LONDON'S GLOBAL UNIVERSITY

Behavioural and Biological Predictors of Depression in Older Age:

The role of Internet use, Insulin-like Growth Factor 1, and cardiovascular disease risk factors in the English Longitudinal Study of Ageing

Thesis submitted for the degree of Doctor of Philosophy

Sungano Chigogora

December 2017

Declaration of originality

I (Sungano Chigogora) declare that the contents of this thesis are my own work. Where the work of others has been used, this has been indicated and appropriately referenced.

Acknowledgements

I am sincerely grateful for the invaluable encouragement, advice and support of my primary supervisor, Professor David Batty, particularly through the most trying of times. His advanced research skills, honest counsel, openness and intuition were instrumental to my development not only as a researcher, but as a growing individual. To Dr Paola Zaninotto, my secondary supervisor, I would like to express my gratitude for the patient statistical guidance, and for helping me to develop and structure my research. In my two supervisors, I had a team that complemented my capabilities, personality and predisposition. I would like to thank my supportive graduate tutors and former lecturers, Professors McMunn and Britton and Doctors Pikhart and Peasey for helping me to navigate my Masters and Doctoral studies. My research was funded by the Economic and Social Research Council and the Medical Research Council, to whom I am extremely grateful. I am also grateful to participants, data collectors and managers of the English Longitudinal Study of Ageing, from which data for my study were taken. My doctoral experience would have been incomplete without the exchange of ideas and networking opportunities with the UCL ELSA group, the IEHC Early Career Forum, the EPH Journal Club, and the Harvard T.H Chan School of Public Health. In particular, I would like to thank Doctors Demakakos and Stegeman from UCL, and Professor Miguel Hernan from Harvard, for paving the way to an amazing opportunity of being a Visiting Research Student at Harvard. I am grateful to my wonderful UCL peers who became very good friends, and to my sister-friends around the world: Nyasha, Prisca, Kudzi, Taurai, Kudzai, Racquel, Henrietta, Vicky, Rebecca, Nathalie, Sonia, Francisca, Elisa, Claire, Nehla, Ruth, and Aly. Your companionship and support have been invaluable. I am grateful to Alex, my obliging proof-reader, and the yin to my yang. I am eternally grateful for the amazing women who have gone beyond the call of duty; Alison, Sasha and Sandra. Lastly, I would like to express my profound love and gratitude to my family: Daddy, Brunette, Adalia, my dearest sister Shamie, and my darling Mum - now and forever my guardian angel.

Abstract

Background: Depression is a leading cause of disability and morbidity. Its determinants are not fully understood. In the present thesis I investigated the potential role of selected behavioural and biological characteristics in predicting depression in older people: Insulin-like Growth Factor 1 (IGF-1), Internet use and cardiovascular disease (CVD) risk factors.

Methods: Participants were recruited from the English Longitudinal Study of Ageing, an ongoing prospective cohort study of adults aged 50 years and over which was established in 2002. With six waves of biennial data collection up to 2012, serum IGF-1 levels were measured from 2008 at each nurse visit. Internet use was ascertained from 2002, and characterised again with greater detail in 2012. Risk factors for CVD were measured from 2004 and investigated according to the QRISK2, Framingham and SCORE algorithms. Depression symptoms were captured using the 8-item Centre for Epidemiologic Studies Depression Scale. Prospective analyses were carried out in individuals free from depressive symptoms at baseline (range dependent on analyses: 3,435 to 7,524 participants).

Results: A'U'-shaped association between IGF-1 and depression was observed, where both lower and higher levels were associated with elevated risk. For instance, relative to men in the lowest quintile of IGF-1, the age-adjusted odds ratio [OR] (95 confidence interval [CI]) for depression symptoms after 4 years of follow-up for increasing quintiles of IGF-1 were: 0.51 (0.28, 0.91), 0.50 (0.27, 0.92), 0.63 (0.35, 1.15) and 0.63 (0.35, 1.13) (P-value for quadratic association 0.002). In multivariable logistic regression analyses, compared with Internet users, non-users were 1.73 times (CI; 1.56, 1.95) more likely to develop depression after 10 years of follow-up. In particular, using the Internet for email communication was associated with a lower risk of depression. Increased risk of depression was observed in women only for all CVD risk algorithms per standard deviation change in score as follows; QRISK2 (OR 1.60: CI; 1.30, 2.00), Framingham model (OR 1.34: CI; 1.13, 1.58), SCORE chart (OR 1.40; CI; 1.11, 1.77).

Conclusion: The present study adds to the understanding of the aetiology of depressive symptoms by suggesting a potential role for IGF-1, Internet use, and elevated CVD risk.

Table of Contents

List of Figures

List of Tables

Appendices

List of abbreviations

BMI	Body Mass Index
CES-D	Centre for Epidemiologic Studies Depression Scale
CI	Confidence Interval
CRP	C - reactive protein
CVD	Cardiovascular disease
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
ELSA	English Longitudinal Study of Ageing
HDL	High Density Lipoprotein
HSE	Health Survey for England
GEE	Generalized Estimating Equations
ICD-10	10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD)
IGF-1	Insulin-like Growth Factor 1
LDL	Low Density Lipoprotein
mmHg	Millimetres of mercury
OR	Odds Ratio
SD	Standard Deviation
SE	Standard Error
SES	Socio-Economic Status
WHO	World Health Organization

Chapter 1: Introduction

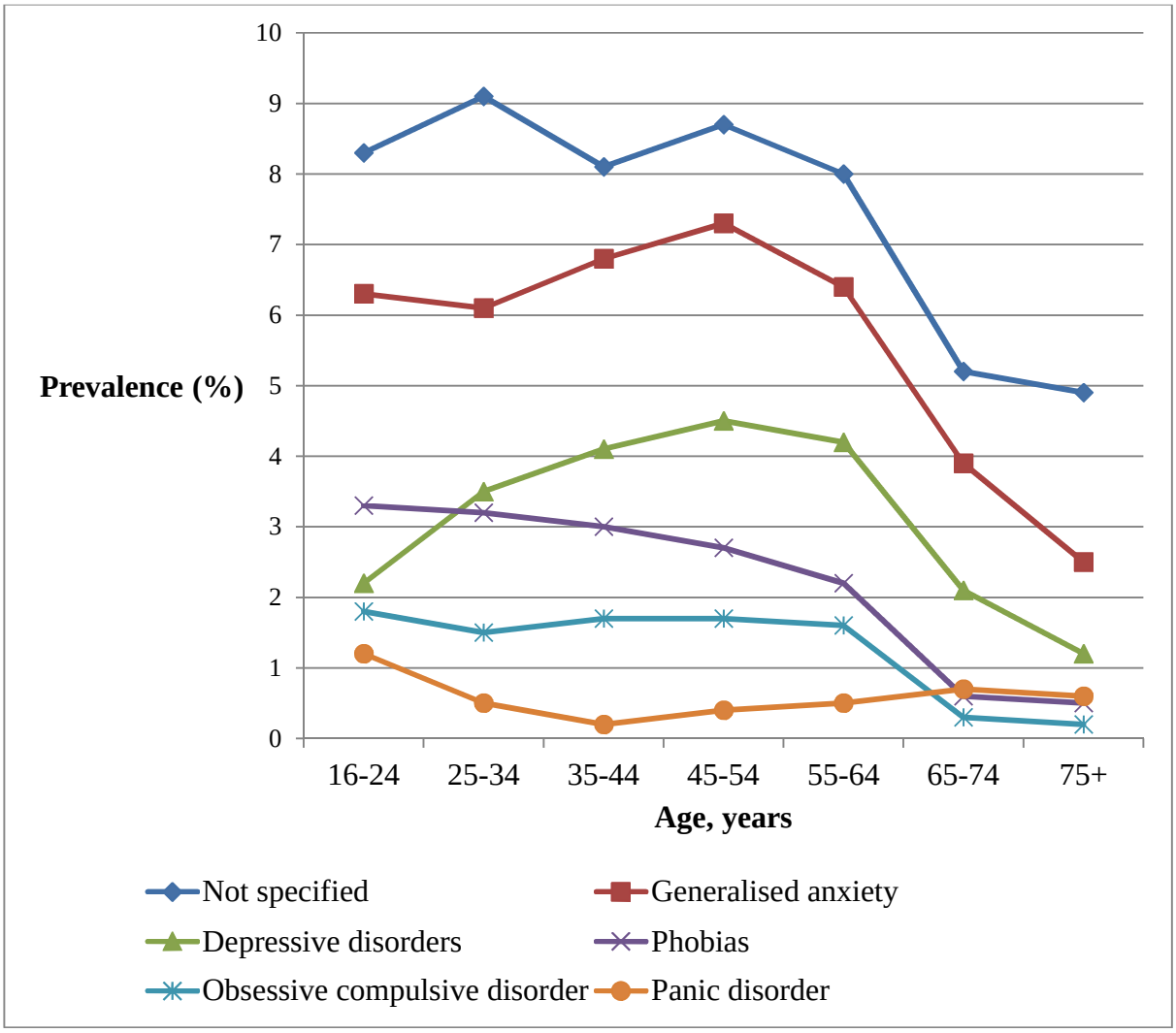
In this first chapter I present an introduction to my doctoral thesis, which details a multi-disciplinary study of novel predictors of depression in older people.

1.1 Depression in older people

Unipolar depression affects around 7% of people aged 60 years and over worldwide,[1] and is associated with a reduction in life expectancy of about 4 to 6 years in this age-group.[2] With the world's population rapidly ageing, the proportion of people aged 60 years and over is projected to double from 11% in the year 2000 to 22% by 2050, and with it the age-specific medical, social, and economic burden of depression.[3] Taking such projections of an ageing population into account, it is likely that the burden of depression in the elderly will also increase.

In the UK, where the median age was 40 years in 2014,[4] about 1 in 5 people aged 16 years and over reported having symptoms of depression and/ or anxiety, with a higher percentage of women (23%) than men (17%).[5] In figure 1, the prevalence of depression in England according to age-group is illustrated in relation to other common mental disorders as reported in the Adult Psychological Morbidity Survey of 2014.[6] Prevalence of depression symptoms started off low in the early teens and then followed a roughly linear increase through middle age and early older age, declining thereafter. Additionally, according to Office of National Statistics data from 2010, an upsurge in the prevalence of both anxiety and depression was observed in the older elderly, who were almost as likely as the middle-aged to report symptoms.[7]

Figure 1: Prevalence of common mental disorders in England by age-group according to the 2014 Adult Psychiatric Morbidity Survey



Globally, more than 300 million people of all ages suffer from depression, which is a leading cause of disability and loss of productivity,[8] and is projected to surpass diarrhoeal and respiratory diseases by the year 2030 to become the leading global cause of disease burden.[9] In 2010, the whole of Europe spent a combined amount of £77 billion on the direct and indirect costs of depression; costs which are projected to result in the loss of a substantial proportion of global economic output due to direct healthcare costs, and depletion of capital and labour. [10]

Defined as a common mental disorder, depression is characterised by negative moods such as sadness and apathy, and usually associated with feelings of tiredness and poor concentration, changes in activity level, disturbed sleep or appetite, feelings of guilt or low self-worth, and regressive and self-punitive wishes.[11] It can be classed as either bipolar or unipolar, with the more severe presentations of unipolar depression diagnosable as major depressive disorder.[12] Although depression is treatable, the largest barrier to this is the fact that sufferers often go undiagnosed due to personal and cultural stigmas and considerations, as well as health service limitations.[13]

In addition to the decreased economic output that results from reduced productivity brought on by sickness absences, disability and early retirement, depression also increases healthcare costs through hospital admissions, medication, and increased contact with community healthcare practitioners.[14] It also negatively affects personal relationships and family life through the behaviour changes of the sufferer and the responses of those around them,[15] and is the most common reason that people end their own lives.[16] As well as being an important disease in its own right, there is evidence that depression may lead to the development of cardiovascular disease (CVD),[17] some cancers,[18] and premature mortality.[19]

Depression in older people has a poor prognosis.[20] While there is no single term that defines the age or characteristics of an older person, most researchers now use the arbitrarily set thresholds of 60 or 65 to define older people.[21] Combined evidence from 12 prospective cohort studies of people aged 60 and over who were depressed at baseline indicated that 33% of them were categorised as ‘well’, 33% ‘still depressed’, and 21% were deceased after 24 months of follow-up.[22] With increasing age, depression is

associated with increased disability and suicide, increased risk of CVD and cancer, and premature mortality.[23, 24]

A review of evidence from community and clinical settings of older people indicates that depression and disability are strongly associated, and sleep disturbance, psychomotor retardation, reduction in body mass index and increased incidence of common disabling illnesses were cited as the possible mechanisms of this association.[25] In this review, cancer and CVD were identified as possible disability-mediating illnesses, with suggestions that depressed individuals may be more susceptible to such illnesses because of behaviours such as smoking or reduced physical activity.[25] However, there are also ongoing debates based on the proposition that depression itself may be an independent risk factor for both cancer and cardiovascular disease, after accounting for all the other known predictors.[26,27]

Depression may be an independent predictor of mortality in older people. [28] In a study of 5,201 elderly community dwellers with high depression symptoms at baseline, 23.9% had an increased risk of dying after 6 years of follow-up compared with those with low symptoms of depression, following adjustment for an extensive array of socio-demographic and physical health control variables. From this study, it was proposed that mortality may be elevated in this group due to what was termed as motivational depletion; finding everything too much of an effort, not having the strength to continue and finally, giving up.[28]

In clinical studies, a meta-analysis of 20 studies which followed cardiovascular disease sufferers whose ages averaged between 53.6 and 74.4 illustrated higher rates of morbidity and mortality among those with diagnosed depression or depression symptoms compared

to those without.[29] Moreover, evidence from a separate review illustrated an increase in mortality from all causes in older people aged 65 years and above with depression compared to those without depression.[30]

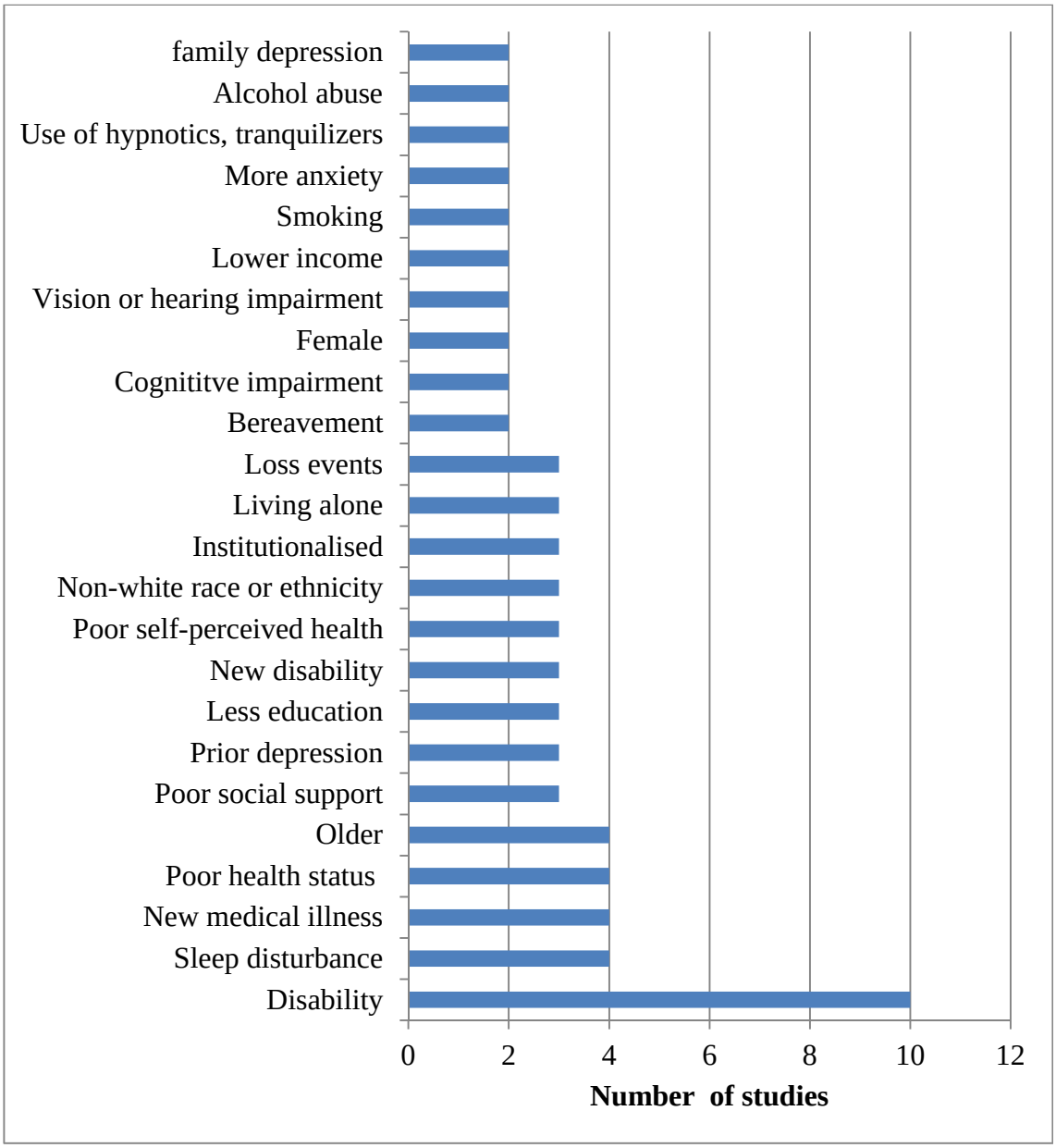
The majority of older people who commit suicide are depressed.[31] Although suicide rates are highest for young people in some individual countries, globally, the highest rate of suicide is in people aged 70 years and over, with women over 70 having twice the risk of committing suicide than that of women aged 15-29 years.[32] While effective treatments for depression are available, the majority of cases among older people remain undiagnosed, and prevention of the disorder remains a major public health priority.[13]

1.2 Risk factors for depression in older people

The aetiology of depression is not fully understood. While early aetiological theories of depression implicated specific neurochemicals and neuropeptides,[33] it is now generally understood that depression is likely to be a result of a combination of social/ personal upheavals and dysfunction of multiple brain regions and/or neurotransmitter systems; conceptualised as a multidimensional, systems-level disorder affecting discrete, but functionally integrated pathways.[34] In addition to not simply being the result of dysfunction in one or more of these elements, depression is portrayed as a complex failure of the remaining functional biological and psycho-social systems to maintain homeostatic emotional control, particularly in times of increased cognitive or somatic stress.[35]

A series of studies have illustrated a range of behavioural and social predictors of depression in later life.[36] Figure 2 displays the most common risk factors for depression in older age as identified through a systematic review of the literature and meta-analysis of available data.[37]

Figure 2: Risk factors for depression in older people as identified in 20 prospective cohort studies



Risk factors collated during a systematic review and meta-analysis of prospective 20 studies of community dwellers aged 50 years or more[37]

While physical disability, diagnosis of a new medical condition, and increasing age have historically been identified as the more important predictors of depression in older age, the evidence also indicates that the effect of these factors is often mitigated by the buffering effects of social support.[38,39] Specifically, the perception of support, particularly from friends (rather than family or significant others) had an important protective effect from depression.[40]

With the exception of weight and inflammation, relatively less attention has been given to the biological predictors of depression. In addition to evidence of a reciprocal relationship between obesity and depression,[41] inflammatory markers such as interleukin-6 and C-reactive protein (CRP) have been shown to be positively related with the development of depression symptoms.[42,43] Relatively smaller bodies of evidence indicate some association between nutritional, protein and endocrine plasma markers with depression,[44,45] while there is some suggestion that a number of neurological disorders may be linked to the development of depression in later life.[46]

1.3 Research Priorities

Given the current and impending burden of depression, increasing knowledge and awareness of the disorder remains a key priority for researchers and policy-makers worldwide. The UK government, through recommendations and guidance from the National Institute for Health and Care Excellence, has made it a priority to improve mental health through research, practice and evaluation, with special focus being paid to promoting improved recognition and treatment of depression.[47]

Although effective treatments are available for some levels of severity, depression in older people remains under-diagnosed.[48] Moreover, while treatment is as effective for older patients as for younger adults, the condition is often under-recognised and under-treated in this age-group.[49] Considering that multiple factors may be responsible for lower diagnoses rates of depression in older people, and given the complex precursors and pathology of depression, identification of a unique biomarker is unlikely. However, identification of a biomarker for depression could be beneficial for informing diagnosis and monitoring for risk. In the case where such a biomarker could also be used to

ascertain severity of disease, it could also potentially play a role in the management of treatment and advancement of therapies through measured responses. Neutrophic factors, which support the growth, survival, and differentiation of both developing and mature neurons, have been implicated in the development of depression.[50] While it is beyond the scope of this project to scrutinise these in their entirety, the role of Insulin-like Growth Factor 1 in the development of depression will be investigated.

Aside from a unique biomarker for depression, identification of a tool where multiple risk factors are combined to predict future risk of depression would be useful for identifying individuals at risk of future disease and coining measures to limit this risk. Such a structured approach, comparable to the use of screening tools for chronic somatic disorders, would put more emphasis on the recognition and treatment of depression, and would likely reduce the stigma and other social, personal and service-based barriers and constraints associated with seeking medical advice for mental illness. Thus, the utility of a cardiovascular disease prediction algorithm in predicting risk of depression will be investigated.

While increasing age, physical limitations and development of chronic medical conditions have often been identified as leading causes of depression in older people, it has also often been noted that the effect of these factors can be buffered by social support.[51] Consideration of changes in forms of social support, particularly in the evolving digital age, may present a psychosocial environment divergent to that previously explored. Data from the Office of National Statistics indicates that Internet use in individuals aged 65 years and over more than tripled between 2006 and 2016, with more than half of this age-group reporting that they used the Internet for communication. [52,53] Thus, with the evolving digital age, there has likely been a cohort effect in which older

people currently using the Internet are more acclimatised to its widespread use, such that a 65-year-old today may be more inclined to engage with and explore its various features than an individual who was 65 years old at the turn of the century. Therefore, consideration of the role of social support in psychological well-being and how it relates to the increasing and ever-changing role of the Internet as a facilitator for social interaction is a perpetual research priority.

While it is understood that depression is likely a result of a combination of social and personal upheavals and dysfunction of multiple brain regions and/or neurotransmitter systems, the multidimensional nature of depression is often not addressed in aetiological studies. Crucially, considering the dynamic changes in societal structures and in the knowledge of disease pathology, there is often oversight in amalgamating biological, behavioural and psychosocial evidence in progressing holistic approaches to understanding this disorder. Considering the progressive agenda in preventative healthcare and the focus on utilising novel methods to identify at-risk individuals, there is a need for more proactive measures to pre-empt depression and potentially modify risk.

As such, current research efforts warrant multidisciplinary approaches where current knowledge is evaluated and advanced with wider scope; where biological, behavioural and psychosocial predictors of depression are considered in relation to our evolving society, and represented where possible. In addition, as there is need to address the lack of a risk prediction tool for depression in first-contact healthcare settings, efforts to identify such a tool remain a priority. Accordingly, this present study addresses these points, focusing on older people in England, who comprise a large proportion of the ageing UK population. Older people in England have some of the highest rates of depression in the country and once they have depression, they tend to experience poorer

outcomes. Furthermore, as older people in England are more likely to attend primary care settings than younger counterparts, it is likely more beneficial to investigate clinical assessment of future risk of disease in this sub-population than in any other.[54]

While mainly concerned with ensuring that the investigation covered all possible perspectives, the multi-disciplinary nature of this study also fulfils the research missions of the joint funders of this research, the Economic and Social Research Council (ESRC),[55] and the Medical Research Council (MRC),[56] whose funding was for a project that combined social and biological determinants of health. Accordingly, the purpose of this present study is to take a multidisciplinary approach to the investigation of depression and to further explore novel biological and psychosocial predictors of depression in the elderly. Following a scoping review of the literature to identify gaps in knowledge, coupled with the data available to me, the potential predictors of depression in older people which I shall investigate in this thesis are:

i. Insulin-like Growth Factor 1, a biomarker,
ii. Internet use, which represents a novel and complex interaction of psychological, social and behavioural traits, and
iii. Cardiovascular disease risk factors, whose role shall be investigated according to individual risk factors, as well as collectively, according to established CVD risk algorithms.

Chapter 2: Aims and objectives

In this thesis, I aim to explore the capacity of IGF-1, Internet use, and CVD risk factors to predict depression symptoms. Based on the literature and the arguments introduced above, I will set out to test the following hypotheses:

- Low IGF-1 is predictive of depression symptoms in older people
- High Internet use, especially for the purpose of social interaction, reduces depression symptoms in older people
- A risk assessment tool used to predict the future probability of CVD can also be used to predict the probability of depression

To achieve the above, I will firstly review current literature on the association between IGF-1 and depression from studies of both animal and human subjects. Based on the evidence to date, my first research objective is to investigate the association between IGF-1 and both prevalent and future development of depression symptoms in individuals aged 50 years and over. Following a review of previous findings, my second objective is to investigate the association between Internet use and future development of depression symptoms in older age, and to investigate the mechanisms by which any relationship (if found) may exist. Due to a commonality of risk factors which I will expand on in the relevant sections of this thesis, my final objective is to investigate whether CVD risk factors as contained within CVD risk assessment tools can be used to predict depression symptoms.

In the next chapter (Chapter 3), I will begin by introducing the analytical sample in which I will investigate novel predictors of depression in older people, which I have taken from the English Longitudinal Study of Ageing (ELSA). While analytical sub-groups for each investigation will differ according to varying eligibility criteria, the core ELSA cohort

that was recruited at the beginning of the study remains the same throughout, and it is this cohort that will form the focus of the next chapter. In addition to describing how participants were recruited to ELSA, I will describe their baseline demographic, socio-economic, behavioural and biological characteristics and the techniques used to quantify these. Characteristics that were only considered for analysis in one investigation (and not in any other) will be described in the analytical methods of the relevant investigation, with only the covariates common to all investigations being illustrated in the next chapter. Of note, the process used to measure depression symptoms in ELSA participants will be described as the ELSA cohort is introduced.

Individual chapters following this shall contain descriptions of my interrogation of each of the possible predictors of depression starting with IGF-1 (Chapter 4), then Internet use (Chapter 5), and finally CVD risk factors (Chapter 6). Each of these chapters will begin with a scoping review of research findings linking the proposed predictors to depression in older people, followed by a short statement of the aims and objectives for that chapter. Based on explicit eligibility criteria, the selection of an analytical sub-sample will then be described prior to enumeration of all chapter-specific covariates. This will be followed by a description of the analytical methods used, and a description of sensitivity analyses used as a comparator to my findings.

I will then describe and tabulate my main findings, which I will relate to the results of sensitivity analyses. Finally, I will discuss my results in relation to previous findings, any key relevant issues identified within my investigation and the strengths and limitations of my analyses. To amalgamate my findings as per my objectives of progressing new evidence in tandem, I will round up my findings in Chapter 7 and suggest how these may impact future research and practice.

Chapter 3: Data Source: The English Longitudinal Study of Ageing

3.1 Selection of study participants

The data for this research come from the English Longitudinal Study of Ageing (ELSA), which is an ongoing prospective cohort study of adults aged 50 years and over who live in private households in the United Kingdom. Initiated in 2001/ 2002, the primary purpose of ELSA is to collect longitudinal objective and subjective data on financial circumstances, health, well-being, behaviours, activities, biological markers and social networks from a representative sample of the English population aged 50 years and older. The overall aim of ELSA is to explore the evolving dynamic relationships between economic status, social networks, health and functioning. It is thus a study of people's quality of life as they get older, in order to understand the factors that contribute to the ageing process.[57]

The original sample for ELSA was recruited from people who had previously participated in the Health Survey for England (HSE). A cross-sectional annual survey, HSE is aimed at monitoring the nation's health through the collection of a wide range of health, lifestyle and biometric information from individuals of all ages living in randomly selected households in England. Full details of the sample design and response rates for HSE have been published elsewhere.[58]

Invitations to participate in ELSA were sent to individuals who had taken part in HSE in one of the years between 1998 and 2001, inclusive, who were born before or on 29 February 1952, and were still resident in a private residential address in England at the time of the ELSA interview. In total, 31,051 households were invited to take part in HSE in the specified years, with 23,132 households actually participating. From these participating households, 11,578 had as residents at least one age-eligible adult who had

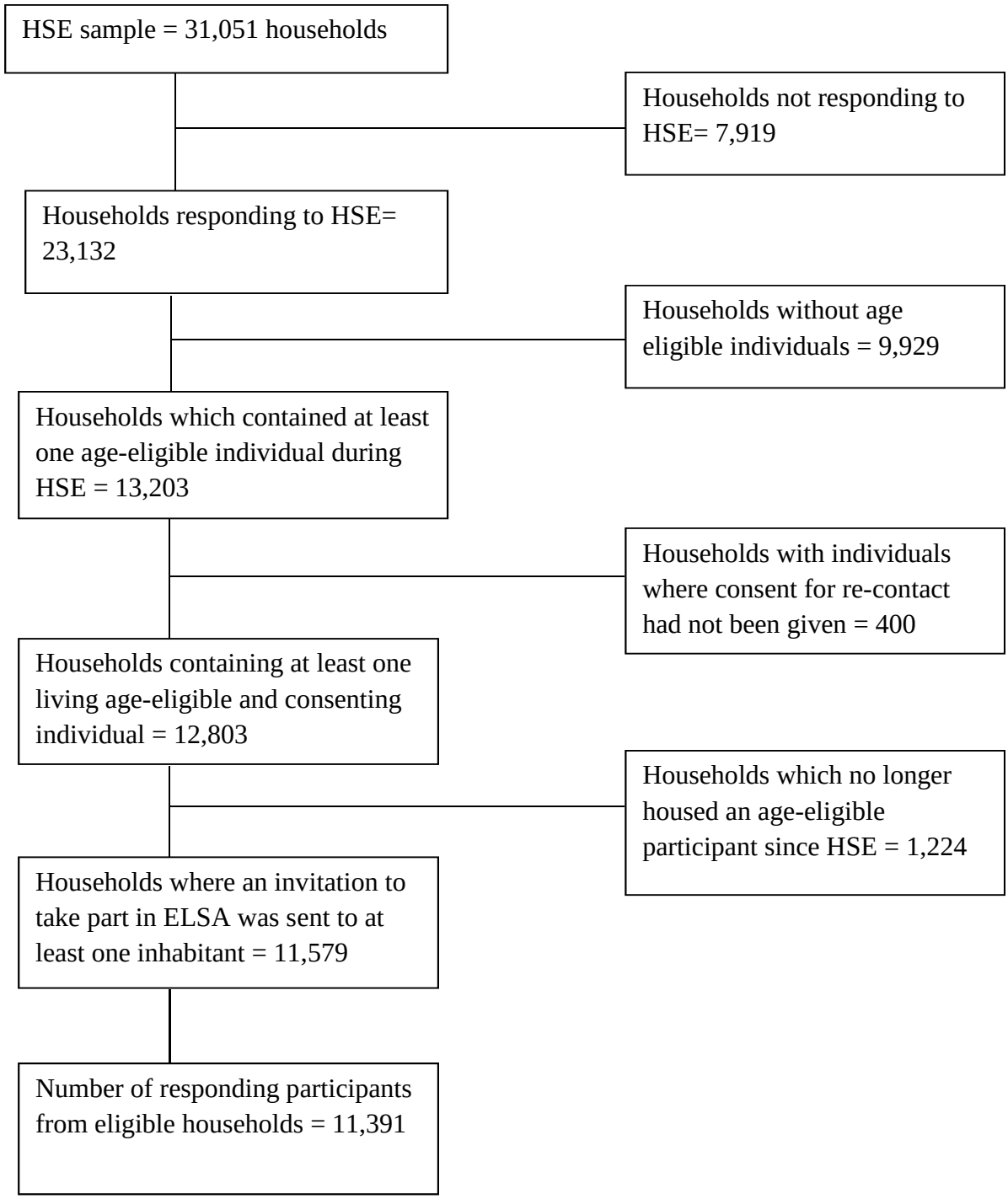
provided consent for re-interview were they selected for participation in ELSA.[59] Figure 3 displays the sample selection stages from HSE to ELSA.

From the 11,579 households invited from HSE, 11,391 individuals took part in ELSA; relating to a response rate of 67%.[60] Also interviewed, but not included in the present study, were 636 partners of eligible participants who were under the age of 50 years, and 72 new partners who had moved into the household since HSE. In total, interviews were thus issued to 12,099 individuals. The 11,391 eligible study members, who shall be referred to here-on as the 'core' participants of ELSA, form the basic level of any sample selection made for the individual investigations contained within this thesis. Additionally, 158 eligible core study members who did not provide responses to the study themselves, but who did so via a proxy will be excluded, as responses via proxy may have introduced reporter bias, and have been identified as being problematic in previous research projects.[61,62]

Data from ELSA participants is collected in two-yearly intervals from the same individuals, with each distinct phase of data collection being referred to as a wave. Core members remain eligible for interview in ongoing waves of ELSA unless they have since died, withdrawn their consent to be interviewed, or emigrated from England. A total of 8,688 core members participated in wave 2 (years 2004/05; response rate 83.7%); 7,382 in wave 3 (2006/07; 75.8%); 6,406 in wave 4 (2008/09; 66.9%), 5,974 in wave 5 (2010/11; 63.9%) and 5,385 in wave 6 (2012/13, response rate unknown at the time of writing). The response rates were calculated by dividing the total respondents to a given wave by total individuals eligible for that wave, where participants who moved into institutions (such as care homes), died or emigrated from England at a particular wave

were not included in the denominator. The calculation of this response rate was not conditional upon response to any previous wave.

Figure 3: Selection of participants to the English Longitudinal Study of Ageing, 2002



In order to maintain the size and representativeness of the ELSA panel, refreshment samples were added in 2006, 2008 and 2012 from subsequent HSE samples. Excluding any young and new partners, and proxy respondents, these refreshments provided 1,261 participants in 2006, a further 2,239 participants in 2008, and 804 participants in 2012. These newer recruits to the ELSA shall be referred to hereon as 'refreshers', who supplement the 'core' sample.

ELSA data are collected mainly through face-to-face interviews by a trained interviewer who captures all the data on a computer using pre-set questions and possible answers. This method of collection is called a computer assisted personal interview, and takes place in ELSA at two yearly intervals. In addition to the interview, consenting individuals receive a visit from a nurse every 4 years who collects biomedical data which includes height, weight, and waist circumference, performs a hearing test, and also takes a blood and saliva sample. Nurse visits have taken place in waves 2, 4 and 6 of ELSA.

The data collected from each participant is more or less the same but has evolved slightly with each wave, with some items added or removed to reflect current interest, issues and concerns, while others were modified to extract a clearer representation of facts. The ELSA study shares a template comparable to that of other studies of ageing in Europe, North America and Asia, whose initial aims, and therefore data collection methods, continue to bear some similarities.[63]

In the following sections, I will describe the data collected from each participant that will be used in more than one investigation in this thesis, and how the information was collected, thus avoiding duplication in subsequent chapters. Ethical approval for all data collection was granted by the National Research and

Ethics Committee. [64] All statistical analyses in this thesis were carried out using StataSE12 software. [65]

3.2 Collection of biological measurements

Biological measurements were collected during the nurse visits, which took place in waves 2, 4 and 6 of ELSA. Full details of the visits are published elsewhere.[66]

Blood pressure: Participants were asked to sit quietly for five minutes to rest prior to blood pressure measurement. They were asked not to smoke, eat or drink during that time. After the five minutes, three blood pressure readings were taken at one minute intervals using an Omron HEM-907 machine. Blood pressure values used in this thesis were derived from the mean of the second and third readings.[67]

Blood sample: Respondents were asked to fast prior to having their blood samples taken, and were given guidelines about when and what they could eat based on their appointment time. During the nurse visit, respondents were then asked when they had last eaten and, if this was in the last 24 hours, what they had eaten. All participants were eligible to have a venous blood sample taken except if they had a clotting disorder, were on anticoagulant drugs or had ever had a fit (including epileptic fit, convulsion or convulsion associated with high fever). Participants who were aged 80 years or over, were diabetic and on treatment, or were considered to be malnourished or otherwise unfit to fast (information obtained from interview) were asked not to fast prior to blood sampling.[66]

Assessment of adequate fasting was carried out using responses to questions asked by the nurse during the visit. Participants were considered to be eligible for a fasting blood sample if they either hadn't eaten or drunk anything (apart from water) on the day of their

nurse visit, or they had not eaten or drunk anything (apart from water) in the 5 hours preceding the appointment, and had only had a light meal (as per appointment record card) or a piece of fruit or drink the last time they ate. Blood was only taken from participants on one occasion at each wave, so if they had fasted adequately then all measurements were recorded as fasting, otherwise they were non-fasting measurements.

All the blood analytes (except blood glucose) were measured for all the blood samples (i.e. both fasting and non-fasting samples). Therefore, in some cases the lipids measures were on fasting samples, and other times not. Blood samples were sent to a single laboratory (Royal Victoria Infirmary, Newcastle, UK) where a number of analyses were carried out, and the levels of certain compounds in the blood were measured. Specific to this thesis, high density lipoprotein (HDL), low density lipoprotein (LDL), and total cholesterol were measured at all nurse visits from wave 2, while IGF-1 was measured for the first time at wave 4 (2008).[66]

In some instances, blood measurements were not taken from participants who had previously given consent to have their samples taken due to events that happened before, during or after the sampling attempt by the nurse. Firstly, sampling was not attempted if the patient reported feeling very anxious or nervous, or feeling faint. That not being the case, sample collection failed in some instances due to low tolerance of having a tourniquet applied, poor or collapsing veins, and failure to draw sufficient blood from a vein. Following sampling, some samples were discarded if they did not contain the required amount of blood. Finally, samples from a number of participants failed to arrive at the laboratory for reasons unknown.

3.3 Measures of depression in the ELSA

Depression was assessed among ELSA participants using two measures of symptomatic mental health; both of which are composite tools made up of distinct questions, and by asking participants if they head been diagnosed of depression by a physician. For this study, one measure of symptomatology was used as the primary measure of depression, while physician-diagnosed depression was used in some cases as a secondary measure.

Primary study outcome: Depression symptoms

The shortened 8-item Center for Epidemiologic Studies Depressive (CES-D 8) scale,[68] applied via the computer assisted personal interview, was used to quantify symptoms of depression among participants. The CES-D has been widely used in population-based epidemiological studies of older groups[69] and has been validated against clinician-assessed depression and clinical ratings of severity of depression to discriminate between psychiatric patients and general population samples.[70] In one study where 8 self-report depression tools for use among geriatric cancer patients were compared, it was noted that the CES-D was the most validated for use among both geriatric and cancer patients[71], while it was concluded in another that depression scores as measured by the CES-D were convergent with clinicians' scores.[72]

Each item of the 8-item CES-D requires a dichotomous (yes/no) response, with scores ranging between 0 and 8 (higher score denotes more severe symptoms). Notably, this shortened CES-D 8 (which shall be referred to simply as the CES-D hereon) has good internal consistency (Cronbach's α 0.78) and similar psychometric properties to the full 20-item scale.[73] Table 1 displays all 8 questions as asked in ELSA. In this study, consistent with other analyses, CES-D scores were converted to a binary variable, with 4 symptoms and above denoting 'caseness' for depression symptoms.[74]

Table 1: The individual components of the 8-item CESD

No.	Questions, led by the leader statement: 'Much of the time during the past week, …'
1	… Have you felt depressed?
2	... Have you felt that everything you did was an effort?
3	… Has your sleep been restless?
4[a]	… Were you happy?
5	… Have you felt lonely?
6[a]	... Have you enjoyed life?
7	… Have you felt sad?
8	… Could you not get going?

[a] Item reverse coded for scoring

Secondary outcome: Physician diagnosis of depression

Ascertainment of physician-diagnosis of depression in ELSA was through solicited self-reporting during the interview. That is, participants were asked if they had been told by a doctor that they had emotional, nervous or psychiatric problems, a question which was then followed up by asking what the specific problem was. Given that depression is often undiagnosed, and that the diagnosis was self-reported, physician-diagnosis of depression is regarded as a secondary outcome in this study where mentioned (relative to symptom reporting), and shall be used in some instances to test convergence of results.

Assessment of depression through self-reports of diagnosis has been validated in a cohort study. There, responses to the question, 'Have you ever been diagnosed of depression by a physician?' were compared to diagnosis according to the Structured Clinical Interview

for DSM-IV (SCID-1) as applied by a psychiatrist or a clinical psychologist. The specificity of self-report assessments, where diagnosed depressed individuals reported as such, was 74.2% (95% confidence interval (CI) 63.3, 85.1), while sensitivity (confirmed non-depression) was 81.1% (95% CI 69.1, 92.9).[75]

3.4 Covariates

Consideration of the covariates that could serve as mediators or confounders of the association between depression symptoms and IGF-1, Internet use, and cardiovascular disease risk factors was based on evidence from the literature and *a priori* knowledge of the separate conditions/factors. Bivariate analyses were used to confirm whether each covariate considered was related to depression symptoms. To simplify interpretation and provide some uniformity, selected covariates were grouped in themes, and shall be described within that context in the next section. Only covariates common to all the three major sub-studies in this thesis shall be described at this point, with any others being discussed in the relevant chapters.

