswaran R et al, 1988; Whincup PH et al, 1991) and with one report on the performance of a similar Dinamap instrument, the 8100 model (Ornstein S et al, 1988). These results contrast with those of studies of the earlier Dinamap 845 model, which all show close overall agreement with sphygmomanometric measurements for systolic pressure. Agreement in diastolic measurement between the Dinamap and sphygmomanometer, by contrast, has been close for all Dinamap models (Figure AI.4). The type of sphygmomanometer used (whether standard or random-zero) appears to have little effect on the result of the comparisons; this is in keeping with earlier reports indicating that, while measurement differences between these types of sphygmomanometer exist, they are small in magnitude (Evans JG and Prior IAM, 1970; De Gaudemaris et al, 1985; O'Brien E et al, 1991). The most likely explanation of these findings is that systolic measurement by the Dinamap 1846SX and 8100 models is not comparable with that of the earlier 845 model, possibly as a result of changes in software programming in the newer model. While studies comparing Dinamap measurement with direct intra-arterial measurement might be expected to clarify these observations, unfortunately they do not do so. Most of those studies were based on the Dinamap 845 and 847, and showed close agreement between Dinamap measurements and direct intra-arterial measurements (Borow KM and

Newburger JW, 1982; Pellegrini-Caliumi G et al, 1982; Colan S et al, 1983; Park MK and Menard SM, 1987). The only study reported on the Dinamap 1846SX was based on neonates and suggested that the Dinamap underestimated intra-arterial systolic pressure (Wareham JA et al, 1987). These contradictory findings emphasize the need for further evaluation of the Dinamap 1846SX, particularly in relation to direct intra-arterial measurement.

The possibility that the level of agreement between the Dinamap and the mercury sphygmomanometer differs at different blood pressure levels has not been reported by earlier investigators, although one study suggested that the Dinamap 845 might overestimate pressures at low blood pressure levels (Johnson CJH and Kerr JH, 1985). A similar study in adults showed an inverse association between blood pressure level and instrument agreement similar to that described in the present study (Whincup PH et al, 1991). However, the study also showed close overall agreement in diastolic blood pressure measurement between the Dinamap and Hawksley instruments, in an adult population with a higher mean diastolic blood pressure level. This inconsistency in the relation between diastolic blood pressure level and instrument differences in these two studies raises the possibility that the apparent relationship between blood pressure level and instrument differences is explained by a factor other than blood pressure level itself.

AI.5.5.4 Implications of results for the Nine Towns Study of Blood Pressure in Children

Consistency of measurement over time was the most important requirement of the study blood pressure instrument. The results of both internal and external validation provided no evidence of systematic measurement drift during the study period. The marked difference in systolic blood pressure measurement between the Dinamap and the random zero sphygmomanometer is important if the results obtained with the Dinamap are to be compared with those of other studies using the sphygmomanometer; in this case a simple correction factor (8.3 mmHg) can be subtracted from systolic blood pressure measurements in the study to render them comparable with sphygmomanometric readings. However, the important hypotheses being examined in the present study were based entirely on comparisons within the study, so that this problem does not arise. More difficult is the question of the inverse association between diastolic blood pressure level and diastolic instrument differences. As discussed earlier, the close overall agreement between diastolic measurements with the Dinamap and Hawksley instruments both in studies of children and adults makes it unlikely that there is a causal association between blood pressure level and instrument differences. If such a relationship were present, its effect would be to raise low Dinamap readings and lower high ones. Thus its influence would tend to reduce rather than to accentuate differences in diastolic blood pressure between population groups.

AI.5.6 INFLUENCE OF OBSERVERS ON BLOOD PRESSURE MEASUREMENT

AI.5.6.1 Considerations in design

The important potential influence of observers on error in blood pressure measurement is well recognized (Rose GA et al, 1982). Inconsistency in the performance of a single observer over time may occur as a result of change in measurement technique, or as a result of observer prejudice. Differences in blood pressure measurement between observers may result from differences in technique, or differences in the extent of observer-subject interaction occurring with different observers. The limitation of observer error was one of the most important reasons for the use of an automated blood pressure recorder. Several other features of study design reflected the need to minimize observer differences in blood pressure measurement and their effect on the study outcome. The number of blood pressure observers in the study was kept to a minimum. Although the use of a single observer would have been ideal in theory, practical considerations dictated the involvement of two observers. To avoid the confounding of between-town differences and observer differences in blood pressure, the study was planned so that each observer would carry out approximately half the measurements in each town. The allocation of observers within each town was designed to ensure that the mean age and proportion of each sex seen by each observer in each town was similar. The observers were trained to make measurements in a standard way with the Dinamap instrument, and were also trained and standardized in the use of a Hawksley random zero sphygmomanometer using training tapes (Rose G, 1965), in case electronic failure necessitated the use of this instrument.

AI.5.6.2 <u>Observer effects on blood pressure measurement</u>
The numbers of subjects measured by each observer in each town and in the study overall are shown in Table AI.4. Measurements were almost equally divided between observers in each town, with the exception of Scunthorpe, where, as a result of illness, observer 2 carried out almost all measurements. A comparison of blood pressure measurements made by the two observers during the course of the study is presented in Figure AI.5. Results are presented as the difference between observers (observer 1 minus observer 2) in systolic and diastolic measurement. For both systolic and diastolic measurement it appeared that observer 1 recorded slightly higher blood pressure measurements than observer 2 in the first two towns of the study, with little difference thereafter. The variation in observer differences between towns was statistically significant, both for systolic pressure (test for observer*town interaction; p = 0.004) and for diastolic pressure (test for observer*town interaction; p = 0.04). However, the sizes of between-observer differences in blood pressure were small in most towns and there were no important overall differences in measurement between observers, either for systolic pressure (observer difference 0.2 mmHg, 95% confidence interval -0.3 mmHg to 0.7 mmHg, p = 0.96) or for diastolic pressure (observer difference 0.2 mmHg, 95% confidence interval -0.2 mmHg to 0.6 mmHg, p = 0.95). In view of this close overall agreement, no adjustment for observer effects on blood pressure measurement was made in subsequent analyses. The explanation and significance of the variation in observer differences between the different study towns remains uncertain. However, there is no evidence that this variation contributed to between-town differences in blood pressure (section 5.4.1.2).

AI.5.7 CUFF SIZE AND BLOOD PRESSURE MEASUREMENT

AI.5.7.1 <u>Considerations in study design</u> The influence of cuff size on blood pressure measurement has been recognized for many years (von Recklinghausen H, 1901). Particular emphasis had been placed in earlier guidelines for blood pressure measurement in children on the need to use a cuff of sufficient size, because of the tendency of small cuffs to produce falsely high blood pressure readings (Prineas RJ et al, 1980a; Petrie JC et al, 1986; Task Force on Blood Pressure Control in Children, 1987; Frohlich ED et al, 1988; de Swiet M et al, 1989). However, there has been little consistency in the detailed advice provided by these reports. While some authors have recommended that cuff size selection should be based on arm circumference (Prineas RJ et al, 1980a; Frohlich ED et al, 1988), others have emphasized the importance of arm length in cuff selection (Task Force on Blood Pressure Control in Children, 1987). Moreover, while some authors have recommended the use of the largest cuff to fit the arm comfortably (Task Force on Blood Pressure Control in Children, 1987; de Swiet M et al, 1989), others have emphasized the tendency of large cuffs to underestimate blood pressure (Frohlich ED et al, 1988). In the present study the American Heart Association guidelines (Frohlich ED et al, 1988), which recommended the use of a cuff bladder size with width corresponding to 40-50% of arm circumference, were followed, because these recommendations were based on the results of earlier comparisons of indirect and direct blood pressure measurement (Robinow M et al, 1939; Moss AJ and Adams FH, 1965). However, the criteria were modified in accordance with the suggestion by Prineas and colleagues that, in addition to a cuff bladder width:arm circumference ratio of 40-50%, cuff bladder length should be sufficient to encompass 90% of arm circumference (Prineas RJ et al, 1980a). As a result, a cuff bladder width/arm circumference ratio of 50% or more was achieved for virtually all subjects. This was consistent with a report on the influence of cuff bladder size on the accuracy of blood pressure measurement with the Dinamap instrument, which suggested that a cuff bladder width corresponding to between 50 and 60% of arm circumference produced blood pressure recordings directly comparable with intra-arterial measurement (Kimble KJ et al, 1981).

AI.5.7.2 <u>Effect of cuff size on blood pressure measurement</u>

(i) <u>Findings in the main study</u> The use of the procedure for cuff size selection outlined above resulted in the use of two Dinamap cuff sizes, the child and the adult, for all study measurements. Of these, 1868

(46%) were made with the child cuff and 2188 (54%) with the adult cuff. The relationship between cuff size and blood pressure measurement was examined by relating arm circumference to blood pressure for each cuff separately. The results are presented in the Figure AI.6 (left-hand, 'unadjusted' figures) for both systolic and diastolic pressure. Blood pressure rises with increasing arm circumference for both child and adult cuff sizes, as might be expected. However, there is a striking fall in blood pressure measurement at the point of changeover from child to adult cuff. Systolic measurements with the adult cuff are approximately 4 mmHg lower than might be expected, while diastolic measurements are approximately 2 mmHg lower than expected on the basis of child cuff measurement.

This difference in blood pressure measurement associated with the change between cuffs of different bladder sizes was sufficiently large to have important potential implications for the analysis of the main study. The implications would be most serious at the individual level, where the presence of these cuff differences in blood pressure measurement would attenuate relations between correlates of arm circumference (including age and all measures of body build) and blood pressure. However, the measurement difference between cuffs would also be of potential importance in the analysis of between-town differences if the proportion of subjects measured with each cuff size differed between towns. The observations on cuff size and blood pressure measurement therefore required further investigation. For the purposes of the main study it was important to confirm that the effect was due to the cuff (rather than some other factor related to the cuff size selection process) and to obtain a precise estimate of the magnitude of the cuff effect on blood pressure measurement so that adjustment for the effect of cuff size could be carried out. These requirements could be most effectively met by a crossover trial, in which subjects were measured with both child and adult cuffs in a randomized order, enabling comparison of blood pressure measurements with child and adult cuff sizes to be carried out on a within-subject basis. However, because the problems of matching blood pressure measurements made with different cuff sizes have received little attention in previous guidelines for blood pressure measurement, it was considered important that the observations should be extended to other sizes of cuff and to the sphygmomanometer as well as the oscillometric blood pressure recorder. Accordingly, the influence of three cuff sizes (adult, child, infant) on blood pressure measurement was examined using a randomized crossover design in both the Dinamap instrument (448 subjects) and the Hawksley random zero sphygmomanometer (390 subjects) in an investigation conducted immediately after the completion of the Nine Towns Study of Blood Pressure in Children. A detailed description of the methodology and the results of the supplementary study are provided elsewhere (Whincup PH et al, 1989, reproduced in Appendix IV). However, those aspects of the study which are directly relevant to the measures taken to standardize blood pressure measurement for the effect of cuff size are described below.

(ii) <u>Results of supplementary study</u> The difference in systolic and diastolic measurement between the child and adult cuffs (presented as child cuff reading minus adult cuff reading) at different levels of arm circumference, based on within-subject comparisons are presented in Figure AI.7. Results are adjusted for the effect of order of measurement. Measured blood pressures are higher with the child cuff than the adult cuff at all levels of arm circumference, both for systolic pressure (mean difference 4.6 mmHg, 95% confidence interval 4.0 to 5.2 mmHg, $p < 0.0001$) and diastolic (mean difference 1.8 mmHg; 95% confidence interval 1.2 to 2.4 mmHg, $p < 0.0001$). The differences in measurement between cuffs show a tendency to increase with arm circumference, both for systolic pressure (0.32 mmHg increase in difference between cuffs per 1 cm increase in arm circumference, 95% confidence limits -0.10 to 0.74 mmHg/cm) and for diastolic pressure (0.36 mmHg increase per 1 cm increase in arm circumference; 95% confidence limits 0.00 to 0.72). The relationship between cuff differences and arm circumference is not statistically significant for systolic pressure ($p = 0.13$) and is of borderline statistical significance for diastolic pressure ($p = 0.05$).

(iii) <u>Development of cuff correction factors</u>

A decision was required on the appropriate method of correcting for the effect of cuff size in the main study, using the results from the supplementary study. The most obvious and simple method was to standardize all measurements to one cuff size. The arm circumferences of children measured in the main survey varied between 14 cm and 25 cm, but 80% of children measured had arm circumferences between 15 cm and 19 cm. It was decided to standardize all measurements to the child cuff size, because the bladder width of that cuff size corresponded more closely to the cuff width/arm circumference ratio of 50-60% which the study by Kimble and his colleagues had suggested might be most appropriate for the Dinamap instrument (Kimble KJ et al, 1981). In order to carry out the correction, a decision was required as to whether a single correction factor should be used at all levels of arm circumference, or whether a different adjustment be used at different levels of arm circumference. While the difference in blood pressure measurement between cuffs appeared to increase with arm circumference in the case of both systolic and diastolic pressure, confidence intervals for both estimates were wide and the effects were of marginal statistical significance. A decision was therefore made to ignore the influence of arm circumference on blood pressure measurement and to make a single overall adjustment, based on measurements made over a range of arm circumferences comparable to that in the study population for which adjustment was required. Because the arm circumference distribution in the Nine Towns Study of Blood Pressure in Children (mean 17.0 cm, median 16.8cm, range 13.2 to 25.2 cm) was very similar to that in the supplementary cuff study (mean 17.1 cm, median 16.9 cm, range 13.8 cm to 24.0cm), adjustments were made to the main study data which matched the overall between-cuff differences defined in the supplementary study, 4.6 mmHg for systolic pressure and 1.8 mmHg for diastolic pressure. The smoothing effect of this adjustment on the relationship between arm circumference and blood pressure, is illustrated in the right hand figures of Figure AI.6. However, the effect of an adjustment for cuff size which took account of the observed variation in between-cuff differences in blood pressure measurement at different arm circumferences was also examined. The use of this more complex adjustment made no important difference to the relationships between age, body build and blood pressure in the study population observed with the simpler adjustment (results not presented). Accordingly, the results of the simpler cuff adjustment are presented throughout.

The observations described here on the relationship between cuff size and blood pressure measurement have important implications for the design of epidemiological studies of blood pressure measurement in children. They emphasize that the use of a cuff which is too small is not the only potential source of error in blood pressure measurement; the use of more than one cuff size may introduce a systematic error into the measurement of blood pressure. Thus, a decision is required as to whether a single cuff size can be used throughout the study, or whether more than one cuff is required. If more than one cuff needs to be used, it may be necessary to establish a correction factor so that all measurements can be standardized to a single cuff size.

AI.5.8 ORDERING OF TOWNS FOR BLOOD PRESSURE MEASUREMENT

The ordering of towns was chosen to minimize the effect of systematic changes in blood pressure measurement on the results of the study. Towns were grouped into three sets, each set having one town with high, one with intermediate and one with low levels of adult town mean blood pressure. Within each set towns were examined in an intermediate-high-low sequence. This ordering offered three advantages over other designs in minimizing the effect of potential measurement drift. First, by examining pairs of high and low towns as closely together as possible (usually within a period of six weeks) the possibility of measurement drift between the high and low towns was kept to a minimum. Second, the ordering ensured that, should measurement drift occur, it would not produce a 'positive' study result (i.e. one in which adult and child blood pressures in each town were related). Third, the design offered the opportunity for conducting analysis <u>within</u> each set of three towns, in order to minimize the influence of measurement drift on the comparison of high and low blood pressure towns. Differences in town mean blood pressures, both within and between town sets are described in chapter 5.