Socio- demographic factors

Although sometimes conflicted, there is a wealth of evidence highlighting the relationship between age and depression. Age is generally considered to be a common modifier of a multitude of risk factors, as the human body and its responses to various stressors and interventions invariably change with time. A large body of evidence highlights how age determines circulating IGF-1 levels,[76] and how it modifies cardiovascular disease risk factors.[77] With regards to Internet use, a small but growing literature describes differences in frequency of access, activities undertaken, and modems of access based on age.[78] In ELSA, age is a continuous variable, measured in years.

Other than age, gender is also often considered as a confounder or effect modifier, and there certainly is evidence of its association with depression,[79] IGF-1,[80] Internet use,[81] and cardiovascular disease risk factors.[82] Evidence from several studies of older people have shown that women are more likely than men to be exposed to factors associated with depression such as low education, lower skilled occupations, lower income and earlier widowhood.[83,84]

Longitudinal research from as early as the 1950s indicates that low socioeconomic status (SES) is significantly and persistently associated with depression and due to the chronic nature of their relationship, it has often been noted that their association at the end of most studies tends to be the same as at the start.[85] With wealth and education often being viewed as composite measures of socio-economic status in studies of older people, it is unsurprising that previous ELSA studies showed that participants who reported low education and low wealth were also more likely to report low quality of life and depression.[86,87]

Wealth, which is considered to be a better measure than education,[88] was ascertained in ELSA through collection of detailed information on different dimensions of wealth, based on the value of financial, physical and housing wealth owned by the household (ie, a single respondent or a responding couple along with any dependent individuals) minus any debt. From this, quintiles of net non-pension wealth were derived by data depositors.[89] Level of education in ELSA was ascertained by asking participants to report their highest qualification from a list provided, as well as the year that they left full-time education. From this, educational qualifications were derived and categorised as 'no qualification', 'completed secondary [high school] education', 'educated beyond secondary education but below degree level', and 'educated beyond degree level'.

Marital status is believed in some cultures and societies to have an effect on one's psychological health, especially in later life.[90] One study of participants from 14 centres in 11 countries across Europe identified an association with depression in some but not all centres, with 2 out of the 3 UK centres adding to the evidence of this association.[91] Marital status also tends to be considered as a confounder in a number of studies as it introduces some form of learned behaviour or pressure than can be attributed to the spouse or partner,[92] and as such it shall be considered in this study, where behaviours such as Internet use, blood sample donation, and cardiovascular disease risk factors can be influenced by another person.

Information on marital status was obtained in ELSA both through the face-to face computer assisted personal interview and via the self-completed questionnaire. From that, a cohabiting status variable was derived in two steps. Firstly, participants were split into 3 groups which reflected whether they (i) were living with a partner (married or not), (ii) were not living with a partner but had previously been married/ cohabiting, or (iii) were not living with a partner and had never been married. From these, two final groups were formed which reflected whether a participant was living with a partner or not (regardless of whether they were married or not).

Behavioural Factors

The association between smoking and depression has more often been investigated in adolescents and young adults, among whom there is strong evidence that smoking is associated with depression. Plausibly due to selective development of chronic illness and mortality among heavy smokers, a phenomenon referred to as the "depletion of susceptibles" effect, smoking typically shows a decline with age which has been found to

be true in ELSA.[93,94] This process of selection and decline may be the reason for the conflicting evidence for the association between smoking and depression in older people, with one study of participants from different age cohorts finding no association in the older cohorts,[95] and another finding an association only among 'heavy' and ex-smokers.[96]

Alcohol consumption has at times been observed to offer paradoxical results with relation to certain health outcomes; hence the term 'the French Paradox', where increased consumption of alcohol was found to be associated with reduced cardiovascular risk.[97] In a similar fashion, previous studies have shown increased alcohol consumption not only to be more prevalent among those of higher social status,[98] but also to be inversely associated with a number of negative health outcomes. In particular, one study illustrated lower levels of cognition and well-being and more depressive symptoms in older people who abstained from alcohol, compared to those who consumed no more than one drink per day. Individuals who drank more than 1 to 2 alcoholic drinks per day had significantly higher levels of cognition and well-being, and fewer depressive symptoms than those who consumed no more than one drink per day.[99]

Participants in ELSA were asked if they had ever smoked, and individuals who responded in the affirmative were asked if they were still smokers at the time of data collection. Participants who responded "yes" to both questions were classed as current smokers,[100] and as such a binary variable for smoking will be used. This measure of smoking status was been validated against saliva cotinine levels in HSE.[101] A number of questions eliciting detailed reports of amounts of alcoholic beverages consumed and frequency of consumption were asked in ELSA. From the reports of frequency, a binary variable has been created for this study which shows if individuals consumed alcohol daily or less than daily in the year preceding year, with consumption on at least 5 days of the week being

classed as daily consumption. This method of classifying alcohol consumption has been used in previous studies of ELSA participants.[102, 103]

Comorbidities

Co-morbidities refer to the presence or absence of physical illness, as well as how participants rated their health. For consideration in this study, a binary variable for physical illness was derived from reports of any physical illness, with a report of at least one illness denoting caseness. Self-rated health, which can be viewed as an indicator of how one views their early life experiences, family history, socio-demographics, and health behaviours,[104] was reported in ELSA ranging from very bad to excellent. This was based on responses to questions asking participants to rate their health, responses to which were categorised for this study as either 'fair to very bad' or 'good to excellent'.

3.5 ELSA sample characteristics

Prior to describing the investigations carried out using data from ELSA, it is useful to gain some understanding of the characteristics of the whole ELSA sample, as different sub-samples of this will be used to investigate different associations. Of the 11,391 core participants of ELSA, 293 had missing values for the main outcome of interest, depression symptoms, and a further 158 responded via a proxy; all 451 participants shall therefore not be included in any analyses of the predictors of depression in this thesis. As such, it is important that any differences between these individuals and the remaining 10,940 be identified, as they may impact on the applicability of the results of this study to the general population.

Table 2 displays the psychological and behavioural characteristics of ELSA participants firstly according to gender, as it is generally accepted that such characteristics may be

different between men and women. The same table also displays baseline characteristics according to depression symptoms, categorised as ‘yes’ (4 symptoms and above), ‘no’ (0 to 3 symptoms), and ‘missing’ (participants with no values for depression symptoms).

The average age of the 11,391 participants of ELSA (6,205 female) was 65.27 years (se, 0.10), and at the start of the study, the average reported CES-D score for all participants was 1.59 (se, 0.02). About a third of ELSA participants perceived their health as being fair to very bad and more than half had at least one chronic physical illness (71.10%; se, 0.42). While the average household size was 2.03 (se, 0.84), a little over 10% of participants reported that they felt lonely, and although 42.70% (0.46) of participants had no educational qualification, less than a fifth of participants were in the lowest wealth quintile, and approximately a third did not live with a partner. Almost a third of ELSA participants reported drinking alcohol daily, while almost 20% reported that they were current smokers. More than half of participants reported that they did not use the Internet at the beginning of the study (62.72; se 0.45).

Female participants were generally older and markedly less educated, poorer, and reported more chronic illness their male counterparts. They also reported having more depression symptoms, having more feelings of loneliness, and were more likely to live alone compared with men. Male participants on the other hand were more likely to drink alcohol daily, use the Internet, and tended to live in somewhat larger households. Even though women reported having more physical co-morbidities, their perception of their health was about the same as that of male participants.

Participants who had symptoms of depression in ELSA (reported 4 or more depression symptoms) were more likely to be female, less educated, poorer and current smokers.

Depressed individuals were also more likely to live alone, and were much more likely to report feeling lonely and had lower perceptions of their health. Somewhat un-intuitively, participants without depression symptoms, compared to those with depression, were more likely to consume alcohol daily.

Participants with missing values for depression symptoms were noticeably older than all other participants. When compared with participants who reported not having depression symptoms, they were also disadvantaged in terms of wealth, education, chronic physical illness - but not to the same extent as those that reported having depression symptoms. The household sizes and reported Internet use of participants with missing values for depression were similar to those who had no depression symptom, with both groups also reporting more Internet use than those who had high depression symptoms. Of all three groups, participants with missing values for depression were the least likely to be current smokers.

Table 2: Baseline characteristics of 11,391 participants from the English Longitudinal Study of Ageing according to gender and depression symptoms in 2002

	Gender		**Depression symptoms ≥ 4**			**All**
Covariates[a]	**Male** (5,186)	**Female** (6,205)	**No** (9,148)	**Yes** (1,792)	**Missing (incl. proxy)** (451)	
Demographics						
Female, %	0 (0)	100 (0)	52.42 (0.52)	65.12 (1.12)	53.65 (2.91)	54.47 (0.47)
Age, years	64.87 (0.14)	65.60 (0.14)	64.83 (0.11)	66.27 (0.26)	70.09 (64.17)	65.27 (0.10)
Does not use the Internet, %	58.00 (0.69)	66.66 (0.60)	62.63 (0.51)	72.21 (1.06)	26.61 (2.08)	62.72 (0.45)
CESD score, mean	1.33 (0.03)	1.81 (0.03)	0.84 (1.03)	5.40 (0.03)	-	1.59 (0.02)
SES, %						
No educational qualifications	36.64 (0.67)	47.77 (0.63)	39.24 (0.51)	58.26 (1.17)	51.00 (2.36)	42.70 (0.46)
Lives alone	21.96 (0.57)	39.15 (0.62)	27.70 (0.47)	49.33 (1.18)	33.26 (2.22)	31.32 (0.43)
Lowest quintile of wealth	17.39 (0.53)	20.55 (0.51)	15.93 (0.38)	33.93 (1.12)	24.83 (2.04)	19.11 (0.37)
Behavioural Factors						
Drinks alcohol daily	35.09 (0.66)	21.41 (0.52)	29.41 (0.48)	21.37 (0.97)	16.85 (2.56)	27.64 (0.42)
Current smoker	17.18 (0.52)	17.84 (0.49)	16.34 (0.39)	25.78 (1.02)	9.09 (1.36)	17.54 (0.36)
Comorbidities, %						
Has chronic physical illness[b]	68.61 (0.60)	73.18 (0.56)	68.69 (0.48)	82.31 (0.90)	75.39 (2.03)	71.10 (0.42)
Fair to very bad self-rated health	31.08 (0.64)	31.49 (0.59)	25.21 (0.45)	62.61 (1.14)	30.60 (2.17)	31.31 (0.43)
Isolation						
Number of people in household, mean	2.17 (0.01)	1.92 (0.01)	2.07 (0.92)	1.84 (0.02)	2.12 (0.05)	2.03 (0.84)
Often feels lonely, %	10.49 (0.43)	15.84 (0.46)	6.17 (0.25)	51.67 (1.18)	8.20 (1.29)	13.41 (0.32)

[a] Percentage or mean (se)

[b] High blood pressure or hypertension, angina, heart attack, congestive heart failure, heart murmur, cardiac arrhythmia, diabetes, cerebral vascular disease (stroke), asthma, chronic lung disease, arthritis, osteoporosis, cancer

Chapter 4: Insulin-like growth factor 1 and risk of depression in older people

4.1 Literature review

4.1.1 Introduction

Human Insulin-like Growth Factor 1 (IGF-1) is a unique, dynamic and complex 70-amino-acid residue single-chain peptide with 3 disulfide bonds; structurally related to human pro-insulin (precursor to insulin).[105] IGF-1 is produced under instruction of the IGF-1 gene, whose complex transcription occurs not only in two variants, but also takes place in at least 2 transcription start sites. The two different variants are expressed either specifically in the liver or in many other tissue sites across the body.[106]

The IGF-1 in circulating serum is generated by the liver under the control of growth hormone, while that produced in other tissue mostly has autocrine effects. Once liver-generated IGF-1 is excreted into the blood-stream, it exerts all of its known physiologic endocrine effects by binding to IGF-1 receptors in various sites, through a process modulated by both growth hormone and multiple IGF-1 binding proteins.[107] Crucially, IGF-1 and growth hormone have a reciprocal relationship (referred to as the somatotrophic axis), where one mediates the production and function of the other; and this lifelong relationship is believed to not only influence growth and development, but also determine some longevity and ageing processes.[108]

Principally recognised as a growth hormone, IGF-1 plays an integral role in mediating the role of growth hormone in prenatal growth and development,[109,110] and while it is more abundantly available in the early years, it continues to affect function and growth through the lifetime. It has been ascertained that IGF-1 directly controls prenatal growth with little input from growth hormone, a role which recedes after infancy and childhood, where growth hormone is the driving force for growth and development.[111] Subsequently,

serum levels of IGF-1 increase during childhood, peaking in puberty in tandem with height velocity, and remaining like this until approximately a year after the height surge has ceased.[112,113] Following this peak, IGF-1 levels return to pre-pubertal levels, and continue to decline with increasing age.[114]

IGF-1 is a potent mediator of cell mitosis and inhibits apoptosis, and is necessary for cell differentiation in normal tissue.[115] Elevated IGF-1 levels are associated with increased skeletal muscle and tissue growth,[116,117] bone mineral density,[118] and risk of selected malignancies,[119,]and cardiovascular disease.[120] Meanwhile, low levels of IGF-1 have been implicated in a number of vascular pathologic states, including atherosclerosis, hypertension and stenosis, as well as angiogenesis and vascular growth responses in insulin-deficient diabetes and hyperinsulinemia. [121,122] Some studies have also shown an association between low IGF-1 and angiographically documented coronary artery disease, ischemic heart disease and myocardial infarction.[123] With increasing age, as both growth hormone and IGF-1 production reduce[124], pathophysiological and functional changes such as loss of muscle mass, skin thickness, and bone mineral content advance.[125, 126] Intriguingly, a meta-analysis of data from 12 studies illustrated that both low and high levels of IGF-1 were associated with increase mortality in the general population, and U-shaped patterns of association were observed for cancer and CVD in particular.[127]

4.1.2 Insulin-like Growth Factor 1 and depression

Although the aetiological role of weight, height, genetics, inflammation and several biomarkers in the development of depression has been examined,[128] relatively less attention has been paid to biological risk factors as a whole. Initial indications that IGF-1 may play a role in the development of depression in humans were observed in clinical

studies where depressed patients exhibited markedly elevated plasma IGF-1 levels, compared to healthy controls.[129,130] Subsequently, it was also identified that IGF-1 levels decreased during acute changes of stress related hormones such as cortisol and norepinephrine, once again indicating that IGF played a role in the pathophysiology of mood disorders.[131]

While the exact molecular and cellular basis of depression is not fully understood, it is characterised as the loss of control of psychological homeostasis, which is believed to result from a multifactorial interplay of neurochemical and/ or neuropeptide imbalances; particularly in the hippocampal region,[132] often connected with lifecourse and/ or environmental stressors, and possibly involving genetic vulnerability and affective temperament.[133] Specifically, disruptions in neuronal production (neurogenesis), and the integrity of the pathways and synapses formed by those neurons (neural plasticity) in the hippocampal region, are believed to play a significant role in the development of depression.[134,135]

Although the hippocampus mainly performs an important role in memory and learning, there is evidence that in disorders such as major depression, schizophrenia and bipolar disorder, the hippocampal complex is reduced in volume,[136] a state which is believed to be partially dependent upon reduced neuronal production, growth, survival and function.[137,138,139] Known precursors for this state include neutrophic factors; a term which includes all biomolecules that are responsible for the growth and survival of neurons, such as IGF-1.[140]

IGF-1 is an important mediator of brain function through a number of actions such as neuroprotection, modulation of neuronal excitability, brain angiogenesis, hippocampal

neurogenesis and neural plasticity.[141] It is also believed to promote and maintain dendritic branching, oligodendrogenesis, and is thought to regulate neurogenesis in a dose-dependent manner.[142] Serum IGF-1, which crosses the blood brain barrier, is needed in the adult brain for both basal hippocampal neurogenesis and exercise-induced increases of neurogenesis.[143] With increasing age, reduction in IGF-1 results in the reduction of hippocampal neurogenesis, and neuroprotection;[144] changes which are believed to be important factors in precipitating episodes of depression.[145]

4.1.3 Animal and laboratory based studies of the relationship between IGF-1 and depression

To date, trials to investigate the effect of IGF-1 on depression have only been carried out in mammals. Evidence from rodent studies showed that the dysregulation of IGF-1 results in marked changes in not only learning and memory, but also in mood. IGF-1 deficient mice displayed worse learning capability and memory skills compared to age-matched control littermates.[146] With regards to mood, it was observed that application of a viral vector to drastically reduce circulating IGF-1 levels resulted in mice showing signs of depression as assessed using standard laboratory mood tests such as the forced swim and tail suspension tests. Furthermore, mice whose IGF-1 had been knocked out exhibited greater immobility in the forced swim test, and qualitatively similar results were found for the tail suspension test.[147]

Results from studies of stressed mice showed that peripheral administration of IGF-1 produced antidepressant-like behaviour, indicating that IGF-1 could induce functional behavioural consequences relevant to depression. Mice that were chronically treated with IGF-1 performed better at the forced swim test than those that had not received IGF-1 infusions. The effect seen was similar to that observed in other studies where mice had

been treated with known antidepressants.[148, 149] A similar study of stressed rats that were treated with IGF-1 and brain-derived neutrophic factor infusions illustrated that the two had similar odds of improving mood as measured by the forced swim test, relative to mice that received no treatment.[150]

Evidence from laboratory studies suggests that expression and function of IGF-1 is similar in humans and rodents.[151,152] In laboratory-based experimental studies of humans, through a range of mechanisms such as altered neuroprotection, modulation of neuronal excitability, brain angiogenesis, hippocampal neurogenesis and neuroplasticity,[153,154] alterations of IGF-1 levels have been linked to hippocampal dysfunction, which in turn have been associated with mood disorders.[155,156] IGF-1 expression in the hippocampus has also been found to be reduced in sufferers of depression, and enhanced by the administration of antidepressants.[157]

4.1.4 Human studies of the association between IGF-1 and depression

Clinical studies of humans have produced apparently contradictory findings of the effects of the somatrotrophic axis on depressive disorders. While potentially a result of social inequalities, individuals with conditions related to growth hormone deficiencies such as dwarfism are known to report higher lifetime affective disorders than the general population. Of note, treatment of these individual with growth hormone infusions have been proven to result in improvements in perceived energy levels and elevation in mood compared to those treated with a placebo.[158] As with growth hormone deficient individuals, higher lifetime affective disorders were also often reported by individuals with conditions of growth hormone excesses such as acromegaly,[159] Moreover, in a study of individuals with prior acromegaly, it was found that they reported worsening quality of life when they experienced subsequent deficiencies in growth hormone following

treatment for their acromegaly.[160] Conversely, depressed patients whose IGF-1 levels were significantly higher compared to their healthy controls exhibited a reduction in those levels after successful antidepressant treatment. [161, 162]

To my knowledge, two general population studies have been carried out to investigate the association between IGF-1 and depression to date. The first consisted of 3,141 participants aged between 20 and 79 who were followed up for five years between 2002 and 2006. From this study, it was illustrated that low IGF-1 levels in women and high levels in men were predictive of depression.[163] However, this study was somewhat limited by the use of a non-Standard scale of measuring depression, which is of unknown validity. Taken from the 12-item Composite International Diagnostic Screener (CID-S), which is used in its full form as a first-line screening tool for a number of psychiatric disorders, a two-item subset was used to assess participants for depressive disorders in this study.

The full CID-S is a WHO tool used to screen for anxiety disorders, panic disorders, social phobia, agoraphobia, general anxiety disorder, specific phobia, and any depressive disorder according to the DSM-IV and ICD-10. Although the CID-S is a highly sensitive in identifying potential cases to be followed up using a secondary tool, it is not itself a diagnostic tool. Furthermore, the CID-S has moderate sensitivity for identifying depressive disorders when compared with some of the other disorders it screens for. Therefore, the two items of the CID-S used in the described study may not by themselves be adequate as measures of depressive disorders in the manner in which they were used.[164]

This study was further limited by very low incidence of depressive disorders observed in some IGF-1 categories. Indeed, only 2 male and 16 female cases with depressive disorders

were identified in one of the three IGF-1 categories, and only 9 females and 12 males were identified in another. This undoubtedly reduced the statistical power of the study, and was cited by the authors as the likely explanation for the sex differences they observed.

The second study consisted of people aged 65 years and over. Cross-sectional analyses based on tertiles of IGF-1 in 1,188 participants indicated that men with normal IGF-1 levels were less likely to have minor depression than men with high levels. In women, a trend toward increased probability of prevalent major depression was observed in respondents with low IGF-1. From longitudinal analyses, it was observed that relative to moderate levels, women with high IGF-1 values experienced an elevated risk of minor depression.[165]

While participants invited to take part in this study may have been nationally representative, bias may have been introduced to the study by non-response and loss to follow-up. According to the authors, non-responders (who formed 21% of the selected sample) were older and had much higher reports of depression symptoms. Individuals lost to follow-up for the prospective analyses were also older and had lower baseline IGF-1 concentrations, indicating that observed associations may have been underestimated. This second study was also limited by very low incidence of depressive disorders in some categories of IGF-1. While only 6 participants (male and female) reported major depression in the middle tertile, 49 reported having symptoms of depression in the same group. With total reports of major depression amounting to 25 participants out of the whole study sample, results were clearly subject to low statistical power.

Accordingly, against this background of study paucity, discordant findings, and methodological concerns, the following study details an examination of the cross-sectional and longitudinal association between IGF-1 and depression symptoms in a large, well-established general population-based study of older adults in England (United Kingdom). Details of this study have been published and presented elsewhere (appendices 1, 2, 3 and 4). [166]

4.2 Aims and objectives

The aim of this present study is to investigate whether IGF-1 is associated with depression symptoms in older people. To meet this objective, the main research questions that I would like to answer are:

- Are individuals with depression symptoms more likely to have low serum levels of IGF-1?
- Are individuals with low serum levels of IGF-1 more likely to develop depression symptoms than those with normal or high levels?
- Are there gender differences in risk of depression in relation to IGF-1

4.3 Methods

4.3.1 Selection of study participants

Participants for the present study were selected from wave 4 of ELSA which took place in 2008. A more detailed description of the ELSA sample can be found in Chapter 3. Biological measurements in ELSA, which were taken during the nurse visit, took place at every other wave, and measurement of serum IGF-1 levels commenced in wave 4, which will represent the 'baseline' for the present analyses. All associations were analysed according to quintiles of IGF-1 for better categorisation of results while allowing

for some comparison according to reference ranges and ensuring adequate sample numbers in each category. Similar categorisation has been used in other studies of ageing and psychological function in relation to IGF-1.[167] Depression was measured at baseline, and at follow-up; which for the purposes of this study, occurred at wave 6.

In Figure 4, the process for selection of participants from core ELSA participants to this present study is illustrated. Of 11,233 participants who were recruited to ELSA in 2002 and had not responded via a proxy, 1,347 had been lost to follow-up by 2008. Of the remainder, 1,688 participants declined a visit from the nurse in wave 4, and were thus excluded because of lack of IGF-1 values. A total of 2,593 'refresher' participants who had consented to a nurse visit (744 recruited in 2006 and 1,849 in 2008) were added to the original core participants, resulting in 8,218 participants that were eligible for investigation of the association between IGF-1 and depression symptoms.

Following the nurse visit, a total of 2,158 participants were excluded from the study as they did not have IGF-1 values. This comprised people who declined to give blood (771), blood sample which were either unsuitable for processing or were lost in transit (395), or failure to obtain blood sample from a participant who had consented (992). Also excluded were participants who had missing values for depression symptoms (43). None of the participants had missing data for physician-diagnosed depression at baseline. The cross-sectional sample therefore comprised 6,017 study members from data collection in 2008.

Participants for longitudinal analysis comprised those participants from cross-sectional analyses as described above, but included only those participants who had values for depression at follow-up. In these analyses, IGF-1 values were based on measures taken in 2008 and were related to new (incident) cases of depression at resurvey in 2012. In

deriving new cases of depression participants who were classed as depressed in 2008 were excluded; limiting longitudinal analyses to only those participants who were free from depression at baseline. This resulted in samples of 4,419 for analysis of depression symptoms and 4,768 for physician-diagnosed depression.

4.3.2 Exposure: Measurement of IGF-1

Whole blood samples were collected from study members and transported to a single laboratory where serum was separated, frozen at 40^{o}C, and batch-assayed (completed in 2008) using the DPC Immulite 2000 method. The inter-assay coefficient of variation for IGF-1 across a range of levels was <=3.7%, and the intra-assay coefficient of variation was <=5.3%. IGF-1 values are reported as whole numbers (range: 3 to 200 nanomoles per litre [nmols/l]).[168] In the ELSA sample, all participants with IGF-1 values recorded as 'less than 3' were assigned a value of 2nmols/l.

4.3.3 Outcomes: Depression symptoms and physician-diagnosis of depression

The main outcome in these analyses is depression symptoms, which were measured using the 8-item CES-D, which is described in detail in Chapter 3.3. Physician diagnosis of depression (also described in Chapter 3.3) was used as a comparator for these present analyses.

4.3.4 Covariates

Covariates, which included potential confounders, were grouped according to theme. Anthropometric measures comprised height and weight which were measured during the nurse visit; body mass index (BMI) (kilograms/metre^{2}) was calculated by dividing each individual's measured weight by height squared. Psychosocial factors were: level of education (no qualification, completed secondary [high school] education, educated

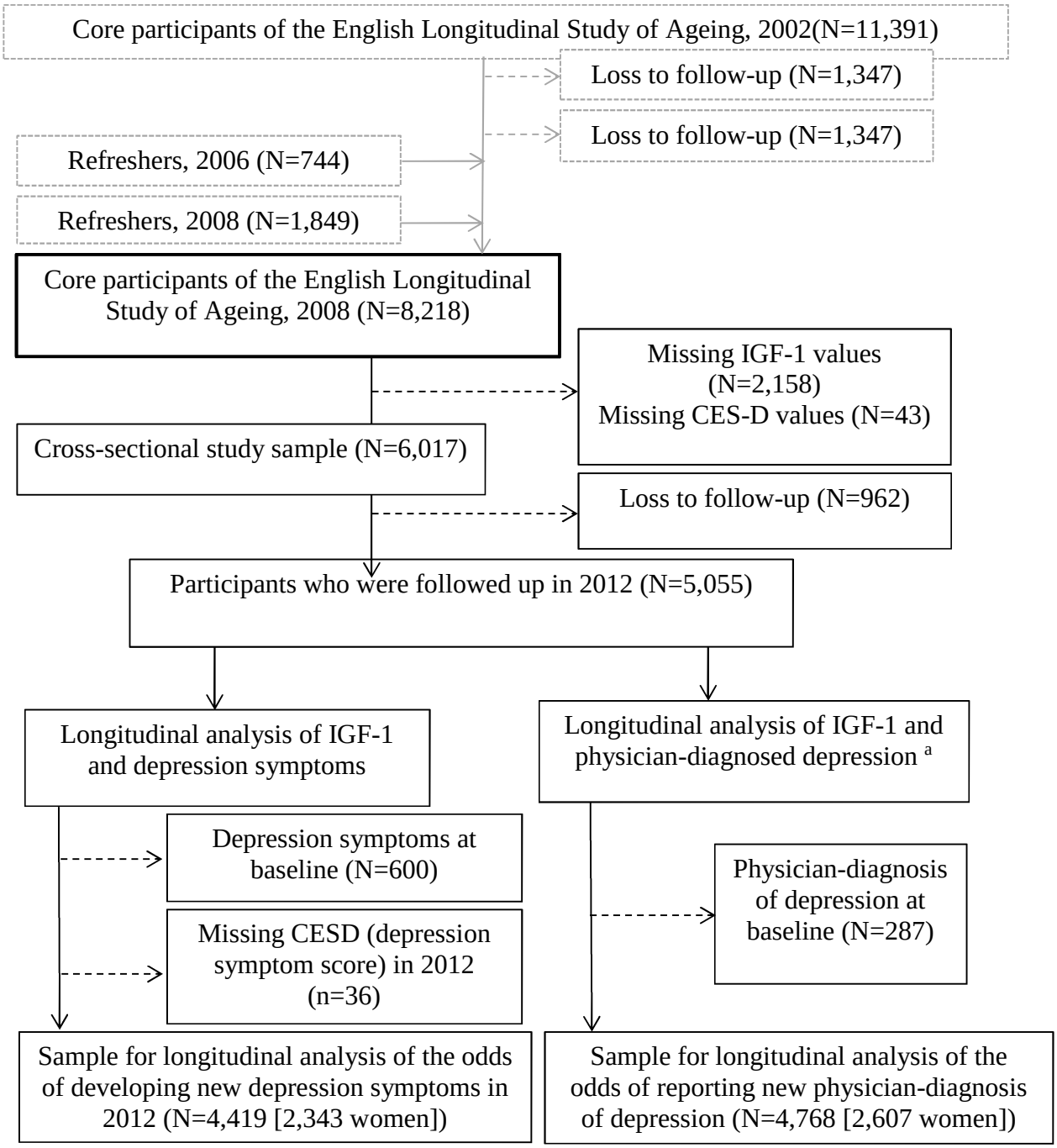
beyond secondary education but below degree level, and educated beyond degree level); quintiles of net non-pension wealth (derived from an estimation of financial wealth and physical assets reported by study participants and their partners, excluding pension savings and net of debts such as credit cards and loans);[169] and marital status (currently living with a partner or not).

Health-related behaviours comprised: smoking status (current, ex-smoker, and never), frequency of alcohol consumption in the past year (less than daily/ daily, with consumption on at least 5 days of the week being classed as daily consumption), and leisure time physical activity (low/sedentary, moderate or high activity of exercises such as jogging, cycling, gardening, walking). Comorbidities were self-reported physician-diagnosis of cancer, diabetes or cardiovascular disease (heart murmur, ischaemic heart disease, abnormal heart rhythm, stroke, valvular heart disease or any other reported heart disease).

4.3.5 Statistical Analysis

Multivariable logistic regression analyses were used to summarise the association of IGF-1 levels with both depression outcomes. The lowest quintile of IGF-1 was used as the referent. There is existing evidence of differential IGF-1–depression relationships in men and women[80] so I present gender-specific analyses here also. Adjustments for known confounders were carries out in a stepwise manner. In these analyses, depression symptomatology was the primary outcome, with physician-diagnosed depression used to test convergence of evidence.

Figure 4: Derivation of the analytical sample for cross-sectional (2008) and longitudinal (2012) analyses of the association between serum IGF-1 and depression in 2012: the English Longitudinal Study of Ageing



[a] All participants had information on doctor-diagnosis of depression both at baseline and follow-up

4.4 Results

4.4.1 Baseline characteristics of study participants

In table 3 (women) and table 4 (men), I present baseline study participant characteristics according to IGF-1 quintiles. As expected, mean IGF-1 values were higher in men

(16.5nmols/l) than women (15.2nmols/l). In both men and women, IGF-1 was inversely associated with age and directly related to height. With regards to somatic conditions, while less than 10% of participants reported having either cancer or diabetes, there was a suggestion that the greatest proportions of sufferers from either disorder had measurements on either extreme of the IGF-1 continuum. Individuals who reported having cardiovascular disease, who constituted almost a quarter of ELSA participants, were also more likely to have IGF-1 measurements in the lowest or highest quintiles of IGF-1.

A socio-economic gradient for IGF-1 levels was observed in participants with the lowest wealth and lowest education, who tended to also have IGF-1 levels in the lowest quintile. Although there was no obvious pattern for distribution of IGF-1 levels according to cohabiting status, having IGF-1 levels in the lowest quintile was typically more prevalent in both men and women who did not have a live-in partner.

A total of 776 participants (12.9%) were 'cases' for depression symptoms at baseline (71.8% were female), and 344 (5.7%) participants reported physician-diagnosis of depression. A higher prevalence of individuals who reported either high depression symptoms or self-declared physician-diagnosed depression was apparent in the lowest and highest quintiles of IGF-1 although the differences across groups were not considerable.

Men and women who were either sedentary or partook in low levels of physical activity were inclined to very low levels of IGF-1, following which they would most likely belong in the highest quintile of IGF-1. In both males and females, current smokers tended to have IGF-1 levels in the highest quintile. There was a

suggestion that women who reported drinking alcohol everyday were more likely to have IGF-1 levels in the highest quintile, while the opposite was true for male drinkers.

4.4.2 IGF-1 and depression symptoms: cross-sectional analyses

In Table 5, the computation of odds ratios for the cross-sectional association between IGF-1 and depression symptoms somewhat supports earlier evidence of an elevated risk of depression symptoms at opposite ends of the IGF-1 continuum in men and women in this study. While men with the highest IGF-1 levels were more likely to report depression symptoms compared to all other groups after accounting for all covariates (OR 1.54; 95% CI 0.90, 1.54), being in the lowest quintile of IGF-1 (referent) was also associated with an elevated risk of depression symptoms, such that individuals who had IGF-1 values in the median range were least likely to report depression symptoms (OR 0.63; 95% CI 0.32, 1.47).

In essence, the relationship between IGF-1 and depression symptoms could be described as U'-shaped. However, statistical significance at conventional levels was not detected. A similar pattern of association was observed in women, but the association was flattened after adjustment for all covariates. The observed attenuation was mostly due to anthropometric measures, and psychosocial factors.

Table 3: Baseline characteristics of study participants according to quintiles of serum IGF-1 in the English Longitudinal Study of Ageing, 2008– 3,311 women

	IGF-1 Quintile (range)					
	1 (2-11 nmols/l)	**2** (12-14 nmols/l)	**3** (15-16 nmols/l)	**4** (17-20 nmols/l)	**5** (21-65 nmols/l)	**All**
Number of participants	861	813	479	681	477	
IGF-1, nmols/l, mean (SE)	9.2 (0.06)	13.0 (0.03)	15.5 (0.02)	18.3 (0.04)	25.2 (0.22)	15.2 (0.10)
Age, years, mean (SE)	68.7 (0.4)	66.2 (0.3)	65.1 (0.4)	64.4 (0.3)	63.2 (0.4)	65.9 (0.2)
Anthropometry mean (SE)						
Height, cm	158.8 (0.3)	159.9 (0.2)	160.4 (0.3)	160.6 (0.2)	160.9 (0.3)	160.0 (0.1)
BMI, kg/m^2	28.7 (0.2)	28.4 (0.2)	27.6 (0.2)	27.7 (0.2)	27.6 (0.2)	28.1 (0.1)
Comorbidities, % (SE)						
Diabetes	8.5 (0.9)	6.0 (0.8)	6.9 (1.2)	5.9 (0.9)	7.8 (1.2)	7.0 (0.4)
Cancer	6.6 (0.8)	4.5 (0.7)	4.6 (1.0)	3.2 (0.7)	6.1 (1.1)	5.0 (0.4)
Cardiovascular disease	26.6 (1.5)	24.4 (1.5)	21.5 (1.9)	18.6 (1.5)	23.9 (2.0)	23.3 (0.7)
Psychosocial factors, % (SE)						
Lowest wealth quintile	23.1 (1.4)	16.0 (1.3)	11.7 (1.5)	15.0 (1.4)	14.5 (1.6)	16.8 (0.7)
No educational qualifications	34.1 (1.6)	30.3 (1.6)	29.0 (2.1)	27.2 (1.7)	23.1 (1.9)	29.4 (0.8)
Lives alone	43.1 (1.7)	37.5 (1.7)	28.4 (2.1)	32.8 (1.8)	36.3 (2.2)	36.5 (0.8)
Behavioural factors, % (SE)						
Sedentary or low physical activity	39.4 (1.7)	30.0 (1.6)	26.5 (2.0)	25.8 (1.7)	30.2 (2.1)	31.1 (0.8)
Current smoking	12.2 (1.1)	13.3 (1.2)	12.7 (1.5)	13.5 (1.3)	16.1 (1.7)	13.4 (0.6)
Daily alcohol intake	15.2 (1.2)	16.0 (1.3)	16.5 (1.7)	15.9 (1.4)	16.8 (1.7)	16.0 (0.6)
Depression						
CESD score, mean *(SE)*	1.8 (0.07)	1.6 (0.07)	1.3 (0.08)	1.5 (0.07)	1.6 (0.09)	1.6 (0.03)
High depression symptoms, % *(SE)*	20.6 (1.3)	15.9 (1.3)	14.4 (1.6)	14.2 (1.3)	17.8 (1.5)	16.8 (0.7)
Physician-diagnosed depression, % *(SE)*	7.1 (0.9)	6.4 (0.9)	5.4 (1.0)	6.5 (0.9)	6.7 (1.1)	6.5 (0.4)

SE = Standard error

Table 4: Baseline characteristics of study participants according to quintiles of serum IGF-1 in the English Longitudinal Study of Ageing, 2008– 2,706 men

	IGF-1 Quintile (range)					
	1 (2-11 nmols/l)	**2** (12-14 nmols/l)	**3** (15-16 nmols/l)	**4** (17-20 nmols/l)	**5** (21-65 nmols/l)	**All**
Number of participants	483	615	384	667	557	
IGF-1, nmols/l (SE)	9.3 (0.08)	13.1 (0.03)	15.5 (0.03)	18.4 (0.04)	25.1 (0.22)	16.5 (0.11)
Age, years, mean (SE)	68.7 (0.5)	65.3 (0.4)	65.0 (0.5)	64.4 (0.3)	64.0 (0.3)	65.4 (0.2)
Anthropometry, mean (SE)						
Height, cm	171.7 (0.3)	172.8(0.3)	173.8 (0.4)	173.8 (0.3)	174.2 (0.3)	173.3 (0.1)
BMI, kg/m^2	28.6 (0.2)	27.8 (0.2)	27.9 (0.2)	28.0 (0.2)	27.9 (0.2)	28.0 (0.1)
Comorbidities, % (SE)						
Diabetes	12.6 (1.5)	6.8 (1.0)	6.3 (1.2)	10.6 (1.2)	11.1 (1.3)	9.6 (5.7)
Cancer	4.8 (1.0)	5.4 (1.0)	4.4 (1.1)	5.2 (0.9)	4.3 (0.9)	4.9 (4.1)
Cardiovascular disease	31.5 (2.1)	24.6 (1.7)	25.7 (2.2)	26.3 (1.7)	27.2 (1.9)	26.9 (0.9)
Psychosocial factors,% (SE)						
Lowest wealth quintile	18.0 (1.8)	13.3 (1.4)	14.3 (1.8)	12.0 (1.3)	13.1 (1.4)	13.9 (0.7)
No educational Qualifications	25.9 (2.0)	20.0 (1.6)	23.4 (2.1)	17.3 (1.5)	16.3 (1.6)	20.1 (0.8)
Lives alone	26.7 (2.0)	20.7 (1.6)	20.8 (2.1)	21.4 (1.6)	16.7 (1.6)	21.1 (0.8)
Behavioural factors, % (SE)						
Sedentary or low physical activity	26.9 (2.0)	18.4 (1.6)	22.1 (2.1)	17.4 (1.5)	21.9 (1.8)	20.9 (0.8)
Current smoking	13.7 (1.6)	12.7 (1.3)	12.8 (1.7)	11.8 (1.3)	14.0 (1.5)	12.9 (0.6)
Daily alcohol intake	28.6 (2.2)	24.7 (1.7)	27.6 (2.2)	26.4 (1.7)	24.1 (1.8)	26.1 (0.8)
Depression						
CESD score, mean *(SE)*	1.0 (0.08)	0.9 (0.06)	0.8 (0.07)	0.9 (0.06)	1.1 (0.07)	0.9 (0.03)
High depression symptoms, % *(SE)*	9.3 (1.3)	7.5 (1.1)	5.7 (1.0)	6.7 (1.0)	11.0 (1.3)	8.1 (0.5)
Physician-diagnosed depression, % *(SE)*	5.2 (1.0)	4.2 (0.8)	4.2 (1.0)	3.9 (0.7)	6.5 (1.0)	4.8 (0.4)

SE = Standard error

Table 5: Odds ratio (95 % Confidence Interval) for the cross-sectional association between serum IGF-1and depression symptoms: the English Longitudinal Study of Ageing, 2008

		IGF-1 Quintile (range)[x]						
		1 (2-11)	**2** (12-14)	**3** (15-16)	**4** (17-20)	**5** (21-65)	P-value for linearity	P-value for quadratic
Women (analytical sample)								
Adjustments	Age (3,311)	1 (ref)	0.76 (0.58, 0.97)	0.69 (0.50, 0.93)	0.68 (0.52, 0.90)	0.91 (0.68, 1.22)	0.027	0.009
	Age, Anthropometric measures[a] (3,181)	1	0.79 (0.61, 1.02)	0.74 (0.54, 1.01)	0.72 (0.54, 0.95)	0.96 (0.71, 1.30)	0.061	0.037
	Age, Co-morbidities[b] (3,308)	1	0.75 (0.58, 0.96)	0.68 (0.50, 0.92)	0.69 (0.52, 0.91)	0.89 (0.66, 1.19)	0.031	0.012
	Age, Psychosocial factors[c] (3,162)	1	0.81 (0.62, 1.06)	0.79 (0.57, 1.09)	0.73 (0.55, 0.98)	0.96 (0.70, 1.30)	0.494	0.026
	Age, Behavioural factors[d] (2,920)	1	0.77 (0.58, 1.02)	0.76 (0.55, 1.06)	0.76 (0.56, 1.02)	0.91 (0.66, 1.25)	0.080	0.078
	Adjusted for all covariates (2,691)	1	0.86 (0.63, 1.16)	0.90 (0.63, 1.29)	0.85 (0.62, 1.29)	1.00 (0.71, 1.41)	0.756	0.199
Men (analytical sample)								
Adjustments	Age (2,706)	1 (ref)	0.75 (0.49, 1.16)	0.56 (0.33, 0.95)	0.66 (0.43, 1.02)	1.12 (0.74, 1.69)	0.008	0.004
	Age, Anthropometric measures[a] (2,627)	1	0.85 (0.54, 1.34)	0.62 (0.35, 1.09)	0.79 (0.50, 1.25)	1.26 (0.81, 1.96)	0.037	0.011
	Age, Co-morbidities[b] (2,696)	1	0.76 (0.49, 1.18)	0.58 (0.34, 0.98)	0.64 (0.41, 0.99)	1.11 (0.73, 1.68)	0.009	0.003
	Age, Psychosocial factors[c] (2,592)	1	0.85 (0.54, 1.34)	0.61 (0.35, 1.06)	0.75 (0.47, 1.19)	1.30 (0.90, 2.16)	0.015	0.045
	Age, Behavioural factors[d] (2,377)	1	0.68 (0.40, 1.16)	0.57 (0.31, 1.06)	0.71 (0.43, 1.18)	1.32 (0.83, 2.12)	0.008	0.052
	Adjusted for all covariates (2,227)	1	0.84 (0.47, 1.50)	0.63 (0.32, 1.24)	0.84 (0.48, 1.47)	1.54 (0.90, 2.64)	0.039	0.153

[x]IGF-1 units are nmols/l
[a] BMI, height
[b]Cancer, diabetes, cardiovascular disease
[c] Own wealth quintile per benefit unit (unit is a couple or single person along with their dependent children), education level
[d]Alcohol consumption, smoking, physical activity

Table 6: Odds ratio (95 % Confidence Interval) for the longitudinal association between serum IGF-1 in 2008 and new depression symptoms in 2012: the English Longitudinal Study of Ageing

		IGF-1 Quintile (range)[x]						
		1 (2-11)	**2** (12-14)	**3** (15-16)	**4** (17-20)	**5** (21-65)	P-value for linearity	P-value for quadratic
Women (analytical sample)								
Adjustments	Age (2,343)	1 (ref)	0.88 (0.60, 1.29)	0.77 (0.51, 1.16)	0.84 (0.53, 1.35)	0.95 (0.60, 1.50)	0.647	0.027
	Age, Anthropometric measures[a] (2,276)	1	0.84 (0.57, 1.25)	0.76 (0.50, 1.16)	0.84 (0.52, 1.36)	0.93 (0.58, 1.48)	0.652	0.033
	Age, Co-morbidities[b] (2,342)	1	0.86 (0.58, 1.26)	0.77 (0.51, 1.16)	0.84 (0.53, 1.35)	0.94 (0.60, 1.49)	0.649	0.014
	Age, Psychosocial factors[c] (2,243)	1	0.90 (0.60, 1.34)	0.86 (0.56, 1.30)	0.90 (0.55, 1.45)	1.06 (0.66, 1.69)	0.816	0.026
	Age, Behavioural factors[d] (2,116)	1	0.91 (0.61, 1.35)	0.76 (0.49, 1.17)	0.86 (0.52, 1.40)	0.93 (0.58, 1.51)	0.915	0.029
	Adjusted for all covariates (1, 969)	1	0.86 (0.56, 1.31)	0.78 (0.50, 1.23)	0.87 (0.52, 1.46)	0.94 (0.56, 1.57)	0.922	0.008
Men (analytical sample)								
Adjustments	Age (2,076)	1 (ref)	0.51 (0.28, 0.91)	0.50 (0.27, 0.92)	0.63 (0.35, 1.15)	0.63 (0.35, 1.13)	0.126	0.002
	Age, Anthropometric measures[a] (2,042)	1	0.51 (0.28, 0.94)	0.50 (0.27, 0.93)	0.66 (0.36, 1.20)	0.63 (0.34, 1.14)	0.142	0.002
	Age, Co-morbidities[b] (2,070)	1	0.52 (0.29, 0.94)	0.56 (0.24, 0.85)	0.64 (0.35, 1.16)	0.65 (0.36, 1.16)	0.098	0.002
	Age, Psychosocial factors[c] (2,031)	1	0.53 (0.29, 0.97)	0.54 (0.29, 0.99)	0.62 (0.33, 1.17)	0.68 (0.37, 1.24)	0.173	0.001
	Age, Behavioural factors[d] (2,076)	1	0.52 (0.27, 0.99)	0.49 (0.25, 0.96)	0.67 (0.35, 1.30)	0.58 (0.30, 1.11)	0.165	0.001
	Adjusted for all covariates (1,765)	1	0.51 (0.25, 1.02)	0.50 (0.22, 0.95)	0.67 (0.33, 1.33)	0.60 (0.30, 1.19)	0.072	0.003

[x]IGF-1 units are nmols/l
[a] BMI, height
[b]Cancer, diabetes, cardiovascular disease
[c] Own wealth quintile per benefit unit (unit is a couple or single person along with their dependent children), education level
[d]Alcohol consumption, smoking, physical activity

4.4.3 IGF-1 and depression: prospective analyses

In total, of the 4419 individuals free from depression symptoms at baseline, 333 individuals (223 female) reported new symptoms of depression at follow-up. In Table 6, the association between IGF-1 and depression symptoms after 4 years of follow-up in participants initially free of depression symptoms at baseline (longitudinal analyses) is depicted. A 'U'-shaped pattern of risk was again observed for the IGF-1–depression association in both genders based on symptomatology. In this instance however, after adjusting for all covariates, men with very low IGF-1 levels (referent) were more likely to develop depression symptoms compared to men with IGF-1 levels were in the highest quintile (OR 0.60; 95% CI 0.30, 1.19). Having IGF-1 levels in the median range was associated with a 50% lower risk of developing depression symptoms after 4 years of follow-up (OR 0.50; 95% CI 0.22, 0.95), compared to having IGF-1 values in the lowest quintile.

In women, risk of developing depression symptoms was similarly elevated for participants whose IGF values in the lowest and highest quintile, while those in the middle quintile were associated with the lowest risk. However, statistical significance at conventional levels was not apparent for these results. There was no statistical evidence that gender modified the IGF-1–depression association (p-value for interaction for the multiply adjusted odds of developing depression symptoms was 0.531)

4.4.4 Sensitivity analyses

Analyses of both cross-sectional and longitudinal associations between IGF-1 and depression were carried out once again as above, with physician diagnosed depression as the outcome. As presented in table 7, in cross-sectional analyses, a 'U'-shaped pattern of

association was apparent in men, such that individuals with IGF-1 levels in the highest quintile (with lowest quintile as referent) had the highest risk of reporting diagnosis of depression (OR 1.04; 95% CI 0.54, 2.00) after adjusting for all covariates. Men with IGF-1 values in the median range had the lowest risk of reporting diagnosis of depression (OR 0.75; 95% CI 0.35, 1.59).

After adjusting for all covariates, women with IGF-1 levels in the lowest quintile were most likely to report physician-diagnosis of depression (referent), followed by those with levels in the second quintile (OR 0.75; 95% CI 0.44, 1.27). Although risk of depression was lower above the 1st quintile, the relationship between IGF-1 and depression in this instance would more appropriately be described as a reverse J-shape, since the lowest risk of physician diagnosed depression was observed in the 5^{th} quintile (OR 0.75; 95% CI 0.49, 1.43). The relationship between IGF-1 and depression was most attenuated by psychosocial factors.

Table 7: Odds ratio (95%Confidence Interval) for the cross-sectional association between serum IGF-1 levels and physician-diagnosed depression: the English Longitudinal Study of Ageing, 2008

		IGF-1 Quintile (range)[x]						
		1 (2-11)	**2** (12-14)	**3** (15-16)	**4** (17-20)	**5** (21-65)	P-value for linearity	P-value for quadratic
Women (analytical sample))								
Adjustments	Age (3,311)	1 (ref)	0.82 (0.56, 1.21)	0.66 (0.41, 1.07)	0.78 (0.52, 1.16)	0.77 (0.49, 1.20)	0.642	0.508
	Age, Anthropometric measures[a] (3,181)	1	0.80 (0.54, 1.19)	0.67 (0.41, 1.08)	0.75 (0.50, 1.15)	0.75 (0.47, 1.19)	0.662	0.671
	Age, Co-morbidities[b] (3,308)	1	0.84 (0.57, 1.23)	0.68 (0.42, 1.09)	0.80 (0.53, 1.21)	0.77 (0.49, 1.21)	0.683	0.676
	Age, Psychosocial factors[c] (3,162)	1	0.87 (0.58, 1.30)	0.73 (0.44, 1.20)	0.81 (0.53, 1.24)	0.75 (0.46, 1.20)	0.396	0.611
	Age, Behavioural factors[d] (2,920)	1	0.80 (0.52, 1.22)	0.71 (0.43, 1.18)	0.77 (0.49, 1.20)	0.78 (0.48, 1.26)	0.169	0.488
	Adjusted for all covariates (2,691)	1	0.88 (0.56, 1.38)	0.83 (0.49, 1.43)	0.86 (0.53, 1.38)	0.75 (0.44, 1.27)	0.483	0.794
Men (analytical sample)								
Adjustments	Age (2,706)	1 (ref)	0.71 (0.40, 1.25)	0.68 (0.36, 1.31)	0.63 (0.36, 1.11)	1.05 (0.62, 1.79)	0.128	0.848
	Age, Anthropometric measures[a] (2,627)	1	0.78 (0.44, 1.40)	0.69 (0.35, 1.36)	0.65 (0.36, 1.17)	1.07 (0.62, 1.87)	0.193	0.865
	Age, Co-morbidities[b] (2,696)	1	0.72 (0.40, 1.26)	0.69 (0.36, 1.32)	0.61 (0.34, 1.08)	1.02 (0.60, 1.75)	0.135	0.841
	Age, Psychosocial factors[c] (2,592)	1	0.74 (0.41, 1.36)	0.69 (0.35, 1.37)	0.63 (0.34, 1.17)	1.30 (0.74, 2.28)	0.003	0.738
	Age, Behavioural factors[d] (2,377)	1	0.72 (0.38, 1.37)	0.81 (0.40, 1.63)	0.71 (0.38, 1.33)	1.05 (0.58, 1.91)	0.420	0.469
	Adjusted for all covariates (2,227)	1	0.75 (0.37, 1.51)	0.75 (0.35, 1.59)	0.64 (0.32, 1.28)	1.04 (0.54, 2.00)	0.353	0.598

[x]IGF-1 units are nmols/l

[a] BMI, height

[b]Cancer, diabetes, cardiovascular disease

[c] Own wealth quintile per benefit unit (unit is a couple or single person along with their dependent children), education level

[d]Alcohol consumption, smoking, physical activity

Table 8: Odds ratio (95% Confidence Interval) for the longitudinal association between serum IGF-1 levels in 2008 and new reports of physician-diagnosed depression in 2012: the English Longitudinal Study of Ageing

		IGF-1 Quintile (range)[x]						
		1 (2-11)	**2** (12-14)	**3** (15-16)	**4** (17-20)	**5** (21-65)	P-value for linearity	P-value for quadratic
Women (analytical sample)								
Adjustments	Age (2,607)	1 (ref)	0.62 (0.32, 1.20)	0.65 (0.33, 1.28)	0.62 (0.28, 1.38)	0.77 (0.38, 1.58)	0.527	0.925
	Age, Anthropometric measures[a] (2,168)	1	0.56 (0.28, 1.11)	0.59 (0.29, 1.17)	0.60 (0.27, 1.33)	0.74 (0.36, 1.52)	0.369	0.824
	Age, Co-morbidities[b] (2,605)	1	0.64 (0.33, 1.26)	0.69 (0.35, 1.36)	0.67 (0.30, 1.48)	0.77 (0.38, 1.57)	0.655	0.840
	Age, Psychosocial factors[c] (2,492)	1	0.52 (0.25, 1.07)	0.64 (0.32, 1.29)	0.58 (0.25, 1.34)	0.78 (0.37, 1.60)	0.315	0.880
	Age, Behavioural factors[d] (2,346)	1	0.49 (0.24, 1.01)	0.58 (0.28, 1.18)	0.68 (0.31, 1.53)	0.63 (0.29, 1.36)	0.046	0.874
	Adjusted for all covariates (2,176)	1	0.39 (0.17, 0.89)	0.51 (0.23, 1.09)	0.65 (0.28, 1.53)	0.61 (0.28, 1.34)	0.174	0.820
Men (analytical sample)								
Adjustments	Age (2,161)	1 (ref)	1.29 (0.48, 3.49)	1.04 (0.37, 2.98)	1.21 (0.42, 3.44)	0.35 (0.09, 1.41)	0.290	0.103
	Age, Anthropometric measures[a] (2,120)	1	1.33 (0.49, 3.58)	1.06 (0.37, 3.03)	1.22 (0.43, 3.50)	0.36 (0.09, 1.47)	0.283	0.114
	Age, Co-morbidities[b] (2,155)	1	1.34 (0.49, 3.62)	1.08 (0.38, 3.08)	1.23 (0.43, 3.52)	0.36 (0.09, 1.45)	0.278	0.111
	Age, Psychosocial factors[c] (2,077)	1	1.37 (0.50, 3.72)	0.82 (0.27, 2.50)	1.30 (0.45, 3.75)	0.38 (0.09, 1.53)	0.649	0.029
	Age, Behavioural factors[d] (1,928)	1	1.15 (0.38, 3.49)	1.08 (0.35, 3.36)	1.31 (0.42, 4.11)	0.38 (0.09, 1.63)	0.563	0.128
	Adjusted for all covariates (1,823)	1	1.34 (0.43, 4.15)	0.92 (0.27, 3.14)	1.52 (0.48, 4.84)	0.45 (0.10, 1.97)	0.686	0.024

[x]IGF-1 units are nmols/l
[a] BMI, height
[b]Cancer, diabetes, cardiovascular disease
[c] Own wealth quintile per benefit unit (unit is a couple or single person along with their dependent children), education level
[d]Alcohol consumption, smoking, physical activity

In total, 113 individuals (74 female) reported that they had been diagnosed with depression by a physician, out of the 4,768 individuals free from depression symptoms at baseline. In longitudinal analyses (table 8), as with depression symptoms, a relationship that could be described as U-shaped was observed for the association between IGF-1 and physician-diagnosed depression; but only in women. Following adjustment for all covariates, women with IGF-1 levels in the lowest quintile (referent) were at highest risk of reporting new diagnosis of depression, while those with levels in the 2nd quintile had the lowest risk (OR 0.39; 95% CI 0.17, 0.89) out of all five quintiles. There was little evidence that IGF-1 was associated with new diagnosis of depression in men as level of risk fluctuated indeterminately across the quintiles. There was no statistical evidence that gender modified the IGF-1–depression association (p-value for interaction after adjustment for all covariates was 0.275).

4.5 Discussion

4.5.1 Main findings of IGF-1 study

The aim of this present study was to investigate whether serum levels of IGF-1 are associated with depression symptoms in older people. The main finding was that, for individuals aged 50 years and over, having serum IGF-1 levels at opposing ends of the continuum was associated with a slightly higher risk of depression symptoms; a relationship best described as U-shaped. Similar results were at times apparent for physician-diagnosis of depression, where a U-shaped of association was observed in cross-sectional analysis of men, and prospective analysis of women.

4.5.2 Comparison with existing studies

The results from this study partially accord with the two population studies on IGF-1 and depression of which I am aware. When compared with data from the Study of Health in Pomerania in Germany,[163] these results were in concordance with the finding that having low levels of circulating IGF-1 was associated with higher risk of developing depression symptoms among women. This present study also highlighted a similar association in men. Present findings were also in partial accordance with evidence from The Longitudinal Aging Study Amsterdam,[165] where associations were found between median levels of IGF-1 and lower risk of both prevalent and incident depression symptoms in women. Once again, the main difference with this present study is that median levels of IGF-1 were associated with lower risk of depression in both men and women.

The 'U'-shaped relationship identified between IGF-1 and depression symptoms is supported by observations of increased reports of lifetime affective disorders in individuals with lower (pituitary dwarfism) and higher (acromegaly) levels of this growth hormone.[170,171,172] As existent general population studies also partially support this U-shaped association between low and high levels of IGF-1, the differential results identified in either study for men and women may be due to statistical instability, and warrants further exploration.

To directly compare the findings, I re-categorised IGF-1 levels in ELSA participants to match the methodology used in the previous studies. In the first instance, as per Sievers et al, I categorised IGF-1 levels at baseline as <10th percentile, between the 10th and the 90th percentile and >90th percentile. Patients with IGF-1 levels between the 10th and

90th percentile were used as the reference group.[163] The results of these analyses in ELSA participants showed that, after 4 years of follow-up, the age-adjusted ORs (95% CI) of depression symptoms for the lowest and highest tenth percentiles of IGF-1 among men were 2.26 (1.25, 4.09) and 1.51 (0.86, 2.68), respectively when compared with those with intermediate levels; while the corresponding results in women were 1.38 (0.93, 2.07) and 1.27 (0.77, 2.10).

Following this, as per van Varsseveld et al, I categorised IGF-1 levels into tertiles, with the last tertile representing the highest IGF-1 concentrations.[165] From these analyses, when compared with the middle tertile, the ORs (95% CI) of depression for the lowest and highest tertiles of IGF-1 among men were 1.14 (0.72, 1.80) and 0.89 (0.55, 1.43) respectively, and corresponding results for women were 1.08 (0.79, 1.49) and 1.14 (0.79, 1.65). Indeed, the combined findings from the two re-categorisation exercises still indicated that having very low and very high IGF-1 levels was associated with increased odds of depression symptoms.

The results from the present analyses are however, partially in contrast with the results from the handful of case-control studies where IGF-1 levels were found to be elevated in patients diagnosed with depression by a physician, compared with healthy controls.[161,162] In the present study, participants were more likely to report that they had already been diagnosed with depression by a physician if they had low levels of IGF-1. Moreover, at follow-up, men who reported new diagnosis of depression were likely to have moderate IGF-1 levels. These results, particularly at follow-up, are likely be due to less statistical power, especially in men, as fewer individuals in ELSA reported diagnosis of depression than reported having symptoms of depression; a scenario often replicated in the elderly

community.[173] As a U-shape pattern of association was indeed observed for IGF-1 and physician-diagnosed depression in women (with more statistical power) at follow-up, it is conceivable that a U-shape likely described the relationship between serum levels of IGF-1 and both diagnosed and undiagnosed depression in both and women.

4.5.3 Antidepressant us and depression state

Possible explanation for inconsistencies in the association between IGF-1 and depression may be due to use of anti-depressants (which was especially explicit in case control studies)[161,162] and their effect on circulating IGF-1 levels. Unfortunately, the role of anti-depressant medication in the relationship between serum IGF-1 levels and depression has often received little attention through the years,[174,175] leading to scant evidence of uncertain value. In addition to indicating that increased levels of IGF-1 reduced symptoms of depression, evidence from animal studies also illustrates how antidepressants may improve expression of IGF-1 and other neutrophic and growth factors in the hippocampus, such that subjects that were given anti-depressants were also more likely to have elevated levels of IGF-1.[148] However, as well as it not being clear whether this would also affect serum levels of IGF-1, there have been suggestions that the animal models used in this context were not relevant to humans.[176]

Indeed, from the present study, having high levels of IGF-1 (as with low) was associated with increased risk of depression symptoms. While anti-depressant use was not recorded, these findings are in partial accord with the results of a large study of the use of antidepressants, where anti-depressant medication-free individuals with current depressive or anxiety disorders – either analysed apart or grouped together – had higher plasma IGF-1 levels compared with healthy controls. Present findings also partially

accord with evidence that depressed individuals who used antidepressants had lower plasma IGF-1 levels relative to controls; a relationship that appeared to be present for most classes of antidepressants and several medications.[177]

To further illustrate the complexity of the IGF-1, depression and antidepressant relationship, it has been proposed that antidepressant use may actually lower peripheral IGF-1 levels both directly, and may indirectly lower GH secretion, resulting in reduced IGF-1 production. However, while reduction of GH indeed has been observed in some studies of some antidepressants,[178] others have demonstrated a blunted response in premenopausal women but not in men,[179] while some even indicated an increase in GH in the elderly population.[180] The impact of anti-depressant use on the association between IGF-1 and depression symptoms observed in this present study is unclear.

Participants selected for this investigation were free from depression symptoms and did not report prior diagnosis at baseline, meaning they were unlikely to be consuming anti-depressants. However, it remains plausible that participants may have been prescribed anti-depressants for mood symptoms without being directly given a diagnosis, or that they were prescribed anti-depressants for disorders unrelated to depression, as indications for these are numerous.[181] In the case that participants were prescribed anti-depressants for previous mood disorders, the likely effect of this would be to weaken present findings, as the real association between anti-depressants use, IGF-1 levels and depression may have created a misleading (confounded) representation of the relationship between IGF-1 and depression. However, this scenario may only apply to a minority of participants, and the observed relationship should not be discounted.

While the effect sizes observed for the associations between IGF-1, depression and use of anti-depressants are often small, the combined evidence may indicate either i) divergence in the relationship between IGF-1 and depression between rodents and humans, ii) complex mechanisms of anti-depressant function through other biological factors, or iii) insufficient capacity of serum measures of IGF-1 to elucidate the relationship with depression in humans. Indeed, it has been argued that cerebrospinal levels of IGF-1 are more relevant in discussions related to psychological homeostasis.[182] Additionally, while evidence from case/ control studies indicates IGF-binding proteins are no different between depressed and non-depressed subjects (whose circulating IGF-1 levels differ),[161] it has been argued that serum IGF-1 may not directly reflect the level of bioactive IGF-1 and that the levels of IGF-binding proteins (IGFBPs) which modulate the bioactivity and -availability of IGF-1, should also be measured.[183]

Based on the evidence leading up to this present study, given the neurotrophic properties ascribed to IGF-1,[141] it should be expected that depressed individuals would have lower IGF-1 levels, which would normalise (i.e. increase) after successful antidepressant treatment. While the use of antidepressants could not be ascertained in the present study, it is possible that the lack of association observed prospectively for men could also be explained by to use of and, adherence to, the antidepressant medication that would most certainly have been provided by the clinician following diagnosis of depression. Such responses following antidepressant therapy have indeed been observed for other neutrophic factors such as brain-derived neutrophic factor, where evidence from meta-analyses showed that serum levels were lower in individuals with major depression compared to healthy controls, whereas antidepressant treatment was related to an increase in levels.[184, 185]

It is thus clear from the above that there are a multitude of variables to consider when investigating the association between IGF-1 and depression. Additionally, it is possible that there are other unknown biological mechanisms related to the state of being diagnosed as depressed which cause serum IGF-1 levels to increase, implying reverse causation in the reported case-control studies, where the depression in the cases had in fact caused the IGF-1 levels to increase. In the present study, attempts were made to circumvent the problem of reverse causality by utilising depression incidence as an outcome in the longitudinal analyses; that is, new cases of depression in participants who, at baseline, were symptom-free and had not previously reported being diagnosed with the condition by a physician.

4.5.4 IGF-1 normal range and relation to deranged IGF-1

The association between IGF-1 and depression symptoms is difficult to interpret based on what are classed as the normal parameters for IGF-1. This interpretation is complicated by the fact that different reference ranges are in place for either gender. However, the lowest quintile of IGF-1 in this study mostly consists of participants with levels of IGF-1 below the normal range, who may be considered to be IGF-1 deficient. My findings with regards to the association between low IGF-1 and depression therefore partially support previous findings that IGF-1 deficient individuals report more affective disorders than the general population.[158] This association requires further investigation in the elderly population.

4.5.5 Strengths and Limitations

The main strength of this study is that it has a large, nationally representative sample of people aged 50 years plus in whom there were high rates of follow up when two standard measures of depression were administered. This study is not without limitations. The observational nature of this study means I am not able to make any assertions about cause and effect. Although suggestions for mechanisms of action have been posited, it remains possible that IGF-1 levels are a proxy for other factors that are causally related to depression (residual confounding).

Although this study was very well characterised, I was not able to control for all possible confounders. Furthermore, although the CES-D is a widely used questionnaire in observational studies which has been validated for the assessment of depression in general population studies and in older people, [71, 73] it does not provide a diagnosis of depression. Conversely, while self-reported physician-diagnosis of depression does (in principle) do this, many people with depression do not seek medical intervention.

The use of anti-depressant medication, which also has some utility in identifying study members with a depression diagnosis, was not gathered in ELSA. It is also the case however, that administration of such therapy does not necessarily imply a diagnosis of depression: anti-depressant medication can be used in the treatment of, amongst other conditions, anxiety and chronic pain disorders. Furthermore, severe liver and kidney disease may influence IGF-1 levels,[186] but these data were not available. While randomisation would have resulted in randomly allocated measured and unmeasured confounding, such a design was not possible in this instance. Furthermore, random allocation of circulating IGF-1 levels would be unethical to implement in human studies.

Other than the above, due to the novelty of this investigation of IGF-1 in relation to depression, it is possible that there are other confounders that have not been considered, or even measured. Future investigations of this association using observational data could benefit from analytical methods where allocation of characteristics can be simulated to emulate a randomised trial, thus reducing potential bias caused by both measured and unmeasured confounding.

Although care was taken to classify potential confounders according to validated and previously employed measures, it remains possible that categorisations used in this study were not optimal for elucidating an effect, or may even have introduced bias. For instance, previous smokers could have had the same IGF-1 properties as current smokers and consideration of them as 'non-smokers' could potentially have masked the association between IGF-1 and depression. However, based on the literature, IGF-1 levels are more likely associated with current smoking, which is believed to lower circulating levels in a dose- response manner.[127] Furthermore, even the best of categorisation is not likely to overcome the problem of under-reporting that is common to self-reported behaviours.[94,97]

Finally, this present study may have been limited by the reduction of sample size effected during selection of participants, which in turn would have reduced cases in each quintile of IGF-1. Thus, while a U shaped association was observed, this was not statistically significant. In particular, the highest quintile of IGF-1, where the relation with depression is likely quite important, was affected by lower numbers of participants, which were reflected by the wider confidence intervals. This reduction in power should be addressed

in future investigations of the association between IGF-1 and depression, where recruitment of a larger sample would be beneficial.

Chapter 5: Internet use and depression symptoms

5.1 Literature review

5.1.1 *The Internet and psychological well-being*

A defining feature of the rapidly evolving 'information age', the Internet has become a popular and commonplace medium for communication, information sharing, transactions, and entertainment.[187] Due to its popularity, concerns were raised about how time spent on the Internet seemed to be displacing time spent on face-to-face interactions and other physically and socially enhancing activities, thus reducing the beneficial effect of those activities on psychological wellbeing.[188] While online communication also facilitates social interaction, relationships made or maintained online have been described as being of poorer quality, characterised by weak ties and distorted reality, which encourage insensitivity, alter expectations and morals, and induce identity crises.[189] While useful for information and resources, these weak Internet based relationships are often viewed as lacking with regards to qualities such as time, affection, and physical support. [190,191]

In contrast, it is proposed that the Internet has opened up doors to extended social lives that were previously limited by geographical location[192] thus apparently enriching some social relationships. Indeed, while interactions on the Internet are viewed as devoid of the buffering effect of strong personal relationships[193] it is suggested that the types of relationships developed on the Internet are particularly complex and varied and that given the right combinations of personality and types of online activities, the Internet could indeed enhance perceptions of social support.[194]

In the first, and most cited, general population based study where the effect of Internet use on psychological well-being was investigated, Kraut et al (1998) found that greater use of the Internet was associated with increased loneliness, stress and depression. [195,196] However, the association with depression, which could only be ascribed to those whose Internet use was defined as 'high', has been challenged, as analytical methods used in that study could only describe a small effect size, suggesting that very little of the everyday distress of the Internet users could be explained in terms of their Internet use.[197] Paradoxically, Kraut et al found that Internet use tended to increase social networks and enabled communication with family and friends.

More recently, a number of small studies modelled on the Kraut study have yielded contradicting results,[198,199,200] with the bulk of evidence (through meta-analysis) indicating a small association between high Internet use and reduced psychological well-being.[201] Of the 40 studies included in this meta-analysis, only 3 focused on people aged 55 years and above, and none assessed the effects of Internet use on depression as component of psychological well-being. While it was proposed that Internet use and 'high' Internet use may be different phenomena and should be treated as such in relation to psychological health, the overwhelming recent global spike in Internet use volumes per individual (and not necessarily psychological distress) suggests a lack of an exclusive causal relationship between high Internet use and psychological health.

Some evidence of the effects of Internet use on depression and social resources in older people can be found in a study of chronically ill individuals aged between 21 and 75+ years (43% aged 50 years and above).[202] In that study, while participants who reported having depression alone as a chronic illness also reported very high Internet use, it was

actually those who had a different chronic illness (diabetes) that reported the most benefit from using the Internet, suggesting that effects of Internet use could be dependent on factors other than volume of use. Indeed, participants who reported using the Internet to expand social circles appeared to benefit the most. Such an association is supported by the online 'social compensation' theory, where people who start off with poor offline social resources (such as those with limiting chronic illness or lifestyles which are diverse in regards to the mainstream) are more likely to benefit the most from meeting and interacting with people online.[203]

5.1.2 Older people, the Internet and depression

To my knowledge, the association between Internet use and depression has been investigated in the elderly population twice to date, in individuals aged 50 and over living in the United States of America. The first of these two, a cross-sectional study of 7,839 retired/ non-working participants of the Health and Retirement Study (HRS), utilised information about Internet use and depression collected in 2006 only. From this study, it was found that Internet use reduced the probability of depression in the elderly by 20-28%.[204] However, as Internet use was only recorded as 'yes' or 'no', the researchers highlighted the need for further investigation using more nuanced measures of Internet use, in order to investigate the specific aspects of Internet use that led to this benefit. Furthermore, direction of effect could not be proven, as both Internet use and depression were assessed on the same occasion.

The second study, also carried out using data from HRS, utilised data collected in 4 waves of biennial interviews encompassing a 6-year period starting from 2002 to 2008.[205] This study was also restricted to non-working, retired individuals aged 50 year and above.

Restriction was based on the hypothesis that the relationship between Internet use and depression was mediated by social interaction, which would be present in very small quantities, if at all, in retired participants. However, such an assumption does not take into account the heterogeneity in retired people, among whom levels of social interaction will vary greatly.

In that second study, while it was highlighted that current depression was dependent on past depression to a large extent, it was also found that Internet use reduced the probability of depression categorisation by 33% at follow-up. These findings were comparable to those found in the initial cross-sectional study. Although the second study established the direction of association, its results can still not be applied to all older people as selection to the study excluded the large proportion of the older population engaged in some form of work. Internet use in this study was once again only measured through a single question which required a yes or no answer, asking individuals if they used the Internet for sending or receiving emails or for any other purpose. Thus, the relationship between Internet use and depression in older people requires further investigation.

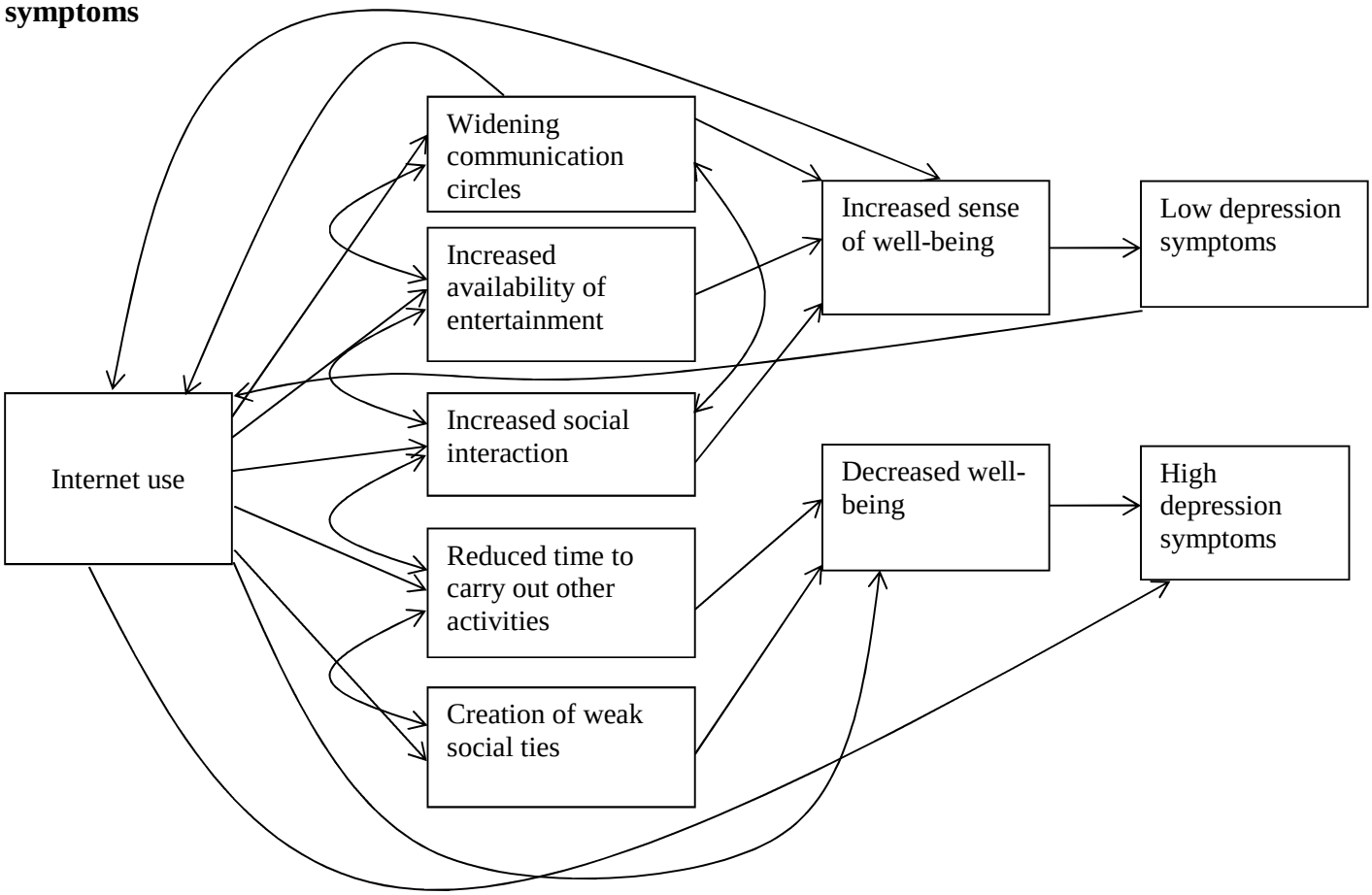
5.2 Aims and objectives

In this the present study I will investigate the association between Internet use and the development of depression symptoms in people aged 50 years and above; retired and non-retired. Additionally, I will explore how the various attributes of Internet use relate to depression symptoms in this population sub-group. While previous studies have shown an association between Internet use and depression symptoms, my aims in carrying out this present study are twofold. Firstly, I will investigate the longitudinal association between Internet use and depression symptoms. Secondly, to advance on the explorations

of previous studies, I will investigate the possible mechanisms by which Internet use may be associated with depression. Ergo, in carrying out this investigation, I will attempt to answer the following question: How does Internet use relate to the risk of developing depression symptoms in older people?

As the investigation shall be carried out in two parts, I shall refer to the first set of analyses as 'Study 1', which will comprise an investigation of the longitudinal association between Internet use and the development of depression symptoms in individuals who were free from depression at the beginning of the study. Following this, the second set of analyses, which I shall refer to as 'Study 2', will comprise multiple cross-sectional investigations of the various attributes of Internet use, and how these are associated with depression symptoms in older people; this second investigation will be based on the conceptual framework illustrated in figure 5. According to this framework, through multiple feed-back processes, Internet use facilitates the widening of communication circles and social interaction, and also avails more entertainment, improving well-being and reducing depression. In turn, individuals who perceive increased well-being and have wider communication circles are more likely to use the Internet to communicate and seek entertainment. Conversely, individuals with low mood are less likely to engage with the Internet. Thus, I will explore attributes of the Internet related to communication, entertainment and the extent to which individuals use the Internet.

Figure 5: Conceptual framework of the association between Internet use and depression symptoms



5.3 Methods for Study 1: The association between Internet use and subsequent development of depression symptoms 2002-2012

5.3.1 Selection of study participants

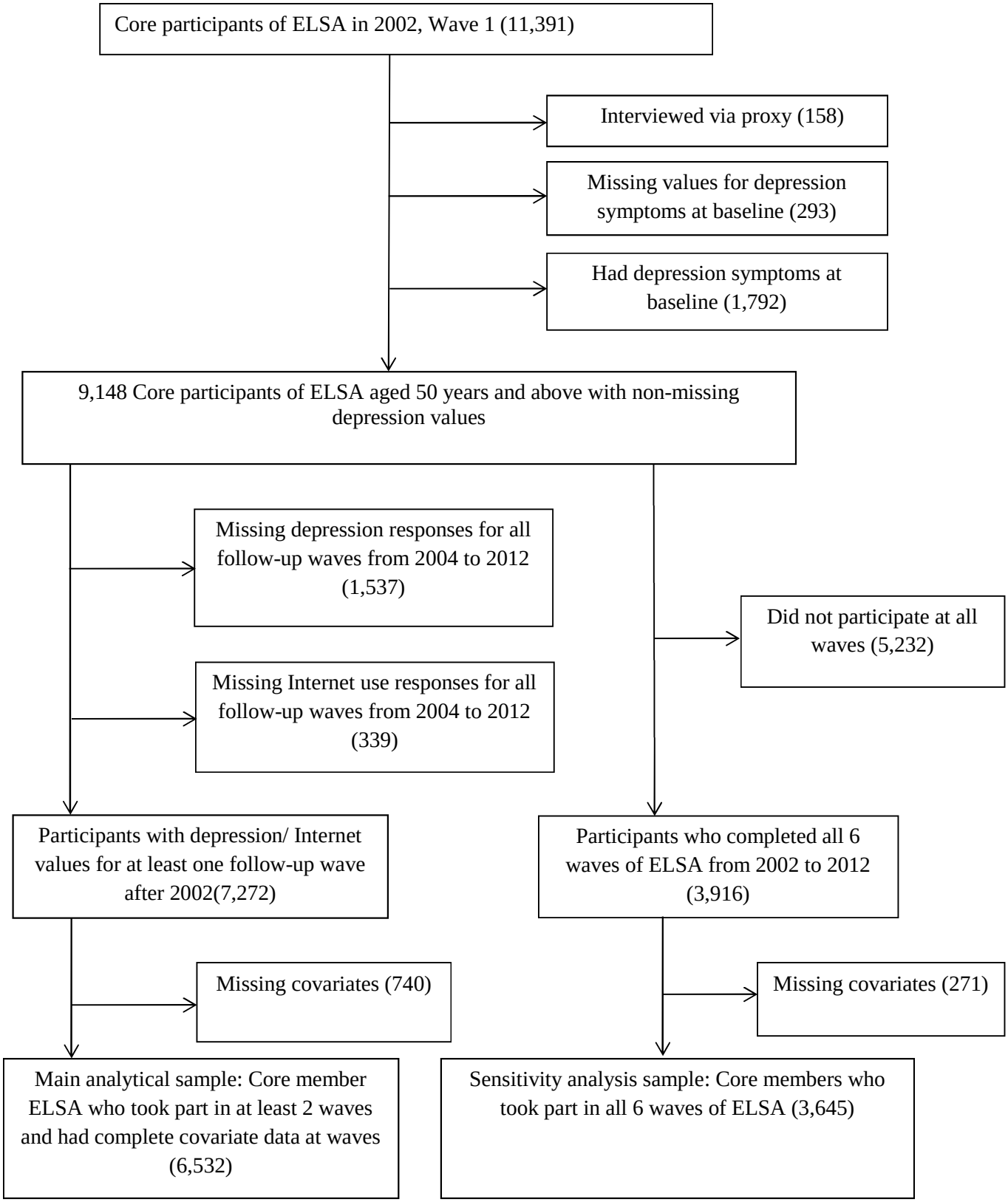
Participants for the present study of the association between Internet use and the development of depression symptoms were selected from wave 1 of ELSA (2002). A detailed description of the full ELSA sample is described in Chapter 3. Figure 6 displays the selection process for the ELSA sub-sample for this present study. From the 11,391 core participants of ELSA who took part in 2002 at the beginning of the study, 158 participants who responded via a proxy were excluded.