TABLE AI.1A PROPORTION OF CHILDREN ATTENDING PRIVATE SCHOOLS BY COUNTY

STUDY TOWN	COUNTY	PROPORTION ATTENDING PRIVATE SCHOOLS (%)
Ipswich	Suffolk	3.6
Maidstone	Kent	5.2
Dunfermline	Fife	0.5
Guildford	Surrey	18.5
Ayr	Ayrshire	0.4
Carlisle	Cumbria	1.5
Exeter	Devon	5.1
Southport	Lancashire	2.1
Merthyr Tydfil	Mid-Glamorgan	0.6
Scunthorpe	Humberside	2.9

(Source: Statistics on Private School attendence, Department of Education and Science, 1986)

TABLE AI.1B COMPARISON OF SOCIAL CLASS COMPOSITION OF STUDY SAMPLE WITH 1981 CENSUS S.A.S. SAMPLE: PILOT TOWN (IPSWICH)

	PROPORTION IN STUDY SAMPLE (%)	PROPORTION IN CENSUS SAMPLE (%)
SOCIAL CLASS		
I	5	4
II	22	22
IIIN	15	16
IIIM	39	37
IV	14	16
V	5	7
% (n) of subjects	100 (404)	100 (2828)

(Social class is based on the occupation of the head of household, as defined by the Office of Population, Censuses and Surveys, 1988).

TABLE AI.2A NUMBERS OF PARTICIPANTS AND RESPONSE RATES: NINE TOWNS STUDY OF BLOOD PRESSURE IN CHILDREN

TOWN	NUMBER INVITED	NUMBER (%) MEASURED		NUMBER (%) WITH QUESTIONNAIRE	
Maidstone	522	429	(82)	395	(76)
Dunfermline	524	451	(86)	408	(78)
Guildford	529	448	(85)	400	(76)
Ayr	532	438	(82)	390	(73)
Carlisle	576	469	(81)	439	(76)
Exeter	525	438	(83)	407	(78)
Southport	571	483	(85)	446	(78)
Merthyr Tydfil	565	488	(86)	435	(77)
Scunthorpe	533	412	(77)	373	(70)
OVERALL	4877	4056	(83)	3693	(76)

(Figures are based on the age-group 5.00 to 7.50 years)

Table AI.2B COMPARISON OF SOCIAL CLASS COMPOSITION OF STUDY SAMPLE (EXPRESSED AS PROPORTION IN MANUAL OCCUPATION) WITH 1981 CENSUS S.A.S. SAMPLE: BY TOWN

	STUDY SAMPLE		CENSUS SAMPLE		STUDY-CENSUS
	N	% manual	N	% manual	% difference
TOWN					
Maidstone	361	50	3202	44	+6
Dunfermline	349	53	1546	65	-12
Guildford	371	45	3352	44	+1
Ayr	363	46	1506	56	-10
Carlisle	406	59	2366	56	+3
Exeter	359	54	2212	50	+4
Southport	424	42	6797	50	-8
Merthyr	397	67	1454	74	-7
Scunthorpe	325	70	1465	74	-4
OVERALL	3355	54	23900	57	-3

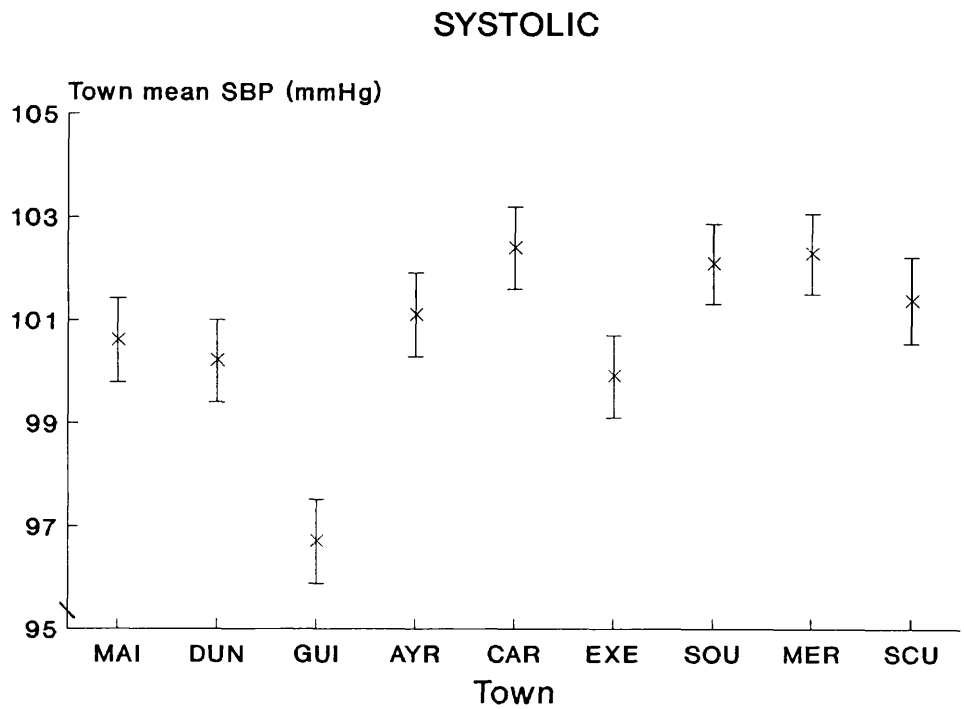
TABLE AI.3 CHARACTERISTICS OF STUDY PARTICIPANTS WITH AND WITHOUT QUESTIONNAIRE RESPONSE

	QUESTIONNAIRE RESPONSE				
	YES (N = 3693)		NO (N = 363)		
	Mean	(s.e.)	Mean	(s.e.)	p (no diff.)
% Female	50.1	--	49.9	--	0.98
Height (cm)	116.9	(0.1)	115.8	(0.3)	0.0005
Weight (kg)	21.4	(0.1)	20.8	(0.2)	0.007
Body mass index (kg/m2)	15.66	(0.02)	15.51	(0.08)	0.07
Systolic B.P.	98.4	(0.2)	97.9	(0.4)	0.26
Diastolic B.P.	58.0	(0.1)	58.0	(0.3)	0.80

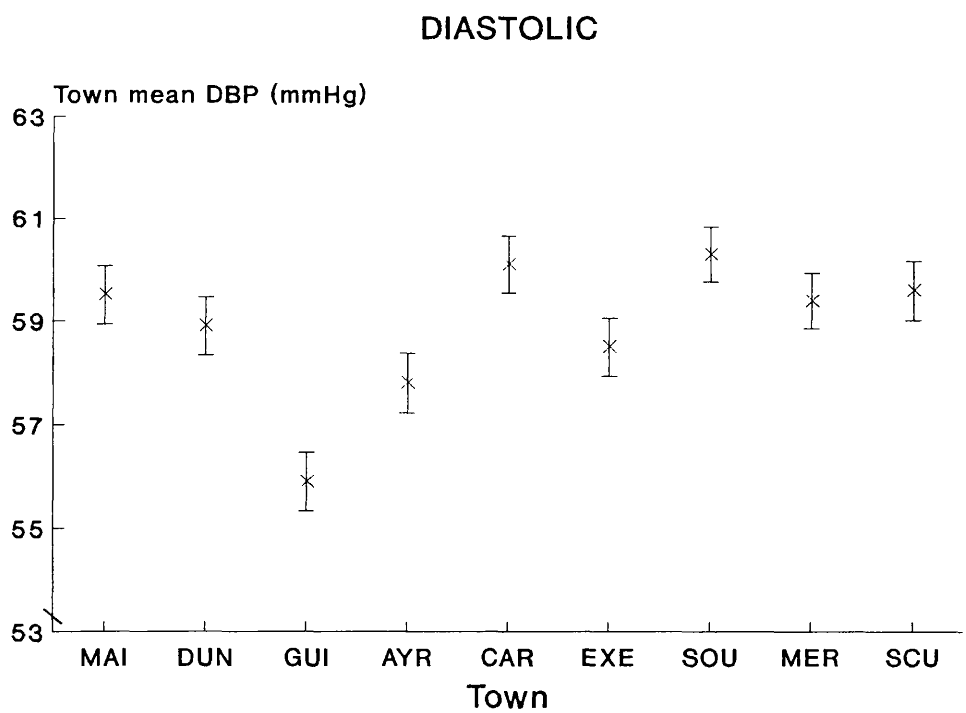
TABLE AI.4 PROPORTION OF BLOOD PRESSURE MEASUREMENTS MADE BY EACH OBSERVER: BY TOWN

	SUBJECTS MEASURED			
	Observer 1		Observer 2	
	N	(%)	N	(%)
TOWN				
Maidstone	193	(45)	236	(55)
Dunfermline	221	(49)	230	(51)
Guildford	228	(51)	220	(49)
Ayr	223	(51)	215	(49)
Carlisle	249	(53)	220	(47)
Exeter	237	(54)	201	(46)
Southport	232	(48)	251	(52)
Merthyr	224	(46)	264	(54)
Scunthorpe	49	(12)	363	(88)
OVERALL	1856	(46)	2200	(54)

Figure AI.1 TOWN MEAN BLOOD PRESSURES BY ORDER OF EXAMINATION



Means and 95% C.I.s



Means and 95% C.I.s

Figure AI.2 BLOOD PRESSURE DIFFERENCES BETWEEN DINAMAP AND HAWKSLEY INSTRUMENTS (PRESENTED AS DINAMAP-HAWKSLEY) AT THREE STAGES (SESSIONS) DURING THE STUDY

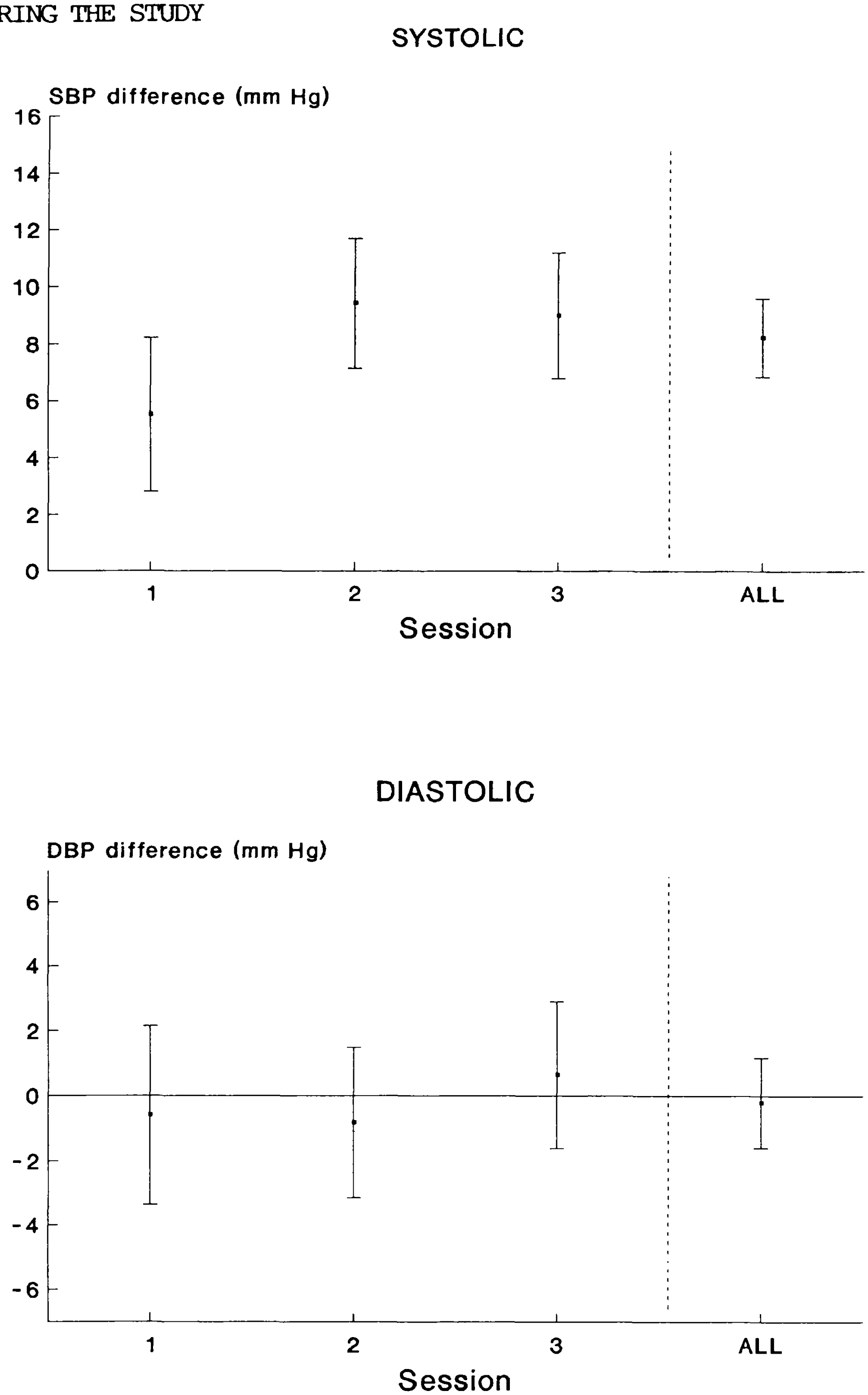


Figure AI.3 BLOOD PRESSURE LEVEL AND DIFFERENCE IN BLOOD PRESSURE MEASUREMENT BETWEEN DINAMAP AND HAWKSLEY INSTRUMENTS.