As the purpose of this present study is to investigate the predictive capacity of Internet use on depression symptoms, the second step taken in selecting the study sample was to exclude participants who had either missing values for depression, or had reported that they had depression symptoms at baseline. Thus, 293 participants with missing values for depression symptoms and 1,792 participants who had reported having depression symptoms were excluded. This left 9,148 participants who had taken part in at least one wave of ELSA and had data on both the exposure and outcome.

The differences in baseline characteristics between included study participants and the two excluded groups who had either (i) reported having symptoms of depression (ii) responded via a proxy/ had missing depression symptoms at baseline are described in Chapter 3.5. While participants who reported having 4 or more symptoms of depression were more likely to be female, excluded participants (male or female) comprised individuals who were older, poorer, less educated and sicker participants than those who were included in the study.

Next, an analytical sample of core members of ELSA who had taken part in at least two study waves and had reported both their Internet use and depression symptoms after baseline was selected. This was done to confine this current study to participants whose exposure and outcome data were recorded on at least two separate time points, in addition to being recorded together at any one time point, so that the association between exposure and outcome could be assessed both longitudinally and cross-sectionally (after baseline) among participants who were free from depression at baseline.

Figure 6: Sample selection for the longitudinal analysis of the association between Internet use and the development of depression symptoms: English Longitudinal Study of Ageing, 2002-2012



To satisfy these requirements, all participants who had missing values for depression symptoms at all follow-up waves of ELSA from wave 2 in 2004 to wave 6 in 2014 were excluded (1, 537), as were participants who had missing values for Internet use for those waves (339), leaving 7,272 participants. Within this selected sample, there were also participants who had exposure and outcome data recorded on more than two separate occasions. Altogether, participant data from all time points were used to create a comprehensive and exhaustive model for the association between Internet use and depression symptoms over time.

Of the selected 7,272 participants, 740 had missing values for at least one of the covariates used in the ensuing multivariate analysis, and to allow for complete case analysis, these participants were also excluded. The final sample for the longitudinal analysis of the association between Internet use and depression symptoms was therefore made up of 6,532 participants.

5.3.2 Exposure Variable: Internet use

For the purpose of this study, the term 'Internet Use' refers to the act of accessing the Internet, and is taken from the question which was posed to ELSA participants within a self-complete questionnaire, which was, 'Which of these statements apply to you?' This question was then followed up with a list of possible situations which could apply to the participants, one of which was 'I use the Internet and/or email', with affirmation denoting 'yes', and the opposite denoting 'no'. Those who did not complete the questionnaire were classed as having missing responses. Internet use was thus defined in this way in ELSA from the start of the study in 2002 until wave 5 in 2010, and refers to the act of having accessed the internet in the 12-month period prior to completion of the study

questionnaire. Based on the Internet use activities reported in wave 6 (2012), it was also possible to derive a binary variable, thus for Study 1, Internet use was measured as a binary variable (yes/no) for waves 1 to 6.

5.3.3 Outcome variable: Depression symptoms

The main outcome in these analyses is depression symptoms, which were measured using the 8-item CES-D, which is described in detail in Chapter 3.3.

5.3.4 Covariates

Selected covariates for this investigation were in themes as described in chapter 3.4 and shall be described in more detail below as relevant.

Demographic factors comprised age and gender. Age also often describes differences in frequency of Internet use and devices used to access the Internet, as well as activities undertaken once online.[78] For instance, in one study carried out in the USA in 2004 it was found that 22% of people aged 65 and over used the Internet, compared to 58% of those aged 50–64, and 75% of those aged 18–49. Interestingly, it was found that when older people did use the Internet, they were usually as capable and as motivated as younger individuals, provided they had the right equipment and skills.[206] In ELSA, age is a continuous variable, which is measured in whole years. With regards to gender, it is unclear whether previously observed differences in Internet use still exit, due to the nature in which gender and technology continue to interact and evolve through time.[81,207]

Socio-economic Status in this investigation comprises wealth, education and marital status, as described in Chapter 3.4. Co-morbidities in this investigation refer to the

presence or absence of one or more physical illnesses. Various studies have shown that the Internet has transformed the way people access health information, with differences being observed in the behaviour of those with medium to long-term illnesses, where their illness was seen either as an incentive[208] or deterrent[209] from engaging with the Internet. Physical illness is recorded as a binary variable, where anyone with one or more of the following ailments was classed as a case, to be compared with individuals with no physical illness: high blood pressure or hypertension, angina, heart attack, congestive heart failure, heart murmur, cardiac arrhythmia, diabetes, cerebral vascular disease (stroke), asthma, chronic lung disease, arthritis, osteoporosis and cancer.

Subjective and objective isolation describe the participant's feelings of loneliness, as well as the number of people living in their household. As per review of the literature, having more face-to face interaction, as facilitated by larger household numbers was expected to result in less internet use and thus fewer negative effects caused by the 'poor quality' social relationships to be found on the internet. With regards to loneliness (subjective isolation), participants were asked whether they had felt lonely for much of the time in the week prior to the interview, the responses to which could only be 'Yes' or 'No'. While the UCLA scale is often used to measure social isolation, the number of people in one's household as opposed to any wider networks was selected. This was based on suggestions that interaction with those in one's immediate environment played a more important role in the association between Internet use and depression than that with wider networks. Further to being the dominant factor underlying the UCLA scale, perceived isolation as measured by a specific question about loneliness seemed more appropriate in illustrating the facet of loneliness that may lead to or result from Internet use than some of the other components within the full scale.[210]

5.3.5 Statistical methods

The longitudinal associations between Internet use and depression symptoms were assessed using logistic regression with Generalized Estimating Equations (GEE) which had an exchangeable correlation matrix, using all data from wave 1 to wave 6 of ELSA. The GEE approach was chosen for this analysis as it accounts for the individual correlation in measures by firstly computing naive standard errors while assuming complete independence of measures, and then computing adjustments to the naive standard errors. This adjustment results in robust standard errors and separates the nuisance variation due to population-wide behaviour from the variation related to trends with time while still incorporating the population-wide variance within its variance structure.[211] Thus, it provides a population average of the association between Internet use and depression symptoms over time.

5.4 Results for Study 1: Association between Internet use and subsequent development of depression symptoms between 2002 and 2012 in 6,532 participants from the English Longitudinal Study of Ageing

5.4.1 Baseline Characteristics of study participants

Results have this study were presented at the ELSA Wave 7 launch event through a poster (appendix 5). Table 9 displays the baseline characteristics of the 9, 148 participants who were aged 50 to 90 years and were free from depression at baseline (reported 3 or less symptoms of depression). The table presents a comparison of participants based on their eligibility for the present study. The ELSA sub-sample selected for this study consisted of participants who had taken part in at least one other study wave where they had values for both depression symptoms and Internet use, with complete covariate data at those participating waves; the completers.

The completers had a similar gender distribution to that of non-completers. As with the core ELSA participants not selected for this study due to missing depression data at baseline (described in Chapter 3.5), the non-completers were older (mean 66.81 years; se, 0.22) than completers (mean 63.96 years; se, 0.12). Although the average proportion of all ELSA participants in the lowest quintile of wealth was about 20%, completers were less likely to be in this group (14.01%; se, 0.53), and were on average more educated and more likely not live with a partner. Although prevalence of chronic physical illness was high for both groups more non-completers reported having at least one illness when compared with completers (67.76%; se, 0.58). Finally, although the average household size was similar for both groups, non-completers reported feeling lonelier in the week prior to the ELSA interview.

After excluding non-completers from the study, the remaining sub-sample of individuals free from depression symptoms was then scrutinised based on reports of Internet use at baseline; table 10 displays their baseline characteristics. It is worth noting at this point that although some participants had missing Internet use values at baseline, they later reported their Internet use status, and were thus eligible for this study according to all criteria as described earlier. Although these participants are represented in table 10, their baseline characteristics according to Internet use status will not be discussed at this point.

Table 9: Baseline characteristics of 9,148 depression-free participants from the English Longitudinal Study of Ageing (2002) according to eligibility for study against the following criteria: non-missing covariates at any participating follow-up wave, 2004 to 2012

Covariates[a]	**Eligible for study** (6,532)	**Missing covariates at follow-up** (2,616)	**95% Confidence Interval for difference**
Demographics, %			
Female	52.73 (0.61)	51.58 (0.98)	-1.22, 3.31
Age, mean, years	63.96 (0.12)	66.81 (0.22)	2.40, 3.30
Does not use the Internet, %	62.52 (0.60)	62.92 (0.94)	5.23, 9.60
SES, %			
No educational qualifications	36.04 (0.59)	47.25 (0.98)	9.02, 13.50
No resident partner	26.21 (0.54)	31.42 (0.91)	3.14, 7.29
Lowest quintile of wealth	14.05 (0.43)	21.64 (0.82)	5.78, 9.41
Comorbidities[b]**, %**			
Has chronic physical illness	67.76 (0.58)	71.02 (0.89)	5.34, 11.90
Subjective and objective isolation, %			
Number of people in household, mean	2.09 (0.01)	2.04 (0.02)	0.02, 0.10
Often feels lonely	5.74 (0.29)	7.22 (0.51)	0.34, 2.63

[a] Percentage or mean (se)

[b] High blood pressure or hypertension, angina, heart attack, congestive heart failure, heart murmur, cardiac arrhythmia, diabetes, cerebral vascular disease (stroke), asthma, chronic lung disease, arthritis, osteoporosis, cancer

About a third (32%) of the 6,532 eligible study participants, whose mean age was 64.0 years (se, 0.1), reported that they used the Internet in the 12 months prior to the first ELSA interview. The non-Internet users group consisted of more women (56.8%) than men, and had a significantly higher mean age (mean 66.27; se, 0.15) than Internet users. Much unlike the Internet users, individuals who reported not using the Internet in 2002 were

more likely to report having a chronic physical illness (71.96%; se, 0.70) compared to Internet users (60.66%; se, 1.04), and were more likely to not live with a partner (30.5% compared to 16.2% of Internet users). More marked differences could be observed in that a larger proportion of non-users of the Internet reported being in the lowest wealth quintile (18.02%; se, 0.60) than users (5.74%; se 0.50), and were also more likely to have no education qualifications (47.0% of non-users, compared to 13.9% of Internet users).

5.4.2 The association between Internet use and depression symptoms

After baseline, where selected participants were free from depression symptoms, the proportion of ELSA participants who reported depression symptoms was stable over time. Where 9.1% of the participants who took part in wave 2 (in 2004) reported depression symptoms, 8.2% reported the same in wave 6, and the highest prevalence of depression symptoms was observed in wave 5 (10%). Although the proportion of participants with depression symptoms did not vary much with each wave, these symptoms did not appear to be a persistent state in individuals, as on average, only about 35% of participants who had reported depression symptoms in any one wave would do so again in the subsequent wave.

Table 10: Baseline characteristics of 6,532 participants according to Internet use: English Longitudinal Study of Ageing 2002

	Internet use			
Covariates[a]	**No** (4,084)	**Yes** (2,196)	**Missing at Wave 1** (252)	**Confidence Interval for difference**[c]
Individual Factors				
Age, years	66.27 (0.15)	59.53 (0.16)	65.29 (0.64)	6.29, 7.20
Female, %	56.83 (0.78)	45.54 (1.06)	48.81 (3.16)	8.71, 13.87
SES, %				
No educational qualifications	47.04 (0.78)	13.89 (0.74)	50.79 (3.16)	31.04, 35.25
No resident partner	30.48 (0.72)	16.21 (0.79)	44.05 (3.13)	12.18, 16.36
Lowest quintile of wealth	18.02 (0.60)	5.74 (0.50)	19.05 (2.48)	10.84, 13.92
Comorbidities[b], **%**				
Has chronic physical illness	71.96 (0.70)	60.66 (1.04)	61.51 (3.07)	8.84, 13.77
Subjective and objective isolation				
Number of people in household, mean	1.97 (0.01)	2.31 (0.02)	2.09 (0.08)	0.30, 0.38
Often feels lonely, %	6.78 (0.39)	3.23 (0.38)	10.44 (1.94)	2.48, 4.61

[a] Percentage or mean (se)

[b] High blood pressure or hypertension, angina, heart attack, congestive heart failure, heart murmur, cardiac arrhythmia, diabetes, cerebral vascular disease (stroke), asthma, chronic lung disease, arthritis, osteoporosis, cancer

[c] Confidence Interval for difference according to Internet use in those with non-missing data

Although the proportion of participants that did not respond to the question about Internet use remained stable over all 6 waves of ELSA, positive responses to the question rose quite significantly at each subsequent wave of data collection. As such, the proportion that reported that they had accessed the Internet rose from 35.5% of participants in wave 1 to 64.2% of participants in wave 6.

Focusing on the fundamental question of whether Internet use was associated with the development of depression symptoms, Table 11 displays the odds ratios and confidence intervals from the GEE models of Internet use as the independent variable, depression symptoms as the dependent variable, with adjustments for each covariate separately. Compared with Internet users, participants that reported not using the Internet were 1.74 times (95% CI 1.56, 1.95) more likely to develop depression symptoms over the 10-year follow-up period of ELSA.

After adding all covariates to the multivariable model, the odds of developing depression symptoms reduced to 1.3 (95% CI, 1.2, 1.5). When assessed according to each separate adjustment, the largest attenuation was observed for loneliness. Other than loneliness, wealth and education, which are the major components of SES, also attenuated the relation between Internet use and depression. The association between internet use and depression symptoms was the same regardless of if one had physical comorbidities or not.

Table 11: Longitudinal Odds Ratio (95 % CI) for the development of depression symptoms in 6,532 participants of the English Longitudinal Study of Ageing who were free from depression in 2002 and completed at least one other study wave from 2004-2012

	Internet users	**No internet use**	
Adjustments		**OR**	**CI**
None	1 (ref)	1.74	1.56, 1.95
Age	1	1.63	1.45, 1.83
Sex	1	1.67	1.49, 1.86
Education	1	1.52	1.35, 1.72
Wealth	1	1.51	1.34, 1.69
Loneliness	1	1.47	1.31, 1.66
Co-morbidities[a]	1	1.72	1.54, 1.92
Number of people in household	1	1.62	1.45, 1.81
Cohabiting status	1	1.69	1.51, 1.89
Adjusted for all covariates	1	1.33	1.16, 1.52

[a] High blood pressure or hypertension, angina, heart attack, congestive heart failure, heart murmur, cardiac arrhythmia, diabetes, cerebral vascular disease (stroke), asthma, chronic lung disease, arthritis, osteoporosis, cancer

5.4.3 Sensitivity analysis

As can be observed in the steps taken to select the sample for this study, the original ELSA population had been reduced by about 40% by the time all ineligible participants were excluded. After exclusion of participants with depression at baseline, further participants were excluded for missing Internet and depression symptoms data at follow-up waves. Where a sample is restricted in this way, bias can be introduced if the reasons

for non-response is not random. In this instance, it is plausible that responses could have been missing because participants had depression symptoms at those wave. As such, a sensitivity analysis of participants with non-missing data at all waves would be a useful comparator for the current study.

The sensitivity analysis for this present study was carried out on only those participants with complete data for all 6 waves of ELSA. Thus, only participants who had completed all six waves of ELSA and had complete data for the exposure, outcome, and all covariates were selected. As illustrated in table 2 (Chapter 3.5), from the 9,178 study participants with non-missing baseline data, a total of 5,232 participants who did not complete all waves were excluded, leaving a sensitivity analysis sample of 3,645 participants.

The same GEE model was re-run using the sensitivity analysis sample and Table 12 displays the association between Internet use and depression symptoms in this sample. As can be observed, the crude odds ratio for developing depression symptoms reduced slightly from 1.74 (as reported for the main Study 1 sample) to 1.61 (95% CI, 1.06 – 1.38) in the sensitivity analysis sample. However, the general pattern of association is much the same as observed with the full study sample above. Once again, loneliness, wealth and education are partially responsible for this observed association. However, after adjusting for all covariates, the odds for developing depression symptoms still remained 20% higher among those that did not use the Internet (95% OR 1.2, CI 1.0–1.4), compared to those who did.

Table 12: Longitudinal odds Ratio (95 % CI) for the development of depression symptoms in 3,645 participants of the English Longitudinal Study of Ageing who completed all waves of the study from 2002-2012

	Internet users	**No Internet use**	
Adjustments		**OR**	**CI**
None	1 (ref)	1.61	1.40, 1.84
Age	1	1.52	1.32, 1.74
Sex	1	1.52	1.33, 1.74
Education	1	1.40	1.21, 1.61
Wealth	1	1.41	1.23, 1.62
Loneliness	1	1.39	1.21, 1.60
Co-morbidities[a]	1	1.59	1.39, 1.82
Number of people in household	1	1.51	1.32, 1.73
Cohabiting status	1	1.57	1.37, 1.79
Adjusted for all covariates	1	1.21	1.04, 1.42

[a] High blood pressure or hypertension, angina, heart attack, congestive heart failure, heart murmur, cardiac arrhythmia, diabetes, cerebral vascular disease (stroke), asthma, chronic lung disease, arthritis, osteoporosis, cancer

5.5 Methods for Study 2: Cross-sectional association between Internet use and depression in 2012, English Longitudinal Study of Ageing

As the aim of this second investigation of the association between Internet use and depression symptoms is to inspect the mechanisms by Internet use reduces the risk of depression symptoms (as observed in Study 1), it is necessary to inspect the various relevant components of Internet use. Instead of being asked whether they used the Internet or not, in 2012/13 (wave 6) participants of ELSA were, for the first time, asked a plethora of questions about how, when and for what they used the Internet. These questions were posed in the self-complete questionnaire; table 13 displays the exact questions asked.

In all, four categories of Internet related information were collected, demonstrating the frequency with which participants used the Internet, the devices they used to access it, at what location they did so, and what activities they pursued once online. As there is as yet no evidence, nor plausible reasoning, to suggest that the location and device used to access the Internet would independently affect mental health in any way, focus hereon shall only be on the utility of frequency of use and types of online activities in indicating risk of depression symptoms.

5.5.1 Exposure Variables: Study 2 – Part 1

Frequency of Internet use

Frequency of Internet use was reported as ‘daily’, ‘weekly’ (not daily), ‘monthly’ (not weekly), ‘at least every three months’(not monthly), ‘less than every 3 months’ and ‘never’ (which equates to not using the Internet). For this present study, these reports were reduced to four categories which reflected daily, weekly, infrequent, and non- use of the Internet.

Participants of ELSA were asked what they used the internet for in the 3 months preceding the study, as detailed in Table 13. In all, there were twelve possible specific activities that individuals could report; any other activity not included in the list could be so reported as 'other'. Thus, participants could report a maximum of 13 activities, with descriptions extensive enough to make the list quite exhaustive.

5.5.2 Statistical methods: Study 2 - Part 1

To analyse the role of 'intensity' of Internet use, the first part of this study will be focused on assessing whether any increase in either time spent on the Internet or number of activities undertaken would be associated with depression symptoms. As such, Internet based 'activities' is denoted by counts of activities per individual. This is with the assumption that, if engaging in activities of any sort on the Internet (thus, 'using' the Internet) is beneficial as identified in Study 1 (Chapter 5.5.1), then engaging in more and more online activities should reduce depression symptoms in a so-called 'dose-response' manner, as described in the Bradford-Hill criteria for disease causation.[212] Due to the low count of participants who reported having more than 10 activities, all such study members will be grouped in one category of those who reported 10 or more activities. The role of Internet use frequency will be assessed in a similar manner, with reports of non- use denoting the lowest level of frequency, and daily–use being the highest.

Table 13: Questions about Internet use posed to participants of the English Longitudinal Study of Ageing in 2012 (Wave6)

Question about Internet use	Possible responses
On average, how often do you use the Internet or email? (participants instructed to select only one responses)	• Every day, or almost every day • At least once a week (but not every day) • At least once a month (but not every week) • At least once every 3 months • Less than every 3 months • Never
In which of the following places have you used the Internet or email in the last 3 months? (participants instructed to select all responses that applied)	• At home • At places of work (other than home) • At place of education • At another person's home • On the move • Other place (library, Internet cafe)
On which of the following devices do you access the Internet? (participants instructed to select all responses that applied)	• Desktop computer • Laptop computer • Tablet computer (e.g. iPad, Samsung Galaxy Tab) • Smartphone (e.g. iPhone, Blackberry) • TV (e.g. games console or set top box) • Other mobile devices • Don't know • Do not access Internet
For which of the following activities did you use the Internet in the last 3 months? (participants instructed to select all responses that applied)	• Sending/receiving e-mails • Finding information about goods and services • Searching for information for learning, research, fact finding • Finances (banking, paying bills) • Shopping/ buying goods or services • Selling goods or services over the Internet e.g. via auctions • Use social networking sites (Facebook, Twitter, Myspace) • Creating, uploading or sharing content (Youtube, blogging or Flickr) • News/ newspaper/ blog websites • Streaming/downloading live or on demand TV/radio (BBC iplayer, 4OD, ITV player, Demand 5) music (iTunes, Spotify), or ebooks • Games • Looking for a job or sending a job application • Other • None of the above

Multivariate logistic regression analyses were used to assess the cross-sectional relationship between (i) frequency of Internet use and depression symptoms, and (ii) number of activities undertaken on the Internet and depression symptoms, with participants who reported no Internet use serving as the reference group. These analyses were adjusted separately for demographic factors, SES, comorbidities and subjective and objective isolation, and then multiply for all the aforementioned.

5.5.3 Exposure Variables: Study 2 – Part 2

For the second part of Study 2, Internet activities will be grouped into themes that best describe the nature of that activity, to allow for a more concise and intuitive inspection of how the Internet could relate to depression symptoms. The first distinct theme identified was 'communication' via email, as that is the only purpose and possible use for email. As it is not possible in ELSA to tell if said communication would have been purely work-related or social, the act of emailing will be viewed simply as an activity enabling communication; which could be work-related, of a social nature, or of any other type as used to facilitate transactions, complaints, queries, etcetera. Participants included in this category may have also reported carrying out other activities online, with the exception of social networking.

The second theme is 'social networking', which is defined as the practice of expanding the number of one's business and/or social contacts (in social contexts) by making connections through individuals.[213] Although this may imply the same thing as communication, social networking can be viewed as being distinct from emailing. In social networking, individuals intentionally seek out popular platforms with the intention of merely connecting with other people, in order to facilitate potential future

communication and to either actively share or passively receive information through site specific tools such as ‘tweets’, ‘posts’, ‘shares’ and ‘direct messages’. As already alluded to, it is an activity that people pursue purely to increase social circles and facilitate interaction. As the size of one’s social circle and the amount of social interaction that they have are some of the mechanisms by which Internet use is believed to affect mood,[195] it is important to assess the relationship between social networking and depression symptoms, relative to any other type of use.

It should be noted that one generally needs an email address to register on almost all social networking sites, therefore it could be assumed and may be expected that most participants who reported using social networks would also report email use. Indeed, only 5 percent of ELSA participants who reported using social networking sites did not report using email (which may or may not have been an omission). As such, although a distinct category exists for email users, and although the category for social networkers also contains email users, social networkers can be viewed as having extra qualities of particular interest to this study (favourable or not) than those who only used email.

The third theme is ‘entertainment’, which is populated by participants who reported using the Internet only to watch television programmes and videos, to upload content for the entertainment of others, to read newspapers and blogs, and to play Internet based games. These participants did not indicate using the Internet for anything else other than entertainment. In the literature, gaming has found to a useful tool in treating depression not only because of its key features of challenge, motivation, and reward, but also because some types of games appear to increase dopamine and endorphin levels, which increase feelings of pleasure.[214] In the same vein, it is plausible that other types of entertainment

may have some effect through their ability to act as distractions from prevailing real-life problems, and may also provide feelings of pleasure in the same manner as gaming.

The final theme is populated by participants who only use the internet for all other activities other than emailing, social networking and entertainment. This theme is thus mainly comprises practical activities such as searching for information about goods and services and for learning, buying and selling goods, organising finances, searching for a job, and all other types of activities not stipulated in the self-complete questionnaire.

5.5.4 Statistical methods: Study 2 - Part 2

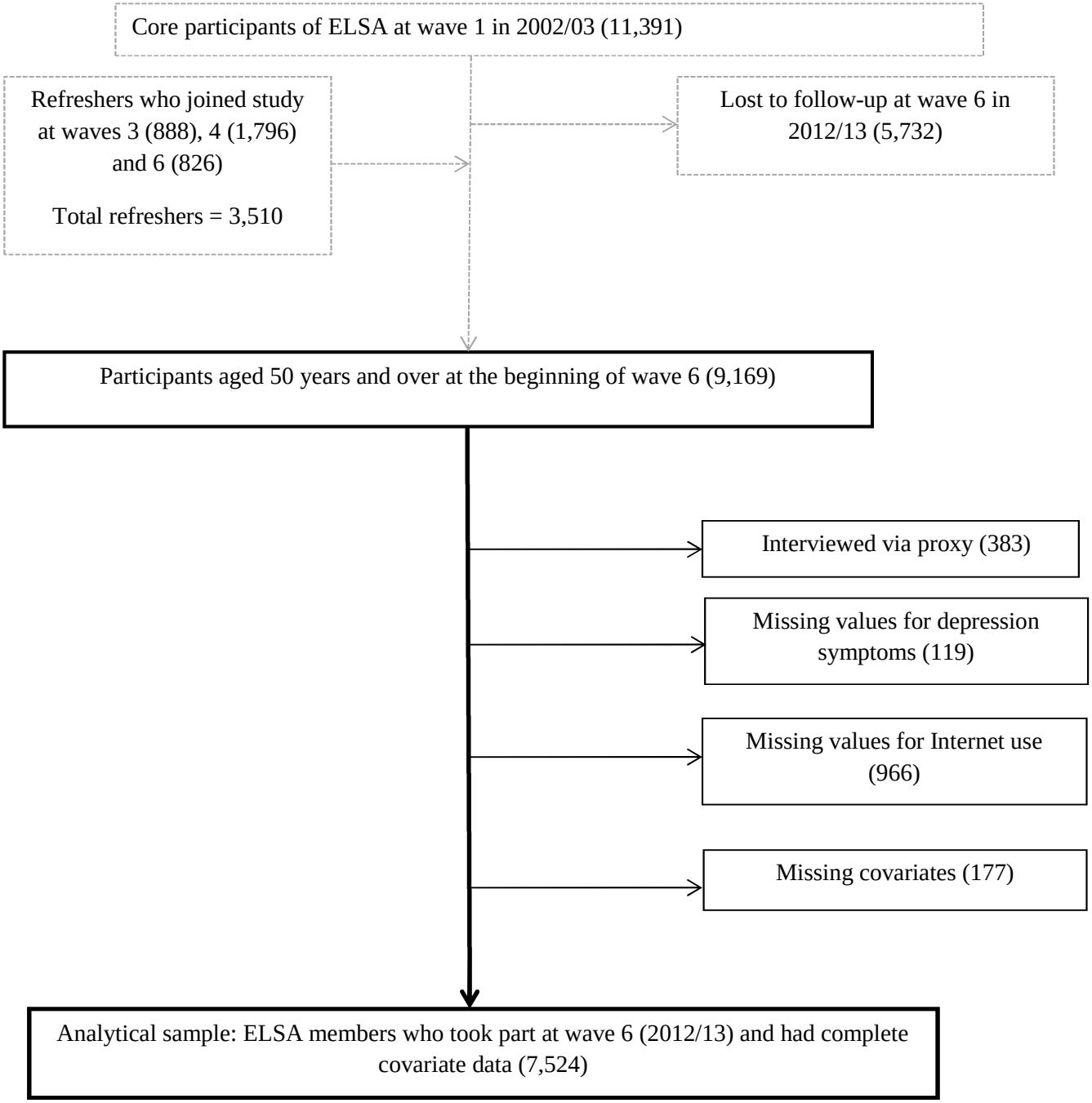
Multivariate logistic regression analyses were also used to assess the cross-sectional relationship between the separate themes of Internet use activities and depression symptoms, with participants who reported no Internet use once again serving as referent. For more detailed scrutiny of the factors that could explain any association, these analyses were adjusted separately for age, sex, educational attainment, wealth, loneliness status, physical comorbidities, number of people living in the household, and cohabiting status. They were then also multiply adjusted for all the stated covariates.

5.5.5 *Selection of participants*

Figure 7 illustrates the sample selection process for the cross-sectional analysis of the association between Internet use and depression symptoms in 2012 (Wave 6). Of 11,391 core participants who enrolled in ELSA wave 1 (2002/03), 5,732 were lost to follow up in wave 6 (2012/13). To maintain representation of individuals aged 50 years and over, ELSA was supplemented with refreshment samples from the same source population at waves 3 (2006/07), 4 (2008/09) and 6 (2012/13), as described in Chapter 3.1. In total,

3,510 eligible new study members joined ELSA by 2013, resulting in a sample size of 9,169 participants in wave 6. A further 1,645 participants who took part in this wave were excluded from the present analyses due to missing covariate data, leaving a final study sample of 7,524 participants.

Figure 7: Sample selection for cross-sectional analysis of the association between Internet use and depression symptoms at wave 6 of the English Longitudinal Study of Ageing, 2012/13



5.6 Results for Study 2: The cross-sectional association between Internet use and depression symptoms in wave 6 of the English Longitudinal Study of Ageing

5.6.1 Baseline characteristics of study participant

Table 14 displays baseline characteristics of the 9,169 participants who took part in wave 6 of ELSA. Compared with the original core 11,391 sample of ELSA at the time of recruitment in 2002 (whose characteristics are described in full in Chapter 3.5) participants at wave 6 had a higher mean age of 67.1 years, compared to 65.2 years in 2002. Furthermore, the core sample members were less educated (43% with no educational qualifications compared to 26.3% in wave 6) and were more likely to live without a partner (31.3% wave 1; 16.5% wave 6), to have a chronic illness (71%), and to report feeling lonely (13.6%). Wealth distribution was similar for the two study periods. As could be expected, participants at wave 1 reported lower Internet use, with 63.6% of participants reporting that they did not use the Internet.

As shown in Table 14, a further 1,645 participants were excluded from the present analyses due to missing covariate data. Although ELSA participants at wave 6 had a higher mean age than core participants at wave 1 (even after supplementation with refresher samples), the participants excluded from these analyses were generally the older members of this wave (mean age 69.96 years, se 0.3). Excluded participants were also poorer (23.59% in lowest wealth quintile; se, 1.05) and less educated (37.69% with no educational qualifications; se, 1.20) than the analytical sample. In addition to living in slightly smaller households (mean household size, 1.95; se, 0.02), excluded participants were also more likely to report often feeling lonely (20.27%; se, 1.16), and having symptoms of depression (21.08, se, 1.20%). Although a third of the excluded participants

did not have data for depression symptoms, their mean CES-D score was still higher than that of the analytical sample (1.87, se 0.07).

The two groups did not appear to differ much with regards to gender distribution, nor whether cohabitation status. Both groups had similarly high prevalence of chronic physical illness (63.16% in the analytical sample, se 0.56). Seemingly deviating from previous findings, participants with non –missing data (i.e., the analytical sample) seemed more likely to report not using the Internet (30.58%, se 0.53); an anomaly explained by the substantial proportion of excluded participants with missing data for Internet use (83.3%).

After excluding proxy interviewees (383), and participants who had missing values for depression (119), Internet use (966) and all other covariates (177), a total of 7,524 participants remained who were eligible for these present analyses. Table 15 displays their Internet-related behaviours according to depression symptoms. It can be observed that the frequency with which participants reported using the Internet differed based on their depression symptom status. Participants classed as cases for depression symptoms were significantly more likely to report that they never used the Internet (45.50%; se 1.63), while conversely, non-cases were much more likely to report that used the Internet daily (52.34%; se, 0.62). Reports of weekly and monthly (but not daily) Internet use were distributed similarly between cases and non-cases.

Table 14: Baseline characteristics of 9,169 participants from wave 6 of the English Longitudinal Study of Ageing (2012/13), based on eligibility for inclusion in analyses of the association between Internet use and depression symptoms

Covariates[a]	Included in analyses (7,524)	Excluded from analyses due to missing covariate data (1,645)	95% Confidence Interval for difference	All
Demographics				
Female, %	55.64 (0.57)	55.32 (1.23)	-2.34, 2.97	55.58 (0.52)
Age, years	67.49 (0.11)	69.96 (0.31)	1.94, 3.01	67.78 (0.10)
Does not use the Internet, %	30.58 (0.53)	27.80 (2.78)	-2.77, 8.33	25.88 (0.46)
Has depression symptoms, %	12.40 (0.38)	21.08 (1.20)	6.21, 11.16	12.80 (0.35)
CESD score, mean	1.29 (0.02)	1.87 (0.07)	0.46, 0.70	1.37 (0.21)
SES, %				
No educational qualifications	23.79 (0.49)	37.69 (1.20)	11.37, 16.43	26.28 (0.46)
No resident partner	16.21 (0.42)	17.99 (0.95)	3.81, 2.55	16.53
Lowest quintile of wealth	15.06 (0.41)	23.59 (1.05)	6.32, 10.73	16.59 (0.39)
Comorbidities[b], %				
Has chronic physical illness	63.16 (0.56)	64.07 (1.18)	3.53, 1.59	63.32 (0.50)
Subjective and objective isolation				
Number of people in household, mean	1.99 (0.97)	1.95 (0.02)	-0.01, 0.09	1.98 (0.91)
Often feels lonely, %	10.70 (0.36)	20.27 (1.16)	7.19, 11.94	11.44 (0.33)

[a] Percentage or mean (se)

[b] High blood pressure or hypertension, angina, heart attack, congestive heart failure, heart murmur, cardiac arrhythmia, diabetes, cerebral vascular disease (stroke), asthma, chronic lung disease, arthritis, osteoporosis, cancer

With regards to activities, non-cases reported higher use of the Internet for sending and receiving emails (62.81%; se, 0.60), organising finances (37.52%; se, 0.60), shopping (49.81%; se, 0.62), seeking information about goods and services (63.24%; se, 0.59), research and learning (53.72%; se, 0.61), and some entertainment; streaming television shows and video clips in particular (24.41%; se, 0.53). On the other hand, cases for depression symptoms reported somewhat higher use of the Internet to search for jobs (6.3%; se, 0.80), albeit that this particular activity was quite rare for both groups of participants, relative to other activities. No clear differences were observed between the two groups for the use of social networking sites (17.90% and 19.39 % in cased and non-cases, respectively), and for uncommon activities such as selling goods or services, and uploading content.

5.6.2 Results for Study 2 – Part 1: Frequency of Internet use

Table 16 displays the risk of reporting depression symptoms relative to the frequency with which participants used the Internet, as well the number of activities that they engaged in. As can be observed in Table 16, increasing Internet use was associated with an average 15% reduction in the odds of reporting depression symptoms. When compared with non-use of the Internet, using the Internet daily was associated with the lowest odds of depression symptoms (age and sex adjusted OR 0.35, CI 0.29, 0.58). Indeed, stepping up from non-use of the Internet to infrequent use was associated with a reduction of the odds of depression symptoms which was surpassed by weekly use, which in turn was surpassed by daily use. The association between frequency of Internet use and depression symptoms was partially explained by SES, comorbidities, and subjective and objective isolation, with the largest attenuation being observed for SES.

Table 15: The Internet use characteristics of 7,524 participants of the English Longitudinal Study of Ageing according to depression symptoms

Internet use characteristics	No depression symptoms (6,591)	Has depression symptoms (933)	95% Confidence Interval for difference
Frequency			
Never	28.46 (0.56)	45.50 (1.63)	13.71, 20.46
Infrequently	6.05 (0.29)	7.72 (0.87)	-3.47, 0.14
Weekly	13.14 (0.42)	11.36 (1.04)	-0.42, 3.97
Daily	52.34 (0.62)	35.37 (1.56)	13.68, 20.27
Activity			
Sending/receiving e-mails	62.81 (0.60)	43.73 (1.65)	15,59, 22, 47
information about goods and services	63.24 (0.59)	44.69 (1.63)	15, 15, 21.94
Information for research, learning	53.72 (0.61)	37.41 (1.59)	12.99, 19.64
Finances (banking, paying bills)	37.52 (0.60)	24.44 (1.41)	10.09, 16.08
Shopping/ buying goods	49.81 (0.62)	33.98 (1.55)	12.56, 19.10
Selling goods or services	6.42 (0.30)	6.11 (0.78)	-1.33, 1.96
Use social networking sites	19.39 (0.49)	17.90 (1.26)	-1.15, 4,13
Uploading content	5.34 (0.28)	3.97 (0.64)	0.01, 2.74
Reading newspapers, blogs	28.21 (0.55)	18.33 (1.27)	71.17, 12.59
Streaming/downloading content (TV shows, YouTube)	24.41 (0.53)	14.90 (1.17)	7.00, 12.02
Gaming	13.99 (0.43)	12.54 (1.08)	-0.84, 3.73
Looking for a job	5.11 (0.27)	6.32 (0.80)	-2.80, 4.39
Other	5.75 (0.29)	4.50 (0.68)	-0.20, 2.69

*Percentage or mean (se)

Table 16: Cross-sectional odds ratios (95% CI) of depression symptoms in 7,524 participants of the English Longitudinal Study of Ageing at wave 6 (2012) based on frequency of Internet use

	No Internet use (2,301)	**Infrequent** (471)	**Weekly** (972)	**Daily** (3,780)	**OR for unit increase in frequency of use**
Adjustments					
Age, sex	1 (ref)	0.68 (0.51, 0.90)	0.46 (0.36, 0.58)	0.35 (0.29, 0.58)	0.70 (0.60, 0.74)
SES	1	0.99 (0.74, 1.31)	0.71 (0.56, 0.91)	0.63 (0.53, 0.75)	0.82 (0.78, 0.87)
Comorbidities[a]	1	0.84 (0.64, 1.11)	0.58 (0.46, 0.73)	0.48 (0.41, 0.56)	0.78 (0.77, 0.87)
Isolation	1	0.96 (0.70, 1.31)	0.68 (0.42, 0.88)	0.56 (0.47, 0.66)	0.82 (0.78, 0.87)
Adjusted for all covariates	1	0.99 (0.72, 1.37)	0.68 (0.51, 0.90)	0.63 (0.50, 0.78)	0.83 (0.77, 0.89)

[a] High blood pressure or hypertension, angina, heart attack, congestive heart failure, heart murmur, cardiac arrhythmia, diabetes, cerebral vascular disease (stroke), asthma, chronic lung disease, arthritis,

5.6.3 Results for Study 2 – Part 1: Internet activities

The number of activities that ELSA participants reported taking part in online was also associated with risk of reporting depression symptoms. Table 17 displays the odds of reporting depression symptoms relative to the number of online activities reported by participants. After adjusting for age and sex, engaging in four to six online activities was associated with the lowest odds of reporting depression symptoms. Participants in this group were 63% less likely to report depression symptoms than participants who did not use the Internet at all (OR 0.37, CI 0.31, 0.45).

Although participants who reported less than 4 or more than 6 activities were also less likely to report depression symptoms than non-users of the Internet, the differences between these two groups were less obvious for either extreme of number of online activities. Results from a likelihood ratio test showed that there was indeed a quadratic relationship between number of online activities and depression symptoms. After

adjusting for all covariates, as well as for a quadratic effect, number of online activities was associated with an average 16% average reduction in the risk of reporting depression symptoms for Internet users when compared to participants who did not use the Internet.

When Internet activities are assessed by theme, it is evident that certain types of activities have are more indicative of the risk of reporting depression symptoms in older people. Table 18 displays the association between Internet activities and depression symptoms when activities are grouped by theme. Here, it can be observed that engaging in any type of online activity was better than not using the Internet at all. However, the risk of reporting depression symptoms was lowest when participants reported using the Internet for communication via email (age adjusted OR 0.33, CI 0.27, 0.39). Although the strength of this association reduced after adjusting for all covariates, participants who communicated via email remained significantly less likely to report depression symptoms (OR 0.64, CI 0.51, 0.80). Aside from communication via email, participants who reported using the Internet for social networking (with or without communication via email) also had a significantly lower risk of reporting depression symptoms (OR 0.65, CI 0.50, 0.84).

As displayed in table 18, the strongest attenuations for the association between the various Internet activities and depression were observed when loneliness was taken into account. After accounting for all other covariates, the association between depression symptoms and using the Internet for entertainment, as well as all other activities, was lost.