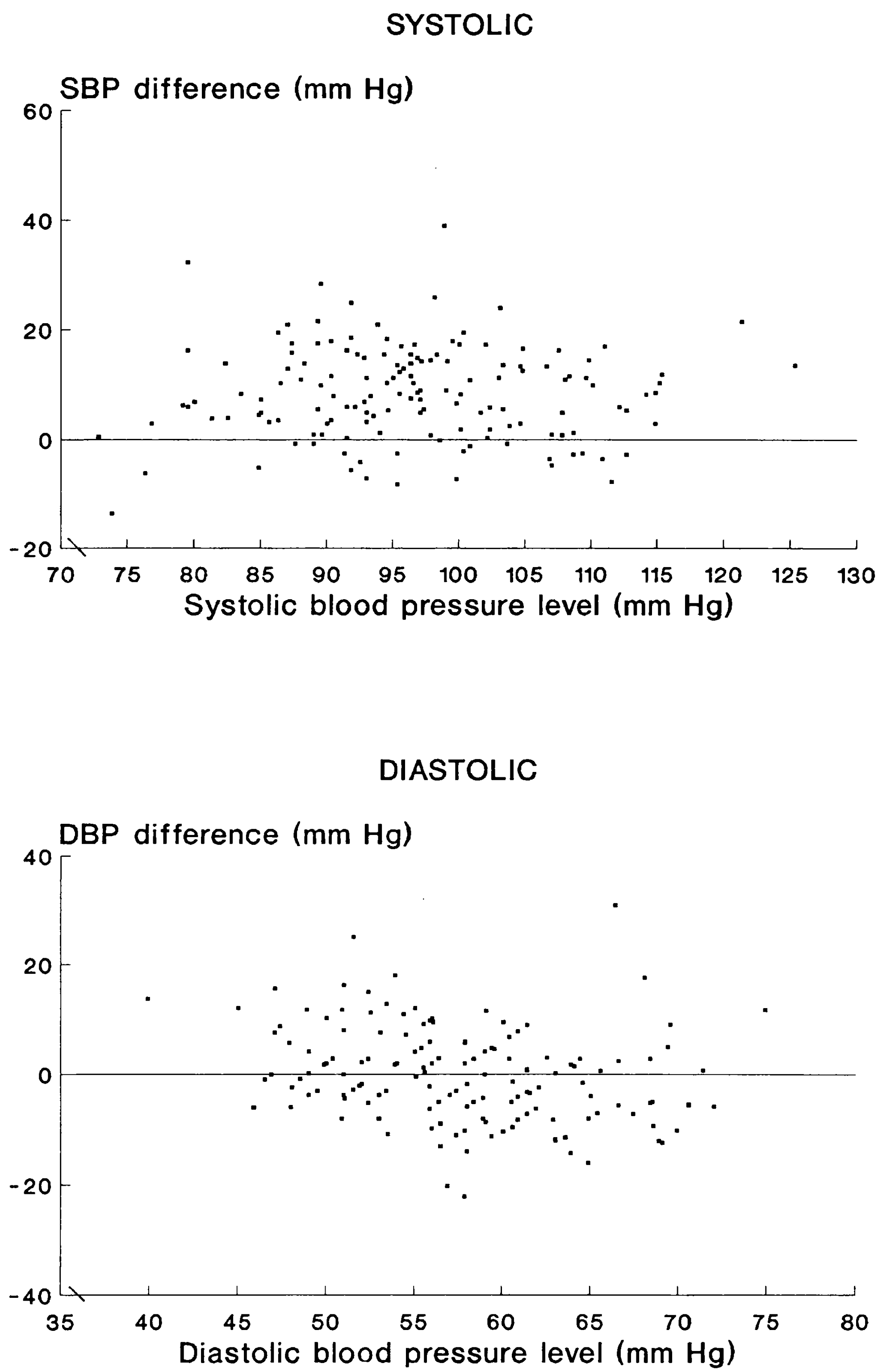
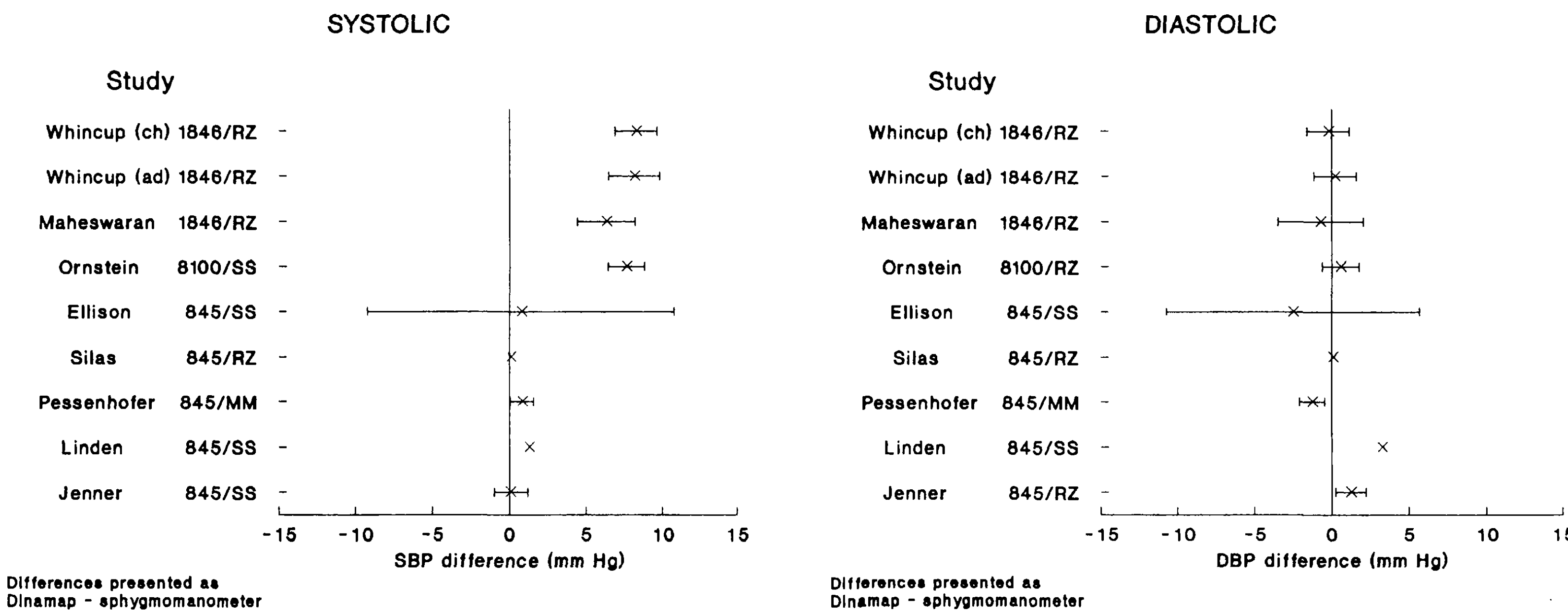


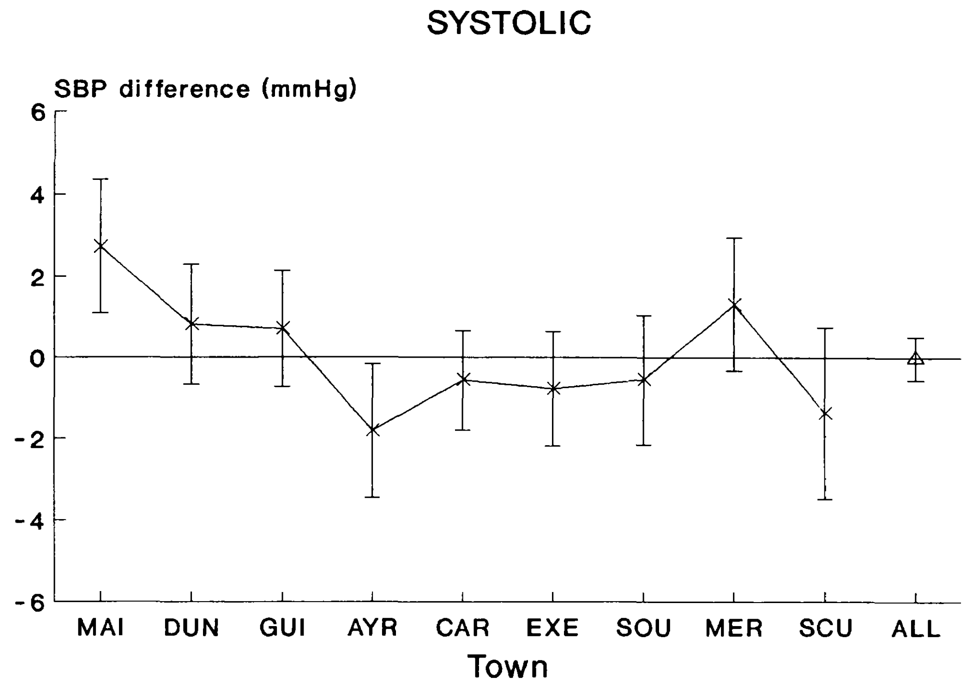
Figure AI.4 COMPARISON OF BLOOD PRESSURE MEASUREMENT BETWEEN THE DINAMAP OSCILLOMETRIC RECORDER AND THE SPHYGMOMANOMETER



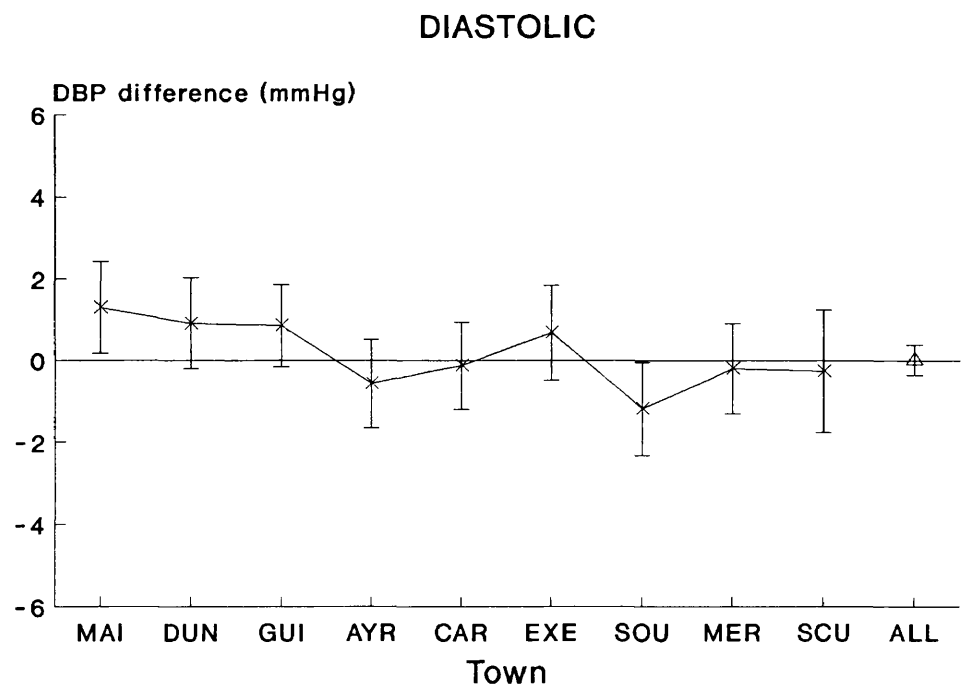
(RZ = random zero spyphygmomanometer,
SS = standard mercury sphygmomanometer
MM = mercury manometer)

Figures refer to Dinamap model used in each case.

Figure AI.5 OBSERVER DIFFERENCES IN BLOOD PRESSURE MEASUREMENT: BY TOWN.



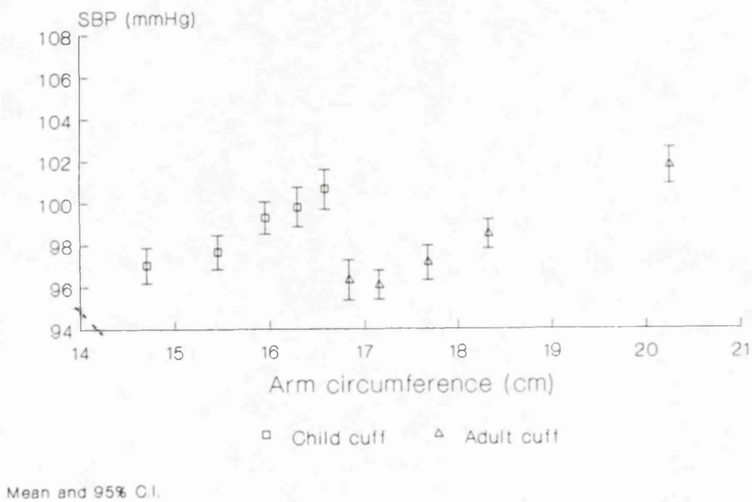
Mean and 95% C.I. shown
(Observer 1 - Observer 2)



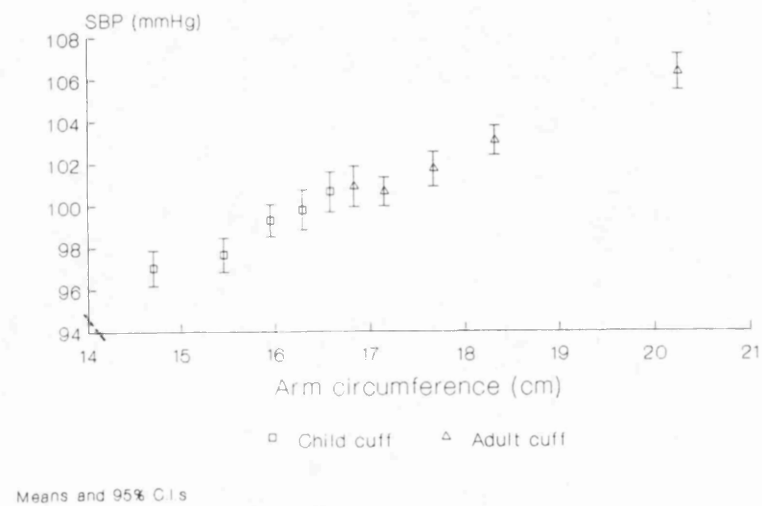
Means and 95% C.I. shown
(Observer 1 - Observer 2)

Figure AI.6 DIFFERENCES IN BLOOD PRESSURE MEASUREMENT BETWEEN CHILD AND ADULT CUFFS: UNADJUSTED AND ADJUSTED.

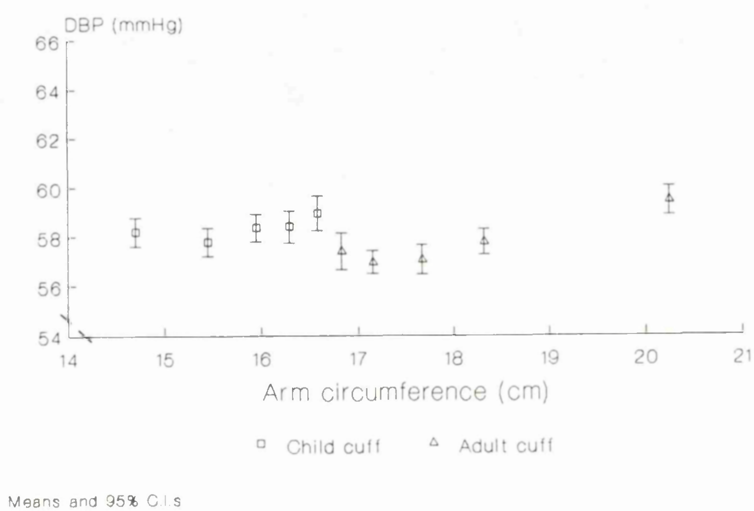
SYSTOLIC: UNADJUSTED



SYSTOLIC: ADJUSTED



DIASTOLIC: UNADJUSTED



DIASTOLIC: ADJUSTED

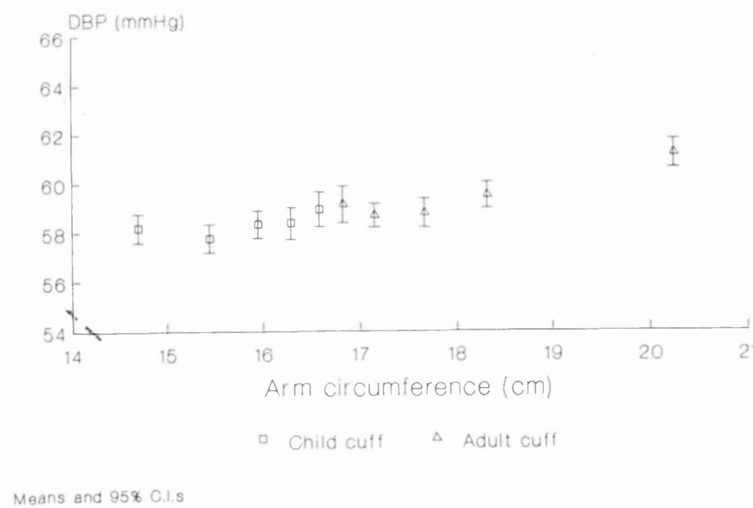
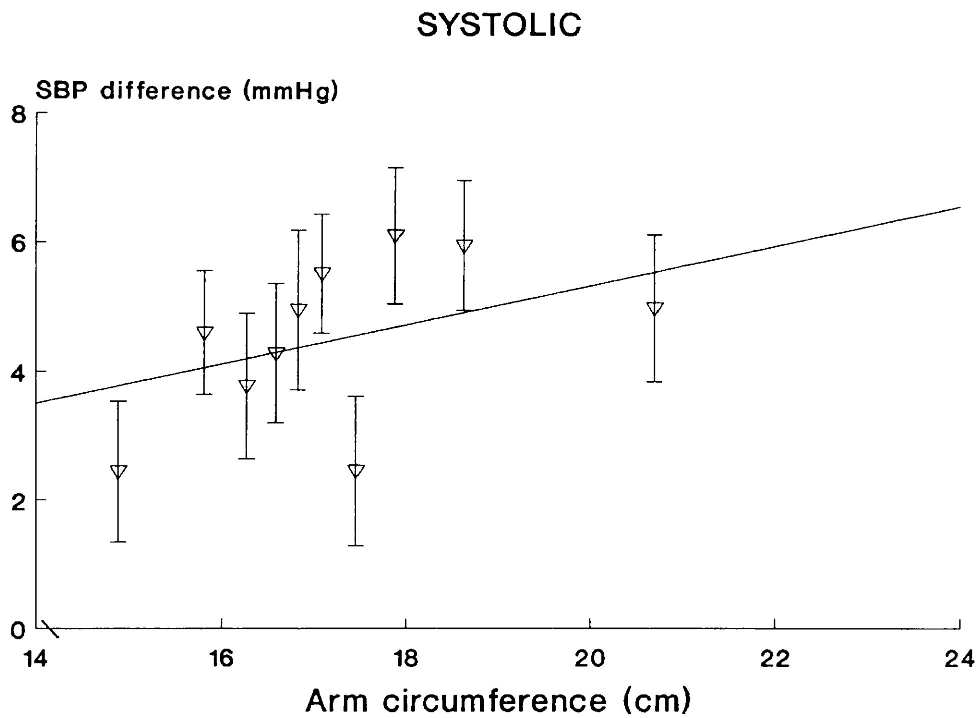
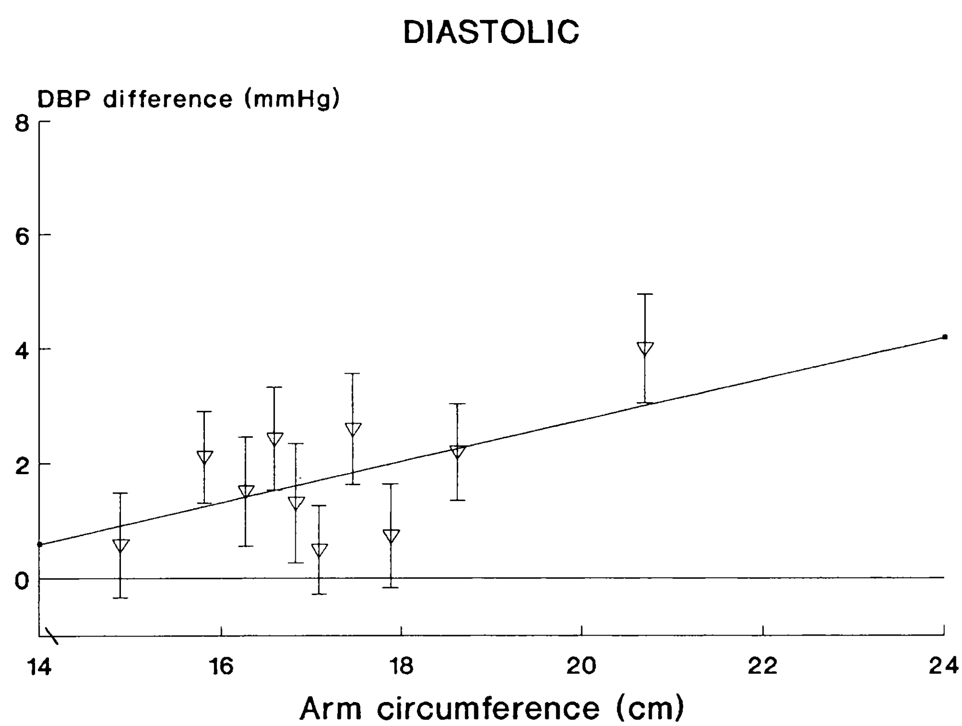


Figure AI.7 DIFFERENCES IN BLOOD PRESSURE MEASUREMENT BETWEEN CHILD AND ADULT CUFFS (CHILD CUFF MEASUREMENT MINUS ADULT CUFF MEASUREMENT) BASED ON WITHIN-SUBJECT COMPARISONS



Mean and S.E.s



Mean and S.E.s

APPENDIX II

STUDIES INCLUDED IN THE REVIEW RELATING POPULATION BLOOD PRESSURES IN MIDDLE-AGE TO THOSE IN EARLY ADULT LIFE AND ADOLESCENCE (SECTION 2.2.4)

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APPENDIX III

QUESTIONNAIRE FROM THE NINE TOWNS STUDY OF BLOOD PRESSURE IN CHILDREN

REGIONAL HEART STUDY

Study Directors
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Dr. S J Pocock

Regional Heart Study
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& General Practice
Royal Free Hospital School
of Medicine
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LONDON NW3 2PF
Telephone 01-794 0500 Ext 3048

Children's Blood Pressure Study:

Dear Parent/Guardian,

Your child has now been examined by our team of nurses. It will help us to interpret the blood pressure results if you can complete the questions below. The answers do not take long to fill in and will be treated in the STRICTEST CONFIDENCE, being seen only by the Research Team.

It is expected that the questionnaire will be completed in most families by the child's mother or female guardian and it is worded accordingly.

To answer the questions please tick the correct box [✓] or write in the spaces provided. When you have finished the questionnaire please put it in the envelope provided (no stamp is required) and post it back to us.

THANK YOU VERY MUCH FOR YOUR HELP.

Peter Whincup

Dr Peter Whincup
(Project Leader)

P.S. You will see that you are not asked to write your name or address on the answer sheet; this helps us to maintain confidentiality.

Please do not write in this column.

first group of questions is about **the child who has been examined** .

| 1 | 8

): What is your relationship to this child ?

Mother	[ ]
Father	[ ]
Other relative	[ ]
Unrelated guardian:-	
Foster parent	[ ]
Adoption parent	[ ]

9

10

): What was this child's date of birth?

(Day)____ (Month)______(Year) 19____

16

): How long has this child lived in this town? ______________(years)

If LESS THAN 1 YEAR, where did this child live before that?

Town______________________ ______________

Region/County_____________________________

Country (if outside U.K.)_________________

17

(4): Was the he/she born in (Scunthorpe?) YES [ ] NO [ ]

20

If NO, where was he/she born?

Town______________________________________

Region/County_____________________________

Country (if outside U.K.)_________________

21

(5): How much did this child weigh at birth?

______lb ______oz OR __________kg

24

Please do not write in this column.

(6): How was this child fed in the first 3 months of life?

Breast fed [ ]
Bottle fed [ ] 27
Fed on a mixture of breast and bottle feeds [ ]

(7): If the child was breast fed, wholly or partly, for how long was this continued from birth?

______________(months) 28

(8): At what age did [redacted] bottle feeding with milk start?______(months) 30

(9): Has your child ever suffered from a urine infection ('water infection')?

YES [ ] 32
NO [ ]

(10): Has your child ever had kidney trouble of any sort? YES [ ] 33
NO [ ]

If YES, please give details if known______________________

______________________________________ 34

(11): Does your child have any other illness or condition of which you are aware?

YES [ ] 35
NO [ ]

If YES please give details______________________ 36

(12): Does your child receive any regular tablets, inhalers or other medications?

YES [ ] 38
NO [ ]

If YES, please give details______________________ 39

write in this column.

3): Please indicate whether your child has been vaccinated against the following illnesses (tick the correct box for each illness).

	Yes	No	Don't know	
Diphtheria	[ ]	[ ]	[ ]	41
Tetanus	[ ]	[ ]	[ ]	42
Whooping cough	[ ]	[ ]	[ ]	43
Polio	[ ]	[ ]	[ ]	44
Measles	[ ]	[ ]	[ ]	45

4): How many children, aged 16 or under, apart from the child examined, live in your household? (Half-brothers and sisters and adopted children should be included) 46

____

Please write the ages of these other children, beginning with the oldest:

____

47 48 49

write in this column.

Questions 15-22 are about **this child's mother or female guardian** . (If she is not living with this child, please tick this box [ ] and leave Questions 15-22 blank).

(15): In what year were you born?________________ 50

(16): Have you ever had your blood pressure measured by a doctor or a nurse?

YES [ ]
NO [ ] 52

(17): If YES, have you ever been told that your blood pressure was high?

YES [ ]
NO [ ] 53

If YES, was this

Only during pregnancy [ ]
Only at other times [ ]
Both [ ] 54

(18): Have you ever taken tablets or other medications for high blood pressure?

YES [ ]
NO [ ] 55

56

If YES, please give the name of the tablets if known______________________

Occupation of Mother or Female Guardian:

(19): Have you ever worked (full-time or part-time)?

YES [ ]
NO [ ] 57

If YES please answer the following questions about your **longest-held** employment.

column.

(a) Your Employer (in longest-held employment)

Please describe clearly what your employer (or you if self-employed) makes or does (made or did)

(For a person in private domestic service write 'Domestic service')

(b) Your Occupation (in longest-held employment)

Please give full and precise details of your occupation (if the job has a special name in the trade or industry please give it):

Please describe the actual work done:

(c) Your Employment Position (in longest-held employment):

Please tick the appropriate box:

- Apprentice or articled trainee [ ]
- Employee not supervising other employees [ ]
- Employee supervising other employees [ ]
- Self-employed not employing others [ ]
- Self-employed employing others [ ]

58

(20): Are you in employment **at present** ?

- Full-time [ ]
- Part-time [ ]
- No [ ]

59

(Please tick correct box/boxes)

If No, are you -a housewife [ ]

-seeking work [ ]

-other [ ]

60

61

write in this column.

(22): Education of female parent or guardian:

At what age did your full-time education (school, college, or university) end?

____ ____ (Age in years) 62

Please give the name of any qualifications obtained since your full-time education ended.

63

Questions 23-26 apply **to your household as a whole**. (All the subjects asked about may be relevant to blood pressure).

Housing:

(23): Are you and your household:-

- -Owner-occupiers (including purchase by mortgage) [ ]
- -Do you rent or lease:-
  - -from a local council [ ]
  - -from a private landlord or company [ ] 64
  - -other (please specify) [ ]

(24): How many rooms does your accommodation contain?______________ 65

Note: Exclude bathrooms, toilets and kitchens less than 6 feet wide.

(25): How many people, including children, live in your household on a regular basis? 67

____

(26): Does your family have a car for normal use? YES [ ] 69

NO [ ]

If YES, please specify how many:

One [ ]
Two [ ]
Three or more [ ]

(This includes cars/vans provided by employers if they are usually available. Vehicles used only for carrying goods should not be included.) 70

write in this column.

Questions 27-36 should be completed on behalf of **the child's father or male guardian** . (If he is not living with this child, please tick here [ ] and leave questions 27-36 blank).

(27): In what year was he born?________________________ 7·

(28): Has he ever had his blood pressure measured by a doctor or a nurse?

YES [ ]
NO [ ] 73

(29): If YES, has he ever been told that his blood pressure is high?

YES [ ] 74
NO [ ]

(30): Has he ever taken tablets or medicines from his doctor for high blood pressure?

YES [ ] 75
NO [ ]

If YES, please give the name of the tablets if known: 76

____

Occupation of Child's Father or Male Guardian:

(31): Please answer the following questions about his **longest-held** employment. (If he has never had a job, please tick this box [ ] and leave the rest of question 31 blank).

(a) His Employer (in longest-held occupation):
Please describe clearly what his employer (or he himself if self-employed) makes or does (made or did):

____

____

column.

(b) His Occupation (in longest-held employment):

Please give full and precise details of his occupation (if the job has a special name in the trade or industry please give it):

[2] 8

____

____

Please describe the actual work done:

____

____

(c) His Employment Position (in longest-held employment):

Please tick the appropriate box:

Apprentice or articled trainee [ ]
Employee not supervising other employees [ ]
Employee supervising other employees [ ]
Self-employed not employing others [ ]
Self-employed employing others [ ]

[ ] 9

(32): Is he in employment **at present** ?

Full time [ ]
Part time [ ]
NO [ ]

[ ] 10

(Tick one box)

If NO, is he -unemployed [ ]
-other [ ]

[ ] 11

If OTHER, please give details

____

[ ] 12

(33) Education of male parent or guardian:

At what age did his full-time education (school, college, or university) end?

___ ___ (Age in years)

[ ] 13

Please give the name(s) of any qualifications acquired since his full-time education ended.

[ ] 14

write in this column.

Eating Habits of Your Child:

Please write down everything your child ate and drank YESTERDAY (that is, the day before you are filling this in), as closely as you can remember it.

Breakfast ______________________________

____

Mid-morning snack: ______________________________

____

Midday meal/Lunch: ______________________________

____

____

Afternoon snack: ______________________________

____

Tea/Dinner: ______________________________

____

Supper: ______________________________

____

Any other meals, snacks not covered above: ______________________________

____

What day of the week was this? ______________________________

THANK YOU VERY MUCH FOR YOUR HELP.

PLEASE CHECK THAT YOU HAVE ATTEMPTED ALL THE QUESTIONS BUT DO NOT WORRY IF

APPENDIX IV

PAPERS AND LETTERS PUBLISHED

Epidemiology

BLOOD PRESSURE IN BRITISH CHILDREN: ASSOCIATIONS WITH ADULT BLOOD PRESSURE AND CARDIOVASCULAR MORTALITY

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Summary Blood pressure was measured in 4186 children aged 5 to 7 years in 9 British towns. 3 towns had high, 3 had intermediate, and 3 had low adult blood pressure levels observed in an earlier study of middle-aged men. Significant differences between the towns were found for the children's mean systolic blood pressure (range 96·7 to 102·4 mm Hg) and diastolic pressure (range 55·9 to 60·3 mm Hg). The pattern of systolic blood pressure differences in children was similar to that observed in the study of middle-aged men ($r = 0·65$). The town mean systolic pressures in children show an association with standardised mortality ratios for cardiovascular disease in adults. The pattern of geographical differences in blood pressure observed in British adult men may have its origins early in life.

INTRODUCTION

THE average rate at which blood pressure rises with age varies widely between different societies,[1,2] and large geographical variations have been found for average blood pressures of adult populations. The determinants of blood pressure in populations are not well understood, but the results of migrant studies suggest that they are predominantly environmental,[3] and the potential importance of sodium and potassium intake has been noted.[4,5]

The age at which differences in population blood pressure first emerge is of interest because the causal factors may be more readily established at that time. Geographical differences in adult blood pressure in British men were found in the British Regional Heart Study,[6,7] in which about 320 middle-aged men were examined in each of 24 towns in different parts of Britain between 1978 and 1980. Striking differences in mean blood pressures of subjects in the different towns were found, with a range of 17·6 mm Hg for systolic pressure and 12·5 mm Hg for diastolic pressure. Our study was set up to establish whether a similar geographical pattern of blood pressure differences was present in children aged 5 to 7 years. This age-group was selected because the rank of blood pressure in the individual is established in infancy—the "tracking" phenomenon[8]—and because previous studies of the effect of migration in children[9] and dietary sodium restriction in infants[10] suggested that environmental factors might influence blood pressure, particularly systolic pressure, at an early age. Systolic pressure was therefore regarded as the more important blood pressure measurement in this study.

SUBJECTS AND METHODS

Sampling Procedures

9 of the 24 towns involved in the British Regional Heart Study were selected for study—3 in which blood pressures in adult men (both systolic and diastolic) were high, 3 in which they were intermediate (medium), and 3 in which they were low (see fig 1). In each town ethical approval was sought, the cooperation of the local education authority secured, and a list of all state schools in the town with children aged between 5·0 and 7·5 years obtained. A random sample of 10 schools stratified by school size, location within the town, and religious denomination was selected in each town. 10 of the 90 invited schools were unable to take part and were replaced by the school that most closely matched. In each school, 2 classes of children were chosen at random to provide 50 to 60 children who were invited to participate. In 2 very large schools which contained substantially more than 10% of the relevant school population in the town, 4 classes (100 to 120 children) were invited. The social representation of the sample obtained was assessed by a pilot study, which showed close agreement between parental social class by occupation in our sample and the social class constitution of the 10% sample for the town in the 1981 census.

Fig 1—Geographical distribution of towns studied.

Towns classified by observed adult male blood pressure as high (H), medium (M), and low (L).

The response rate was 85% (range 79 to 88%) in the different towns. 4186 children, 2101 boys and 2085 girls, with a mean age of 6·24 years, were examined. The mean number of children examined in each town was 465 (range 425 to 498).

Survey Procedures

All measurements were made between May, 1987, and February, 1988. Towns were examined in three sets, each set containing one town with intermediate, one with high, and one with low adult pressure, surveyed in that order (fig 2). Each set was examined in the shortest possible period, usually ten weeks, to minimise changes in climate or measurement technique. Individual towns were surveyed within 2 weeks; individual schools were visited for 1 day (or 2 days for the exceptionally large schools).

All measurements were made by 2 trained nurses. Each observer made half the blood pressure observations in each town (with the exception of Scunthorpe where, because of illness, one observer made all measurements). Working procedures were standardised for all schools and measurements were done in the medical room or similar accommodation. All children were examined in underclothes without shoes, after resting for approximately 5 minutes.

Height was measured to the nearest millimetre with a Holtain electronic stadiometer. Weight was measured to the nearest 0·1 kg with a Soehnle digital electronic weighing scale. Right arm circumference was measured to the last complete millimetre at the midpoint between the acromial process and the olecranon and was used to determine cuff size for blood pressure measurement.