Table 17: Cross-sectional odds ratios (95% CI) of depression symptoms in 7,524 participants of the English Longitudinal Study of Ageing at wave 6 (2012) based on the number of online activities

	Zero activities/ No Internet use (ref) (2,301)	**One to three** (1,125)	**Four to six** (2,372)	**Seven to ten** (1,726)	**OR for each additional online activity**
Adjustments					
Age, sex	1 (ref)	0.49 (0.39, 0.61)	0.37 (0.31, 0.45)	0.39 (0.31, 0.48)	0.69 (0.65, 0.75)
SES	1	0.72 (0.58, 0.90)	0.65 (0.54, 0.79)	0.71 (0.57, 0.87)	0.87 (0.81, 0.93)
Comorbidities[a]	1	0.60 (0.48, 0.74)	0.47 (0.40, 0.57)	0.55 (0.45, 0.66)	0.80 (0.73, 0.83)
Isolation	1	0.73 (0.57, 0.93)	0.56 (0.46, 0.68)	0.63 (0.51, 0.78)	0.83 (0.77, 0.86)
Adjusted for all covariates	1	0.77 (0.60, 0.99)	0.63 (0.50, 0.80)	0.69 (0.53, 0.90)	0.86 (0.79, 0.94)

[a] High blood pressure or hypertension, angina, heart attack, congestive heart failure, heart murmur, cardiac arrhythmia, diabetes, cerebral vascular disease (stroke), asthma, chronic lung disease, arthritis, osteoporosis, cancer

5.7 Discussion

5.7.1 Main findings of Internet use study

The study shows that among people aged 50 years and above, using the Internet was associated with a reduced risk of developing depression symptoms over a 10-year follow-up period. This relationship was partially explained by loneliness, low educational attainment and low wealth. Age, gender, physical comorbidities, number of people in the household and cohabiting status made little difference to the association between Internet use and depression.

From cross-sectional analyses of the various attributes of Internet use, it is illustrated that participants were less likely to report depression symptoms if they also reported that they used the Internet; an association which was most pronounced among those that reported using the Internet for communication via email. Additionally, 'intensity' of Internet use was also inversely associated depression symptoms, such that the more an individuals used the Internet, the less likely they were to report depression symptoms. From measures of frequency used in this study, it can be seen that using the Internet regularly was associated with lower reports of depression symptoms than irregular use, which in turn provided better odds than not using the Internet at all. Although this association was even stronger when age was taken into account, it was once again attenuated by loneliness, wealth and education.

Concurrently, using the Internet for an increasing number of different activities reduced risk of reporting depression symptoms, albeit modestly. As such, individuals who reported using the Internet for multiple activities were a little less likely to report depression symptoms than those who used it for a single activity; who in turn were less likely to report depression symptoms compared to those who did not use the Internet at all. The modest risk reduction proffered by each additional activity increased when age was taken into account, but was once again reduced when other covariates are taken into account, such that marginal reduction in risk of depression symptoms was observed as the number of activities increased.

Table 18: Odds ratios (95% CI) of depression symptoms in 7,524 participants of the English Longitudinal Study of Ageing according to the type of Internet activity

	No Internet use (ref) (2,301)	**Communication via email (no social networking)** (3,176)	**Social networking plus email** (1,445)	**Entertainment only OR (CI)** (145)	**All other activities** (457)
Adjustments					
Age	1 (ref)	0.33 (0.27, 0.39)	0.44 (0.36, 0.55)	0.61 (0.38, 0.99)	0.62 (0.47, 0.83)
Sex	1	0.41 (0.35, 0.49)	0.58 (0.48, 0.70)	0.79 (0.49, 1.27)	0.75 (0.56, 1.00)
Education	1	0.48 (0.40, 0.57)	0.70 (0.57, 0.86)	0.80 (0.50, 1.29)	0.80 (0.60, 1.06)
Wealth	1	0.56 (0.47, 0.67)	0.69 (0.57, 0.84)	0.83 (0.52, 1.35)	0.82 (0.61, 1.09)
Loneliness	1	0.55 (0.45, 0.66)	0.75 (0.60, 0.93)	0.98 (0.57, 1.67)	0.96 (0.69, 1.32)
Comorbidities[a]	1	0.43 (0.36, 0.51)	0.65 (0.53, 0.79)	0.82 (0.51, 1.33)	0.77 (0.58, 1.03)
Number of people in household	1	0.40 (0.34, 0.47)	0.60 (0.49, 0.73)	0.78 (0.48, 1.25)	0.74 (0.56, 0.99)
Cohabiting status	1	0.40 (0.34, 0.47)	0.56 (0.46, 0.68)	0.77 (0.48, 1.24)	0.73 (0.55, 0.97)
Adjusted for all covariates	1	0.64 (0.51, 0.80)	0.65 (0.50, 0.84)	0.86 (0.50, 1.51)	0.92 (0.66, 1.30)

[a] High blood pressure or hypertension, angina, heart attack, congestive heart failure, heart murmur, cardiac arrhythmia, diabetes, cerebral vascular disease (stroke), asthma, chronic lung disease, arthritis, osteoporosis, cancer

While cross-sectional analyses were carried out in an attempt to determine how Internet use was associated with the reduced risk of developing depression symptoms observed in longitudinal analyses, caution should be applied before inferring causation based on the individual attributes of Internet use. Although longitudinal analyses illustrated reduced risk of depression among those who used the Internet, it is plausible that because of

reverse causation at the time of cross-sectional analyses, participants who reported using the Internet less frequently or less for activities such as communication via email abstained because they were depressed. However, these current findings would be useful in informing future research efforts.

5.7.2 Comparison with existing studies

Findings from this study affirm the findings from the two existent population studies of the association between Internet use and depression in older people, where individuals who used the Internet had a lower probability of developing depression symptoms compared with those who did not.[204,205] Such was the case even though previous investigations were carried out only among retired participants, who were viewed as heterogeneous from the non-retired due to their increased likelihood of being socially isolated.

Aside from the hypothesised differences in social interaction characteristics, it was further proposed that non-retired individuals would be more likely to report work-related Internet use, which would result in the term 'Internet use' having different meanings for the two sub-populations. However, while retired and non-retired participants may not display similar use of the Internet, variations in use are somewhat irrelevant in a study that probes the absolute role of Internet use as measured by yes or no responses, as these activities may be heterogeneous even among the retired, and may be homogenous through other unexplored ways. For instance, an individual could benefit from spending their time on the Internet responding to emails, while another only accesses it to read the daily paper as illustrated in a review of the literature and statistics on Internet use behaviour in older

people.[215] Conversely, partaking in either of these activities could result in reduced symptoms of depression related to some aspect of the act of engaging with technology.

While Internet use was found be stable over the 4 wave of HRS,[205] this was not the case in the present study, where Internet use was observed to increase markedly with each following wave. Indeed, the findings of the present study in relation to the steep rise of Internet use over time resound with findings from other studies, where it has on occasion been noted that the widespread use of the Internet has resulted in an entire world that can be likened to a 'global village'.[187] In the UK, the communications regulator, Ofcom noted in 2010 that internet access at home was growing faster for the older age groups than in any other, and the highest absolute growth in uptake was observed amongst the 55-64 and the 65-74 age groups.[216] By 2016, younger seniors in the USA (65-69 year-olds) were subscribing to the Internet at the same rate as younger users, indicating that while Internet use was found to be stable in the previous study between 2002 and 2008, changes in Internet use practices during that period are likely more in line with those reflected in the present study.[217]

In addition to the findings which were similar to those of previous studies as detailed above, this present study is the first which shows that among older people, unlike any other age group, increased frequency of Internet use reduces risk of depression. While the view shown in the media indicates that the Internet increases risk of depression in the whole population, the evidence of this association can only be found in studies of younger people. Often, the effect of the Internet on depression is attributed to malicious behaviours whose names have been adapted for the digital sphere in which they are now being observed. In particular, 'cyberbullying' and 'trolling' are associated with not only

the posting of intimidating and harassing statements online, but also disruptive and anti-social behaviour like inciting arguments, upsetting people, and posting inflammatory, extraneous, or off-topic messages on social media with the deliberate intent of provoking readers into an emotional response. [218] Such behaviours, as with bullying in the traditional sense, are more often observed among younger people,[219] who may also be more susceptible to their effects because of their age-specific biology and social norms.

Thus, although studies of younger people have shown that social networking in particular is adversely associated with depression symptoms,[220] this study shows that such Internet activities may have the opposite effect on people aged 50 years and over. While crude analysis shows that social networking does not have the same strength of association with depression symptoms as communication via email in the present study, multiple adjustments for all covariates result in similar odds of depression symptoms for both groups. This suggests that, all things considered, using the Internet for communication via email and for social networking may convey similar protection from depression in older people. This also suggests that while social networkers may have more unfavourable individual attributes (in relation to depression) compared to individuals who use the Internet for emailing, once all attributes are taken into account, using the Internet for social networking and emailing are activities that carry similar benefit in relation to depression symptoms.

5.7.3 Subjective and objective isolation

While using the Internet for communication via email and social networking were activities that were strongly associated with fewer depression symptoms, the strength of these associations was weakened most when loneliness was taken into account. Thus, it

would seem that participants who perceived themselves to be socially isolated were not only more likely to report depression symptoms, but also less likely to use the Internet. Indeed, assessment of the baseline characteristics of core ELSA participants proves this to be the case, as most of those who reported depression symptoms as baseline were much more likely to report feeling lonely in the week preceding the study, compared to those without depression symptoms. Participants who were depressed at baseline were also more likely to report that they did not use the Internet.

While one line of reasoning implies that introverts and socially anxious people, and other types of people that struggle to form friendships, are more likely to use the Internet because they substitute online contacts for an undesirable offline social network (Social Compensation theory),[221] this is clearly not the case in ELSA, and may be another phenomenon related to youth. As demonstrated, lonely ELSA participants were less likely to report that they used the Internet. Moreover, there was no evidence that Internet use was more beneficial for people who started off with poor social resources at baseline, such as those with chronic illness, who according to this theory are meant to benefit most from meeting people online.

Based on characteristics of the HRS sample, previous investigations of the association between Internet use and depression indicated that living alone made individuals more vulnerable to isolation and loneliness than those who lived in larger households, where they were could enjoy more social interaction. As such, it was surmised that living alone would lead to more reports of loneliness, and thus more reports of depression. While it is clear from this present study that loneliness was indeed associated with both Internet

use and depression symptoms, such that it often partially explained this relationship, this was certainly not the case for objective isolation.

Among ELSA participants the number of people that lived in a household was not only unrelated to a participant's likelihood of reporting feelings of loneliness, but it also clearly had no relation with either their use of the Internet or subsequent reports of depression symptoms. Indeed, rounded to whole figures (as would be the actual case) the number of inhabitants per household was quite similar across ELSA, with most people living in households with an average of 2 occupants. As such, subjective and objective isolation had distinct relationships with both Internet use and risk of depression, and objective isolation had no effect on their association. It is likely therefore that feelings of loneliness may have been hinged much more on the nature and quality of relationships in and out of the households, than on the number of people in the immediate surroundings.

While Kraut et al pointed to the isolating effects of Internet use, and indicated this to be the mediator for poor psychological well-being; it is possible that the effects they observed were due to the tainted quality of relationships, as opposed to the reduced quantity.[195] However, with broad reference to quality of relationships, the evidence from this present study opposes the notion that having fewer people in one's immediate environment mediates the association between Internet use and depression. Indeed, the difference in reports of depression symptoms in ELSA were substantially (but not totally) explained by reports of loneliness or perceived/ subjective isolation, and not by objective isolation.

Thus, although previous evidence has shown an association between Internet use and increased isolation[195] and loneliness,[222] this present study illustrates that while loneliness may explain the association between Internet use and depression, objective isolation (where individuals may have little interaction with others due to ill health, reduced mobility or other factors) does not play the same role. Indeed, unlike observations made in the previous longitudinal study, having poor health did not explain the association between Internet use and depression symptoms among ELSA participants. Ultimately, this present study highlights that even after taking subjective and objective isolation into account, using the Internet significantly reduced the risk of reporting depression symptoms, relative to not using the Internet at all.

Given that the benefit of using the Internet seemed to be associated with activities that involve communication, it would appear that any possible isolating effects of the act of using the Internet (as per Kraut's isolation hypothesis) are outweighed by the benefits of communicating online. Pertaining to that, the findings of this present study support earlier proponents of Internet use, who suggested that the Internet may reduce depression in older people by increasing social support, social contact and social connectedness.[223, 224, 225] While increasing frequency of Internet use may help to reduce depression symptoms, it should be noted that efforts to increase time spent online should be balanced against other factors which are also essential for well-being, such as maintaining adequate physical activity, and performing basic (personal hygiene) and instrumental (bathing, dressing and grooming) activities of daily living. [226]

5.7.4 Social interaction, Internet use and depression

Although it has previously been suggested that the Internet could impact social relationships in much the same way as its technological predecessors and that the social ties formed or maintained on the Internet would be weaker than real life ties,[227] what this study illustrates is that although the qualities of physical social ties may be different, they are not necessarily any better than those developed or maintained on the Internet. Furthermore, evidence from this study challenges the idea that physical social ties provide more protection from depression than online ties by offering more buffering from stressful events.[228]

While the number of people per household may not fully describe subjective isolation, it does illustrate the number of people who may be readily available to an individual if they needed support and buffering from stressful events. However, based on the role of communication via email observed in this study, it is plausible that online communication offers the same benefits as one-to-one interactions. Considering busy lifestyles and distance between family members (such as children and grandchildren who live far away), the Internet may indeed be a place where support can be more readily available than in one's physical space. Nowadays, with online features that allow for voice and video conversations, online communications are just a short step of the imagination away from being just the same as 'face-to-face'.

Thus, social ties in the digital/ information age are not necessarily dependent on physical distance, and social interactions on the Internet can be used to enhance the buffering attributes of any social relation; just as they could be damaging and be toxic.[229, 230] Although the Internet obviously cannot be used to provide physical assistance in the way

that people in the immediate environment can, it is possible that the importance of physical support with regards to depression is over-emphasised, and that psychological well-being is much more dependent on the intangible aspects of relationships. Furthermore, in England, it is likely that physical help (where required) is received from a professional or volunteer when help from family and friends is not available, thereby reducing some psychological effects of physical deficiencies.

As indicated in the review of the literature, it has been proposed that it may take a certain personality type to perceive communication via the Internet as being emotionally supportive.[194] As such it is possible that ELSA participants in this study subscribe to the personality traits that fulfil the social enhancement theory, where individuals who have healthy social circles engage readily with others online, and continue to expand their already large offline network of friends and family.[231] However, as personality traits were not reviewed in this study, such a relationship would need to be explored in future research.

Apart from maintaining supportive relationships, the Internet makes it easier to find and communicate with people who have similar interests or have had similar experiences. For instance, it is now common practice for people to email each other in cancer, bereavement and chronic illness support groups.[232] It is likely that as in other scenarios where circumstances are shared and where people are more conscious of each other than normal, the essence of interacting in a seemingly isolating environment as the Internet is captured by the philosopher Alain de Botton when he writes, 'In roadside diners and late-night cafeterias, hotel lobbies and station cafes we may dilute a feeling of isolation in a lonely place and hence rediscover a distinctive sense of community'.[233] Aside from this type of

online emotional support, other online support platforms have mushroomed in recent years, where individuals can get help with fixing malfunctioning appliances, report various problems and join causes of different types. How the Internet has expanded and enhanced communication channels cannot be understated.

5.7.5 Other factors: SES, entertainment

While Internet use patterns have changed over time, there is evidence that during the time data for this study were collected; Internet access and use remained structured along socio-economic and educational lines, which were believed to work against already disadvantaged groups. This has remained the case despite considerable technological change and policy interventions specifically targeting marginalised sections of society at the time.[234] From the present study, it is evident that SES, specifically wealth and education level, largely attenuated the relationship between Internet use and depression symptoms. Thus, the risk of depression symptoms was largely dependent on the level of education and wealth status, as was access to the Internet. Conceivably, Internet access was limited by lack of access to computers and smartphones, as well as limited ability to perform various activities once on them. For instance low education may have resulted in less confidence in using the computer, and may have led lack of resourcefulness online, limiting the benefit that could otherwise be given by Internet use. However, even considering this disadvantage, wealth and education still do not fully explain the association between Internet use and depression.

Although the most benefit observed is in the use of the Internet for communicating, it is worth noting that there may be some merit to encouraging use of the Internet for entertainment. Although there is little evidence from the present study that using the

Internet for entertainment reduces the risk of depression symptoms, other studies have shown that this type of pastime improves psychological well-being. For instance, one study showed that college students who engaged in online video game-like exercises that involved identifying shapes stayed more focused and were less likely to be anxious than those who did not.[235] Employed in this manner, online games may distract players from the life factors that may lead to depression, such as social isolation, thereby reducing their perception of their reality and thus any low mood that may come with it.

5.7.6 Strengths and limitations

The main strength of this study is that it has a large, nationally representative sample of people aged 50 years, who have been well retained over the follow-up period to date. Furthermore, the longitudinal aspect of this study allows for an assessment of directionality, highlighting in this instance that Internet use preceded depression symptoms. Additionally, this study employs a comprehensive and validated depression symptomatology tool, the CES-D, which has been used in a number of studies of the elderly. [71, 73]

Compared to previous studies of depression in older people, this present study not only utilises data from participants who are followed up over a long period, but also uses multiple measures of Internet use to ascertain associations with depression symptoms. To my awareness, the assessment of frequency of Internet use and activities pursued online has not been performed in relation to depression symptoms at any point prior to this current study. This study therefore offers novel evidence in increasing the knowledge on Internet use and depression in older people.

This study also has a number of limitations. The observational nature of information sourcing makes it impossible to make any firm assertions about cause and effect. Both Internet use and depression symptoms were self-reported by participants, which may introduce some elements of reporter and recall bias. Some of the covariates such as diagnosis of a chronic illness and loneliness were self-reported and thus would be prone to the same bias.

While suggestions for mechanisms of action have been posited, it remains possible that Internet use is a proxy for other factors that are causally related to depression (residual confounding). Although this present study is very well characterised, it is not possible to control for all possible confounders. Aside from potential confounders such as quality of online and offline social networks, and personality types not being measured, it also the case that some potential confounders were not considered for analyses. While reduced cognitive function, vision impairment and frailty could have reduced the likelihood of using the Internet, these factors could also increase the risk of depression. It is recommended that these factors be considered for future investigations. In particular, such measures that may affect access to Internet and could affect well-being should be considered when implementing measures to reduce inequalities in Internet use, and interventions to achieve this will be proposed in a later section of this thesis.

While rationale has been provided for the classification of objective and subjective isolation in this study with consideration to Internet use, it is plausible that these measure do not capture these attributes appropriately. This could have led to misclassification of these attributes, which could result in incomplete adjustment for confounding. Furthermore, it is possible that co-morbidities could have been further characterised to

allow for assessment of severity of physical limitations, and the effect this would have on present findings. Accordingly, further consideration of confounding is recommended for future research.

Although the present study adds valuable information to Internet research in that the various attributes if Internet use are explored in relation to depression symptoms, it is important to note that such explorations are carried out using cross-sectional data. Thus, even though intensity of Internet use and the number of activities pursued online are shown to reduce the risk of developing depression symptoms, it remains possible that the risk of reporting depression symptoms at one time-point is not necessarily dependent on these factors, and that it is in fact the condition of being depressed that makes individuals spend more time on the Internet. However, based on findings form the longitudinal study, where depressed individuals were less likely to report that they used the Internet, this reverse causation is highly unlikely.

With regards to methodology, there is a possibility that some over-adjustment may have occurred when analysing the association between Internet use and depression relative to SES. This is because while each of the three separate measures used to measure SES had an individual effect on the overall association, the combined way in which they described SES may have been over-emphasised in the multiple adjustment. However, as wealth, education status and cohabitation status all describe different aspects of a complex measure of SES, the inclusion of all three was necessary for elucidating the complex nature of individual characteristics that may affect the relationship under investigation. Therefore, when possible over-estimation is taken into account, it is likely that the results

reported in this study are under-estimated, and that Internet use may be more beneficial to older people than illustrated in this study.

Finally, during the process of selecting study participants, a substantial proportion of individuals were excluded from the present study. ELSA participants who could not be included in this study (mainly due to having depression symptoms at baseline) were generally older, poorer and less educated than those who were included. Thus, when considering the fact that socio-economic status does not fully explain the relationship between Internet use and depressions symptoms, it is important to note that excluded participants were more deprived than those included, whose inclusion may have affected the relationship between Internet use and depression symptoms.

Chapter 6: Cardiovascular disease risk factors and cardiovascular disease risk algorithms in relation to the development of depression symptoms in older people

6.1 Literature review

6.1.1 Cardiovascular disease burden and risk prediction tools

Cardiovascular disease (CVD), which encompasses all diseases of the heart and circulation, is the leading cause of death worldwide.[236] Approximately 7 million people live with CVD in the UK, where it is responsible for more than a quarter (26%) of all deaths each year.[237] The bulk of these CVD deaths are attributable to the atherosclerotic narrowing of coronary arteries, known as coronary heart disease (CHD). [238]

According to the British Heart Foundation, CHD is currently responsible for about 73,000 deaths per year in the UK, most of which occur as a result of myocardial infarction (MI); more commonly known as heart attack. [239] Of the estimated 2.3million people who live with CHD, most are known to be affected by chest pain (angina) and it is this pain that is recognised as one of the classic signs of CHD, the other signs being chronic heart failure and heart attack.[238] While it is often a consequence of arterial plaque build-up, CVD also notably comprises congenital, inflammatory and rheumatic heart disease, as well as venous thromboembolism, and both ischemic and haemorrhagic stroke.[240]

To predict risk of CVD among individuals in the UK, the use of any of the following tools is recommended by the National Institute for Health and Care Excellence: The Framingham model, the QRISK2 calculator, and the Systematic COronary Risk Evaluation (SCORE) chart. [241]

The Framingham model

The Framingham model is the oldest CVD prediction tools currently in use. Developed using evidence from the Framingham Heart Study, an ongoing prospective, single-centre study of community-based adults in the USA,[242] the Framingham model is a sex-specific multivariable risk factor algorithm that is used to assess 10-year risk of CHD in individuals aged 20 to 79 years.[243]

While it was deemed to have satisfactory discriminative abilities in some American[244] and European settings,[245] the main criticism for use of the Framingham model is that it was developed using data from a mainly white, middle class sample, at the peak of CVD incidence in the USA, and could not be generalised to other populations, particularly those with lower risk profiles.[246] A systematic review of the Framingham model's performance in multiple countries showed it often either over- or under-estimated CVD risk in low and high-risk populations, respectively, with predicted versus observed risk ratios varying from 0.43 to 2.87.[247] In the British population, the uncalibrated Framingham model not only overestimated risk of CVD (by as much as 5% for men), but also underestimated risk in some socioeconomic groups.[248]

Women have a higher baseline Framingham score than men, as the value allocated to each component of the score is higher for the female gender than that for a male with the exact same attributes. For instance, a woman who is 70 years old, currently smokes cigarettes, has a systolic blood pressure of 140mmHg, a total cholesterol level of 6.2 and HDL cholesterol level of 1.03 will have a Framingham score of 21, while a man with the exact same characteristics will have a Framingham score of 16. Thus, the average woman

will always have a higher Framingham score than the average man; which, importantly, does not relate to proportionally higher risk of CVD.

To reflect the fact that women actually have lower baseline risk of CVD than men, the gender differences in scores is corrected for when Framingham scores are translated into 10-year percentage risk of a fatal or non-fatal CVD event, at which point they actually reflect overall a lower points-based risk for females than males. For instance, a woman with a Framingham score of 15 will only have a 3% risk of experiencing a CVD event, while a man with the same score will face a 20% chance of experiencing a similar event.

The QRISK calculator

Packaged as advancement in CVD risk prediction in the UK, the QRISK risk calculator is a multifactorial algorithm that was developed to provide accurate assessment of CVD in people in England and Wales, and was validated for use in the UK.[249] Prior to its use, clinicians in England and Wales used a modified version of the Framingham risk score. However, due to the limitations of the Framingham scale in isolating 'at risk' individuals in the population at a time when there was an eminent national initiative to lower the threshold of using statins for primary CVD prevention,[250] a study was carried out to derive and validate an improved cardiovascular disease risk scoring equation for use in the UK.

The QRISK calculator is a computer based CVD prediction tool, whose main purpose is to predict risk of suffering a heart attack or stroke over a 10 year period in individuals aged 25 to 84 years using information about their demographics, health behaviours and some clinical information.[251] Although intended for use as a web-based calculator which would normally be applied by a clinician in a primary care setting, the QRISK can be

used by any individual with access to the Internet. Since its development, in addition to annual updates, the QRISK calculator has been modified to incorporate additional risk factor components to increase its efficiency in predicting CVD, resulting in a release of the QRISK2 in 2016,[252] and the QRISK3 in the latter part of 2017.[253]

To derive this equation the researchers utilised prospective data from a large, validated electronic database (www.qresearch.org) representative of primary care and containing the health records of 10 million patients over a 17 year period from 529 general practices. After randomly selecting two thirds of participants for the study and development of the equation, the remaining one third of the dataset was used to validate the algorithm.[254] The derivation sample comprised a cohort of patients aged 35-74 at the date of study entry, drawn from patients registered with eligible practices from 1 January 1995 to 1 April 2007; all without a diagnosis of cardiovascular disease or diabetes before their entry date.

Following *a priori* selection of risk factors to be used in the model based on traditional risk scores, Cox proportional hazard models were used to compute strength of association with each variable, and to test for interactions. Each patient's probability of experiencing a cardiovascular event (heart attack or stroke) within 10 years was then calculated using the characteristics of the patient and the baseline survivor function of all participants. Performance of the resultant QRISK equation was tested and calibrated using the validation dataset[249] and later revised and re-validated externally,[255] whereon the QRISK calculator was deemed the best available tool for predicting risk of CVD among individuals aged 25 to 84 years in the UK.

The SCORE chart

The Systematic COronary Risk Evaluation (SCORE) charts are recommended as simple, straightforward tools which can be used as first-line screening tools all across Europe.[256] Replacing the borrowed New Zealand risk charts in previous guidelines, [257] and also descendent from the Framingham score, the purpose of the original SCORE chart was to predict 10-year risk of fatal CVD in 40-65 year-old men and women across Europe who had no pre-existing atherosclerotic CVD.[258]

Based on risk functions used in the Framingham model, and enhanced for simplicity of use by adopting the traffic light colour coded graphics of the New Zealand charts,[259] the SCORE chart is advertised as a fool-proof first-line screening tool, meant to prompt further screening and intervention once an individual was found to have a 10-year absolute risk of 20% or more.[260] However, even as it was implemented, there were demonstrable concerns that the chart was not entirely appropriate for the whole European population as it used the same Framingham model which was known to either over- or under- estimate risk in some populations, and whose end-points were not the same as those used in other cohort studies and clinical trials.[247] Thus, dependent on their country's background CVD risk profile, low- and high-risk versions of the SCORE chart have since been developed, with the users in the UK advised to use the low-risk chart.

6.1.2 Gender differences in risk of CVD

The development and application of the CVD risk prediction tools above indicates gender differences in risk of CVD which are supported by the literature.[261] The differences in risk arise mainly from individual risk factors that often favour women; the most important being age, whose effect is largely attributed to circulating oestrogens present in women

of fertile age.[262] Additionally, differences in lipid regulation[263] and vascular tone (dues to sex hormones) also proffer pre-menopausal women with more resistance to the ramifications of high blood pressure than men and post-menopausal women. [264] Further explanation of gender differences in CVD incidence and mortality up to menopausal age has been offered through the observation that risk factors such as smoking, heavy drinking and poor dietary habits often accumulate more in younger men.[265]

Menopause transition is associated with a worsening CHD risk profile,[266] and although often underestimated, the risk of CHD in women rapidly becomes comparable to that of male counterparts after menopause. Indeed, evidence from longitudinal data illustrates increases in CVD incidence and mortality among post-menopausal women.[267] While it is suggested that the increased incidence and mortality may be due to the over-representation of women in older age due to higher life-expectancy,[268] steeper rises in central obesity, cholesterol and blood pressure, are often observed in women, [269, 270] often resulting in worse cardiac outcomes than those of men with similar risk profiles.[261] In addition, older women are more likely to be diagnosed with type II diabetes and as a result, as highlighted by evidence from 37 prospective cohort studies, they develop higher risk of fatal CHD (of up to 50% in some instances) compared to male diabetes sufferers.[271]

Barring the protective effect of gonadal hormones, women are more susceptible to the effects of smoking, which is considered the second most important determinant of the sex difference in CHD risk.[272] Smoking increase the risk of MI incidence and CVD by about 50% among women compared to men who smoke similar amounts of tobacco per day.[273] Furthermore, low physical activity is associated with worse outcomes for women, as illustrated by evidence from a worldwide study of physical activity, which shows that the

prevalence of obesity increased more rapidly in women as the number of footsteps taken per day reduced (232% obesity increase for females versus 67% increase for males; comparing lowest versus highest activity).[274] To a lesser extent, various genes that regulate insulin resistance and body fat distribution may also preferentially predispose men to lower risk of CVD. [275, 276]

6.1.3 Depression and cardiovascular disease

There is growing evidence that CVD and depression may have similar origins. While evidence from a systematic review and meta-analysis of longitudinal data indicates that prevalent CVD and stroke both predict depression in later life,[277] there is evidence that risk of CVD, in people apparently free of the disease, also predicts depression. Although the mechanisms of this effect are unclear, biomarkers such as hyperglycaemia, obesity/excessive weight, dyslipidaemia and hypertension have been implicated in the development of depression,[278] while specific cardiovascular disorders such as angina,[279] hypertension[280] and atrial fibrillation[281] have also been linked in the development of depression. The evidence of a relationship between circulating cholesterol levels and development of depression is somewhat ambiguous.[282]

Although not limited to the following, other important risk factors strongly linked to both CVD and depression are age, sex, smoking and socio-economic status.[283] In addition, individuals who eventually develop either disorder are also more likely to have pre-existing diabetes[284,285] obesity,[286] chronic kidney disease[287, 288] and rheumatoid arthritis[289, 290] than the general population. Moreover, psycho-social factors such as loneliness and social isolation have been implicated in the development of both CVD and depression. [291]

Following a causal model where risk factors for depression have been identified as similar to those CVD, irrespective of the eventual relation in existent disease, an exploration of a range of classic CVD risk factors in relation to depression may indicate whether a standard algorithm for CVD may have predictive utility for depression. Dual use of such an algorithm would increase the likelihood of identifying individuals at risk of depression, thus creating an opportunity for early intervention as is the case for CVD. Furthermore, as the use of such a tool would not increase either financial or time commitments of either the clinician or the patient, it would be beneficial to all key stakeholders.

Although existent algorithms specific to depression would be most appropriate in this endeavour, the use of a CVD risk prediction algorithm for predicting depression would be beneficial for a number of reasons. While tools developed to predict anxiety and depression like PredictD[292] and PredictA[293] tool have been identified as having good discriminatory characteristics, they are disadvantaged by being impractical for application in primary care as they require information (Short Form 12 scores) not normally available to general practitioners (GPs).[294] The same is the case with regards to evidence that social media could be used to aid detection and diagnosis of depressive disorders[295] by observing online behaviour, where implementation of such would only apply to individuals who engage with social medial – whereas a tool applied by a physician would likely capture more individuals during routine primary care visits.

The importance of carrying out early interventions for mental health has previously been emphasised based on evidence that it is value for money.[296] At present, individuals who are identified as being at high risk of CVD are offered lifestyle advice such as increasing exercise and reducing alcohol consumption and smoking;[240] factors which are also

implicated in the development of depression. Pertinent to this, there is evidence that pre-emptive interventions involving exercise and cognitive behavioural therapy could be used to prevent new onset of anxiety and depression in older adults living with osteoarthritis.[297]

From the study above, it was proposed that interventions which engage older adults in interventions to manage disabling and nuisance conditions (like pain) and also mental health-promoting qualities (like CBT and exercise) could be an efficient approach to optimising both physical and mental health.[297] Accordingly, in addition to dual prediction of risk of CVD and depression, current CVD lifestyle interventions could be augmented and monitored in relation to depression.

6.2 Aims and objectives

It is apparent that depression and CVD have a number of have mutual risk factors, such that elevated risk of one disorder often indicates risk of the other. Thus, the aim of the present study is to investigate whether a disease prediction algorithm used to predict CVD can also be used to predict depression symptoms.

Based on the commonality of risk factors between depression and CVD, my hypothesis for this present study is that a CVD risk prediction tool can also be used to predict future depression. Considering that the QRISK2 was introduced in the UK as advancement in CVD risk prediction tailored for the UK population, it is also my hypothesis that the QRISK2is likely to provide the most utility in predicting depression in older people in England, if any is to be found.

6.3 Methods

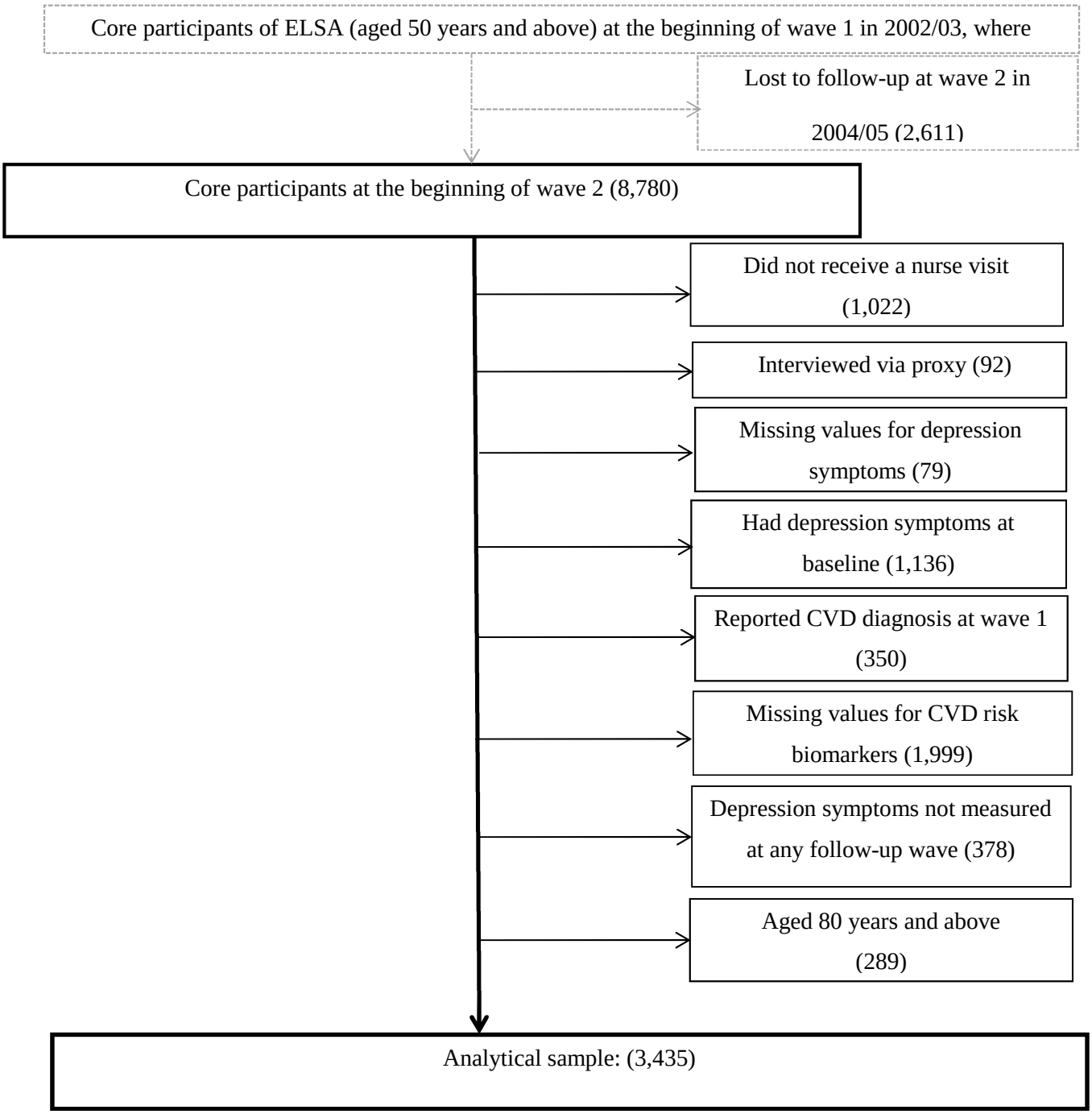
6.3.1 Selection of study participants

The data for this investigation were taken from wave 2 of ELSA (2004/2005), which is when measurement of biological CVD measurements was first taken. Figure 8 displays the selection process of the ELSA subsample for the present study. To start with, from the 11,391 core participants of ELSA who took part in the first wave (2002/2003) of the study, 2,611 were lost to follow-up at wave 2. Of the remaining 8,780 participants who took part in wave 2, a total of 92 participants who participated via a proxy were automatically excluded.

Furthermore 1,022 participants who had not received a nurse visit (and thus had no measures for biological risk factors), and an additional 1,999 participants who did not have blood samples taken were excluded. Reasons for failure to acquire biological measure where consent to a nurse visit had been given (such as failure to obtain an adequate blood sample), are described in detail in Chapter 3.2. A total of 350 participants who had reported physician's diagnosis of CVD prior to or in 2004/2005 were also excluded, in order to limit the study to 'at-risk' participants only.

Next, 79 participants who had missing values for depression symptoms at baseline, and 1,136 who had reported having depression symptoms were excluded. A total of 378 participants who had not provided responses to any of the questions about depression at any subsequent wave (after wave 2) were also excluded. Finally, for valid comparability between the QRISK2 score and Framingham model, analysis was limited to individuals aged up to 79 years, thus 289 participants aged 80 years and above were excluded. This resulted in a final analytical sample of 3,435 participants.

Figure 8: Sample selection for longitudinal analysis of the association between CVD risk factors and development of depression symptoms: the English Longitudinal Study of Ageing, 2004/05



6.3.2 Exposures: Cardiovascular disease prediction algorithms

1. The Framingham Model

Framingham scores were measured in ELSA participants firstly by ascertaining their (1) gender, which is then used to calculate scores dependent on their (2) age, (3) systolic blood pressure, (4) current smoking, serum levels of (5) total cholesterol and (6) high-density lipoprotein cholesterol, (7) diabetes, and (8) the use of antihypertensive treatment. Appendix 6 illustrates the allocation of scores according to the Framingham model for both women and men, which were applied accordingly to each participant in this study. Additionally, appendix 7 illustrates the allocation of Framingham 10-year percentage risk of fatal and non-fatal CVD.

2. The QRISK2 calculator

The QRISK2, which was the prevalent version of the QRISK calculator at the time of these analyses, contains some of the traditional risk factors as employed in the Framingham score such as (1) age, (2) sex, (3) systolic blood pressure, (4) smoking status and (5) use of antihypertensive medication, and also has additional components used to quantify the risk related to (6) total serum cholesterol to high density lipoprotein (HDL) ratio, (7) body mass index (BMI), (8) family history of cardiovascular disease, (9) social deprivation (derived from the Townsend score, which is extrapolated from the participant's postal code) and (10) ethnicity. Although initially not present when it was first implemented, the updated version of QRISK2 (2016) also factors in pre-existing diagnoses of (11) diabetes, (12) kidney disease, (13) rheumatoid arthritis, and (14) atrial fibrillation.[298] Calculation of CVD risk according to QRISK calculator were carried out using the online calculator for each individual, and rounded to the nearest fifth percentile

point. An image of the 2016 online version of the QRISK2 calculator is presented in appendix 8.

3. SCORE chart

Composed of two independent charts for use in different parts of Europe, both SCORE charts contain the appropriate scores to be applied to individuals in correspondence with their (1) gender, (2) age, (3) total cholesterol, (4) systolic blood pressure and (5) smoking status. These scores are aggregated in a risk chart with colour-coded risk cells, whose colour scheme represents a traffic light style warning system, such that green reflects low risk of CVD and red indicates very high risk of cardiovascular event within the following 10 years. Appendix 9 displays the low risk SCORE chart, which was employed to calculate CVD risk for each participant in this present study.

6.3.3 CVD risk factors in ELSA

Table 19 displays the components of the QRISK2 calculator, the Framingham model and SCORE chart, illustrating which CVD risk algorithm each component belongs to, and showing components which are common to more than one algorithm. In addition, the table contains a description of how the components are recorded in ELSA and how data were collected from participants. Of note, family history of CVD and diagnosis of atrial fibrillation, which are components of the QRISK2 calculator, were only recorded in the 1998 cycle of HSE only, resulting in missing data for participants recruited from the 1999 and 2001 HSE surveys.