The Dinamap '1846 SX P' automatic oscillometric blood pressure recorder was used to record three blood pressure measurements at 1-minute intervals, with the child seated and the arm supported at chest level. Systolic and diastolic measurements

AGE-STANDARDISED TOWN BLOOD PRESSURES IN CHILDREN 5 TO 7 YEARS OLD

Town	n	Systolic	Diastolic
Carlisle	473	102·4 (8·6)	60·1 (6·0)
Merthyr Tydfil	493	102·3 (8·6)	59·4 (5·95)
Southport	487	102·1 (8·6)	60·3 (6·0)
Scunthorpe	416	101·4 (8·6)	59·6 (6·0)
Ayr	442	101·1 (8·7)	57·8 (6·0)
Maidstone	441	100·6 (8·6)	59·5 (5·9)
Dunfermline	452	100·2 (8·6)	58·9 (6·0)
Exeter	461	99·9 (8·6)	58·5 (5·95)
Guildford	451	96·7 (8·6)	55·9 (5·95)

Values shown as mean (SD); towns ranked by systolic pressure.

by this instrument have been validated by comparison with intra-arterial pressure measurement;[11,12] diastolic pressure measurement corresponds to disappearance of sounds (phase V) with the mercury sphygmomanometer.[13] Cuff size was selected according to the recommendations of Prineas et al[14] based on earlier recommendations of the American Heart Association.[15] Two sizes of cuff were used in the study with cuff bladder dimensions of 15 × 9 cm and 22 × 12 cm: a systematic difference in blood pressure measurement between the two cuff sizes was observed. Adjustments for the effect of cuff size were made from the results of a supplementary study (to be described elsewhere) which provided estimates of differences between the two cuffs, based on within-subject cuff comparisons in 479 subjects who did not take part in the main study. Although cuff-adjusted blood pressure results are used throughout this paper, the effect on the results was very small because the proportion of children measured with each of the two cuffs was similar in all the towns.

Room temperature was recorded to the nearest 0·1°C with an RS digital thermometer and thermocouple with each set of measurements. Hourly external temperature data, from local meteorological stations, were provided by the Meteorological Office.

The Dinamap blood pressure recorder was checked and calibrated daily throughout the study with a reference mercury column. A comparison of blood pressure measurement with a random zero sphygmomanometer[16] was also done in 50 subjects at intervals through the study. No evidence of systematic measurement drift was found.

Statistical Methods

Age-standardised mean town blood pressures in childhood and the significance of between-town differences in these measurements were derived from an analysis of covariance in which blood pressure was regressed on age fitted as a continuous variable and town fitted as a factor with 9 levels. The relation between the mean child blood pressures and the mean adult blood pressures was assessed by regression of the mean age-adjusted blood pressure for children on the mean age-adjusted blood pressure for adults[7] in that town and by calculation of an unweighted correlation coefficient.

Standardised mortality ratios (SMRs) for heart disease between 1979 and 1983 were determined by comparison of the observed number of deaths in adults aged 35 to 64 years from all cardiovascular disease (except rheumatic heart disease) in each town with the number expected, calculated by applying age-sex-specific rates for England, Wales, and Scotland combined to town populations. 10 year age stratification was used.

RESULTS

Data presented here are based on the 3 blood pressure measurements combined and are restricted to 4116 children in whom complete triplicate blood pressure measurements were recorded. No important differences in blood pressure between the sexes were found, therefore the results are presented for both sexes combined. No systematic inter-observer variation occurred.

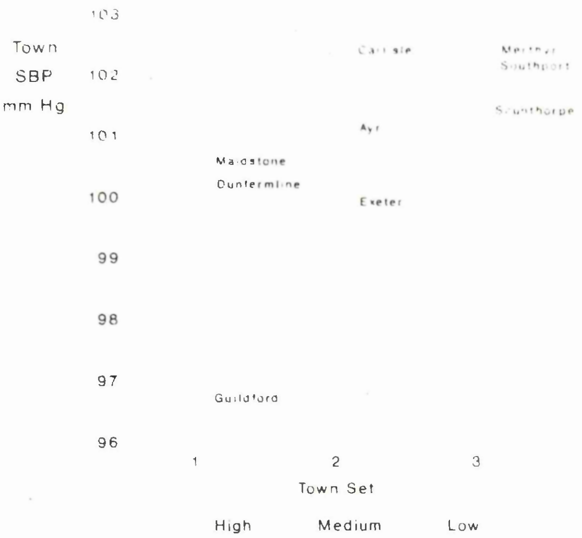

Fig 2—Age-standardised mean systolic blood pressure (SBP) for each set of towns.

Towns classified as for fig 1 in each set.

Mean Blood Pressures

The table shows age-standardised town mean blood pressures: town mean systolic pressures ranged from 102·4 mm Hg in Carlisle to 96·7 mm Hg in Guildford; town mean diastolic pressures ranged from 60·3 mm Hg in Southport to 55·9 mm Hg in Guildford. One-way analysis of variance shows that between-town differences are very unlikely to be explained by chance ($p < 0{\cdot}0001$ for both systolic and diastolic pressures). If the most extreme value (Guildford) is excluded from the analysis, the differences are still statistically significant. The differences observed cannot be explained by differences in height, weight, pulse rate, or temperature (room or external).

Mean Blood Pressures within Town Sets

Fig 2 shows the age-standardised systolic blood pressures for the towns in each of the 3 sets. In all 3 sets, the systolic pressure of the town with high adult pressure is greater than that in which adult pressure was low, with the medium town occupying an intermediate position in 2 sets. A similar, though less striking, pattern is seen for diastolic pressure (data not presented). When the overall blood pressure differences between the 3 high and 3 low towns are examined the differences are less striking, because the systolic pressure in the high town of the first set is below that of the low town in the third set. With the sets combined the overall mean difference in systolic blood pressure between children in the high towns and those in the low towns was 2·5 mm Hg (95% confidence intervals [CI] 1·8, 3·2); that for diastolic pressure was 1·6 mm Hg (95% CI 1·1, 2·1).

Blood Pressures in Children and Adults

The overall relation between age-standardised mean town systolic pressures in childhood and those in middle age is shown in fig 3. There is an apparent increase in mean town pressure in childhood with an increased mean town pressure in adulthood, although the relation is heavily dependent on the lowest town, Guildford. The regression coefficient is

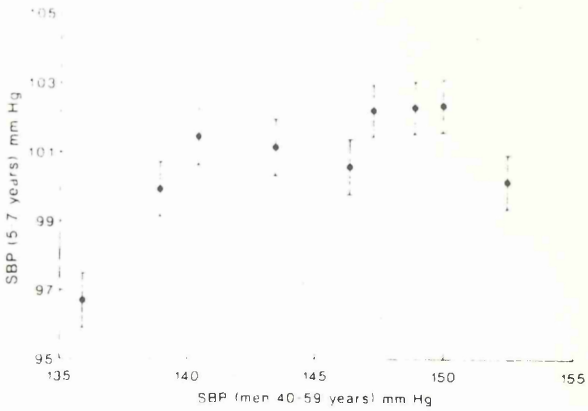

Fig 3—Relation between adult and child mean systolic blood pressures.

Means and 95% CI shown for children.

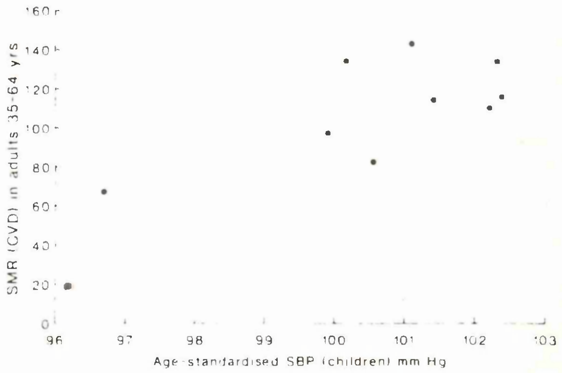

Fig 4—Relation between child mean systolic blood pressure and town SMR for cardiovascular disease.

0·21 ($r = 0{\cdot}65$, $p = 0{\cdot}058$). If a linear relation does exist, a difference of approximately 0·2 mm Hg in town mean systolic pressure in childhood occurs for each 1 mm Hg difference in town mean adult systolic pressure. A similar, although weaker, pattern is found for diastolic pressure ($r = 0{\cdot}49$).

Childhood Blood Pressure and Cardiovascular Mortality

The scatter diagram (fig 4) describes the relation between mean town systolic pressure in childhood and the SMR for all cardiovascular disease (excluding rheumatic heart disease) in men and women aged 35 to 64 years. There is a positive association between childhood mean systolic pressure and cardiovascular mortality ($r = 0{\cdot}66$), although again this relation is very dependent on the lowest town, Guildford.

DISCUSSION

The findings indicate that important geographical differences in the average blood pressures of children are present at the age of 5 to 7 years, and that the pattern resembles that previously observed in middle-aged men.[6] The validity of these observations depends on the contribution of biases, particularly of sampling and measurement. Standardised sampling procedures with uniformly high response rates should have reduced the possibility of sampling bias within the state schools examined. Although the proportion of children who attended independent schools differed between towns, this variation cannot explain the results: the most recent estimates of the proportion of children at independent schools was highest (18·5%) in Guildford (< 6% in all other towns),[17] which would be expected to reduce the proportion of children with parents in non-manual occupations in the Guildford sample. As these excluded children might be expected to have lower blood pressures than average,[18] any bias in the Guildford sample would have tended to raise the estimates of mean blood pressure in that town. Important measurement bias between the towns is unlikely because of the standardised procedures and regular instrument checks. Although the observers were aware of the general hypothesis under test, the use of a fully automated blood pressure recorder with a data printout should have limited the potential for observer bias. The differences in blood pressure between towns could not be explained by differences in temperature (room or external), weight, height, or pulse rate.

The association between adult and childhood pressures is unlikely to be explained by systematic error because procedures for sampling and measurement were quite different in the two studies. The association is strongly influenced by the lowest town coordinate, Guildford (fig 3): we are confident that the Guildford estimate in children, which has narrow confidence intervals and is similar for both sexes, is valid. The adult estimate for Guildford has been supported by the results of a further study in that town (N. Bruce, personal communication). The dependence of our findings on the Guildford results emphasises that the consistency of the association between systolic blood pressure patterns in adults and children is not as great as had been anticipated at the outset of this study. Population blood pressure levels in adults may be affected by factors which are of less importance in childhood (particularly alcohol consumption[19,20]), or which do not differ to the same extent between children as between adults (particularly body build[6]).

Mean town blood pressure levels in adults have been shown to be associated with cardiovascular mortality.[6] Fig 4 shows an association between childhood blood pressure and adult cardiovascular mortality, although again the observation is heavily dependent on Guildford. A stronger association would have been surprising because of the very indirect relation between blood pressure and outcome, and the importance of other factors (eg, blood cholesterol level, smoking) which influence adult cardiovascular mortality. Childhood blood pressure and adult stroke mortality showed a similar relation (data not shown).

The blood pressure differences and associations described in this study are too small to be clinically important in childhood. However, the establishment of population differences in blood pressure from an early age could be of aetiological importance. It is not known whether systematic differences in the blood pressures of populations are present at birth, but a randomised controlled trial by Hofman and colleagues[10] indicated that sodium intake might influence population blood pressure levels as early as 6 months of age. Previous evidence on the relation between population blood pressures in children and adults is inconclusive. Many investigators have concluded that population blood pressure levels in childhood are similar, irrespective of adult levels.[21] However, the results of at least one standardised international study[22] have suggested that adult differences in blood pressure may be manifest before 20 years of age. Furthermore, in the Tokelau Island migrant study,[9,23] children as young as 2 years of age showed a striking rise in blood pressure on migration.

Blood pressure patterns may therefore be established from an early age, which would be consistent with reports that emphasise the importance of childhood in the origins of cardiovascular disease.[24] If population differences in blood pressure identified in middle age are indeed present in early childhood, the determinants of population blood pressures may act from an early age. Study of the determinants of population blood pressures in the first years of life may enhance our understanding of the causes, and hence the means of primary prevention, of high blood pressure in adults.

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Blood pressure measurement in children: the importance of cuff bladder size

Peter H. Whincup, Derek G. Cook and A. Gerald Shaper

The effect of cuff bladder size on blood pressure measurement has been investigated in 838 children aged 5–7 years, using a Dinamap oscillometric automated blood pressure recorder and a Hawksley random zero sphygmomanometer. With both instruments the smallest (infant) cuffs recorded higher pressures than the child cuffs (mean systolic differences: Dinamap 4.6 mmHg, Hawksley 6.6 mmHg), which in turn recorded higher pressures than the largest (adult) cuffs (mean systolic differences: Dinamap 5.5 mmHg, Hawksley 8.1 mmHg). These differences in measurement between cuffs are sufficiently large as to be of concern in both clinical and epidemiological studies. Since they are little affected by arm circumference, their occurrence cannot be prevented simply by following current guidelines for selection of cuff size. Methods of dealing with these problems are discussed.

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Keywords: Blood pressure determination in children.

Introduction

The increasing importance attributed in recent years to blood pressure in childhood has emphasized the need for accuracy and comparability in the measurement of blood pressure in children. The importance of using a cuff with an appropriate bladder size is widely recognized and has been discussed in several recent publications which make recommendations about blood pressure measurement in children [1–5]. However, considerable disagreement is apparent in several areas. Opinion is divided as to whether arm circumference is a sufficient basis for determining the appropriate cuff size [1,3] or whether upper arm length also needs to be taken into account [2,4]. There is conflicting advice about the consequences of using a large cuff, with one authority recommending the use of the largest cuff which will fit the child's arm comfortably [2], while others emphasize the tendency of large cuffs to underestimate blood pressure [1,4]. The paucity of reports documenting the effects of different cuff sizes on blood pressure measurement and the relation of cuff size to arm size in children has undoubtedly contributed to the existing disagreement.

This study has compared indirect blood pressure measurements made using three different sizes of cuff (infant, child and adult) with two instruments, the Dinamap oscillometric automated blood pressure recorder (Critikon Inc., Tampa, Florida, USA) and the Hawksley random zero sphygmomanometer (Hawksley and Sons Ltd, Lancing, UK). The specific purpose of the study was to quantify differences in blood pressure measurement between the child and adult cuffs with the Dinamap recorder. However, the results allow more general conclusions about the relationship between cuff bladder size and blood pressure measurement which have important implications for the conduct of future blood pressure studies in children.

Subjects and methods

Selection and recruitment of subjects

The study was carried out in a single British town (Gloucester) as an adjunct to a nationwide investigation of blood pressure in childhood [6]. Ethical approval was sought and local education authority co-operation obtained. Schoolchildren aged 5–7 years (n = 1012) attending nine local primary schools were invited to participate. A total of 884 subjects (87%) were examined.

Measurements

Subjects were examined in school medical rooms or similar accommodation, after resting for approximately 5 min. All blood pressure measurements were made on the right arm with the child seated. Arm length (right side) was recorded to the last complete millimetre between the acromial process and the olecranon on the right side, with the

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elbow flexed at 90°. Arm circumference was measured at the midpoint of the right arm to the last complete millimetre.

Blood pressure

Instruments

Two blood pressure instruments were used, a Dinamap 1846 SXP oscillometric blood pressure recorder [7,8] and a Hawksley random zero sphygmomanometer [9] (fitted with a 20 mmHg cam to reduce discomfort). The cuff sizes used in each case were those which were commercially available. For the Dinamap, Velcro® cuffs with bladder sizes 22 cm × 12 cm (adult), 15 cm × 9 cm (child) and 12 cm × 7 cm (infant) were used; for the Hawksley, V-Lok cuffs (Hawksley and Sons Ltd) with bladder sizes 23 cm × 12 cm (adult), 18 cm × 9 cm (child) and 12 cm × 6 cm (infant). All cuff bladder sizes were verified before use. Children were called for examination in age order and allocated to examination at the first available instrument station; this procedure resulted in a slightly larger number of children being examined with the Dinamap instrument. The age and sex distributions of the groups measured with each instrument were very similar.

Observers

Two observers carried out all measurements; each made approximately half the blood pressure recordings with each instrument. For measurements with the Hawksley instrument, standard training procedures in auscultatory blood pressure measurement were employed [10] and diastolic phase IV readings used because of their greater reliability in children [1].

Cuff selection and order of measurement

Dinamap oscillometric blood pressure recorder

One measurement of blood pressure was recorded with each of three cuffs (adult, child and infant) in all subjects (arm circumference range 14–24 cm). Measurements were made at 1 min intervals. The first two readings were made with the child and adult cuffs in random order; the third reading was made with the infant cuff throughout. This ordering was used because it was critical for our nationwide blood pressure study [6] to make accurate estimates of child–adult cuff differences. Since blood pressure tends to fall with successive readings, measurements made with the infant cuff should be lower on average because they were made last. We have made no allowance for this bias in the data reported here. However, because measurements made with the infant cuff were actually on average higher than those made with the other cuffs, the results represent an underestimate of the differences in blood pressure measurement between the infant cuff and other cuffs. The extent of underestimation is likely to be small and can be inferred from the magnitude of the fall between successive blood pressure readings in our nationwide study, which was 1.96 mmHg for systolic pressure [95% confidence interval (CI) 1.80–2.12] and 1.51 mmHg for diastolic pressure (95% CI 1.37–1.65).

Random zero sphygmomanometer

One measurement of blood pressure was recorded with each of two cuffs at 1 min intervals. The child and infant cuffs were used in children with arm circumference 14–18.9 cm and the adult and child cuffs in children with arm circumference 19–24 cm. The order in which the pairs of cuffs were applied was random. Only two blood pressure measurements were made with the random zero sphygmomanometer because children tolerated further readings poorly.

Statistical methods

For the analyses presented in Figs 1 and 2, subjects were ranked according to arm circumference and then grouped. For the Dinamap recordings, 10 equal-sized groups were used. For the Hawksley measurements, subjects with arm circumference < 19 cm (n = 336) were divided into eight groups and those with arm circumference ≥ 19 cm (n = 54) were divided into two groups. Mean blood pressure values were plotted against mean arm circumference values for each group. The corresponding regression lines were determined using data on individual subjects, not the grouped data. The analyses of differences between cuffs, listed in Tables 1 and 2, were based on the individual differences in blood pressure measurements using the two cuffs. In Table 2, these differences are regressed on arm circumference. Adjustment for order effects (where appropriate) was made by fitting order as a dichotomous variable in the regression analyses.

Results

The results presented here are restricted to the 838 subjects in whom it was possible to make complete blood pressure measurements, 448 with the Dinamap and 390 with the Hawksley instrument. Age, sex and observer had no consistent effect on the differences in blood pressure measurement between cuffs and have therefore been ignored in these analyses. The height, weight and arm length of the subjects had no effect on differences in blood pressure measurement between cuffs, once arm circumference had been taken into account, and have also been ignored in our analyses. An order effect was observed with the Dinamap instrument (with a fall of 1 mmHg systolic and 2 mmHg diastolic blood pressure between first and second readings) and has been taken into account in the results presented. No order effect was observed with the Hawksley instrument.

Table 1. Average differences in blood pressure measurement between cuffs

	Dinamap			Hawksley		
	n	Mean	s.e.	n	Mean	s.e.
Child – adult						
SBP	448	4.6	0.3	54	6.6	1.0
DBP	448	1.8	0.3	54	2.4	0.8
Infant – child						
SBP	448	5.5	0.3	336	8.1	0.4
DBP	448	2.0	0.3	336	6.5	0.4

Means and standard errors (s.e.), measured in mmHg, are presented for each cuff pair. SBP, systolic blood pressure; DBP, diastolic blood pressure.

Cuff size and blood pressure

The relationship between cuff size and systolic blood pressure over the measured ranges of arm circumference are

Table 2. Differences in blood pressure measurement between cuffs: the effect of arm circumference

	Dinamap			Hawksley		
	b	s.e.	*P*	b	s.e.	*P*
Child – adult						
SBP	0.32	0.21	0.13	2.33	0.79	< 0.01
DBP	0.36	0.18	0.05	0.76	0.71	0.2
Infant – child						
SBP	0.37	0.22	0.09	1.00	0.39	0.01
DBP	−0.11	0.19	0.57	−0.10	0.30	0.74

Regression coefficients (b), measured in mmHg/cm, (representing change in blood pressure difference between cuffs per cm change in arm circumference) are presented with their standard errors (s.e.) and *P* values for each regression slope. SBP, systolic blood pressure; DBP, diastolic blood pressure.

shown in Fig. 1 (Dinamap) and Fig. 2 (Hawksley). The pattern of results appears broadly similar for both instruments. In both cases, the smallest cuff sizes are associated with the highest blood pressure measurements and the largest cuff sizes with the lowest measurements.

The most precise estimates of differences in blood pressure measurement between cuffs are those based on comparisons of cuffs in individual subjects (i.e. within-subject comparisons). Estimates of differences in blood pressure measurement between cuffs, based on within-subject comparisons, are presented for both the Dinamap and Hawksley instruments in Table 1. With both instruments, average differences in blood pressure measurements between cuffs were greater for systolic than for diastolic pressures. Differences between cuffs in both systolic and diastolic blood pressure measurement appeared to be greater for the Hawksley instrument than for the Dinamap throughout, although this discrepancy between the instruments was only statistically significant for the infant–child cuff comparisons ($P < 0.001$).

Are average differences in blood pressure measurement between cuffs related to arm circumference?

The relationship between arm circumference and differences in blood pressure measurement between cuffs can be assessed visually from the differences between the slopes for each cuff in Figs 1 and 2, and more accurately from the regression coefficients (based on within-subject comparisons) which are presented in Table 2. It can be seen in Fig. 1 that with the Dinamap instrument, differences in systolic pressure measurement between both infant and child cuffs, and child and adult cuffs appear to increase slightly with arm circumference. However, the regression coefficients (Table 2) which represent change in between-cuff differences in systolic blood pressure measurement (measured in mmHg) for each unit change in arm circumference (measured in cm) are small and do not reach conventional levels of statistical significance for the Dinamap. The regression coefficients for diastolic pressure (also Table 2) are inconsistent, one being positive and the other negative, and do not suggest any systematic influence of arm circumference on between-cuff differences in diastolic blood pressure measurement.

The results for the Hawksley instrument are more difficult to interpret. The findings presented in Fig. 2 suggest that arm circumference has little or no effect on the magnitude of the differences in blood pressure measurement between cuffs. However, the regression coefficients based on within-subject comparisons (Table 2) suggest that between-cuff differences in blood pressure measurement do increase markedly with arm circumference. The reason for this discrepancy is that the slope relating arm circumference and blood pressure with the child cuff is considerably steeper when arm circumference exceeds 19 cm. This can be seen from the data points in Fig. 2; a line representing a 'best fit' for the first eight points for the child cuff (arm circumference < 19 cm) is clearly shallower than that for the upper two points (arm circumfer-

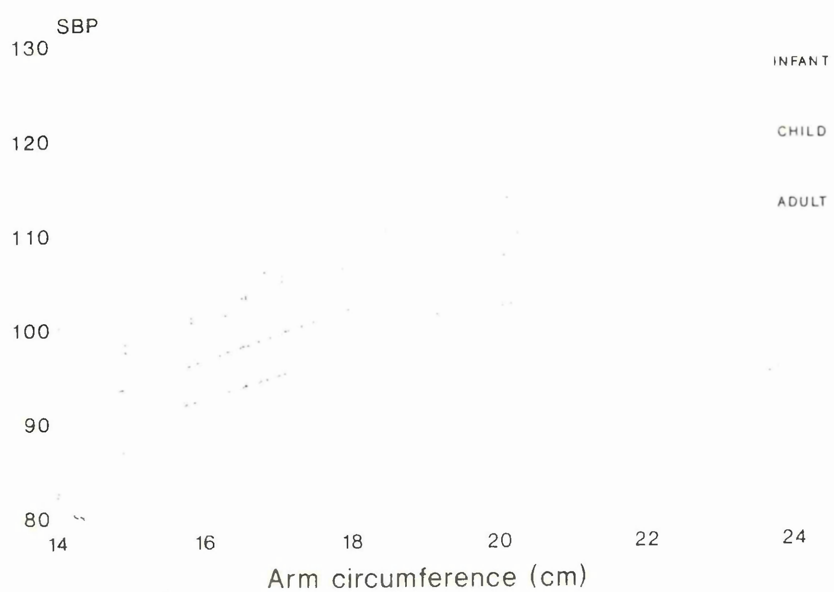

Fig. 1. Dinamap oscillometric blood pressure recorder. Mean systolic blood pressures (SBP) measured with infant, child and adult cuffs in relation to arm circumference. Data points represent 10 groups of approximately 45 subjects each. Regression lines are based on data for all individual subjects. +, infant cuff; □, child cuff; △, adult cuff.

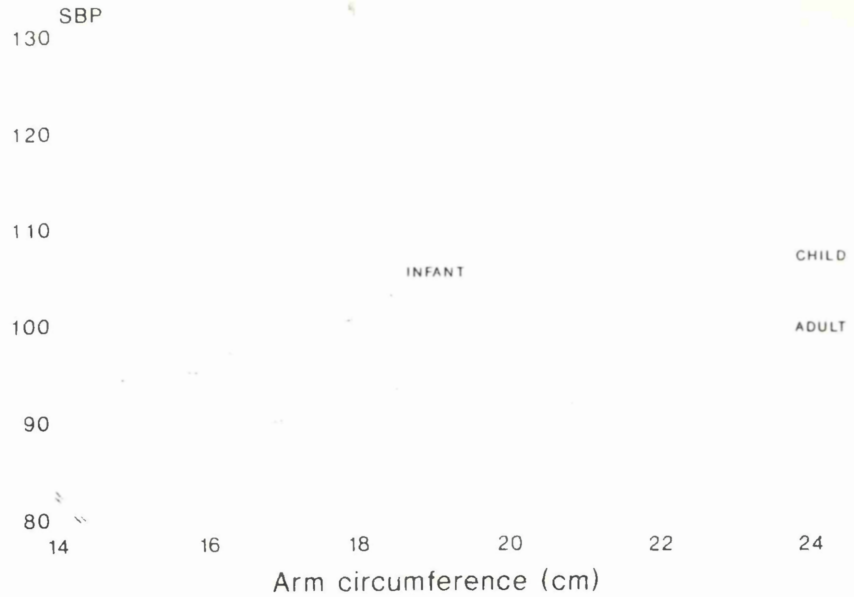

Fig. 2. Hawksley random zero sphygmomanometer. Mean systolic blood pressures (SBP) measured with infant, child and adult cuffs in relation to arm circumference. Data points represent (at arm circumferences < 19 cm) eight groups of approximately 42 subjects each and (at arm circumferences ≥ 19 cm) two groups of 27 subjects each. Regression lines are based on data for all individual subjects. +, infant cuff; □, child cuff; △, adult cuff.

ence ≥ 19 cm). This finding makes interpretation of the within-subject comparisons for the Hawksley instrument extremely difficult. Overall, the data suggest that the differences in blood pressure measurement between cuffs observed with the Hawksley instrument are also largely independent of arm circumference.

Discussion

Effects of small and large cuffs

It has long been recognized that cuff bladder size influences blood pressure measurement [11]. The results of the present study emphasize the importance of cuff bladder size in the measurement of blood pressure in children. The average differences in blood pressure recorded with cuffs of different bladder sizes are similar in direction and magnitude to those observed in studies of neonates [12], infants [13] and older children [14–16]. These systematic differences in measurement may be sufficiently large as to interfere with blood pressure measurement in both clinical and research settings. However, the relative importance of this effect in the clinical context is reduced by the presence of two other important sources of variation between readings, within-subject variation and between-observer variation [17]. In the research context, where repeated measurements and observer standardization are used to reduce these sources of error [17], between-cuff differences in blood pressure measurement may be sufficiently great as to interfere with the detection of systematic differences or changes in blood pressure between groups. They may also confound analyses relating blood pressure to factors associated with arm circumference, particularly body build.

Why the differences in blood pressure measurement between cuffs are greater with the Hawksley instrument than with the Dinamap remains uncertain. Cuff bladder width is not a factor, as it is identical for the two instruments in the case of the child and adult cuffs and very similar in the case of the infant cuffs.

Arm circumference and cuff effects

Although the blood pressure measurement differences between cuffs of various sizes appear in most cases to increase slightly with arm circumference, the effects are small over the range of arm circumferences studied and, at least for the Dinamap, did not consistently achieve conventional levels of statistical significance ($P = 0.05$). In the case of the Dinamap child cuff (for which the most information is available), a change in arm circumference of 10.2 cm (cuff width : arm circumference ratio 37–64%) is associated with a change of < 4 mmHg in the systolic blood pressure measurement differences betweeen this cuff and the adjacent infant and adult cuff sizes. The findings suggest that the blood pressure measurement differences between any particular cuff and smaller and larger cuff sizes remain fairly consistent over a wide range of cuff width : arm circumference ratios. They also imply that the size of the cuff bladder is at least as important as its relationship to the dimensions of the arm in determining the blood pressure recorded. These observations are consistent with the findings of Long and colleagues in children [14] and those of Simpson and colleagues in adults [18].

Implications for current guidelines on cuff bladder size

The observation that the effects of cuff bladder size on blood pressure measurement persist across a wide range of arm circumferences raises difficulties for recent recommendations on cuff bladder size for blood pressure measurement [1–4]. These emphasize the need to use cuff sizes selected according to arm circumference [1,3] or a combination of arm circumference and arm length [2,4]. Adherence to any of these recommendations will result in a series of 'steps' in blood pressure measurement at the points where changes between cuff bladder sizes are made. As an example, the effects of following the recommendations of the American Heart Association (changing to a larger cuff when the cuff width : arm circumference ratio falls below 40%) are presented in Fig. 3 using our data obtained with the Dinamap recorder. The 'steps' which occur with the change to successively larger cuffs can be clearly seen. This problem (which also occurs with the Hawksley instrument) will arise whichever set of recommendations is followed and irrespective of whether arm circumference, arm length or both of these are used as a basis for the selection of cuff size. This is a problem which receives little attention in current recommendations for blood pressure measurement in children; its further consideration is warranted in future guidelines.

Implications for design of studies measuring blood pressure in children

We have drawn attention to the possibility of bias in blood pressure measurement being introduced by the use of different cuff bladder sizes. In order to reduce or eliminate this bias in a study, the use of a single cuff bladder size throughout is desirable. Because between-cuff differences appear reasonably similar over a wide range of cuff width : arm circumference ratios, the use of a single cuff may often be feasible. Where this is not the case, adjustment for the effect of cuff bladder size can be carried out (see below). In either situation, a further step in many analyses will be to standardize measured blood pressures for the effects of arm circumference. However, these measures, aimed at minimizing the effect of between-cuff bias, conflict with the advice given in the American Heart Association guidelines [1] and the studies on which they are based [19,20] which suggest that a cuff width : arm circumference ratio of 40% should always be used to obtain auscultatory measurements comparable with those obtained by direct intra-arterial recordings. These conflicting demands need to be taken into account when the protocol for choice of cuff size is selected. In particular, a decision is required as to whether the outcome of the study will be seriously affected by between-cuff bias and whether the comparability of the measurements with direct intra-arterial pressure recordings is of great importance.

In comparative studies, between-cuff biases are an important potential source of error which must be avoided. The use of a single cuff size is therefore recommended in this situation. Where this is not possible, correction for the effect of different cuff bladder sizes should be carried out in the analysis. This option requires careful documentation of the cuff sizes used for all subjects in the study. The simplest form of correction available is to adjust all measurements to a single cuff size. An adjustment factor for cuff size could be derived internally from the arm circumference–blood pressure relationship in subjects measured with different cuff sizes, a procedure which requires that a sufficient number of subjects be measured with each cuff. Alternatively, an external adjustment could be made using the results of within-subject comparisons of various cuff sizes carried out in a separate population. A comparison of the data from our previous study of blood pressure in 5–7-year-olds [6] with that from the present study suggests that the two methods produce similar results. Whether a single cuff is used or whether results are standardized to the measurements of a single cuff, it would seem logical to use the cuff size which corresponds most closely with the American Heart Association recommendation (cuff width : arm circumference ratio = 40%) for the mean arm circumference of the study population.