Table 19: Components of the cardiovascular disease risk prediction algorithms and how they are recorded in the English Longitudinal Study of Ageing 2004

CVD risk factors	F	S	Q	Type of variable and how the information is collected in ELSA
Gender	●	●	●	Binary
Age	●	●	●	Continuous (Measured in whole years)
Systolic blood pressure	●	●	●	Continuous (Blood pressure was measured three times during the nurse visit using an Omron blood pressure monitor with the participant seated and then averaged. Reported as millimetres of mercury (mmHg))
Smoking status	●	●	●	Binary (Yes/ No. Participants were asked if they had ever smoked, and individuals who responded in the affirmative were asked if they were still smokers at the time of data collection. Participants who responded "yes" to both questions were classed as current smokers)
HDL cholesterol	●			Continuous (Whole blood samples taken from consenting participants and stored in plain tubes. Serum samples were assayed for total and HDL cholesterol at the Royal Victoria Infirmary, Newcastle-upon-Tyne, UK.[299] Reported as millimoles per litre (mmol/l))
Total cholesterol	●	●		Continuous (As above)
Cholesterol/HDL ratio			●	Continuous (As above)
BMI	●		●	Continuous (Height and weight without shoes was measured to the nearest millimetre using a portable stadiometer and 0.1 kg using a portable electronic scale, respectively. BMI (kg/m2) calculated by dividing each individual's measured weight by height squared.)[300]
Material deprivation			●	Categorical, quintiles (A measure of socio-economic status assessed using the index of multiple deprivation (IMD) score; a weighted composite derived from income, employment, health deprivation and disability, education skills and training, barriers to housing and services, crime, and living environment. Matched to ELSA participants using their postal codes. Scores were divided into quintiles, with the least deprived participants belonging to the lowest quintile)[301]
Ethnicity			●	Categorical (White or not stated, Indian, Pakistani, Bangladeshi, Other Asian, Black African, Black Caribbean, Chinese, Other)
Family history of CVD			●	Binary (Yes/ No). Recorded in 1998 HSE wave 0 only
Kidney disease			●	Binary (Yes/ No, Self-report of physician's diagnosis). Recorded in 1998 HSE wave 0 only
Rheumatoid arthritis			●	Binary (Yes/ No, Self-report of physician's diagnosis)
Atrial Fibrillation			●	Binary (Yes/ No, Self-report of physician's diagnosis)
Diabetes	●		●	Binary (Yes/ No, Self-report of physician's diagnosis)
Antihypertensive medication use	●		●	Binary (Yes/No). Participants asked whether they were taking drugs prescribed for blood pressure

F Components of the Framingham model
S Component of SCORE chart
Q Components of QRISK2 calculator

6.3.4 Outcome: Depression Symptoms

The main outcome of this study is depression symptoms, measured using the 8-itme CES-D, which is described in Chapter 3.3.

6.3.5 Statistical methods

Firstly, the distribution of each individual component of the three CVD risk algorithms was assessed according to gender, and differences between means and proportions were tested using the Chi^2 test and analysis of variance (ANOVA). Following this, the odds for developing depression symptoms over an 8 year follow-up period were computed for each CVD risk factor using Generalized Estimating Equations (GEE) logistic regressions with exchangeable correlation matrices. This was done using data from all participation waves from wave 2 (baseline) to wave 6 of ELSA; also according to gender. Risk was assessed according to standard deviation change for all continuous variables. Due to lack of ethnic variation in ELSA, adjustments for ethnicity were not made in any analyses, and because of the volume of missing data for this factors, atrial fibrillation and family history of CVD were excluded from some analyses.

The GEE approach was chosen for this analysis as it accounts for the individual correlation in reports of depression symptoms by firstly computing naive standard errors while assuming complete independence of measures, and then computing adjustments to the naive standard errors. This adjustment results in robust standard errors and separates the nuisance variation due to population-wide behaviour from the variation related to trends with time while still incorporating the population-wide variance within its variance structure.[302] Thus, it provides a population average of the association between each CVD risk factor (time non-varying) and depression symptoms (time-varying) over time.

Finally, risk of CVD was calculated for each participant according to the Framingham model, the QRISK2 calculator, and the SCORE chart. As the SCORE chart is intended for calculation of CVD risk up to 65 years, age was truncated such that individuals who were older than 65 years were allocated the same SCORE risk as those aged 65 years. Bivariate logistic regressions were used to investigate the odds of developing depression symptoms after 8 years of follow-up according to each of the three algorithms. To serve as sensitivity analyses, bivariate logistic regressions were used to assess the predictive capacity of each individual CVD risk factor in predicting a CVD event; that is, either mortality, MI, stroke, CHF or angina. Further sensitivity analyses were carried out for each CVD risk algorithm, testing for their capacity for predicting CVD event following 8 years of follow-up in ELSA.

6.4 Results

6.4.1 Baseline Characteristics of study participants

In total, 3,435 ELSA participants were eligible for the present analyses – that is, people who were free of depression at baseline, had not been previously diagnosed with CVD, and had non-missing data for biological CVD risk factors at baseline. Compared with ELSA participants who were not eligible for this study, this eligible sub-sample were younger, and comprised a smaller proportion of women (53.3% compared to 56.2%) (see table 20). Participants in this group had somewhat lower BMI, and higher mean HDL and total cholesterol. While there were no clear group differences according to systolic blood pressure and family history of CVD, eligible participants were significantly less likely to report kidney disease, rheumatoid arthritis, atrial fibrillation and diabetes, and were also less likely to be using antihypertensive medication. Notably, eligible study participants were wealthier than those excluded.

Table 21 displays the baseline characteristics of the 3,435 eligible study participants, who were aged 52 years and above and were free from depression at baseline (reported 3 or less symptoms of depression). The table presents a comparison of participants according to their gender, where it can be observed that women had significantly higher HDL and total cholesterol than men, and were less likely to report diagnosis of diabetes. Of the 3,345 participants, only 1,519 had data for family history of CVD and atrial fibrillation, and while there was no difference between men and women with regards to family history of CVD, women were more likely to report diagnosis of atrial fibrillation.

Mean Framingham scores for women were only marginally higher than those for men (15.20 compared to 12.85), indicating that the correlating 10-year risk of a CVD event for men would actually be higher for men than for women. Indeed, when Framingham scores were converted into 10-year risk of suffering a fatal or non-fatal CVD event, it was evident that men actually had a higher mean 10-year percentage risk (5.39) than women (4.34). The same was observed for the SCORE chart, according to which the mean 10-year risk of suffering a fatal CVD event remained lower for women than men (1.46% compared to 2.96%). While the average 10-year risk of a CVD event was remarkably higher for both men and women according to QRISK calculator compared to predictions based on either the Framingham model or SCORE chart, similar gender differences could once again be observed, such that men had a higher mean QRISK percentage (22.76) than women (16.42).

Table 20: Baseline characteristics of 8,780 depression and CVD free participants of the English Longitudinal Study of Ageing in 2004/5 according to eligibility criteria[a] for the CVD risk factors/depression study

CVD risk factors	F	S	Q	Eligible N=3,435	Not eligible N=5,345	All
Female, % (s.e.)	●	●	●	53.28 (0.85)	56.15 (0.70)	55.02 (0.53)
Age (years), mean (s.e.)	●	●	●	63.59 (0.13)	69.20 (0.15)	66.93 (0.11)
Systolic Blood pressure (mmHg), mean (s.e.)	●	●	●	134.23 (0.31)	136.44 (0.35)	135.30 (0.23)
Current smoker, % (s.e.)	●	●	●	11.21 (0.54)	17.66 (0.52)	15.14 (0.38)
HDL cholesterol (mg/dl), mean (s.e.)	●			1.54 (0.01)	1.50 (0.01)	1.52 (0.01)
Total cholesterol (mg/dl), mean (s.e.)	●	●		6.00 (0.02)	5.79 (0.03)	5.91 (0.02)
Cholesterol/HDL ratio, mean (s.e.)			●	4.04 (0.02)	2.80 (0.02)	4.03 (0.01)
BMI (kg/m^2), mean (s.e.)	●		●	27.83 (0.08)	28.02 (0.08)	27.92 (0.06)
Highest quintile of material deprivation, % (s.e.)			●	9.05 (0.49)	17.40 (0.52)	14.13 (0.37)
Family history of CVD[b,] % (s.e.)			●	15.67 (0.93)	16.52 (0.80)	16.17 (0.61)
Kidney disease, % (s.e.)			●	0.76 (0.15)	1.53 (0.17)	1.23 (0.12)
Rheumatoid arthritis, % (s.e.)			●	4.60 (0.36)	8.38 (0.38)	6.90 (0.27)
Atrial Fibrillation[b,] , % (s.e.)			●	4.95 (0.50)	8.51 (0.59)	6.64 (0.41)
Diabetes, % (s.e.)	●		●	5.62 (0.39)	9.80 (0.42)	8.17 (0.29)
Antihypertensive medication use, % (s.e.)	●		●	12.98 (0.57)	16.22 (0.50)	14.95 (0.38)

[a] Eligibility criteria were: No depression symptoms and CVD diagnosis at baseline, no missing CVD risk factor measures, and had values for depression symptoms on at least one occasion at follow-up

F Components of the Framingham model

S Component of SCORE chart

Q Components of QRISK2 calculator

[b] Only 3,692 participants had these data collected in HSE survey

Table 21: Baseline characteristics of 3,435 depression-free participants with no previous diagnosis of CVD and non-missing CVD risk factor values: the English Longitudinal Study of Ageing, 2004/5

	F	S	Q	Female (N = 1,830)	Male (N = 1,605)	All
Age (years), mean (SE)	●	●	●	63.47 (0.17)	63.73 (0.21)	63.59 (0.15)
Systolic Blood pressure(mmHg), mean (SE)	●	●	●	133.06 (0.45)	135.58 (0.42)	134.23 (0.31)
HDL cholesterol (mg/dl), mean (SE)	●			1.68 (0.01)	1.39 (0.01)	1.54 (0.01)
Total cholesterol (mg/dl), mean (SE)	●	●		6.23 (0.03)	5.74 (0.03)	6.00 (0.02)
Cholesterol/HDL ratio, mean (SE)			●	3.85 (0.02)	4.25 (0.02)	4.03 (0.02)
BMI (kg/m^2), mean (SE)	●		●	27.89 (0.12)	27.76 (0.10)	27.83 (0.08)
Current smoker, % (SE)	●	●	●	11.04 (0.73)	11.40 (0.79)	10.21 (0.54)
Highest quintile of material deprivation, % (SE)			●	9.13 (0.67)	8.97 (0.71)	9.05 (0.48)
Family history of CVD [b], % (SE)			●	15.08 (1.25)	16.36 (1.40)	15.67 (0.93)
Kidney disease, % (SE)			●	0.87 (0.22)	0.62 (0.20)	0.76 (0.15)
Rheumatoid arthritis, % (SE)			●	4.97 (0.51)	4.17 (0.50)	4.59 (0.36)
Atrial fibrillation[b], % (SE)	●		●	4.50 (0.72)	3.30 (0.67)	3.94 (0.50)
Diabetes, % (SE)	●		●	4.64 (0.49)	6.73 (0.63)	5.62 (0.39)
Antihypertensive medication use, % (SE)	●		●	12.90 (0.78)	13.08 (0.84)	12.98 (0.57)
Risk Scores						
Framingham score, mean (SE)	●			15.20 (0.08)	12.85 (0.05)	14.10 (0.05)
Framingham 10 year % risk of CVD, mean (SE)	●			4.34 (0.10)	5.39 (0.23)	4.83 (0.12)
SCORE 10 year % risk of fatal CVD, mean (SE)		●		1.46 (0.03)	2.96 (0.05)	2.16 (0.03)
QRISK 10 year % risk of heart attack or stroke, mean (SE)			●	16.42 (0.21)	22.76 (0.25)	19.38 (0.17)

F Components of the Framingham model
S Component of SCORE chart
Q Components of QRISK2 calculator
[b] Only 1,519 participants with these data; values excluded from final QRISK2 calculation

6.4.2 The association between individual CVD risk factors and depression

After baseline, the prevalence of people reporting incident depression symptoms was stable over time. The prevalence of depression at each wave and proportion of recurrent cases is displayed in table 22.

Table 22: Prevalence and recurrence of depression by wave

Reports of symptoms ≥ 4 by wave					
	Wave 2	Wave 3	Wave 4	Wave 5	Wave 6
Number of participants	3,435	3,294	2,970	2,593	2,651
Prevalence % (n)	0	7.01 (231)	7.31 (217)	7.76 (218)	8.07 (214)
Reported depression in previous wave %, (n)	N/A	0	28.43 (58)	32.46 (62)	38.89 (70)

Where 7.0% of the participants who took part in wave 3 (in 2006) reported depression symptoms, 8.1% reported the same in wave 6, which was the highest proportion or depression incidence for all waves. Although the proportion of participants with depression symptoms did not vary much with each wave, these symptoms did not appear to be a persistent state in individuals, as on average, just over a quarter of participants who reported depression symptoms in any one wave would have done so in a previous wave. Similar proportions of depression prevalence and recurrence were observed for the whole ELSA sample.

The relationship between the development of depression symptoms in these ELSA participants and each CVD risk factor that is included in either the Framingham model, SCORE chart or QRISK2 calculator is displayed in table 23.

For the 3,435 participants in these analyses, increasing age, higher BMI, current smoking, use of antihypertensive medication, being materially deprived and having a diagnosis of either rheumatoid arthritis or atrial fibrillation were all associated with increased risk of developing depression symptoms for both men and women. Of note having the following characteristics was associated with an increased risk greater than 50% compared to individuals who did not possess them: atrial fibrillation (OR, 1.70; 95% CI 1.02, 2.83), material deprivation (1.80; 1.33, 2.46), rheumatoid arthritis (1.61; 1.15, 2.27), use of antihypertensive medication (1.57; 1.26, 1.97), and smoking (1.51; 1.19; 1.93)

When these associations were stratified according to gender, the increased risk of depression symptoms associated with atrial fibrillation, material deprivation, rheumatoid arthritis and BMI was only apparent in women. Thus, the only CVD risk components which were significantly associated with depression symptoms in men were use of antihypertensive medication (OR 1.88, 95% CI 1.31, 2.70), material deprivation (2.01; 1.15, 3.47) and current smoking (1.71 95% CI 1.15, 2.55).

Table 23: Odds Ratio (95% confidence intervals) for the relation of CVD risk factors with the risk of developing depression symptoms over an 8 year follow-up period among 3,435 participants in the English Longitudinal Study of Ageing, 2004/5

Risk factors Referent is absence of risk, or SD increase for continuous variables	**F**	**S**	**Q**	**Women** (610 new cases)	**Men** (270 new cases)	**OR* (CI)** (All participants)	**P value for gender interaction**
Age (years)	●	●	●	1.28 (1.12, 1.45)	1.06 (0.88, 1.27)	1.20 (1.08, 1.33)	0.116
Systolic Blood pressure, (mmHg)	●	●	●	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.07 (0.98, 1.17)	0.676
Current smoker	●	●	●	1.43 (1.06, 1.94)	1.71 (1.15, 2.55)	1.51 (1.19, 1.93)	0.443
HDL cholesterol (mg/dl)	●			0.89 (0.80, 1.00)	0.86 (0.72, 1.03)	1.02 (0.93, 1.11)	0.994
Total cholesterol (mg/dl)	●	●		1.01 (0.91, 1.12)	0.95 (0.82, 1.12)	1.07 (0.99, 1.17)	0.629
Cholesterol/HDL ratio			●	1.13 (1.02, 1.26)	1.09 (0.95, 1.26)	1.03 (0.95, 1.12)	0.453
BMI, (kg/m^2)	●		●	1.19 (1.09, 1.30)	1.11 (0.95, 1.31)	1.19 (1.10, 1.29)	0.933
Highest quintile of deprivation [a]			●	1.72 (1.19, 2.49)	2.01 (1.15, 3.47)	1.80 (1.33, 2.46)	0.872
Family history of CVD [b]			●	0.90 (0.58, 1.39)	1.31 (0.77, 2.21)	1.01 (0.72, 1.42)	0.109
Kidney disease			●	1.29 (0.47, 3.53)	2.49 (0.67, 8.85)	1.66 (0.75, 3.69)	0.161
Rheumatoid arthritis			●	1.68 (1.12, 2.51)	1.30 (0.67, 2.56)	1.61 (1.15, 2.27)	0.411
Atrial fibrillation [b]			●	2.25 (1.30, 3.90)	0.38 (0.07, 2.19)	1.70 (1.02, 2.83)	0.126
Diabetes	●		●	1.18 (0.73, 1.89)	1.47 (0.87, 2.47)	1.20 (0.84, 1.71)	0.451
Antihypertensive medication use	●		●	1.46 (1.10, 1.93)	1.88 (1.31, 2.70)	1.57 (1.26, 1.97)	0.521

F Components of the Framingham model
S Component of SCORE chart
Q Components of QRISK2 calculator
[a] Referent is lowest quintile of material deprivation
[b,] Only 1,519 participants with feed-forward data from HSE; values excluded from final QRISK2 calculation

6.4.3 The association between CVD risk score and depression symptoms

Following application of CVD risk scores to individuals according to the respective algorithms, it can be observed from table 24 that having a higher Framingham risk score was significantly associated with increased risk of developing depression symptoms in women only (OR 1.34; 95% CI 1.13, 1.58 per standard deviation change). Although results were not significant according to traditional thresholds, it could also be inferred that a standard deviation change in Framingham scores was also associated with increased risk of depression symptoms for men (OR 1.22: 95% CI 0.83, 1.82). Pooled gender analyses were not appropriate for the Framingham score as the model is applied differently according to gender.

Table 24: Odds Ratio for development of depression symptoms after 8 years of follow-up according to CVD risk algorithm at baseline: English Longitudinal Study of Ageing 2004/5

CVD Risk algorithm	**Women** (New cases = 417)	**Men** (New cases = 203)	**OR (CI) for Men and Women** (New cases = 620)
Per-point increase in Framingham risk (%)	1.10 (1.04, 1.16)	1.07 (0.94, 1.21)	1.13 (1.08, 1.19)
SD change in Framingham score	1.34 (1.13, 1.58)	1.22 (0.83, 1.82)	N/A*
Per-point increase in SCORE (%)	1.20 (1.06, 1.37)	1.16 (1.04, 1.29)	1.05 (0.98, 1.14)
SD change in SCORE (%)	1.40 (1.11, 1.77)	1.31 (1.08, 1.60)	1.10 (0.96, 1.27)
Per-point increase in QRISK (%)	1.04 (1.02, 1.06)	1.02 (0.99, 1.04)	1.02 (1.00, 1.03)
SD change in total QRISK (%)**	1.61 (1.30, 2.00)	1.24 (0.92, 1.68)	1.23 (1.04, 1.46)

* Women have a higher baseline Framingham score than men, therefore pooled score is not appropriate.

** Family history of CVD and atrial fibrillation excluded from QRISK calculation due to missing data

As these gender differences are reflected in the final Framingham 10-year risk prediction percentage, a pooled gender analysis is appropriate according to this measure of risk prediction. Accordingly, the pooled gender analysis shows that a single percentage point increase in 10-year risk of fatal or non-fatal CVD as predicted by the Framingham model is associated with a 13% increase in the risk of developing depression symptoms (OR 1.13; CI 1.08, 1.19). As such, a 1% increase in CVD risk is associated with a 13% risk in developing depression symptom. However, taking into account that Framingham risk only increments in single units up to a certain point and then increments exponentially after the 6% mark; it is also true that an increase in CVD risk from 20% to 25% is also associated with a 13% increase in risk of developing depression symptoms. When assessed according to gender, the association between Framingham risk and depression symptoms is once again more prominent in women, for who increased 10-year risk of CVD is associated with a 10% increase in the risk of developing depression symptoms (OR 1.10; CI 1.04, 1.16).

With regards to the SCORE risk chart, the pooled gender analysis showed that increased CVD risk according to this algorithm did not predict depression symptoms. However, when assessed by gender, increased risk of CVD does also relate to increased risk of depression in both men and women. According to the SCORE chart, a single percentage increase in the 10-year risk of fatal CVD increased the odds of developing depression by 20% over an 8-year follow-up period in women (OR 1.20; CI 1.06, 1.37), and a slightly more modest increase in men (1.16; 1.04, 1.29).

Finally, prediction of depression risk according to the QRISK2 calculator indicated that a standard deviation increase in CVD risk related to a 23% increase in risk of developing depression symptoms after 8 years of follow-up (OR 1.23, 95% CI 1.04, 1.46). Women were once again at higher risk of developing depression symptoms according to the QRISK2 calculator when compared with men (OR for women 1.61, 95% CI 1.30, 2.00; OR for men 1.24, 95% CI 0.92, 1.68).

6.4.4 Sensitivity analyses

Sensitivity analyses for the predictive capacity of individual CVD risk factors in predicting CVD events are displayed in table 25. As expected, increasing age, systolic blood pressure, material deprivation, use of antihypertensive medication and diagnosis of diabetes were associated with increased risk of developing CVD for both men and women. However, the pooled gender analysis did not reveal an association between development of CVD and cholesterol, smoking status, family history of CVD, diagnosis of atrial fibrillation and BMI, all factors which tend to be implicated in the development of CVD.

From these analyses, it can be observed that the risk of developing CVD more than doubled as a result of diagnoses of diabetes (OR 2.61; 95% CI 1.84, 3.70), use of antihypertensive medication (2.40; 1.86, 3.11) and material deprivation (2.40; 1.68, 3.44). Gender differences were observed for rheumatoid arthritis, for which increased odds of developing CVD were observed for women but not for men. Additionally, the effect of total cholesterol on development of CVD was different according to gender (p value for interaction = 0.030).

Thus, with regards to developing either depression symptoms or CVD, increased risk was observed in both cases for age, systolic blood pressure, use of antihypertensive medication, material deprivation and diabetes if diabetes for both women and men, while diagnosis of atrial fibrillation increased the risk of both conditions in women only. Interestingly, in this sample, current smoking, which is often reported as being a large risk factor for CVD was only associated with development of depression symptoms but not CVD in this sample.

Sensitivity analyses performed for each risk prediction tool against its ability to predict CVD events demonstrated that the Framingham model, SCORE chart and QRISK2 calculator all strongly predicted CVD events in the 8-year follow-up period in ELSA (see table 26). While a single percentage increase does not equate to a one point increase in risk of CVD for any of the algorithms, it is worth noting that the increments in each of the calculators are not strictly single unit increments, as described in chapter 7.1.2.

In summary, the above sensitivity analyses illustrated that the CVD risk algorithms above appropriately indicated increased risk of CVD. Notably, CVD risk prediction according to the QRISK2 calculator was most aligned to expected predictions, as a 1% increase in risk according to QRISK2 related to a similar increase in risk of CVD event in the analytic sample.

Table 25: Odds Ratio (95% confidence intervals) for the relation of CVD risk factors with the risk of new CVD events (fatal and non-fatal) after 8 years of follow-up among 3,435 participants in the English Longitudinal Study of Ageing, 2004/5

Risk factors Referent is absence of risk, or SD increase for continuous variables	**F**	**S**		**Q**	**OR (CI) for Women only** (179 new cases)	**OR (CI) for Men only** (214 new cases)	**OR* (CI)**	**P value for interaction**
Age (years)	●	●		●	2.32 (1.90, 2.82)	1.95 (1.63, 2.33)	2.12 (1.85, 2.41)	0.204
Systolic Blood pressure (mmHg)	●	●		●	1.41 (1.22, 1.62)	1.26 (1.08, 1.47)	1.34 (1.21, 1.49)	0.308
Current smoker	●	●		●	1.28 (0.81, 2.02)	1.20 (0.78, 1.85)	1.24 (0.91, 1.70)	0.839
HDL cholesterol (mg/dl)	●				0.77 (0.65, 0.92)	0.70 (0.58, 0.85)	0.72 (0.64, 0.81)	0.425
Total cholesterol (mg/dl)	●	●			0.85 (0.72, 1.00)	0.66 (0.56, 0.78)	0.73 (0.65, 0.81)	0.030
Cholesterol/HDL ratio				●	1.13 (0.96, 1.31)	0.92 (0.80, 1.06)	1.04 (0.94, 1.16)	0.062
BMI, (kg/m^2)	●			●	1.06 (0.93, 1.21)	1.18 (1.00, 1.38)	1.10 (1.00, 1.22)	0.325
Highest quintile of deprivation*				●	2.23 (1.30, 3.83)	2.59 (1.60, 4.21)	2.40 (1.68, 3.44)	0.905
Has family history of CVD**				●	1.37 (0.77, 2.46)	0.95 (0.55, 1.65)	1.13 (0.76, 1.69)	0.370
Rheumatoid arthritis				●	1.90 (1.06, 3.37)	1.60 (0.86, 2.99)	1.72 (1.13, 2.62)	0.697
Atrial fibrillation**				●	1.75 (0.71, 4.34)	1.85 (0.71, 4.80)	1.71 (0.89, 3.28)	0.937
Diabetes				●	2.25 (1.28, 3.97)	2.74 (1.75, 4.30)	2.61 (1.84, 3.70)	0.589
Antihypertensive medication use	●			●	1.90 (1.29, 2.81)	2.93 (2.10, 4.15)	2.40 (1.86, 3.11)	0.101

F Components of the Framingham model
S Component of SCORE chart
Q Components of QRISK2 calculator
* Referent is lowest quintile of material deprivation
** Only 1,649 participants with feed-forward data from HSE

Table 26: Odds Ratio (95% confidence intervals) for development of fatal or non-fatal CVD event during follow-up according to CVD risk at baseline as predicted by CVD risk algorithms: English Longitudinal Study of Ageing 2004/5 -2012/13

CVD Risk algorithm	**Women** (New cases = 179)	**Men** (New cases = 214)	**All participants** (New cases = 393)
Per-point increase in Framingham risk (%)	1.20 (1.15, 1.27)	1.30 (1.20, 1.40)	1.14 (1.10, 1.18)
SD change in Framingham score	1.81 (1.55, 2.12)	2.26 (1.77, 2.88)	N/A
Per-point increase in SCORE (%)	1.40 (1.27, 1.56)	1.16 (1.09, 1.23)	1.22 (1.16, 1.28)
SD change in SCORE%	1.84 (1.53, 2.23)	1.29 (1.16, 1.45)	1.43 (1.30, 1.55)
Per-point increase in QRISK (%)	1.06 (1.05, 1.09)	1.06 (1.05, 1.08)	1.06 (1.05, 1.08)
SD change in total QRISK %**	2.20 (1.83, 2.63)	2.06 (1.75, 2.43)	2.10 (1.87, 2.36)

** Family history of CVD and atrial fibrillation excluded from QRISK calculation due to missing data

6.5 Discussion

6.5.1 Main findings of the CVD risk factors study

This study shows that among people aged 52 years and above, increased 10-year risk of a CVD event as predicted by the QRISK2 and Framingham model also indicated increased risk of developing depression symptoms after 8 years of follow-up in women only. Increased risk of CVD according to the SCORE chart was associated with increased risk of depression symptoms after 8 years of follow-up in men and women separately, but not in pooled gender analyses. Material deprivation and use of antihypertensive medication were associated with risk of both depression symptoms and CVD, while elevated cholesterol levels, systolic blood pressure, family history of CVD, and diagnosis of kidney disease and diabetes were not associated with risk of depression.

6.5.2: Relation of present findings with existing literature

Traditionally, risk of depression in the elderly has been ascribed to extrinsic socio-economic and behavioural factors such as poor social network and living conditions, stressful events, and lower level of education and income.[37] Additionally, age and being of female gender are often associated with increased risk of depression in older people. Increasingly however, biomarkers indicating cardio-metabolic disorders such as diabetes mellitus, obesity/excessive weight, dyslipidaemia and hypertension have also been implicated in the development of depression.[278] Moreover, there is growing evidence that those socio-economic factors usually associated with depression (loneliness, social isolation) also lead to development of CVD.[291]

This present study illustrates that risk of future depression and of experiencing a CVD event is associated with material deprivation and use of hypertensive medication. Congruent with these findings age, sex, smoking and social status are often identified as the most important indicators of risk of CVD and depression.[283] In addition, various sources also identify diabetes, obesity, loneliness, isolation,[291] chronic kidney disease, rheumatoid arthritis angina, hypertension, atrial fibrillation, and cholesterol as risk factors for both.[284,285,286,325,288,287] While mechanisms of association were not explored and thus remain unclear, this study strengthens the proposition that risk of CVD can predict risk of depression.

Although multiple behavioural factors such as smoking, sedentary behaviour and alcohol consumption have been implicated in the development of both CVD and depression,[265] it is notable that only smoking is contained in the CVD prediction tools employed for this study. Due to challenges in quantification, and interaction with other risk factors,

sedentary behaviour in particular was excluded in the development of the Framingham model,[243] possibly presenting similar challenges in the development of other algorithms. However, awareness of these additional shared risk factors further illustrates the co-existence of CVD risk and depression risk, and strengthens the argument for further consideration of shared risk prediction processes.

It has been suggested that this common risk not only progresses to cause the individual disorders, but that once contracted, the combined effect of depression and CVD results in increased mortality, such that mortality rates for one disorder would reduce if the other were not present.[303] While this present study was focused on extrapolating the relation between risk factors for CVD and future risk of depression, a wealth of studies of prevalent CVD has illustrated that CVD events may be an independent predictor of depression.[304]

Conceivably, the reality of being diagnosed with CVD, or suffering a CVD event, is often accompanied by feeling of sadness and a negative outlook on life. Beyond that, evidence from multiple studies has highlighted increased rates of depression among people with CVD, with significantly higher rates of depression being observed in patients who had suffered from stroke in particular,[305] whose depression rates appeared to increase steadily over time.[306] While further extensive research is required to affirm current findings, this present study goes a step further in affirming suggestions that *risk* of CVD (prior to any CVD events or diagnosis) is also indicative of risk of depression; as indicated by commonality of risk factors.

Although mechanisms of association are unclear, evidence from imaging studies show that in older age depression can be a direct outcome of subcortical brain lesions on strategic brain areas caused by cerebral atherosclerosis, which may disrupt the striato-pallido-thalamo-cortical pathway, resulting in a condition known as 'post-stroke depression'.[307] This indicates that some of the structural changes that eventually lead to and ultimately characterise CHD are also linked with risk and development of depression, particularly when they occur in the prefrontal cortex, amygdala, hippocampus and the subcortical regions.[308] However, while there are other causes of depression, this theory offers no explanation for the CVD/ depression link when depression has been known to precede vascular disease.[309]

Another proposition for the mechanisms that link vascular disorders to depression is that of inflammatory pathways. It is believed that inflammation is an intrinsic part of atherosclerosis in which the deposits that characterise this condition invoke (i) the production of local and systemic cytokines such as interleukin-6 (IL-6), (ii) hepatocytic acute-phase reactants such as C-reactive protein (CRP), and (iii) the expression and endothelial shedding of soluble intercellular adhesion molecules (sICAMs) such as sICAM-1.[310,311] Due to the chronicity of atherosclerosis, the systemic low grade immune response (known as the acute phase response due to the constant presence of acute phase proteins) tends to persist in patients with CVD, and is especially prominent when acute cardiac events are observed.[312]

Intriguingly, it has been noted that patients with depression show similar patterns of immune activation to those just described,[313] further illustrated through a meta-analysis of samples of depressed patients without CVD, among whom the most consistent patterns

of immune activation involved high circulating levels of IL-6.[314] In addition, it has been highlighted that individuals with either major depression or depression symptoms tend to have high elevated circulatory levels of other inflammatory markers associated with CVD, such as CRP, albumin and white blood cells.[315] However, while similar instruments may either play some precursory or featuring roles, it is yet to be proven that the exact inflammatory pathways which lead to CVD are the exact same pathways which also lead to depression.

6.5.3 Gender difference in CVD risk

While multiple risk factors may act cumulatively to cause CVD, a multifactorial approach, one that takes into consideration all the risk factors separately, is probably the best for investigating gender-specific differences in the CVD-depression link. Primarily, the CVD risk factors that are more common among women in ELSA may explain why the CVD prediction algorithms are more inclined to analogously predict depression among them. While gender differences in baseline characteristics in ELSA are not remarkable enough to fully explain the differences in risk of depression, some explanation may lie in the fact that women tend to have higher rates of depression in general.[316] Furthermore, study results indicating higher female mortality rates after MI may suggest higher susceptibility to not only the outcomes of CVD, but to the overall effect of individual risk factors, particularly with regards to development of depression. This may be the case for diabetes, for instance.

While men were more likely to report diagnosis of diabetes in the ELSA sample, it has been demonstrated that diabetes substantially increased the risk of depression in women in much the same way as it has been shown to markedly increase the risk of death from

coronary heart disease, compared to men.[317] Extraneous to having higher risk of mortality from CVD than men,[318] women who were previously known to have a history of depression or attempted suicide were also found to have a 14-fold hazard ratio for ischemic heart disease death, while men had a much lower hazard ratio of 3.5.[319]

It has been posited that the greater adverse outcomes observed for women who have diabetes may be explained by the less favourable cardiovascular profiles with regards to blood pressure and lipid levels compared to men who have diabetes.[320] Furthermore, it has also been suggested that women respond differently physiologically to stressors such as life trauma by producing more cortisol, which in turn increases obesity, dyslipidaemia and other metabolic abnormalities over time; thus increasing the risk of both CVD and depression.[321] Intriguingly, one study showed that stress reduction customised for women improved their prognosis in relation to coronary artery disease, while the same result was not observed in men.[322]

While it is acknowledged that low socio-economic status (SES) predicts CVD, it is not clear how it contributes to severity of disease and outcomes. It is however, widely accepted that women suffer more exposure to low SES than men, and are more likely to occupy the lower grades employment, income and wealth.[323] Moreover, it is thought that they are also more vulnerable to the effects of low wealth and income.[324] Thus, low SES is often cited as a reason why women are more likely to report depression symptoms.[325] The observation made in this study of the lack of gender interaction between low SES and depression may well signal that SES as a risk factor should be viewed differently for CVD and depression. Taking into account that this present sample composed of participants who were generally wealthier than the full ELSA sample, it would be prudent

to investigate this relationship further in a sample that has wider representation of socio-economic gradients.

6.5.4 Differences in depression risk according to theQRISK2 and Framingham model

The risk prediction algorithms employed in the present study are administered according to gender with regards to CVD, so it would likely follow that they would behave differently dependent on if they were applied to males or females. This seems to be the case for the all the three algorithms in relation to depression risk, which is not uniform when assessed according to gender.

Aside from the gender differences, it is notable that not all components common to the CVD prediction algorithms are independently predictive of depression symptoms in this present study. Though comparison of all three algorithms in relation to both CVD and depression may shed light on the aspects of CVD risk that predict depression, as age was truncated at 65 years for the calculation of CVD risk according to the SCORE chart, comparison of the three tools would not be completely valid in this context. Therefore, the QRISK2 calculator and Framingham model will be compared hereon.

While only three of the eight components of the Framingham model (smoking, age and use of hypertensive medication) were independently predictive of depression symptoms particularly in women, seven components of the QRISK2's twelve components were independently predictive of depression. This difference in 'proportional representation' may partially explain the stronger capacity of the QRISK2 not only in predicting CVD, but also in predicting depression symptoms in the ELSA sample. Additional rationale for the absolute differences in the risk score may lie behind the methodology behind the

formulation of each algorithms, and thus the weight placed upon each risk factor. As such, it may be that the components of CVD risk which predict depression carry more weight in the QRISK2 equation than in the Framingham algorithm. Ultimately, the two risk factors similarly predict increased risk of depression in women.

In addition to the predictive strength that each instrumental risk factor may have added to the QRISK2, it may be suggested that the QRISK2 may be a more efficient tool for predicting depression in the English population than the Framingham score simply because it was tailored for use on subjects in England. As illustrated in sensitivity analyses, while a single unit increase Framingham risk equated to an increased risk of a CVD event greater than 10%, each unit increase in QRISK2 indicated similarly raised risk of CVD in the ELSA sample. Given that the predictive capacity of the QRISK2 has been validated as more appropriate for the English population, so may it be that the risk estimates drawn from it are also more appropriate in this context. However, based on risk estimates for depression symptoms, there is a possibility that the QRISK2 calculator actually overestimates risk of depression in the ELSA sample, and may not necessarily be more appropriate in this context.

Further focus on the individual components of each of the risk factors strongly associated with risk of depression also displays their roles as indicators of some loss of function or negative life circumstances. As such, it is conceivable that the pathway by which these risk factors are related may not be purely biological. While as the pathophysiology of rheumatoid arthritis, treated hypertension and atrial fibrillation for instance may be linked with the mechanisms by which risk of CVD contributes to risk of depression, it is equally likely that an individual living with a chronic condition may develop depression

symptoms purely because they have a chronic condition, as described earlier in the scenario where one may become depressed due to diagnosis of CVD.

Thus, all considered, while the evidence from this study shows that cardiovascular risk prediction tools could be used to predict depression, particularly in women, further studies would be required to not only cement or refute this evidence, but to explore possible biological mechanisms. Furthermore, replications of this present study would be required in larger samples encompassing wider age ranges, to arrive at risk estimates that could be applied to the general population.

If findings from the present study are indeed reflective of the true relation between CVD prediction algorithms and depression, further research would be especially important in order to quantify CVD risk scores that can easily be related to risk of depression. From present findings, a 1% increase in risk of CVD does not necessarily relate to a 1% increase in risk of depression symptoms, as illustrated in the case of the Framingham model, where risk of depression in women according to each unit increase the risk score was 10% in the ELSA sample. Attempting to use either of these CVD risk prediction tools to quantify risk of depression would be challenging at the very least, and much more investigation into feasibility of application would be required. Contrastingly, with diversity of the general UK population in mind, as the Framingham model has also been known to over-predict CVD in some Mediterranean and European populations, it could be suggested that it may well also over-predict depression symptoms in the same manner, in which case it may then actually modest capacity for predicting depression symptoms. As such, this particular association requires further investigation.

As partially implied, part of the reason the Framingham model may not show congruent results may be due to the characteristics of this present sample, who when compared with the rest of ELSA participants were significantly healthier, wealthier, and younger. Risk of disease in the general population is likely to be higher than that observed in this study. As such, further studies of the CVD – depression association, which dictates that participants with existent disease and missing risk factor measures be excluded, should preferably be further investigated in a trial in clinical practice.

6.5.5 Strengths and limitations

The main strength of this study is that it has a large, nationally representative sample of people aged 50 years, who have been well retained over the follow-up period to date. Furthermore, the longitudinal nature of this study allows for an assessment of directionality, highlighting in this instance that CVD risk factors are associated with development of depression symptoms, and that a CVD prediction algorithm can be used to predict depression symptoms.

An additional strength of this study is that it employs a comprehensive depression symptomatology tool, the CES-D, which has been used in a number of studies of the elderly. Compared to a host of studies of depression in older people, this present study not only utilises data from participants who are followed up over a long period, but also assess the predictive capacity of CVD risk prediction algorithms in predicting depression; an association of clinical importance that to my awareness has not been tested before. This study therefore offers novel evidence that shows that it may be possible to predict depression in older people, in a way that is simple and inexpensive.

This study also has some limitations. The lack of sufficient participant data for some risk factor components has resulted in a much more limited sample than would have been desired, and may have introduced some selection bias. In some instances, participants had missing values for some of the components which would have been used to calculate QRISK scores (family history of CVD and atrial fibrillation). However, it is likely that the effect of those missing values actually under-estimated the risk of depression as opposed to over-estimating it, in which case the QRISK2 calculator is likely to have better utility for predicting depression symptoms than represented in this study.

Aside from missing aggregate data, it was identified in this study that minority ethnic groups were severely under-represented, leading to omission of this risk factor in the calculation of CVD risk. As such, findings from this study cannot be generalised to ethnicities other than Caucasians. Indeed, as risk profiles are known to differ in relation to ethnicity,[298] this should also be considered in the development of depression. Finally, as restrictions were made in selecting the analytical sample to limit the study to those who had values for CVD risk factors, the analytical sample for this study was less than half of the total ELSA sample. Such restrictions likely reduced statistical power, which could explain the lack of a significant association between CVD and depression in men. As such, further investigations using larger, and more widely characterised samples according so ethnicity and socio-economic status, are warranted.

Chapter 7: Overarching discussion

The aim of this study was to carry out a multidisciplinary exploration of predictors of depression in older people by investigating the relation of IGF-1, Internet use and CVD risk factor with depression symptoms in individuals aged 50 years and over. Based on the literature, my primary hypothesis was that low levels of circulating IGF-1 would predict future symptoms of depression in older people. It was also my hypothesis that high Internet use, especially for the purpose of social interaction, would reduce the risk of developing depression symptoms in people aged 50 years and over. Finally, I hypothesised that a risk assessment tool used to predict the future probability of CVD could also be used to predict the future probability of depression.

With respect to my first research objective, I found that having serum IGF-1 levels at opposing ends of the continuum was associated with a slightly higher risk of depression symptoms, while having median levels was associated with the lowest risk; an association which could best be described as U-shaped. These results were in concordance with previous findings that having low levels of circulating IGF-1 was associated with higher risk of developing depression symptoms and that having median levels of IGF-1 was associated with lower risk of both prevalent and incident depression symptoms. [163, 165]

The second investigation in this thesis illustrated that using the Internet was associated with a reduced risk of developing depression symptoms. While this relationship was partially explained by loneliness, low educational attainment and low wealth, it appeared from cross-sectional analyses that the reduced risk of depression related to Internet use could be linked to communication via email. Additionally, increased intensity of Internet use was associated with reduced risk of depression such that a ‘dose response’ effect

could be intimated. However, due to the possibility of reverse causation, these findings are relayed with caution.

The third investigation illustrated that while CVD risk factors as clustered within the QRISK2 calculator, Framingham model and SCORE chart were predictive of depression symptoms in women; this relation was often not observed in men. Sensitivity analyses to assess the capacity of CVD risk algorithms to predict CVD events in ELSA participants indicated that increased risk of CVD at baseline according to all three algorithms correctly indicated increased risk of a CVD event at follow-up.

7.1 Implications

This study contributes to a better understanding of predictors of depression in older people, and adds to the understanding of the origins of depression by illustrating the potential role for IGF-1, Internet use, and elevated CVD risk. The main motivation for this research was to advance research efforts in recognition of the wider scope of biological, behavioural and psychosocial evidence to date, and attempt to move the knowledge base forward in harmony. Thus, novel predictors of depression were considered in relation to these themes and in relation to our evolving society, and represented according to available data.

Altogether this study advances knowledge of risk factors for depression in older people, and taking into account the current burden of depression, these findings can be utilised to further research efforts and to inform practice. While it is unclear whether awareness of depression risk necessarily reduces future incidence, some evidence indicates that

identification and pro-active management of depression risk may be value for money,[296] particularly when individuals suffer from other chronic conditions.[297]

My findings of an association between IGF-1 and depression symptoms are not sufficient to be utilised for diagnosis of depression, in the same way as awareness of Internet use practices would not necessarily aid identification of individuals at risk of depression. However, taking into account that depression is usually a result of the malfunction of a combination of social and biological systems, the findings from this study could be used in conjunction with information about other factors to paint a more informative picture of the profile of an individual at risk of depression.

While not investigated in the present study, it has been indicated in previous studies that anti-depressants may play a role in the relationship between IGF-1 and depression. Although it has been suggested that the use of some antidepressants may increase expression of IGF-1,[178] thereby resulting in elevation of mood, other evidence indicates either no effect,[179] or even the opposite.[180] As such, the role of IGF-1 should be considered in relation to assessment of the effect of anti-depressants, and possibly in the development of future therapies.

While the association between IGF-1 and depression symptoms is difficult to interpret in relation to implications for healthcare practice, the results of this and other studies of the role of IGF-1 indicate that it would be of value to maintain 'normal' levels of IGF-1. While this may be achievable through dietary interventions, such a goal may require more invasive manipulations of IGF-1. While licensed IGF-1 therapies do exist, any move to

manipulate circulating levels requires more extensive research to ascertain safety and feasibility.

Taking into account the buffering role of social support,[193] associations observed in this present study in relation to use of the Internet for communication allude to the need for more proactive ways of not only investigating novel risk factors, but of considering changes in the social environment and the role that known predictors play. Indeed, with dynamic social and relationship structures and evolving modes of communication, combinations of risk factors for depression will likely require continuous assessment for relevance to prevalent social norms.

Importantly, unlike in any other age group, this study illustrated that increased frequency of Internet use was associated with lower odds of depression symptoms by older people. Although these findings were cross-sectional and thus may have been subject to reverse-causation, unlike in young people where 'generous' Internet use is often cautioned against due to the fact that it reduces time spent with other people in the immediate environment and increases exposure to cyberbullying and trolling,[218] the opposite is likely true in older people, among whom the Internet likely engenders an extension to social interactions, connectedness and support. Indeed, while previous researchers have pointed to the potentially isolating effects of the Internet,[195] this present study highlights that individual who report higher Internet use are not only less likely to report that they feel isolated, but are also less likely to report symptoms of depression.

While it has previously been suggested that social ties formed or maintained on the Internet were likely to be weaker than real life ties,[190] this study illustrates that physical

social ties are not necessarily any better than those developed or maintained on the Internet with regards to depression. Moreover, online social ties are often formed with individuals that one had/ has physical ties, and serve to extend that relationship across the barriers of distance and busy lifestyles. The fact that one can also connect with strangers who have similar interests, and engage in other forms of entertainment, is almost certainly an added bonus.

With recent features that allow voice and video conversations, online communications are indeed just a short step of the imagination away from being almost like 'face-to-face' interactions. Although physical assistance cannot be provided over the Internet, it is likely that psychological well-being is much more dependent on the intangible aspects of relationships, and that the importance of physical support (especially where suitably provided by health and social services) is over-emphasised.

As it has been observed that online communication is likely beneficial to older people, this study implies that Internet access for all older people should be encouraged and facilitated, where possible. Understandably, there are a number of barriers for such an encompassing intervention. To start with, there are age-related issues such as impaired vision, problems with manual dexterity and mobility, memory and cognition challenges, and limitations with activities of daily life.[326] Some of the characteristics of the technology such as complex screens, small print, computer keyboard formats, usability issues with system designs, computer jargon, and the fact that some technologies are complex to use or simply do not work well may put some individuals off attempting to use the Internet.[327] As older age can be accompanied by physical, cognitive and/or behavioural change that can either support or limit Internet use, measures to enhance

engagement may include the use of large screen devices with large keys, voice prompts and responsive keypads.

It has been noted that the elderly generation tend to be suspicious of newer technology,[328] and may not only perceive any benefit from using the Internet, but may also believe that it as dangerous, unnecessarily expensive, and too difficult and complicated to learn; which in turn will lower their confidence and ability to use the technology.[329] Furthermore, those that do want to engage with the Internet may struggle to get access to training and support as they may not afford it, or just do not know how to access the support that they need, particularly from trainers who are sensitive of the needs of older learners.[330]

Additionally, frail older people may need more support than younger individuals and more physically able older people. As such, it is encouraged that communities set up meetings or home visits aimed at opening up the world of online communication where older people are given information about online social platforms, and given instructions on how to navigate them safely through individualised assessments of learning times, speed of performance, retention over time and subjective satisfaction.

Although the cost of Internet access has reduced dramatically over the years, increasing access at affordable cost can be an expensive exercise for local authorities, charities, or any other interested parties, as it will still include set-up and maintenance. As such, all these measures which require further funding would benefit from wider dissemination and discussion, so that whoever is able does their part in improving access and use of the Internet for older people. However, as cautioned earlier, efforts to increase the time spent

online by older people should be balanced against other factors which are also essential for well-being, such as maintaining adequate physical activity, and performing basic (personal hygiene) and instrumental (housework, preparing meals) activities of daily living.[226]

The evolving characteristics of risk factors for depression may explain how the QRISK2 calculator, as the most comprehensive and advanced of CVD risk factor algorithms, had stronger capacity to predict depression than the Framingham model. Components of the QRISK2 calculator, such as the measure of material deprivation and information on diagnoses of rheumatoid arthritis and atrial fibrillation may have reflected incorporation of the dynamism of risk factors for depression, and may explain the higher risk estimates derived from it in a UK population. As such, further scrutiny of the link between dynamic risk factors for both CVD and depression may be of some utility in predicting depression, thus advancing the agenda for preventative healthcare.

While there is some evidence that CVD risk prediction tools could have some utility in predicting depression in older people, particularly in women, increased risk of CVD according to the algorithms does not equate to depression risk, which introduces some challenges about how this could be useful for quantifying and interpreting risk of depression in clinical practice. As such, it would be premature at this point to stress any of the present findings without carrying out further studies in samples that encompass wider age-groups, ethnic and socio-economic backgrounds. A natural next step would be to consider the role and utility of those risk factors imbedded within the present CVD prediction algorithms that also predict depression symptoms in older people.

While the results presented in this thesis suggest that a CVD risk prediction algorithm could be used to predict depression, this relationship requires extensive research before any firm conclusions can be reached. Indeed, the evidence mostly points to this likely being the case for women only. From this present investigation, CVD prediction algorithms indicate increased risk of depression in women only, and it may prudent to consider this in relation to women who have increased risk of CVD, even though it is not possible to measure the exact extent of their increased risk of depression. This information could be used to guide assessment of long term female patients who have increased risk of CVD with regards to their elevated risk of also suffering from depression. While caution is stressed with regards to the inconclusiveness of these findings, were any actions to be taken in relation to these, they should be balanced against the potential impact on doctors' decision making and patient outcomes, as actions may result in overmedication of female patients.

7.2 Recommendations for future research

The first recommendation for future research following the investigations above is for further and more intensive investigations of the association between IGF-1 and depression to be carried out. The next ideal step would be in the form of a large randomised trial. However, considering the challenges involved in randomising circulating IGF-1 levels, it is likely that larger observational studies in socio-economically diverse populations of all age-groups would be more plausible, results of which could be used to build on current evidence. From these observational studies, causal inference methods such as Mendelian randomisation could be employed, and would be conducive for establishing whether a causal relationship exists between IGF-1 and depression. This type of study could be performed using data such as employed in

the present study, interrogating an instrumental variable in the form of a genetic marker for IGF-1, which would then be regarded in a similar way to random assignment in a clinical trial.

While it has been found that IGF-1 levels were elevated in patients already diagnosed with depression,[161,162] the role of anti-depressants in this predicament has not been investigated much in humans. Evidence from animal studies on the other hand has indicated that antidepressants may improve expression of IGF-1 and other neutrophic and growth factors in the hippocampus, such that subjects that were given anti-depressants were also more likely to have elevated levels of IGF-1, and increased levels of IGF-1 resulted in reduced symptoms of depression.[148] While it has been argued that these animal models are not relevant to humans,[176] it is feasible that a key route by which antidepressants correct mood is either through adjustments of the somatotrophic axis, or the expression and function of neutrophic factors such as IGF-1.

Indeed such findings of the antidepressant/ IGF-1 interplay are being indicated in antidepressant development studies.[331] Considering the complex mechanisms by which antidepressants may affect IGF-1 levels and thus psychological homeostasis, it is recommended that future research be focused on investigating how manipulation of the somatotrophic axis, and cerebrospinal or serum IGF-1 levels in particular, influences mood. To this end, interventions such as increasing exercise and infusing recombinant IGF-1 have been shown to increase or normalise levels,[143,148] both of which may be of consideration for the future.

While the exact relationship between IGF-1 and depression is unclear, it is evident that having 'normal' levels of IGF-1 is linked with lower risk of both somatic and physical illness, and that it is also often associated with other social and lifestyle factors that often predict positive health outcomes. Further studies are needed to examine if the observed association with depression symptoms is likely to be causal before meaningful discussions about normalising IGF-1 levels with drugs could be useful in the prevention of depressive symptoms in older people.

As proposed through the social enhancement theory, it is plausible that the benefits of online communication are only perceived by certainly personality types. As such, it is recommended that future researchers on this matter explore how personality features may affect the relationship between Internet use and depression. Furthermore, it may be useful to have some qualitative data on how exactly the Internet affects mood in people of different ethnicities, gender, personality, sexuality and religion.

In consideration of the role and utility of risk factors imbedded within CVD prediction algorithms and how they predict depression symptoms in older people, sub-analyses of these risk factors may be may be useful in forming a risk prediction algorithm within another risk prediction algorithm. Thus, the CVD prediction tool would continue to be applied as per current practice, and only those factors that predict depression would be used to predict depression, such that a secondary calculator (for depression) would be embedded within a CVD prediction tool.

In particular, the role of higher BMI, current smoking, use of antihypertensive medication, material deprivation and having a diagnosis of any circulatory disorder

should be investigated. Supplementary to the above, a trial in which development of depression is assessed following CVD risk factors modification would shed more light on the CVD risk / depression link. Such a trial could be made up two or more groups, where at least group would have particular risk factors modified through improved education or pharmacological intervention. Development of depression over time following such interventions could then be assessed.

Considering the challenges and expense of developing and implementing a bespoke risk prediction tool for depression, further investigation of the use of a CVD risk prediction tool for dual use could also be explored not only placing more weight on the strongest predictors of depression already embedded in the model, but also considering addition of more components. These additional components would only contribute to prediction of depression once all the values are added to the calculator. Thus, the possibility of embedding a secondary calculator within any CVD prediction tool could be explored, using only the components that strongly predict depression, and arriving at a risk scores that predict both risk of CVD and depression over time. Extensive research is required before any of the CVD prediction tools interrogated in this investigation could be used to predict risk of depression in the general population.

While the study was carried out rigorously using an accepted measure of depression, the consistency of the above CVD-depression finding could be examined using different measures of depression, and possibly additional CVD risk prediction algorithms. It would be of particular interest to elucidate any gender differences in risk of depression according to CVD risk factors, and to ascertain the direction of future research in relation to these. Research encompassing wider age-groups would also add value to the present findings,

and advance investigations into depression risk prediction that would be applicable to all ages. Following this, more work would be needed to evaluate the performance of different models across countries, allowing for the models to be tailored to different subpopulations.

Taking all the investigation in this thesis together, considering changes in social relationships in the information age, the role of Internet use should be explored further in older people, with particular focus on enabling communication and shedding more light on other types of activities that could enhance psychological well-being. Furthermore, there is scope for trials to shed more light on the relationship between IGF-1, CVD risk factors and depression in older people. Finally, while more information has been added to current knowledge on depression, consideration of all possible risk factors has not been exhausted, and future researchers are encouraged to consider other possible predictors of depression in older people.

7.3 Strengths and limitations

As indicated throughout this thesis, the main strength of this study is that it used data from a large, nationally representative sample of people aged 50 years and over. Considering the effect of chronic illness and mortality on this age-group, approximately 70% of core participants responded to waves at least up to wave 3, with refresher waves also being added regularly to keep the study representative of the general population.[332] The longitudinal aspects of the study allowed for an assessment of directionality, highlighting associations between IGF-1, Internet use, and CVD risk factors and future development of depression symptoms.

The study made use of IGF-1 measures that had been collected by a nurse and process in a recognised laboratory using validated techniques. Other measures utilised in predicting risk of depression which were measured and reported in a similarly rigorous manner were BMI, systolic blood pressure and serum cholesterol. While random error could still have affected the measurements, each of the investigations in this thesis involved relatively large analytical samples, whose biological measurement were repeated and averaged in some instances.

This study also owes much of its strength to the use CES-D, which is a well-validated and comprehensive depression symptomatology tool, and has been used in a number of epidemiologic studies of the elderly.[71,73] While the CES-D is a widely used questionnaire in observational studies, it does not itself provide a diagnosis of depression. Nevertheless, investigators have found the CES-D to be highly sensitive and specific when used in population samples, with a sensitivity of range of 70% to 99%, a specificity to range of 56% to 94%, in various population samples.[333,334] In this context, sensitivity refers to the level to which the CES-D could isolate individuals truly suffering from depression (i.e., true positives) as determined by established independent and respectably valid criterion such as clinical diagnoses of depression, and by the same criterion, specificity was its capability to accurately identify individuals that were not suffering from depression (i.e., true negatives).

While this is a novel study which illustrates important results with potentially large public health implications, it is prone to the effects of missing data that can be found in any observational study of its nature. Although ELSA participants were generally well-retained through the course of the study, in this present study a proportion of the 9,148

depression-free individuals who were initially recruited to ELSA in 2002 were at times excluded from analyses due to loss to follow-up or for missing data such as item or unit non-response.

Some measurements such as Internet use and other behaviour-related covariates like alcohol consumption, physical activity and smoking were self-reported, which may have introduced some reporter and recall bias. However, it is often not possible to collect this type of information without being exceptionally intrusive, which would likely reduce participation rates. In the meantime, multiple alternatives which involve the use of technology and biological proxies are being explored and would add value to this type of research in the future.

While observational nature of information sourcing employed in ELSA makes it impossible to make any firm assertions about cause and effect, findings from this present study add value to considerations of direct of associations. In all three investigations in this thesis, participants were free from depression at baseline, and possible confounders were accounted for using advanced statistical techniques. additionally, the approach used to adjust for confounding in this present study make it make it simple to consider the role of biological, psychological, social, economic and health factors. Such considerations can be used to inform the structure of future investigations in older people in relation to these or other predictors.

Although multiple factors were considered in relation to possible confounding, through oversight or lack of data, not all confounders were accounted for in this study. For instance, with regards to the investigation of the association between IGF-1 and

depression, severe kidney disease, which is known to be associated with both IGF-1 and depression was not measured.[186] While this lack of measurement would not matter in a randomised trial, where it would be expected that potential confounders such as acute kidney disease would also be randomly distributed, randomisation is not always possible or ethical in human studies. It may however be possible to identify an instrumental variable such as a genetic marker which would essentially be randomly assigned, and could be utilised in future research as indicated above.

Factors such as quality of online and offline social networks, and personality types may play a role in the relationship between Internet use and depression, but were not measured, and so could not be accounted for. As an example, it may be the case that extroverts are more likely to use the Internet, and that they too are less likely to develop depression. Were this confounding to be accounted for, it could shift the association between Internet use and depression towards the null. However, it has been shown in some instances that adjusting for a known confounder does not necessarily remove bias.[335]

While consideration of potential confounders were made with reference to existent literature and bivariate analysis, there may have been some oversight in not adjusting for potential confounders that were actually measured in ELSA but not accounted for in this study. For instance, cognitive impairment, vision/hearing impairment or functioning/frailty may alter the relationship between Internet use and depression. It is likely that an individual with increasing frailty may be less likely to use the Internet, and may also be more likely to be depressed. An awareness of this limitation can be addressed in future research.

Due to the observational nature of this study, it remains possible that that there is residual confounding that is both unmeasured through omission or as yet unknown in the context of the investigations in this thesis. However, it has been argued that strong associations are unlikely to be solely attributable to confounding, as strong confounders are likely to be detected in the study population or documented in the literature as strong confounders.[336] However, due to the novelty of some of the studies in this thesis, it is plausible that that there are strong confounders that have not been considered either in the past or on this occasion, and thus would not have been measured or adjusted for.

Finally, with regards to confounding, associations observed in this study may have been affected by how some covariates were classed. While rationale was given for the method in which covariates were classified, such as in the case of objective and subjective isolation, there is a potential that some variables may have been misclassified, which in turn would have introduce bias.[337] Indeed, even where rationale were given, variables may still have been misclassified, in which case it would be prudent to consider handling them differently in future research. In general, although there were challenges in classifying some measures such as co-morbidities (as these are addressed in a variety of ways in the literature), efforts were made to measure confounders according to validated measures.

Missing data are a common problem in depression studies, and are often more pronounced in studies where self –report instruments are used such as the present,[338] and an awareness of the amount of missing data and the reason that is missing is often useful for creating strategies to ensure studies are fit for purpose and can be used to make inferences to the source population. Methods such as the application of weights (where greater weight is

given to some responders based on similarities to non-responders) and imputation (where missing values are estimated based on other characteristics of non-responders) are often used to circumvent potential bias. [339, 340] While imputation produces unbiased estimates of the mean when the data are missing completely at random or missing at random, it can produce biased measures of association through over-estimation of values derived from correlated observations.

Based on the objectives of this study, ascribing values through imputations was unlikely to add value where biological associations did indeed exist, and may have over-complicated analyses and introduced bias through analytical methodology. Additionally, while it is recommended that weights (generated from HSE and ELSA data) be used when certain types of data manipulation such as clustering are used,[339] that has not been the case in the present study. It was against these considerations that the differences in sample according to missing data were scrutinised, and analytical techniques applied to adjust for these.

As indicated throughout, excluded participants were generally socio-economically disadvantaged and often carried less desirable attributes in relation to depression. In turn, these aspects have been considered and discussed in each individual study, often indicating that associations would still have been observed regardless of missing data. This being the case, present findings are potentially not generalisable to certain populations groups. For instance, findings related to CVD risk factors and depression cannot be generalised to individuals of ethnicities other than white, as the sample in which the investigation was carried almost completely consisted of white participants. Furthermore, although differences according to socio-economic advantage have been

described in the context of each investigation and adjusted for in analyses, caution should be exercised when relating findings to socio-economically disadvantaged populations. While Internet use has generally been described as having a positive association with emotional well-being in older people, further consideration within that population such as sexuality and religion should be made before blanket measures are applied.

Were the results of the study only to be ascribed to the population sub-sample with attributes of the participants in the present study, the sample size in this thesis is suitably large to make inferences to a sizeable proportion of people aged 50 years and over living in England. Additionally, to account for differences that may have been introduced by non-response after baseline, sensitivity analyses were carried out in subjects with complete data at all waves, also adjusted for difference in baseline characteristics. However, such restrictions, as with restrictions made in selecting the analytical sample resulted in a reduction in sample size which have may have reduced statistical power in some instances. As such, further investigation using larger samples sizes are called for, particular in the studies such that of IGF-1 and depression, and CVD risk factors in men, where some patterns of association were observed, but could not be strongly asserted due to lack of significance according to traditional thresholds.

7.4 Conclusion

This research expands on current understanding of the predictors of depression in older people, and has illustrated the predictive capacity of IGF-1, Internet use and CVD risk factors in predicting depression symptoms. Firstly, it was identified that a U-shaped relationship described the relationship between IGF-1 and depression symptoms, such that participants with low and high serum levels had slightly higher risk of depression,

and those with median levels experienced the lowest risk. Secondly, it was illustrated that increased use of the Internet, particularly for communication via email, was associated with reduced risk of depression. Finally, it was determined that CVD risk factors could be used to predict risk of depression – particularly in women, and that risk factors as encompassed within the QRISK2 calculator had better utility than the Framingham model.

While the association between CVD risk factors in particular certainly requires further investigation, the identification of a U-shaped relationship between IGF-1 and depression not only affirms findings from the two existent population studies, but adds valuable information about elevated levels of IGF-1 that should also be noted where interventions that may alter IGF-1 levels are planned. While also affirming previous findings of the association between Internet use and depression in older people, this study has been the first to identify that increased intensity of Internet use, particularly for social interactions, is associated with lower risk of reporting depression symptoms. Thus, while caution is stressed with regards to balancing this with other activities of daily living, measures to increase confident use of the Internet by older people should be explored.

Finally, it should be noted that while this study has identified relatively novel predictors of depression in older people, the need for exploration of any further causal or protective factors remains a priority. This will likely continue to be the case in perpetually changing social and economic environments, which will require proactive explorations and interventions from researchers and policy-makers.

References

1. World Health Organization. *Mental Health and Older Adults. Fact Sheet No 381*; September 2013. Available at: http://www.who.int/mediacentre/factsheets/fs381/en/ [accessed on 13 January 2015].

2. S.L. Reynolds, W.E. Haley, N. Kozlenko. The impact of depressive symptoms and chronic diseases on active life expectancy in older Americans. *American Journal of Geriatric Psychiatry 2008*; **16**(5): 425–432.

3. World Health Organization. *Ageing and Life Course: Facts about ageing*; September 2014. Available at: http://www.who.int/ageing/about/facts/en/ [accessed on 13 January 2015].

4. Office of National Statistics. Statistical bulletin: Annual Mid-year Population Estimates: 2014. Estimates of the usual resident population in the United Kingdom and its constituent countries.

5. Mental Health Foundation. *Fundamental facts about mental health 2016*. Available at: https://www.mentalhealth.org.uk/sites/default/files/fundamental-facts-about-mental-health-2016.pdf [accessed on 20 October 2017].

6. Stansfeld L, Clark C, Bebbington P, King M, Jenkins R, Hinchliffe S. Common mental disorders. Mental health and wellbeing in England: adult psychiatric morbidity survey, 2014. Available at: http://digital.nhs.uk/catalogue/PUB21748 [accessed 30 October 2017].

7. Beaumont J, Lofts H. Measuring National Well-being - Health, 2013.*Office of National Statistics, 2013.* Available at: http://webarchive.nationalarchives.gov.uk/20160105160709/http://www.ons.gov.uk/ons/dcp171766_310300.pdf[accessed on 11 January 2016].

8. World Health Organization. Depression. *Fact sheet No. 369*; Updated February 2017. Available at: http://www.who.int/mediacentre/factsheets/fs369/en/ [accessed on 15August 2017].

9. World Health Organization. *The Global Burden of Disease: 2004 Update*. Geneva: World Health Organization, 2008. Available at: http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf [accessed on 14 January 2014].

10. Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jonsson B. The economic cost of brain disorders in Europe. *European Journal of Neurology 2012*; **19**: 155–162.

11. World Health Organization. *Depression*; 2014. Available at: http://www.who.int/topics/depression/en/ [accessed on 13 January 2015].

12. World Health Organisation. *International Statistical Classification of Diseases and Related Health Problems 10th Revision*; 2015. Available at: http://apps.who.int/classifications/icd10/browse/2015/en#/V [accessed on 21 January 2015].

13. World Health Organization. *An Estimation of the economic impact of chronic non-communicable diseases in selected countries (Working paper);* 2006. Available at: http://www.who.int/chp/working_paper_growth%20model29may.pdf. [accessed on 14 January 2014].

14. NHS England. Older People. Available at https://www.england.nhs.uk/mental-health/adults/iapt/older-people/ [accessed on 9 February 2018].

15. Birtchnell, J. Depression and family relationships. A study of young, married women on a London housing estate. *The British Journal of Psychiatry 1988;* **153**(6), 758-769.

16. Bell S, Russ TC, Kivimäki M, Stamatakis E, Batty GD. Dose-response association between psychological distress and risk of completed suicide in the general population. *JAMA psychiatry 2015*; **11**, 1-3.

17. Daskalopoulou M, George J, Walters K, Osborn DP, Batty GD, Stogiannis D, et al. Depression as a Risk Factor for the Initial Presentation of Twelve Cardiac, Cerebrovascular, and Peripheral Arterial Diseases: Data Linkage Study of 1.9 Million Women and Men. *PLOS One 2016*; **11**(4):e0153838.

18. Currier MB, Nemeroff CB. Depression as a Risk Factor for Cancer: From Pathophysiological Advances to Treatment Implications. *Annual Review of Medicine 2014*; **65**: 203-221.

19. Russ TC, Stamatakis E, Hamer M, Starr JM, Kivimaki M, Batty, G. D. Association between psychological distress and mortality: individual participant pooled analysis of 10 prospective cohort studies. *BMJ 2012;* **345**: e4933.

20. World Health Organization. *Defining of an older or elderly person. Proposed working definition of an Older Person in Africa for the MDS project*. Available at: http://www.who.int/healthinfo/survey/ageingdefnolder/en/ [accessed on 12 January 2015].

21. Mitchell AJ, Subramaniam H. Prognosis of depression in old age compared to middle age: a systematic review of comparative studies. *American Journal of Psychiatry 2005*; **162**(9):1588-601.

22. Cole MG, Bellavance F, Mansour A. Prognosis of depression in elderly community and primary care populations: a systematic review and meta-analysis. *American Journal of Psychiatry 1999*; **156**(8): 1182-1189.

23. Davidson IA, Dewey ME, Copeland JRM. The relationship between mortality and mental disorder: evidence from the Liverpool Longitudinal Study. *International Journal of Geriatric Psychiatry 1988*; **3**:95-98.

24. Hare DL, Toukhsati SR, Johansson P, Jaarsma, T. Depression and cardiovascular disease: a clinical review. *European Heart Journal 2014*; **35**(21): 1365-U13.

25. Lenze EJ, Rogers JC, MartireLM, Mulsant BH, Rollman BL, Dew MA, Schulz R, Reynolds Iii CF. The Association of Late-Life Depression and Anxiety With Physical Disability: A Review of the Literature and Prospectus for Future Research. *The American Journal of Geriatric Psychiatry 2001;* **9**(2): 113-135.

26. Garssen B. Psychological factors and cancer development: evidence after 30 years of research. *Clinical psychology review 2004*;**24**(3):315-38.

27. Rugulies R. Depression as a predictor for coronary heart disease: a review and meta-analysis. *American Journal of Preventative Medicine 2002*; **23**: 51–61.

28. Schulz R, Beach SR, Ives DG, Martire LM, Ariyo AA, Kop WJ. Association between depression and mortality in older adults: the Cardiovascular Health Study. *Archives of Internal Medicine 2000*; **160**(12): 1761-1768.

29. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosomatic Medicine 2004;***66**(6): 802-813.

30. Saz P, Dewey ME. Depression, depressive symptoms and mortality in persons aged 65 and over living in the community: a systematic review of the literature. *International Journal of Geriatric Psychiatry 200*1; **16**(6): 622-630.

31. Manthorpe J, Iliffe S. Suicide in later life: public health and practitioner perspectives. *International Journal of Geriatric Psychiatry 2010*; **25**(12): 1230-1238.

32. World Health Organization. *Preventing suicide: a global imperative (Executive summary)*; 2012. Available at: http://www.who.int/mental_health/suicide-prevention/exe_summary_english.pdf?ua=1[accessed on 19 January 2015].

33. Fava M, Kendler KS. Major depressive disorder. *Neuron 2000*; **28**(2):335-41.

34. Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. *The Journal of neuropsychiatry and clinical neurosciences, 1997*.

35. Mayberg HS. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. *British medical bulletin 2003*; **65**(1):193-207.

36. Djernes JK, Prevalence and predictors of depression in populations of elderly: a review. *Acta Psychiatrica Scandinavica 2006*; **113**(5): 372-387.

37. Cole MG, and Dendukuri N. Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. *American Journal of Psychiatry 2003*; **160**(6): 1147-1156.

38. Neugebauer A, Katz PP. Impact of social support on valued activity disability and depressive symptoms in patients with rheumatoid arthritis. *Arthritis Care & Research 2004*; **51**(4):586-92.

39. Travis LA, Lyness JM, Shields CG, King DA, Cox C. Social support, depression, and functional disability in older adult primary-care patients. *The American Journal of Geriatric Psychiatry 2004*; **12**(3):265-71.

40. Jensen MP, Smith AE, Bombardier CH, Yorkston KM, Miró J, Molton IR. Social support, depression, and physical disability: age and diagnostic group effects. *Disability and health journal 2014*;**7**(2):164-72.

41. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: A systematic review and meta-analysis of longitudinal studies. *Archives of General Psychiatry 2010;***67**(3): 220-229.

42. Gimeno D, Kivimäki M, Brunner EJ, Elovainio M, De Vogli R, Steptoe A, Kumari M, Lowe GD, Rumley A, Marmot MG, Ferrie JE. Associations of C-reactive

protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. *Psychological medicine 2009*; **39**(3):413-23.

43. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosomatic medicine 2009*; **71**(2):171-86.

44. Blazer DG, Hybels CF (2005).Origins of depression in later life. *Psychological Medicine 2005*; **35**(09): 1241-1252.

45. Blumberger DM, Daskalakis ZJ, Mulsant BH. Biomarkers in geriatric psychiatry: searching for the holy grail? *Current Opinion in Psychiatry 2008*; **21**(6): 533-539.

46. Aziz, R. and D. C. Steffens. What are the causes of late-life depression? *Psychiatric Clinics of North America 2013*; **36**(4): 497-516.

47. National Institute of Clinical Excellence.Depression in adults: recognition and management. Available at: https://www.nice.org.uk/guidance/cg90 [accessed on 16 August 2017].

48. Volkert J, Schulz H, Härter M, Wlodarczyk O, Andreas S. The prevalence of mental disorders in older people in Western countries – a meta-analysis. *Ageing Research Reviews 2013*; **12**(1): 339-3.

49. Rodda J, Walker Z, Carter J. Depression in older adults. *BMJ 2011*; **343**: d5219.

50. Krishnan V, Nestler EJ. The molecular neurobiology of depression. *Nature 2008*; **455**(7215):894.

51. Uchino BN. Social support and health: a review of physiological processes potentially underlying links to disease outcomes. *Journal of behavioral medicine 2006*; 29(4):377-87.

52. Age UK. The Internet and Older People in the UK – Key Statistics July 2016. Available at: https://www.ageuk.org.uk/globalassets/age-uk/documents/reports-and-

publications/reports-and-briefings/active-communities/rb_july16_older_people_and_internet_use_stats.pdf [accessed on 9 February 2018].

53. Office of National Statistics. Statistical bulletin: Internet access – households and individuals: 2016. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/householdcharacteristics/homeinternetandsocialmediausage/bulletins/internetaccesshouseholdsandindividuals/2016 [accessed on 9 February 2018].

54. Hobbs FR, Bankhead C, Mukhtar T, Stevens S, Perera-Salazar R, Holt T, Salisbury C. Clinical workload in UK primary care: a retrospective analysis of 100 million consultations in England, 2007–14. *The Lancet 2016*;**387**(10035):2323-30.

55. Economic and Social Research Council. Strategy and Priorities. Available at: http://www.esrc.ac.uk/about-us/strategy-and-priorities/ [accessed on 14 August 2017].

56. Medical Research Council. About the Medical Research Foundation. Available at: https://www.mrc.ac.uk/about/what-we-do/medical-research-foundation/ [accessed on 14 August 2017].

57. Natcen Social Research. *English Longitudinal Study of Ageing (ELSA): What we do*. Available at: http://www.elsa-project.ac.uk/about-ELSA [accessed on 20 January 2015].

58. Mindell J, Biddulph JP, Hirani V, Stamatakis E, Craig R, Nunn S, Shelton N. Cohort Profile: The Health Survey for England. *International Journal of Epidemiology 2012*; **41**(6): 1585-1593.

59. Taylor R, Conway L, Calderwood L, Lessof C, Cheshire H, Cox K and Scholes S. *Health, wealth and lifestyles of the older population in England: The 2002 English Longitudinal Study of Ageing: Technical Report*; 2007. Available at: http://www.ifs.org.uk/elsa/report03/w1_tech.pdf [accessed on 15 March 2016].

60. Marmot M, Banks J, Blundell R, Lessof C and Nazroo J. Health, wealth and lifestyles of the older population in England: The 2002 English Longitudinal Study of Ageing; 2003 Available at: http://www.elsa-project.ac.uk/reportWave1 [accessed on 14 March 2016].

61. Jönsson L, Andreasen N, Kilander L, Soininen H, Waldemar G, Nygaard H, Winblad B, Jönhagen ME, Hallikainen M, Wimo A. Patient- and Proxy-Reported Utility in Alzheimer Disease Using the EuroQoL. *Alzheimer Disease & Associated Disorders 2006*; **20**(1): 49-55.

62. Magaziner J, Simonsick EM, Kashner TM, Hebel JR. Patient-proxy response comparability on measures of patient health and functional status. *Journal of Clinical Epidemiology 1988*; **41**(11): 1065-1074.

63. Banks, James; Muriel, Alastair; Smith, James P. Attrition and health in ageing studies: evidence from ELSA and HRS. *Longitudinal and Life Course Studies, May 2011* [S.l.]; **2**(2), 101 - 126.

64. Natcen Social Research. English Longitudinal Study of Ageing (ELSA): Wave One to Wave Five - User Guide to the datasets. Available at: http://www.ifs.org.uk/elsa/user_guides/waves_1_5_datasets_user_guide.pdf [accessed on 22 January 2015].

65. StataCorp LP. Stata 12. StataCorp, College Station. 2011.

66. ELSA Project. Documentation. Available at: https://www.elsa-project.ac.uk/documentation [accessed on 17 August 2017].

67. ELSA Project. User Guide for the ELSA Wave 2 Nurse Visit Data (version 2). Available at: http://www.elsa-

project.ac.uk/uploads/elsa/user_guides/Wave_2_Nurse_Visit_User_Guide.pdf[accessed on 17 August 2017].

68. RadloffLS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Applied Psychological Measurement 1977*; 1: 385

69. Karim J, Weisz R, Bibi Z, and urRehman S. (2014). Validation of the Eight-Item Center for Epidemiologic Studies Depression Scale (CES-D) Among Older Adults. *Current Psychology 2014*: 1-20.

70. Gotlib IH, Lewinsohn PM, Seeley JR. Symptoms versus a diagnosis of depression: differences in psychosocial functioning. *Journal of consulting and clinical psychology 1995*; **63**(1):90.

71. Nelson CJ, Cho C, Berk AR, Holland J, Roth AJ. Are gold standard depression measures appropriate for use in geriatric cancer patients? A systematic evaluation of self-report depression instruments used with geriatric, cancer, and geriatric cancer samples. *Journal of Clinical Oncology 2010*; **28**(2), 348-356.

72. Reinecke MA, Schultz. Comparison of self–report and clinician ratings of depression among outpatient adolescents. *Depression 1995*; **3**(3), 139-145.

73. Turvey CL, Wallace RB, Herzog R. A revised CES-D measure of depressive symptoms and a DSM-based measure of major depressive episodes in the elderly. *International Psychogeriatrics 1999*; **11**(2): 139-148.

74. Steffick DE. *Documentation of Affective Functioning Measures in the Health and Retirement Study.HRS; 2*000. Survey Research Center University of Michigan Ann Arbor, MI

75. Sanchez-Villegas A, Schlatter J, Ortuno F, Lahortiga F, Pla J, Benito S, Martinez-Gonzalez MA. Validity of a self-reported diagnosis of depression among participants in a cohort study using the Structured Clinical Interview for DSM-IV (SCID-I). *BMC psychiatry 2008*; **8**(1), 43.

76. Perrini S, Laviola L, Carreira MC, Cignarelli A, Natalicchio A, Giorgino F. The GH/IGF1 axis and signaling pathways in the muscle and bone: mechanisms underlying age-related skeletal muscle wasting and osteoporosis. *Journal of Endocrinology. 2010 Jun 1*; **205**(3):201-10.

77. Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. *Circulation 1993*; **88**(4):1973-98.

78. Zickuhr K, Madden M. Older adults and Internet use. *Pew Internet & American Life Project 2012 Jun 6*; 6.

79. Piccinelli M, Wilkinson G. Gender differences in depression Critical review. *The British Journal of Psychiatry 2000*; **177**(6):486-92.

80. Goodman-Gruen D, Barrett-Connor E. Epidemiology of Insulin-like Growth Factor-I in Elderly Men and Women: The Rancho Bernardo Study. *American Journal of Epidemiology 1997*; **145**(11): 970-976.

81. Li N, Kirkup G. Gender and cultural differences in Internet use: A study of China and the UK. *Computers & Education 2007*; **48**(2):301-17.

82. Regitz-Zagrosek V, Lehmkuhl E, Weickert MO. Gender differences in the metabolic syndrome and their role for cardiovascular disease. *Clinical Research in Cardiology. 2006 Mar 1*; **95**(3):147.

83. Barefoot JC, Mortensen EL, Helms MJ, Avlund K, Schroll M. A longitudinal study of gender differences in depressive symptoms from age 50 to 80. *Psychology and Aging 2001*; **16**(2), 342-345

84. Arber S, Cooper H. Gender differences in health in later life: the new paradox? *Social Science & Medicine 1999*; **48**(1), 61-76

85. Murphy JM, Olivier DC, Monson RR, Sobol AM, Federman EB, Leighton AH. Depression and anxiety in relation to social status: A prospective epidemiologic study. *Archives of General Psychiatry 1991*; 48(3):223-9.

86. Netuveli G, Wiggins RD, Hildon Z, Montgomery SM, Blane D. Quality of life at older ages: evidence from the English longitudinal study of aging (wave 1). *Journal of Epidemiology and Community Health, 2006*; **60**(4), 357-363

87. Demakakos P, Nazroo J, Breeze E, Marmot M. Socioeconomic status and health: the role of subjective social status. *Social science & medicine 2008*; **67**(2):330-40.

88. Pinquart M, Sörensen S. Influences of socioeconomic status, social network, and competence on subjective well-being in later life: a meta-analysis. *Psychology and aging 2000*; **15**(2):187.

89. Banks J, Breeze E, Lessof C, Nazroo J. *Living in the 21st century: older people in England ELSA 2006 (Wave 3), 2008.* London, The Institute for Fiscal Studies.

90. Stack S, Eshleman JR. Marital status and happiness: A 17-nation study. *Journal of Marriage and the Family 1998 May 1*; 527-36.

91. Prince MJ, Beekman AT, Deeg DJ, Fuhrer R, Kivela SL, Lawlor BA, Lobo A, Magnusson H, Meller I, Van Oyen H, Reischies F. Depression symptoms in late life assessed using the EURO-D scale. Effect of age, gender and marital status in 14 European centres.*The British Journal of Psychiatry 1999*; **174**(4):339-45.

92. Wyke S, Ford G. Competing explanations for associations between marital status and health. *Social science & medicine 1992*; **34**(5):523-32.

93. Tournier M, Moride Y, Lesk M, Ducruet T, Rochon S. The depletion of susceptibles effect in the assessment of burden-of-illness: the example of age-related macular degeneration in the community-dwelling elderly population of Quebec. *Canadian Journal of Clinical Pharmacology 2008*;15:e22-35

94. Mons U, Müezzinler A, Gellert C, Schöttker B, Abnet CC, Bobak M, de Groot L, Freedman ND, Jansen E, Kee F, Kromhout D. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. *BMJ 2015*; 350:h1551.