For those studies aimed primarily at comparability with direct intra-arterial pressure measurement, it will be more appropriate to ensure that a cuff width : arm circumference ratio as close to 40% as possible is used throughout the study. This may involve the use of several cuffs

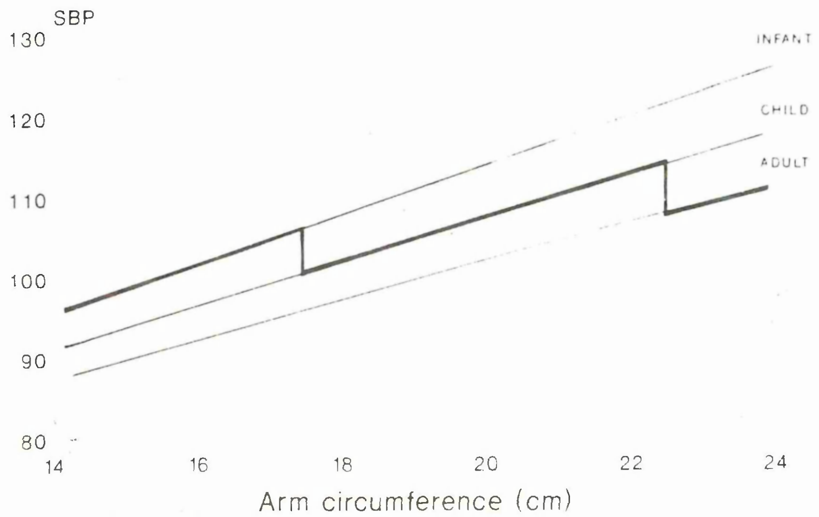

Fig. 3. Dinamap oscillometric blood pressure recorder. The effect on blood pressure measurement of using the guidelines of the American Heart Association (i.e. the change to a larger cuff is made when the cuff width : arm circumference ratio falls below 40%). Regression lines are as in Fig. 1. SBP, systolic blood pressure.

with changes between them as necessary. In order to maintain comparability with direct intra-arterial measurement and at the same time compensate for between-cuff bias, more complex adjustments would be needed. However, the validity of any such adjustment would depend critically upon the cuff width : arm circumference ratio considered optimal for comparability with direct intra-arterial measurement. There is evidence to suggest that this optimal ratio is probably not constant for all instruments and may well be higher than 40% for instruments using ultrasound [12,21] and oscillometric [22] methods.

Conclusions

The choice of an appropriate cuff bladder size is important for the accurate measurement of blood pressure in children, particularly in epidemiological studies. If more than one cuff size is used, systematic 'steps' in blood pressure occur between measurements made using cuffs with different bladder sizes. This problem may be overcome either by the use of a single cuff throughout or by using several cuffs and standardizing results to a single cuff size.

Standardization can be carried out using adjustments derived from the study population blood pressure data, provided that an adequate number of subjects have been examined with each cuff size. Alternatively, a separate study of within-subject comparisons of different cuff sizes can be carried out. While adjustments can provide effective standardization to a single cuff size, they do not necessary ensure that measurements are comparable with intra-arterial pressure. Adjustments that could take account of both cuff size and intra-arterial pressure are beyond the scope of present knowledge, particularly with oscillometric instruments.

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PAPERS

Early influences on blood pressure: a study of children aged 5-7 years

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Abstract

Objective—To examine factors that influence blood pressure in children.

Design—Cross sectional study of children aged 5·0-7·0 years who had blood pressure measurements and for whom parental questionnaires were completed.

Setting—School based survey.

Subjects—3591 Children aged 5·0-7·5 years selected by stratified random sampling of primary schools in nine British towns (response rate 72%); 3591 were examined and their parental questionnaires were completed. Data were complete for birth rank in 3559, maternal age in 3542, maternal history of hypertension in 3524, and paternal history in 2633.

Results—Birth weight was inversely related to mean systolic blood pressure but only when standardised for current weight (weight standardised regression coefficient −1·83 mm Hg/kg (95% confidence interval −1·31 to −2·35). Mean diastolic pressure was similarly related to birth weight. Maternal age, birth rank, and a parental history of hypertension were all related to blood pressure. After standardisation for current weight a 10 year increase in maternal age was associated with a 1·0 mm Hg (0·4 to 1·6) rise in systolic pressure; first born children had systolic blood pressure on average 2·53 mm Hg (0·81 to 4·25) higher than those whose birth rank was ≥4; and a maternal history of hypertension was associated with a systolic pressure on average 0·96 mm Hg (0·41 to 1·51) higher than in those with no such history. The effects described were largely independent of one another and of age and social class. The relation for birth rank was, however, closely related to that for family size.

Conclusions—Influences acting in early life may be important determinants of blood pressure in the first decade. The relation between birth weight and blood pressure may reflect the rate of weight gain in infancy. The reasons for the relation with birth rank and maternal age are unknown; if confirmed they imply that delayed motherhood and smaller family size may be associated with higher blood pressure in offspring.

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Introduction

A growing body of evidence suggests that influences acting in the first years of life may influence blood pressure in adulthood. This includes observations that blood pressure rank in individual subjects is established at an early age[1,2] and that familial influences on blood pressure are apparent in the first decade.[3] Some studies have suggested that differences in blood pressure among populations may be established at an early age[4,5] and that environmental factors (including diet) may act in the same way in infancy as in adulthood.[6,7] Barker and Osmond reported a relation between infant mortality and adult mortality from stroke, which they suggested may be mediated by differences in blood pressure.[8] For these reasons there has been a considerable interest in factors that influence blood pressure early in life; many studies, however, have been handicapped by limitations in measuring blood pressure[9,10] or have focused on children whose mothers were hypertensive in pregnancy.[11] We have measured the blood pressures of 3591 children aged 5-7 years from nine British towns with particular attention to standardising measurements.[5] We report the relation between blood pressure and birth weight, infant feeding, maternal age, birth rank, and a parental history of hypertension.

Subjects and methods

Full details of the nine towns study of blood pressure in children have been described.[5] The study took place in nine British towns selected to give a wide range of mean blood pressures in adults living in towns.[12] Within each town a sample of 10 primary schools stratified by size, location within the town, and religious denomination gave a sample of children that was socially representative of each.

All blood pressure measurements and over 96% of other measurements were carried out by two research nurses, who had been trained in all measurement procedures and whose procedures had been standardised.

Blood pressure was measured in triplicate at one minute intervals with a Dinamap 1846 SX P automatic oscillometric blood pressure recorder, with the child seated and the arm supported at chest level. The size of the cuff was chosen according to the circumference of the arm (measured at the midpoint of the right arm) following recommendations based on those of the American Heart Association.[13] Two sizes of cuff (bladder dimensions 15×9 cm (child cuff) and 22×12 cm (adult cuff) were used. A systematic difference in blood pressure measurement between the two cuff sizes was observed. Accordingly, all measurements were standardised to the child cuff with correction factors derived from a study of 497 children not included in this study population.[14]

Current weight was measured to the nearest 0·1 kg with a Soehnle digital electronic weighing scale.

A self administered questionnaire was sent to the parents of all participating children to give information on:

Birth weight—Mothers were asked to record the child's birth weight as accurately as possible. The reliability of maternal recall after a five to seven year interval has previously been shown.[15]

Birth rank—The number of living siblings older than the child in question aged ≤16 years was used to give a measure of birth rank; first born children were and so on.

Younger siblings—The number of living siblings younger than the child in question.

Maternal age—The age of the mother when the child was born.

Feeding in infancy—Mothers were asked to specify the method of feeding in the first three months of the child's life: breast feeding, bottle feeding, or both. The duration of breast feeding in months (when applicable) was also recorded.

Maternal history of high blood pressure—Mothers were asked whether they had ever had their blood pressure measured and, if so, whether it had been high at any time. Mothers who answered yes were asked to specify whether this had been in pregnancy, at other times, or both.

Paternal history of high blood pressure—Fathers were asked whether they had ever had their blood pressure measured and, if so, whether it had been high at any time.

Social class—Both parents were asked for their longest held occupation. This was classified according to the registrar general's six social classes with the 1980 manual of the Office of Population Censuses and Surveys. The analyses presented relate to the occupation of the head of the household (male in 89%) as defined in the classification of social class for children by the Office of Population Censuses and Surveys.[7]

Statistical analysis

Weight, birth weight, and maternal age were treated as continuous variables in the analysis. All standardisation procedures were carried out by linear regression techniques. When appropriate data were standardised for weight, which in the study population also provided standardisation for age and body build. A family history of high blood pressure was treated as a 0/1 variable and birth rank as a class variable. Standardisation for differences in blood pressure among towns described earlier had no effect on the results and was therefore not used.

Results

Results are presented here for 3591 children (72%) who attended for examination and for whom parental questionnaires were completed. Analyses of birth rank were restricted to 3559 children for whom data were complete and those of maternal age were restricted to 3542 subjects for whom the information had been given. Analyses including parental history of high blood pressure were restricted to those children whose parents reported having had their blood pressure

TABLE I—*Mean systolic blood pressure (mm Hg) according to birth weight and current weight as fifths of their distributions in boys and girls*

	Current weight (kg)					
	Boys (n=1789)					
Birth weight (g)	13·1-18·8	18·9-20·4	20·5-21·7	21·8-23·7	23·8-47·8	Mean (SD)
90-2999	96·5	100·6	100·8	103·1	108·6	100·2 (9·0)
00-3289	97·3	99·9	100·4	103·6	106·5	101·0 (8·6)
290-3529	94·8	98·9	100·5	102·6	106·8	101·1 (9·2)
30-3799	96·0	99·7	100·3	102·3	104·3	101·1 (8·5)
00-5469	96·4	98·0	99·7	100·8	104·4	101·0 (8·0)
Mean (SD)	96·4 (8·3)	99·6 (7·6)	100·2 (7·7)	102·3 (8·2)	105·4 (8·7)	
	Girls (n=1802)					
	13·3-18·1	18·2-20·0	20·1-21·4	21·5-23·6	23·7-47·0	Mean (SD)
40-2819	97·7	99·7	102·6	105·3	105·5	101·1 (9·4)
20-3169	97·7	100·1	100·8	102·0	107·8	101·0 (9·2)
70-3389	94·5	97·7	100·6	103·2	103·7	100·0 (8·8)
90-3659	96·6	99·0	99·7	102·4	105·8	101·0 (8·0)
90-5299	95·6	97·9	98·9	99·5	104·5	100·4 (8·9)
Mean (SD)	96·8 (9·0)	98·9 (8·2)	100·4 (7·6)	102·1 (8·4)	105·2 (8·8)	

2633 for paternal history).

Birth weight and current weight

Univariate analysis showed no evidence of a relation between birth weight and systolic or diastolic blood pressure in either sex (systolic pressure r=0·003 in boys, r=0·035 in girls). Adjustment for age made no difference to this finding. Current weight, however, was positively associated with birth weight (r=0·27) as well as with systolic blood pressure (r=0·35) and diastolic pressure (r=0·21). The relation between birth weight and blood pressure was therefore examined taking current weight into account. Table I shows the mean systolic blood pressures at different birth weight intervals within each fifth of the distribution of current weight in boys and girls separately. In both sexes birth weight and blood pressure were inversely related within each fifth of the current weight. The overall magnitude of the effect seemed to be similar in boys and girls, with weight standardised regression coefficients (representing change in blood pressure/kg change in birth weight) of −1·58 mm Hg/kg in boys (95% confidence interval −2·33 to −0·83) and −2·03 mm Hg/kg in girls (−2·76 to −1·30). A similar pattern of associations was observed for diastolic blood pressure (not shown). The regression slopes relating birth weight and systolic blood pressure within each fifth of current weight are presented in the figure. In boys the relation between birth weight and mean systolic blood pressure was apparently stronger in those with higher current weights; this was confirmed by a formal test for interaction (p=0·002). No such difference, however, was apparent in girls.

Maternal age

Table II shows the univariate relation between maternal age and mean systolic blood pressure in boys and girls combined. With increasing maternal age both

TABLE II—*Relation between maternal age and mean (standard error) blood pressure (mm Hg) in boys and girls*

Maternal age (years)	No of children	Systolic blood pressure	Diastolic blood pressure
15·0-22·4	787	99·8 (0·3)	58·2 (0·2)
22·5-25·4	720	100·7 (0·3)	58·9 (0·2)
25·5-27·4	567	100·5 (0·4)	58·9 (0·2)
27·5-30·4	679	101·1 (0·3)	59·1 (0·2)
≥30·5	789	101·8 (0·3)	59·3 (0·2)

the mean systolic and the mean diastolic pressure increased. The regression coefficients for blood pressure associated with maternal age controlling for current weight were 0·10 mm Hg/year for systolic pressure (p=0·0002) and 0·05 mm Hg/year for diastolic pressure (p=0·005), implying an increase of 1·0 mm Hg in systolic pressure and 0·5 mm Hg in diastolic pressure for each 10 year increase in maternal age. For systolic pressure this relation seemed to be similar in boys and girls; for diastolic pressure the effect seemed to be stronger in girls (p=0·004).

Birth rank and number of younger siblings

Table III shows the univariate relation between birth rank and blood pressure. A stepwise fall in both mean systolic and mean diastolic blood pressures was observed with increasing birth rank, with a mean difference of 2·3 mm Hg in systolic blood pressure and 1·9 mm Hg in mean diastolic blood pressure between birth rank 1 (that is, first born children) and birth rank ≥4. When adjusted for current weight the effect of birth rank was slightly more apparent and remained highly significant for both systolic (p=0·0007) and diastolic (p <0·0001) pressures. To examine whether any other aspect of family size might be important the *blood pressure (mm Hg) in boys and girls*

Birth rank	No of children	Systolic blood pressure	Diastolic blood pressure
1	1653	101·4 (0·2)	59·4 (0·2)
2	1390	100·4 (0·2)	58·5 (0·2)
3	424	100·0 (0·4)	58·3 (0·3)
≥4	92	99·1 (0·9)	57·5 (0·6)

TABLE IV—*Mean (standard error) systolic blood pressure (mm Hg) by birth rank and number of younger siblings in boys and girls**

No of younger siblings	Birth rank 1	2	3	≥4
0	102·1 (0·4) (n=450)	100·9 (0·3) (n=969)	100·3 (0·5) (n=328)	99·0 (1·0) (n=58)
1	101·3 (0·3) (n=944)	99·2 (0·5) (n=347)	99·0 (1·0) (n=83)	
≥2	100·4 (0·5) (n=259)	99·2 (1·0) (n=74)		

*Categories based on fewer than 25 subjects were excluded.

association of birth rank and number of younger siblings with blood pressure was examined; table IV shows the results for mean systolic pressure. The inverse association between birth rank and blood pressure was observed for each number of younger siblings. An increasing number of younger siblings, however, was associated with a fall in mean systolic pressure even after birth rank had been taken into account.

Infant feeding

Blood pressures of children who had been fed exclusively with either breast milk or bottled milk were compared. Both systolic and diastolic blood pressures were identical in the two groups (mean systolic pressure 100·7 mm Hg, mean diastolic pressure 58·8 mm Hg; 95% confidence interval for difference −0·62 mm Hg to 0·62 mm Hg systolic pressure, −0·25 mm Hg to 0·25 mm Hg diastolic pressure).

Maternal and paternal history of high blood pressure

The mean systolic and diastolic blood pressures of children whose mothers or fathers had reported a history of high blood pressure were compared with

TABLE V—*Relation between parental history of hypertension and mean blood pressure (mm Hg) in boys and girls*

	Maternal history: Present	Maternal history: Absent	Paternal history: Present	Paternal history: Absent
No of children	1409	2115	257	2376
Mean (SE) blood pressure:				
Systolic	101·6 (0·2)	100·3 (0·2)	101·8 (0·5)	100·7 (0·2)
Diastolic	59·3 (0·2)	58·6 (0·1)	60·1 (0·4)	58·9 (0·1)

TABLE VI—*Multiple regression analysis of current weight, birth weight, maternal age, birth order, and maternal history of hypertension and systolic blood pressure in childhood*

Variable	Regression coefficients adjusted for current weight alone: Regression coefficient	Standard error	p Value	Regression coefficients adjusted for all factors: Regression coefficient	Standard error	p Value
Current weight (mm Hg/kg)*	0·89	0·04	<0·0005	0·91	0·04	<0·0005
Birth weight (mm Hg/kg)	−1·83	0·26	<0·0005	−1·73	0·27	<0·0005
Maternal age (mm Hg/kg)	0·10	0·03	<0·0005	0·15	0·03	<0·0005
Birth rank 1	0·00			0·00		
2	−0·86	0·30	<0·005	−0·94	0·31	<0·0005
3	−1·16	0·44		−1·34	0·46	
≥4	−2·53	0·88		−2·70	0·89	
Maternal history of hypertension:						
Absent	0·00		<0·005	0·00		<0·005
Present	0·96	0·28		0·90	0·28	

*Excluded from current weight adjustment.

reported (table V). The children in whom both parents had a history of high blood pressure constituted too small a group to be treated separately. The results seemed to be similar for boys and girls. Children in whom either parent had reported a history of high blood pressure had systolic blood pressures that were on average ≥1·0 mm Hg higher than those whose parents had not and diastolic pressures on average ≥0·7 mm Hg higher. These differences were significant in analyses of both paternal and maternal history. Adjustment for current weight reduced the magnitude of the effects slightly, but the effect in maternal history remained highly significant in both systolic ($p=0·0007$) and diastolic ($p=0·009$) pressures.

Interrelations of factors

The independent contributions of maternal age, birth rank, birth weight, and maternal history of high blood pressure to childhood blood pressure were examined in a multiple regression analysis, which took all these variables and current weight into account. Paternal history of high blood pressure was excluded because it would have considerably restricted the number of children that could be included in the analysis. Table VI shows the results for systolic pressure. Regression coefficients are given for the relation between each variable and systolic pressure adjusted for current weight alone and then for current weight and all other factors in a simultaneous regression model. The effects of current weight, birth weight, maternal age, birth rank, and maternal history of hypertension remained significant in the multiple regression model and were little affected by the addition of the other factors. The strengths of relations between maternal age and blood pressure and between birth rank and blood pressure were increased by taking the other factors into account; this resulted from the association between maternal age and birth rank (greater maternal age being associated with high birth rank), which has opposing effects on blood pressure. A similar pattern was observed for diastolic pressure (results not shown). Because adjustment for a maternal history of high blood pressure as a 0/1 variable is unlikely to take the factor into account completely, the relation of birth weight, maternal age, and birth rank with blood pressure were re-examined in children with a maternal history of high blood pressure and those without. The results suggested that the relations were similar in both groups.

Discussion

The data examined in this report have two important strengths; firstly, they are based on a sample of children from nine British towns (six in England, two in Scotland, and one in Wales) carefully selected to represent all social classes in each town, and, secondly, measurement of blood pressure was standardised by using the same observers and procedures and the same calibrated automated instrument throughout. Errors introduced by the retrospective collection of data on potential blood pressure determinants are likely to be random, leading to underestimation rather than overestimation of the strength of associations with blood pressure. The absence of appreciable differences in blood pressure based on social class and the lack of awareness about blood pressure measurements in the parents make major recall bias unlikely.

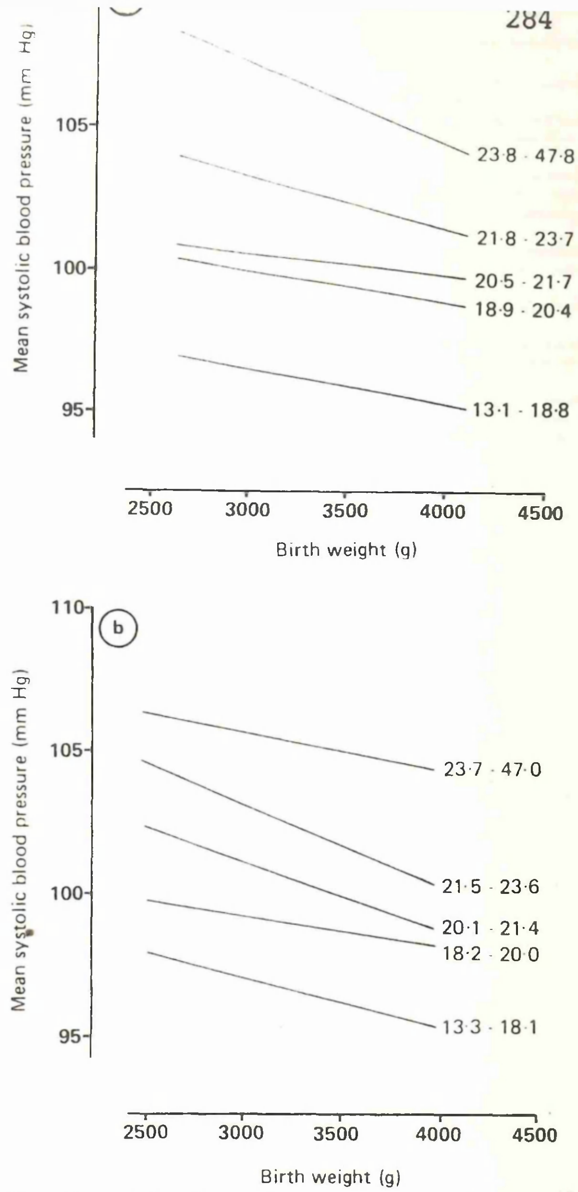
Negative associations between birth weight and blood pressure have been described in two studies of 7 year olds[11 17] and in two populations of 10 year olds.[10 18] In our study population the relation was observed only when the effect of current weight was taken into account. This presumably reflects the strong associaearly years of life, which becomes increasingly attenuated with age. When compared with the effect of current weight the magnitude of the association between birth weight and blood pressure is small; the change in systolic blood pressure for a change of one standard deviation in current weight is 3·11 mm Hg compared with −0·98 mm Hg for birth weight. The importance of the relation between birth weight and blood pressure depends on whether it persists into adult life; earlier reports have suggested that this may be the case.[9 10 19] The basis of the association remains unknown, although unspecified intrauterine factors have been suggested to be important.[10] The negative relation between birth weight and blood pressure, however, does not seem to be present at birth. Studies examining this relation in full term infants found either a positive association[20 21] or no association.[22] Studies of infants of low birth weight have found a consistently positive association between birth weight and blood pressure at birth.[23-25] These findings imply that the relation between birth weight and blood pressure develops in infancy or early childhood. One factor that may be important in its development is weight gain, which is particularly pronounced in infants of low birth weight,[26] particularly during the first year of life.[27] The indication from our data, at least in boys, that blood pressures are highest in those who have gained most weight since birth (figure) is consistent with this hypothesis.[11]

Maternal age and birth rank

We could not identify previous descriptions of the relation between maternal age and blood pressure and between birth rank and blood pressure. These relations are in opposing directions; by taking both factors into account the strengths of the individual associations with blood pressure are increased. The magnitude of the effects are comparable with those of birth weight; the change in systolic blood pressure for a change of one standard deviation in maternal age is 0·51 mm Hg, compared with −0·98 mm Hg for birth weight. These relations seem to be independent of birth weight, current weight, and social class. The causality and mechanisms underlying these associations, however, remain to be established. For birth rank the relation may be particularly complex; the finding that the number of younger siblings is related to blood pressure after birth rank has been taken into account suggests that family size or factors related to it may be aetiologically important. The extent to which maternal age and birth rank are related to blood pressure at birth is of considerable interest. Assessment of the public health importance of these relations must, however, wait until they have been shown to persist into adult life. If this is confirmed it implies that the tendency towards smaller families and rising maternal age in pregnancy in Britain during the past two decades[28 29] may be associated with higher blood pressure in children.

Infant feeding methods

The relation of feeding method to blood pressure is particularly interesting because of the differing sodium content of breast milk and bottle milk, which is considerably higher in bottled preparations.[30] The feeding methods used in the first months of life did not seem to influence blood pressure at age 5-7 years. This remained the case even when adjustment was made (unpublished data) for slight differences in current weight observed between breast fed and bottle fed groups (in agreement with a previous report[31]). Our results are consistent with the findings of other retrospective studies, which observed no relation between blood pressure in infancy or childhood and previous



Regression analysis of birth weight and mean systolic blood pressure by fifths of current weight (kg) in boys (top) and girls (bottom). Numbers are ranges in each fifth of distribution

feeding methods.[32 33] They are, however, challenged by the results of a randomised controlled trial of sodium restriction in neonates, in which a difference of 2 mm Hg in systolic blood pressure was observed after a six month intervention period.[7] In our observational study the differences in sodium intake between the groups may well have been much less than those under trial conditions. If a difference of even half the magnitude reported,[7] however, persisted to age 5-7 years we should have been able to detect it without difficulty. This inconsistency may imply that the results of the previous study were incorrect; alternatively, it may indicate that the influence of sodium intake in infancy on blood pressure is not sustained after the restriction is withdrawn or that the effect is small when compared with the influence of other factors, particularly weight gain.

Influence of parental history of hypertension

A parental history of high blood pressure was associated with higher blood pressure in childhood. Self reported assessments are a crude index of blood pressure, and the strength of the familial relationship is probably being underestimated; better estimates of the strength of relations in blood pressure in parents and children can be obtained from studies in which interesting, however, that the relation between birth weight, maternal age, and birth rank and blood pressure were largely unaffected by adjustment for reported parental history of high blood pressure and seemed to be similar in children with and without a maternal history of hypertension. These findings suggest that the means by which familial influences on blood pressure are mediated are quite separate from those of the other factors discussed.

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...rther important point is that 20-30% of the ...ation in the Paddington and North Kensing... ...is not registered with a general practitioner ...ould therefore not be included in any screen... ...ogramme that is based on the family practi... ...committee register. This is a cause of some ...n and necessitates the implementation of ...ative strategies, which bear an additional ...

...also emphasise that the problem of cervical ...ning is not one of simply contacting women ...achieving a response. It is worrying that our ...showed that even having received an invita... ...letter, a significant number, particularly of ...women, chose not to attend for a smear test. ...our health authority valuable resources have ...spent in terms of time, money, and energy in ...menting a particular screening system. We ...m unconvinced that it is appropriate for inner ...lon, and we would like to see the available ...rces put to more effective use in an attempt to ...an impact on the incidence of cervical cancer ...y.

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...uidelines for medical audit

...—Drs Charles D Shaw and David W Costain ...nforce the wishful thinking of the medical ...fession that medical audit is primarily a matter ...clinicians.[1] There are three serious objections to ...s view.

Firstly, while it may be possible to tease out the ...iquely medical contribution to the process of ...re, outcomes reflect the interaction of the patient ...th a range of clinical and supporting staff. ...condly, quality assurance (and therefore audit) ...a responsibility not only of clinicians but also of ...blic health staff and managers, and doctors are ...be found in all three roles. Thirdly, audit is a ...echanism for improving the quality of care by ...creasing the accountability of health care profes... ...onals to the outside world, including managers, ...vil servants, politicians, and the general public. ...he illusion that it can be conducted by doctors for ...octors out of sight of the prying eyes of laymen ...hould be abandoned.

Obviously, there exists a tension between the ...inical and managerial uses of audit which must be ...solved, for audit cannot be effectively pursued in ...n atmosphere of mutual suspicion. To be credible ...he audit structures about to be established must ...e seen to be free from vested interests. Since ...either clinical divisions nor health authorities ...ulfil this criterion, we need to create a properly ...esourced independent national audit commission ...with regional subdivisions (empowered to investi... ...gate all levels of the service including management ...and to publicise its findings. The alternative is to ...permit the current misunderstandings about the ...nature of audit to drag on to the point where open ...onflict between clinicians and managers becomes ...nevitable.

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Measurement of blood pressure in children

SIR,—We welcome the British Hypertension Society's timely report on the measurement of blood pressure in children, which offers clear recommendations for standardising sphygmomanometric blood pressure measurement in clinical practice. We are, however, concerned about the aspects of these recommendations that refer to cuff size.

Firstly, the working party recommends that "the widest cuff that can be applied to the arm should be used." If this recommendation is followed in children the width of the cuff may equal or exceed 70% of the arm circumference in many subjects. Although most attention has been paid to the systematic overestimation of blood pressure that results from using a cuff that is too narrow, there is evidence that a cuff bladder width equal to 40% of arm circumference provides the most consistent agreement with direct intra-arterial pressure[2] and that an excessively wide cuff underestimates blood pressure.[3-5] For these reasons the American Heart Association recommends that the ideal cuff bladder width is 40% of arm circumference and that a range between 40 and 50% is acceptable.[6] This advice is difficult to follow, however, because the range of cuff sizes available is limited, and the best compromise may therefore be to use the available cuff which has a bladder width nearest to but preferably not much less than 40% of arm circumference.

Secondly, although the report emphasises that several cuff sizes are needed for the wide range of arm circumferences found in children, it does not emphasise that the recorded blood pressure is considerably influenced by cuff size, being lower with larger cuffs.[7,8] Changes between cuffs of different sizes may therefore result in considerable changes in recorded blood pressure, which may be important in a child who is being observed over a period of time.

In children who require repeated accurate blood pressure measurements over time we suggest the following:

(1) The choice of cuff size should be based on measurement of arm circumference.

(2) Cuff bladder width should be as close as possible to, and preferably not less than, 40% of arm circumference. A simple guide can be used to show the best available cuff width for a particular arm circumference (figure). The diagonal line represents ratios of cuff width to arm circumference of 40%. This is used to determine the maximum desirable arm circumference for the bladder widths of the available cuffs (for example, 20 cm for the 8 cm cuff). Each cuff is used over a range of arm circumferences between its maximum desirable arm circumference and that of the next cuff size down (for example, from 20 cm down to 10 cm for the 8 cm cuff).

(3) Unnecessary changes in cuff size should be avoided, and the size of cuff bladder used should be recorded. Clear marking of cuff bladder size by manufacturers would be helpful in this context.

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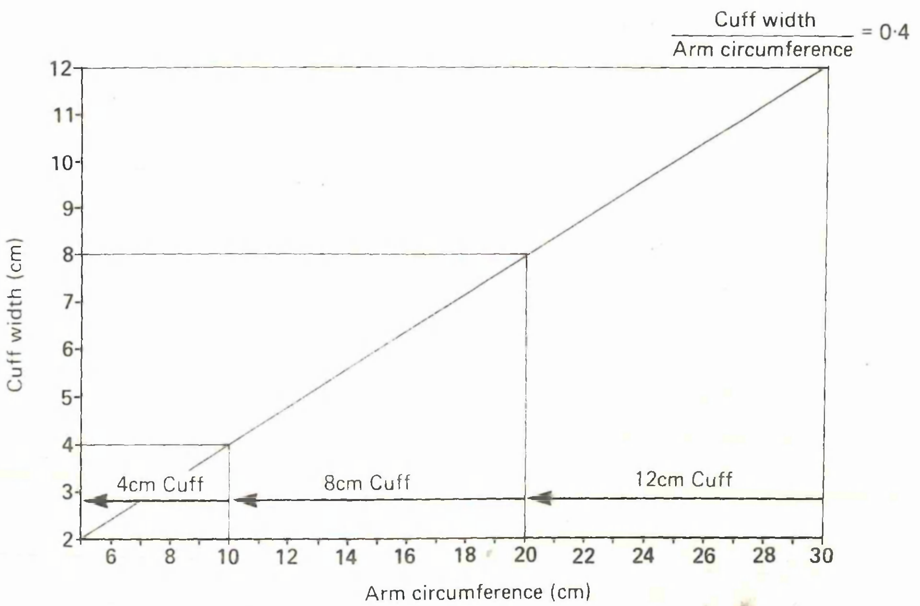
AUTHORS' REPLY,—We are aware that there are problems in choosing the correct size of cuff, but we do not believe that the technique advocated by Dr P H Whincup and colleagues is necessarily any more correct than ours. They found that blood pressure is not independent of cuff size in their recent study.[1] The recommendation of a cuff width of 40% of arm circumference[2] seems to have been made from one study in which arterial blood pressures in sedated children were compared with retrospective indirect blood pressure measure-



Guide to selecting an appropriate cuff bladder width for blood pressure measurement in children based on arm circumference. Most appropriate cuff width for a particular arm circumference is indicated above arm circumference scale. Cuffs with bladder widths of 4, 8, and 12 cm (as in the British Hypertension Society recommendations) are assumed to be available. The diagram can, however, be modified to include other cuff sizes

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