95. Murphy JM, Horton NJ, Monson RR, Laird NM, Sobol AM, Leighton AH. Cigarette smoking in relation to depression: historical trends from the Stirling County Study. *American Journal of Psychiatry 2003*; **160**(9):1663-9.

96. Almeida OP, Pfaff JJ. Depression and smoking amongst older general practice patients. *Journal of affective disorders 2005*; **86**(2):317-21.

97. Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet 1992*; **339**(8808):1523–1526.

98. McMunn A, Hyde M, Janevic M and Kumari M. Health. In, Marmot M, Banks J, Blundell R, Lessof C, Nazroo J. *Health, wealth and the lifestyles of the older population in England: The 2002 English Longitudinal Study of Ageing*. Available at: http://www.elsa-project.ac.uk/reportWave1 [accessed on 8 April 2015].

99. Lang I, Wallace RB, Huppert FA, Melzer D. Moderate alcohol consumption in older adults is associated with better cognition and well-being than abstinence. *Age and ageing 2007*; **36**(3):256-61.

100. Shankar A, McMunn A, Banks J, Steptoe A. Loneliness, social isolation, and behavioral and biological health indicators in older adults. *Health Psychology 2011*; 30(4):377.

101. Erens B, Primatesta P. *Health Survey for England 2000: Cardiovascular disease, 2001*. London: The Stationery Office

102. Bostock S, Steptoe A. Association between low functional health literacy and mortality in older adults: longitudinal cohort study. *BMJ 2012*; **344**:e1602.

103. Hamer M, Molloy GJ, de Oliveira C, Demakakos P. Leisure time physical activity, risk of depressive symptoms, and inflammatory mediators: the English Longitudinal Study of Ageing. *Psychoneuroendocrinology 2009*; 34(7):1050-5.

104. Singh-Manoux A, Martikainen P, Ferrie J, Zins M, Marmot M, Goldberg M. What does self-rated health measure? Results from the British Whitehall II and French Gazel cohort studies. J*ournal of epidemiology and community health 2006*; **60**(4):364-72.

105. Daughaday WH, Hall K, Salmon Jr WD, Van den Brande JL, Van Wyk JJ. Letter to the editor: On the nomenclature of the somatomedins and insulin-like growth factors. *Endocrinology 1987*; **121**(5):1911-2.

106. Kim SW, Lajara R, Rotwein P. Structure and function of a human insulin-like growth factor-I gene promoter. *Molecular Endocrinology 1991*; **5**(12), 1964-1972.

107. Delafontaine P. Insulin-like growth factor I and its binding proteins in the cardiovascular system.*Cardiovascular Research 1995*; 30:825–834.

108. Bartke A. Minireview: role of the growth hormone/insulin-like growth factor system in mammalian aging. *Endocrinology 2005*; **146**(9):3718-23.

109. Giustina A, Mazziotti G, Canalis E. Growth hormone, insulin-like growth factors, and the skeleton. *Endocrine reviews 2008*; **29**(5):535-59.

110. Gluckman PD, Pinal CS. Regulation of fetal growth by the somatotrophic axis. *The Journal of nutrition 2003*; **133**(5):1741S-6S.

111. Randhawa R, Cohen P. The role of the insulin-like growth factor system in prenatal growth. *Molecular Genetics and Metabolism 2005*; **86**(1–2): 84-90.

112. Tanner JM, Davies PS. Clinical longitudinal standards for height and height velocity for North American children. *The Journal of paediatrics 1985*; **107**(3):317-29.

113. Juul A, Dalgaard P, Blum WF, Bang PE, Hall K, Michaelsen KF, Müller J, Skakkebaek NE. Serum levels of insulin-like growth factor (IGF)-binding protein-3 (IGFBP-3) in healthy infants, children, and adolescents: the relation to IGF-1, IGF-1I, IGFBP-1, IGFBP-2, age, sex, body mass index, and pubertal maturation. *The Journal of Clinical Endocrinology & Metabolism 1995*; **80**(8):2534-42.

114. Juul A, Holm K, Kastrup KW, Pedersen SA, Michaelsen KF, Scheike T, Rasmussen S, Müller J, Skakkebæk NE. Free insulin-like growth factor I serum levels in 1430 healthy children and adults, and its diagnostic value in patients suspected of growth hormone deficiency. *The Journal of Clinical Endocrinology & Metabolism 1997*; **82**(8):2497-502.

115. Stewart CE, Rotwein P. Growth, differentiation, and survival: multiple physiological functions for insulin-like growth factors. *Physiological reviews 1996*; **76**(4):1005-26.

116. Philippou A, Maridaki M, Halapas A, Koutsilieris M. The role of the insulin-like growth factor 1 (IGF-1) in skeletal muscle physiology. *In vivo 2007*; **21**(1), 45-54.

117. Wit JM, Walenkamp MJ.Role of insulin-like growth factors in growth, development and feeding. *Nutrition and Growth 2013*; **106**; 60-05

118. Rosen CJ. Insulin-like growth factor I and bone mineral density: experience from animal models and human observational studies. *Best Practice & Research Clinical Endocrinology & Metabolism 2004*; **18**(3): 423-435.

119. Chhabra Y, Waters MJ, Brooks AJ. Role of the growth hormone-IGF-1 axis in cancer. *Expert Review in Endocrinology and Metabolism 2011*; **6**(1), 71–84

120. Anisimov VN, Bartke A. The key role of growth hormone–insulin–IGF-1 signaling in aging and cancer. *Critical reviews in oncology/hematology 2013*; **87**(3):201-23.

121. Le Roith D. Seminars in medicine of the Beth Israel Deaconess Medical Center. Insulin-like growth factors. *New England Journal of Medicine 1997*; 336:633–640.

122. Bikle DD, Tahimic C, Chang W, Wang Y, Philippou A, Barton ER. Role of IGF-1 signaling in muscle bone interactions. *Bone 2015*; **80**:79-88.

123. Delafontaine P, Song YH, Li Y. (2004). Expression, regulation, and function of IGF-1, IGF-1R, and IGF-1 binding proteins in blood vessels. *Arteriosclerosis Thrombosis and Vascular Biology 2004*; **24**(3): 435-444.

124. Sytze van Dam P, Aleman A. Insulin-like growth factor-I, cognition and brain aging. *European Journal of Pharmacology 2004*; **490**(1–3): 87-95.

125. Lamberts SWJ, van den Beld AW, van der Lely AJ. The Endocrinology of Aging. *Science 1997*; **278**(5337): 419-424.

126. van Dam PS, Aleman A, de VriesWR,Deijen JB, van der Veen EA, de Haan EHF, KoppeschaarHPF.Growth hormone, insulin-like growth factor I and cognitive function in adults.*Growth Horm IGF Res 2000*; **10** (Suppl B): S69-73.

127. Burgers AM, Biermasz NR, Schoones JW, Pereira AM, Renehan AG, Zwahlen M, Egger M, Dekkers OM. Meta-analysis and dose-response metaregression: circulating insulin-like growth factor I (IGF-1) and mortality. *The Journal of Clinical Endocrinology & Metabolism 2011*; **96**(9):2912-20.

128. Kalia M, Costa e Silva J. Biomarkers of psychiatric diseases: Current status and future prospects. *Metabolism 2015*; 64(3, Supplement 1): S11-S15.

129. Lesch KP, Rupprecht R, Müller U, Pfüller H, Beckmann H. Insulin-like growth factor I in depressed patients and controls. *Acta Psychiatrica Scandinavica 1988*; **78**(6):684-8.

130. Rupprecht R, Rupprecht C, Rupprecht M, Noder M, Lesch KP, Mössner J. Effects of glucocorticoids on the regulation of the hypothalamic-pituitary-somatotropic system in depression. *Journal of affective disorders 1989*; **17**(1):9-16.

131. Ferraccioli G, Guerra P, Rizzi V, Baraldo M, Salaffi F, Furlanut M, Bartoli E. Somatomedin C (insulin-like growth factor 1) levels decrease during acute changes of stress related hormones. Relevance for fibromyalgia. *The Journal of rheumatology 1994*; **21**(7):1332-4.

132. Veiel HO. A preliminary profile of neuropsychological deficits associated with major depression. *Journal of clinical and experimental neuropsychology 1997*; **19**(4):587-603.

133. Kendler KS, Thornton LM, Gardner CO. Genetic risk, number of previous depressive episodes, and stressful life events in predicting onset of major depression. *American Journal of Psychiatry 2001*; **158**(4):582-6.

134. Paslakis G, Blum WF, Deuschle M. Intranasal insulin-like growth factor I (IGF-1) as a plausible future treatment of depression. *Medical Hypotheses 2012*; **79**(2): 222-225.

135. Malberg JE, Blendy JA. Antidepressant action: to the nucleus and beyond. *Trends Pharmacological Sciences 2005*; 26:631–8

136. Videbech P, Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. *American Journal of Psychiatry 2004*; *161*(11):1957-66.

137. Llorens-Martin M, Torres-Aleman I, Trejo JL. Mechanisms mediating brain plasticity: IGF1 and adult hippocampal neurogenesis. *Neuroscientist* 2009; **15**(2): 134-148.

138. Eriksson PS, Perfilieva E, Björk-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH. Neurogenesis in the adult human hippocampus. *Nature medicine 1998*; **4**(11).

139. Cotter DR, Pariante CM, Everall IP. Glial cell abnormalities in major psychiatric disorders: the evidence and implications. *Brain research bulletin 2001*; **55**(5):585-95.

140. Trejo JL, Carro E, Torres-Aleman I. Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. *Journal of Neuroscience 2001*;**21**(5): 1628-1634.

141. Torres Aleman, I. Role of insulin-like growth factors in neuronal plasticity and neuroprotection. *Advances in Experimental Medicine and Biology 2005*; **567**: 243-258.

142. Schneider HJ, Pagotto U,Stall GK. Central effects of the somatotropic system. *European Journal of Endocrinology 2003*; **149**(5): 377-392.

143. Trejo JL, Piriz J, Llorens-Martin MV, Fernandez AM, Bolos M, LeRoith D, Nunez A, Torres-Aleman I. Central actions of liver-derived insulin-like growth factor I underlying its pro-cognitive effects. *Molecular Psychiatry 2007*;**12**(12): 1118-1128.

144. Anderson MF, Aberg MA, Nilsson M, Ericsson PS. Insulin-like growth factor-I and neurogenesis in the adult mammalian brain. *Brain Research. Developmental Brain Research 2002*; **134**(1-2): 115-122.

145. Jacobs BL, van Praag H, Gage FH. Adult brain neurogenesis and psychiatry: a novel theory of depression. *Molecular Psychiatry 2000*; **5**(3): 262-269.

146. Svensson J,Diez M, Engel J, Wass C, Tivesten A, Jansson JO, Isaksson O, Archer T, Hokfelt T, Ohlsson C. Endocrine, liver-derived IGF-1 is of importance for spatial learning and memory in old mice. *Journal of Endocrinology 2006*;**189**(3): 617-627.

147. Mitschelen M, Yan H, Farley JA, Warrington JP, Han S, Hereñú CB, Csiszar A, Ungvari Z, Bailey-Downs LC, Bass CE, Sonntag WE. Long-term deficiency of circulating and hippocampal insulin-like growth factor I induces depressive behavior in adult mice: a potential model of geriatric depression. *Neuroscience 2011*;**185**(0): 50-60.

148. Duman CH, Schlesinger L, Terwilliger R, Russell DS, Newton SS, Duman RS. Peripheral insulin-like growth factor-I produces antidepressant-like behavior and contributes to the effect of exercise. *Behavioural Brain Research 2009*;**198**(2): 366-371.

149. Dulawa SC, Hen R. Recent advances in animal models of chronic antidepressant effects: the novelty-induced hypophagia test. *Neuroscience & Biobehavioral Reviews 2005*; **29**(4):771-83.

150. Hoshaw BA, MalbergJE, Lucki I. Central administration of IGF-1 and BDNF leads to long-lasting antidepressant-like effects. *Brain Research 2005*; **1037**(1-2): 204-208.

151. Humbel RE, (1990). Insulin-like growth factors I and II. *European Journal of Biochemistry 1990*; **190**(3): 445-462.

152. Junnila RK, List EO, Berryman DE, Murrey, JW, Kopchick JJ. The GH/IGF-1 axis in ageing and longevity. *Nature Reviews Endocrinology 2013*; **9**(6): 366-376.

153. Bondy CA, Cheng CM. Signaling by insulin-like growth factor 1 in brain. *European Journal of Pharmacology 2004*; 490: 25– 31.

154. Szczesny E, Slusarczyk J, Glombik K, Budziszewska B, Kubera M, Lason W, et al. Possible contribution of IGF-1 to depressive disorder. *Pharmacological Reports 2013*; **65**(6): 1622-1631.

155. Schneider HJ, Pagotto U, Stalla GK. Central effects of the somatotropic system. *European Journal of Endocrinology 2003*; **149**(5): 377-392.

156. Jacobs BL, van Praag H, Gage FH. Adult brain neurogenesis and psychiatry: a novel theory of depression. *Molecular Psychiatry 2000*; **5**(3): 262-269.

157. Torres Aleman, I. Role of insulin-like growth factors in neuronal plasticity and neuroprotection. *Advances in Experimental Medicine and Biology 2005*; **567**: 243-258.

158. McGauley GA, Cuneo RC, Salomon F, Sonksen PH. Psychological well-being before and after growth hormone treatment in adults with growth hormone deficiency. *Hormone Research 1990*; **33 (**Suppl 4): 52-54.

159. Sievers C, Dimopoulou C, Pfister H, Lieb R, Steffin B, Roemmler J, Schopohl J, Mueller M, Schneider HJ, Ising M, Wittchen HU, Stalla GK. Prevalence of mental disorders in acromegaly: a cross-sectional study in 81 acromegalic patients. *Clinical Endocrinology (Oxford) 2009*; **71**(5): 691-701.

160. Wexler T, Gunnell L, Omer Z, Kuhlthau K, Beauregard C, Graham G, Utz AL, Biller B, Nachtigall L, Loeffler J, Swearingen B, Klibanski A, Miller KK. Hormone Deficiency Is Associated with Decreased Quality of Life in Patients with Prior Acromegaly. *The Journal of Clinical Endocrinology & Metabolism 2009*; **94**(7): 2471-2477.

161. Franz B, Buysse DJ, Cherry CR, Gray NS, Grochocinski VJ, Frank E, Kupfer DJ. Insulin-like growth factor 1 and growth hormone binding protein in depression: a preliminary communication. *Journal of Psychiatric Research 1999*; **33**(2): 121-127.

162. Deuschle M, Blum WF, Strasburger CJ, Schweiger U, Weber B, Korner A, Standhardt H, Gotthardt U, Schmider J, Pflaum C-D, Heuser I. Insulin-like growth factor-I (IGF-1) plasma concentrations are increased in depressed patients. *Psychoneuroendocrinology 1997*; **22**(7): 493-503.

163. Sievers C, Auer MK, Klotsche J, Athanasoulia AP, Schneider HJ, Nauck M, Volzke H, John U, Schulz A, Freyberger HJ, Friedrich N, Biffar R, Stalla GK, Wallaschofski H, Grabe HJ. IGF-1 levels and depressive disorders: Results from the

Study of Health in Pomerania (SHIP). *European Neuropsychopharmacol 2014*; 24(6): 890-6.

164. Wittchen HU, Höfler M, Gander F, Pfister H, Storz S, Üstün B, Müller N, Kessler RC. Screening for mental disorders: performance of the Composite International Diagnostic–Screener (CID–S). *International Journal of Methods in Psychiatric Research 1999;* 8(2): 59-70.

165. van Varsseveld NC, van Bunderen, Sohl E, Comijs HC, Penninx BWJH, Lips P, et al. Serum insulin-like growth factor 1 and late-life depression: A population-based study. *Psychoneuroendocrinology 2015*;**54**:31-40.

166. Chigogora S, Zaninotto P, Kivimaki M, Steptoe A, Batty GD. Insulin-like growth factor 1 and risk of depression in older people: the English Longitudinal Study of Ageing. *Translational psychiatry 2016*; **6**(9):e898.

167. Frater J, Lie D, Bartlett P, McGrath JJ. Insulin-like Growth Factor 1 (IGF-1) as a marker of cognitive decline in normal ageing: A review. *Ageing research reviews 2018*; 42:14-27.

168. Freeman Laboratories Newcastle (2012).*DPC Immulite 2000 – IGF-1.*(Laboratory summary of methods used up to 02.02.2012, available from laboratory on request)

169. Banks J, Breeze E, Crawford R, Demakakos P, de Oliveira C, Gjonça E, et al. (2010). *Financial circumstances, health and well-being of the older population in England: The 2008 English Longitudinal Study of Ageing (wave 4).* Institute of Fiscal Studies, London

170. Sievers C, Dimopoulou C, Pfister H, Lieb R, Steffin B, Roemmler J, et al. Prevalence of mental disorders in acromegaly: a cross-sectional study in 81 acromegalic patients. *Clinical Endocrinology (Oxford) 2009*; **71**(5): 691-701.

171. McGauley GA, Cuneo RC, Salomon F, Sonksen PH. Psychological well-being before and after growth hormone treatment in adults with growth hormone deficiency. *Horm Res 1990*; **33 (**Suppl 4): 52-54.

172. Wexler T, Gunnell L, Omer Z, Kuhlthau K, Beauregard C, Graham G, et al. Hormone Deficiency Is Associated with Decreased Quality of Life in Patients with Prior Acromegaly. *The Journal of Clinical Endocrinology & Metabolism 2009*; **94**(7): 2471-2477.

173. VanItallie TB. Subsyndromal depression in the elderly: underdiagnosed and undertreated. *Metabolism 2005*; **54**(5):39-44.

174. Kopczak A, Stalla GK, Uhr M, Lucae S, Hennings J, Ising M, Holsboer F, Kloiber S. IGF-1 in major depression and antidepressant treatment response. *European Neuropsychopharmacology 2015*; **25**(6):864-72.

175. Weber-Hamann B, Blum WF, Kratzsch J, Gilles M, Heuser I, Deuschle M. Insulin-like growth factor-I (IGF-1) serum concentrations in depressed patients: relationship to saliva cortisol and changes during antidepressant treatment. *Pharmacopsychiatry 2009*; **42**(01):23-8.

176. Molendijk ML, de Kloet ER. Immobility in the forced swim test is adaptive and does not reflect depression. *Psychoneuroendocrinology 2015*; **62**:389-91.

177. Bot M, Milaneschi Y, Penninx BW, Drent ML. Plasma insulin-like growth factor I levels are higher in depressive and anxiety disorders, but lower in antidepressant medication users. *Psychoneuroendocrinology 2016*; **68**:148-55.

178. O'Flynn K, O'Keane V, Lucey JV, Dinan TG. Effect of fluoxetine on noradrenergic mediated growth hormone release: a double blind, placebo-controlled study. *Biological psychiatry 1991*; **30**(4):377-82.

179. Meesters P, Kerkhofs M, Charles G, Decoster C, Vanderelst M, Mendlewicz J. Growth hormone release after desipramine in depressive illness. European Archives of Psychiatry and Clinical *Neuroscience 1985*; **235**(3):140-2.

180. Wilkins JN, Spar JE, Carlson HE. Desipramine increases circulating growth hormone in elderly depressed patients: a pilot study. P*sychoneuroendocrinology 1989*; **14**(3):195-202.

181. RxList. Antidepressants. Available at: https://www.rxlist.com/antidepressants/drugs-condition.htm#toc [accessed on 17 February 2018]

182. Schilling C, Blum WF, Heuser I, Paslakis G, Wudy SA, Deuschle M. Treatment with antidepressants increases insulin-like growth factor-I in cerebrospinal fluid. *Journal of clinical psychopharmacology 2011*; **31**(3):390-2.

183. Delafontaine P, Song YH, Li Y. Expression, regulation, and function of IGF-1, IGF-1R, and IGF-1 binding proteins in blood vessels. *Arteriosclerosis, thrombosis, and vascular biology 2004*; **24**(3):435-44.

184. Molendijk ML, Spinhoven P, Polak M, Bus BA, Penninx BW, Elzinga BM. Serum BDNF concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analyses on 179 associations (N= 9484). *Molecular psychiatry 2014*; 19(7):791.

185. Sen S, Duman R, Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. *Biological psychiatry 2008*; **64**(6):527-32.

186. Zoccali C, Mallamaci F, Tripepi G, Benedetto FA, Cutrupi S, Parlongo S, Malatino LS, Bonanno G, Seminara G, Rapisarda F, Fatuzzo P. Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease. *Journal of the American Society of Nephrology 2002*; **13**(1):134-41.

187. Castells M. *The rise of the network society: The information age: Economy, society, and culture*. John Wiley & Sons; 2011 Aug 24.

188. Robinson J, Godbey G. *Time for life: The surprising ways Americans use their time;* 2010. Penn State Press.

189. Gibson, W. Neuromancer. Cited in, Turkle S. *Life on the Screen: Identity in the Age of the Internet*; 1997. Simon & Schuster

190. Granovetter, M. The strength of weak ties. *American Journal of Sociology 1973*: **78**(6), 1360-1380.

191. Krackhardt, D. The strength of strong ties: the importance of Philos in Organizations, In, N, Nohriaand RGEccle (eds), *Networks and organizations*; 1992, pp. 216-39.

192. Rheingold, H. *The virtual community: Homesteading on the electronic frontier*; 1993. MIT press.

193. Cohen S, Wills TA. Stress, social support, and the buffering hypothesis. *Psychological bulletin 1985*: **98**(2), 310.

194. Swickert RJ, Hittner JB, Harris JL, Herring JA. Relationships among Internet use, personality, and social support. *Computers in human behavior 2002*;**18**(4):437-51.

195. Kraut R, Patterson M, Lundmark V, Kiesler S, Mukopadhyay T, Scherlis W. Internet paradox - A social technology that reduces social involvement and psychological well-being? *American Psychologist 1998*: **53**(9): 1017-1031.

196. Carnegie Mellon University.*CMU HomeNet Study*. Available at: http://cs.stanford.edu/people/eroberts/cs201/projects/personal-lives/cmu.html [accessed on 26 September 2016].

197. Rierdan J. Internet-depressionlink? *American Psychologist 1999*; **54**(9)781-782

198. Wästlund E, Norlander T, Archer T. Internet blues revisited: Replication and extension of an Internet paradox study. *CyberPsychology & Behavior 2001*; **4**(3), 385-391.

199. Shaw LH, Gant LM. Users divided? Exploring the gender gap in Internet use. *CyberPsychology & Behavior 2002*; **5**(6): 517-527.

200. Pressman S, Kiesler S, Kraut R. Effects of Internet Use on Health and Depression: A Longitudinal Study. *Journal of Medical Internet Research 2010*; **12**(1): 4-4

201. Huang C. Internet use and psychological well-being: A meta-analysis. *Cyberpsychology, Behavior, and Social Networking 2010*; **13**(3):241-9.

202. Kiesler S, Kraut R, Boneva BS. Effects of Internet Use and Social Resources on Changes in Depression. *Information, Communication & Society 2008*; **11**(1): 47-70.

203. McKenna KYA, Bargh J. Coming out in the age of the Internet: identity 'demarginalization' through virtual group participation. *Journal of Personality and Social Psychology 1998*; **75**(3), 681–694

204. Cotten SR, Ford G, Ford S, Hale, TM. Internet use and depression among older adults. *Computers in Human Behavior 2012;***28**(2): 496-499.

205. Cotten SR, Ford G, Ford S, Hale, TM. Internet use and depression Among retired older adults in the United States: A longitudinal analysis. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences 2014*; **69**(5),763-71.

206. Pew Internet & American Life .*Older Americans and the Internet, 2004*. Available at: http://www.pewinternet.org/2004/03/28/older-americans-and-the-internet/ [accessed on 4 February 2016].

207. Silva EB.The cook, the cooker and the gendering of the kitchen. *The Sociological Review 2000*; **48**(4), 612-629

208. Dumitru RC, Bürkle T, Potapov S, Lausen B, Wiese B, Prokosch HU. Use and perception of internet for health related purposes in Germany: results of a national survey. *International Journal of Public Health 2007*; **52**(5):275-85.

209. Murray E, Lo B, Pollack L, Donelan K, Catania J, White M, Zapert K, Turner R. The impact of health information on the internet on the physician-patient relationship: patient perceptions. *Archives of Internal Medicine 2003*; **163**(14):1727-34.

210. Hawkley LC, Burleson MH, Berntson GG, Cacioppo JT. Loneliness in everyday life: cardiovascular activity, psychosocial context, and health behaviors. *Journal of personality and social psychology 2003*; **85**(1):105.

211. Russell D, Peplau LA, Cutrona CE. The revised UCLA Loneliness Scale: Concurrent and discriminant validity evidence. *Journal of personality and social psychology 1980*; **39**(3):472.

212. Yee JL, Niemeier D. Advantages and disadvantages: Longitudinal vs. repeated cross-section surveys. *Project Battelle 1996*; **94**(16).

213. Hill AB. The environment and disease: association or causation? *Proceedings of the Royal society of Medicine 1965*; **58**(5), 295.

214. WhatIs.com. Definition: *Social networking*: Available at: http://whatis.techtarget.com/definition/social-networking [accessed on 6 July 2016].

215. Li J, Theng YL, Foo S. Game-based digital interventions for depression therapy: a systematic review and meta-analysis. *Cyberpsychology, Behavior, and Social Networking 2014*; **17**(8), 519-27.

216. Nominet Trust. *Ageing and the use of the internet: current engagement and future needs*. Available at: https://www.nominettrust.org.uk/sites/default/files/NT%20SoA%20-

%20Ageing%20and%20the%20use%20of%20the%20internet_0.pdf [accessed on 4 August 2017]

217. Ofcom. *The communications market report 2016*. Available at:https://www.ofcom.org.uk/research-and-data/multi-sector-research/cmr/cmr16 [accessed on 5 August 2017].

218. Pew research Centre. *Internet & technology*. Available at: http://www.pewinternet.org/2017/05/17/technology-use-among-seniors/ [accessed on 4 August 2017].

219. Collins English Dictionary. *Definition of troll.* Available at: http://www.collinsdictionary.com/dictionary/english/troll [accessed on 3 October 2016).

220. Bullyingstatus.com. *Bullying statistics*. Available at: http://www.bullyingstatistics.org/content/bullying-statistics.html [accessed on 4 October 2016]

221. Pantic I, Damjanovic A, Todorovic J, Topalovic D, Bojovic-Jovic D, Ristic S, Pantic S. Association between online social networking and depression in high school students: behavioral physiology viewpoint. *Psychiatria Danubina 2012*; **24**(1), 90-3.

222. Valkenburg PM, Schouten AP, Peter J. Adolescents' identity experiments on the Internet. *New Media & Society 2005*; **7**(3), 383–402.

223. Moody EJ.Internet use and its relationship to loneliness. *CyberPsychology&Behavior 2001*; **4**(3), 393-401.

224. Bradley, N, Poppen W. Assistive technology, computers and Internet may decrease sense of isolation for homebound elderly and disabled persons. *Technology and Disability 2003*; **15**, 19–25.

225. Cotten SR, Goldner M, Hale TM, Drentea P. The Importance of Type, Amount, and Timing of Internet Use for Understanding Psychological Distress*. *Social Science Quarterly 2011*; **92**(1), 119-39.

226. Gatto SL, Tak SH. Computer, Internet, and e-mail use among older adults: Benefits and barriers. *Educational Gerontology 2008;* 34, 800–811.

227. Foti DI, Kanazawa L. Activities of daily living. In, Pendelton HM, Schultz-Krohn (eds) *Pedretti's Occupational Therapy: Practice Skills for Physical Dysfunction 2008*; 6:146-94. Elsevier, St Louis.

228. Kraut R, Mukhopadhyay T, Szczypula J, Kiesler S, Scherlis W. Communication and information: Alternative uses of the Internet in households. In, *Proceedings of the SIGCHI conference on Human factors in computing systems*; January 1998. pp. 368-375. ACM Press/Addison-Wesley Publishing Co.

229. Cohen S, Wills T A. Stress, social support, and the buffering hypothesis. *Psychological bulletin 1985*; **98**(2), 310.

230. Sum S, Mathews RM, Hughes I, Campbell A. Internet use and loneliness in older adults. *CyberPsychology & Behavior 2008*; **11**, 208–211

231. Winstead V, Anderson WA, Yost EA, Cotten SR, Warr A, Berkowsky RW. You can teach an old dog new tricks a qualitative analysis of how residents of senior living communities may use the web to overcome spatial and social barriers. *Journal of Applied Gerontology 2013*; **32**(5):540-60.

232. Kraut R, Kiesler S, Boneva B, Cummings J, Helgeson V, Crawford A. Internet paradox revisited. *Journal of Social Issues 2002;* **58**(1), 49–74.

233. Patient. *Support Groups*. Available at: http://patient.info/selfhelp [accessed on 5 July 2016]

234. De Botton A. *The art of travel*. Penguin UK; 2003, pp 283

235. White P, Selwyn N. Moving on-line?An analysis of patterns of adult Internet use in the UK, 2002–2010. *Information, Communication & Society 2013*; **16**(1):1-27.

236. Moser JS, Moran TP, Leber AB. Manipulating attention to non-emotional distractors influences state anxiety: a proof-of-concept study in low-and high-anxious college students. *Behavior therapy 2015*; **46**(6), 834-43.

237. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet 2015*;385:117–71

238. British Heart Foundation. *CVD Statistics – BHF UK Factsheet*. Last reviewed and updated 20 September 2016. Available at: https://www.bhf.org.uk/-/media/files/research/heart-statistics/bhf-cvd-statistics---uk-factsheet.pdf?la=en [accessed on 17 October 2016].

239. British Heart Foundation. *Coronary heart disease*. Available at: https://www.bhf.org.uk/heart-health/conditions/coronary-heart-disease [accessed on 12 December 2016[.

240. British Heart Foundation. *Coronary heart disease is leading cause of avoidable deaths*. Available at: https://www.bhf.org.uk/news-from-the-bhf/news-archive/2015/may/coronary-heart-disease-is-leading-cause-of-avoidable-deaths [accessed on 17 July 2017)]

241. Mendis S, Puska P, Norrving B (eds). *Global Atlas on Cardiovascular Disease Prevention and Control*. World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization, 2011: pp. 3–18.

242. National Clinical Institute of Excellence (NICE). *CVD risk assessment and management.* Available at: https://cks.nice.org.uk/cvd-risk-assessment-and-management#!scenariorecommendation [accessed 22 November 2016].

243. Framingham Heart Study. Available at: https://www.framinghamheartstudy.org/ [accessed 22 November 2016].

244. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation 1998*; **97**(18):1837-47.

245. Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham Study. *American Journal of Cardiology 1976*; **38**(1):46-51.

246. Empana JP, Ducimetiere P, Arveiler D, Ferrieres J, Evans A, Ruidavets JB et al. Are the Framingham and PROCAM coronary heart disease risk functions applicable to different European populations? The PRIME Study. *European Heart Journal* 2003; **24**(21):1903-1911.

247. Pyorala K. Assessment of coronary heart disease risk in populations with different levels of risk. *European Heart Journal* 2000; **21**(5):348-350.

248. Brindle P, Beswick A, Fahey T, Ebrahim S. Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systematic review. *Heart* 2006; **92**(12):1752-1759.

249. Brindle PM, McConnachie A, Upton MN, Hart CL, Smith GD, Watt GCM. The accuracy of the Framingham risk-score in different socioeconomic groups: a prospective study. *British Journal of General Practice 2005*; **55**(520): 838-845.

250. Hippisley-Cox JJ, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, Brindle P. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ 2008*; **336**(7659): 1475-1482.

251. North of England Hypertension Guideline Development Group. *Essential hypertension: managing adult patients in primary care (NICE guideline)*. University of Newcastle upon Tyne: Centre for Health Services Research 2004.

252. Welcome to the QRISK2-2016 Calculator. Available at: https://qrisk.org/2016/ [accessed 22 November 2016].

253. QRISK2. Explaining annual updates. Available at: https://qrisk.org/ [accessed on 20 February 2018]

254. ClinRisk. Wlecome to the QRISK3-2017 Calculator. Available at: https://qrisk.org/three/ [accessed on 20 February 2018].

255. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. *BMJ 2007*; **335**:136.

256. Collins GS, Altman DG. An independent external validation and evaluation of QRISK cardiovascular risk prediction: a prospective open cohort study. *BMJ 2009*; **339**:b2584.

257. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R et al. European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *European Journal of Cardiovascular Prevention and Rehabilitation 2007*; **14** Suppl 2:S1-113.

258. New Zealand Guidelines group. Evidence-Based Practice Guidelines: The assessment and management of cardiovascular risk. Available at: https://www.health.govt.nz/system/files/documents/publications/cvd_risk_full.pdf [accessed on 19 July 2017].

259. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *European Heart Journal* 2003; **24**(11):987-1003.

260. Cooney MT, Dudina AL, Graham IM. Value and limitations of existing scores for the assessment of cardiovascular risk: a review for clinicians. *Journal of the American College of Cardiology 2009*; **54**(14):1209-27.

261. Score risk charts. The European cardiovascular disease risk assessment model. Available at: http://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/SCORE-Risk-Charts [accessed on 21 November 2016].

262. Mendelsohn ME, Karas RH.Molecular and cellular basis of cardiovascular gender differences. *Science 2005*; **308**(5728):1583-7.

263. Mikkola TS, Gissler M, Merikukka M, Tuomikoski P, Ylikorkala O. Sex differences in age-related cardiovascular mortality. *PLOS One 2013*; **8**(5):e63347.

264. Knopp RH, Paramsothy P, Retzlaff BM, Fish B, Walden C, Dowdy A, Tsunehara C, Aikawa K, Cheung MC. Gender differences in lipoprotein metabolism and dietary response: basis in hormonal differences and implications for cardiovascular disease. *Current atherosclerosis reports 2005*; **7**(6):472-9.

265. Dubey RK, OparilS, Imthurn B, Jackson EK. Sex hormones and hypertension. *Cardiovascular research 2002*; **53**(3):688-708.

266. Vartiainen E, Laatikainen T, Peltonen M, Juolevi A, Männistö S, Sundvall J, Jousilahti P, Salomaa V, Valsta L, Puska P. Thirty-five-year trends in cardiovascular risk factors in Finland. *International journal of epidemiology 2009*; **39**(2):504-18.

267. Matthews KA, Meilahn EN, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. *New England Journal of Medicine 1989*; **321**:641-6

268. Mondul AM, Rodriguez C, Jacobs EJ, Calle EE. Age at natural menopause and cause-specific mortality. *American journal of epidemiology 2005*; **162**(11):1089-97.

269. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention. *Circulation 2011*; **124**(19):2145-54.

270. Barton M, Meyer MR. Postmenopausal hypertension. Mechanisms and therapy. *Hypertension 2009*; **54**:1118.

271. Kip KE, Marroquin OC, Kelley DE, et al. Clinical importance of obesity versus the metabolic syndrome in cardiovascular risk in women. *Circulation 2004*; **109**:706-13

272. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ 2006*; 332(7533):73-8.

273. Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, age, cardiovascular risk factors, and coronary heart disease. *Circulation 1999*; **99**(9):1165-72.

274. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *The Lancet 2011*; **378**(9799):1297-305.

275. Althoff T, Hicks JL, King AC, Delp SL, Leskovec J. Large-scale physical activity data reveal worldwide activity inequality. *Nature 2017*; 547(336-339).

276. Charchar FJ, Tomaszewski M, Strahorn P, Champagne B, Dominiczak AF. Y is there a risk to being male?. *Trends in Endocrinology & Metabolism 2003*;**14**(4):163-8.

277. McCarthy JJ. Gene by sex interaction in the etiology of coronary heart disease and the preceding metabolic syndrome. *Nutrition, metabolism and cardiovascular diseases 2007*;**17(**2):153-61.

278. Valkanova V, Ebmeier KP. Vascular risk factors and depression in later life: a systematic review and meta-analysis. *Biological psychiatry 2013*; **73**(5), 406-413.

279. Pan A, Keum N, Okereke OI, Sun Q, Kivimaki M, Rubin RR, Hu FB. Bidirectional Association Between Depression and Metabolic Syndrome A systematic review and meta-analysis of epidemiological studies. *Diabetes care 2012*; **35**(5):1171-80.

280. Lespérance F, Frasure-Smith N, Juneau M, Théroux P. Depression and 1-year prognosis in unstable angina. *Archives of Internal Medicine 2000*; ***160***(9), 1354-1360.

281. Scuteri A, Spazzafumo L, Cipriani L, Gianni W, Corsonello A, Cravello L, Repetto L, Bustacchini S, Lattanzio F. Sebastiani M. Depression, hypertension, and comorbidity: disentangling their specific effect on disability and cognitive impairment in older subjects. *Archives of gerontology and geriatrics 2011*; **52**(3), 253-257.

282. Thrall G, Lip GY, Carroll D, Lane D. Depression, anxiety, and quality of life in patients with atrial fibrillation. *CHEST Journal 2007*; **132**(4), 1259-1264.

283. Papakostas GI, Öngür D, Iosifescu DV, Mischoulon D, Fava M. Cholesterol in mood and anxiety disorders: review of the literature and new hypotheses. *European Neuropsychopharmacology 2004*; 14(2):135-42.

284. Joynt KE, Whellan DJ, O'Connor CM. Depression and cardiovascular disease: mechanisms of interaction. *Biological psychiatry 2003*; **54**(3):248-61.

285. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes - A meta-analysis. *Diabetes Care 2001;* **24**(6): 1069-1078.

286. Ford ES, Zhao G, Li C. Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. *Journal of the American College of Cardiology 2010*; **55**(13):1310-7.

287. Huxley R, Mendis S, Zheleznyakov E, Reddy S, Chan J. Body mass index, waist circumference and waist: hip ratio as predictors of cardiovascular risk—a review of the literature. *European journal of clinical nutrition 2010*; **64**(1):16-22.

288. Palmer S, Vecchio M, Craig JC, Tonelli M, Johnson DW, Nicolucci A, Pellegrini F, Saglimbene V, Logroscino G, Fishbane S, Strippoli GFM. Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. *Kidney International 2013*; **84**(1): 179-191.

289. Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, Salem DN, Levey AS, Sarnak MJ. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. *Journal of the American Society of Nephrology 2004*; **15(**5):1307-15.

290. Dickens C, McGowan L, Clark-Carter D, Creed F. Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis. *Psychosomatic Medicine 2002*; ***64***(1), 52-60.

291. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: A meta-analysis of observational studies. *Arthritis Care & Research 2008*; **59**(12):1690-7.

292. Valtorta NK, Kanaan M, Gilbody S, Ronzi S, Hanratty B. Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies. *Heart 2016*; **102**(13):1009-16.

293. King M, Walker C, Levy G, Bottomley C, Royston P, Weich S, Bellón-Saameño JÁ, Moreno B, Švab I, Rotar D, Rifel J. Development and validation of an international risk prediction algorithm for episodes of major depression in general practice attendees: the PredictD study. *Archives of General Psychiatry 2008*; **65(**12):1368-76.

294. Nichols L, Ryan R, Connor C, Birchwood M, Marshall T. Derivation of a prediction model for a diagnosis of depression in young adults: a matched case–control study using electronic primary care records. *Early intervention in psychiatry 2016*.

295. De Choudhury M, Gamon M, Counts S, Horvitz E. Predicting depression via social media. *ICWSM 2013*; **13**:1-0.

296. Knapp M, McDaid D, Parsonage M. Mental health promotion and mental illness prevention: The economic case. Available at: http://eprints.lse.ac.uk/32311/ [accessed on 13 February 2018].

297. King M, Bottomley C, Bellon-Saameno JA, Torres-Gonzalez F, Švab I, Rifel J, Maaroos HI, Aluoja A, Geerlings MI, Xavier M, Carraca I. An international risk prediction algorithm for the onset of generalized anxiety and panic syndromes in general practice attendees: predictA. *Psychological medicine 2011*; **41**(8):1625-39.

298. Karp JF, Dew MA, Wahed AS, Fitzgerald K, Bolon CA, Weiner DK, Morse JQ, Albert S, Butters M, Gildengers A, Reynolds CF. Challenges and solutions for depression prevention research: methodology for a depression prevention trial for older adults with knee arthritis and emotional distress. *The American Journal of Geriatric Psychiatry 2016*; **24**(6):433-43

299. Hippisley-Cox J, Coupland C, Brindle P. The performance of seven QPrediction risk scores in an independent external sample of patients from general practice: a validation study. *BMJ open 2014*; **4**(8):e005809.

300. ELSA Project. English Longitudinal Study of Ageing (ELSA) Health and lifestyles of people aged 50 years and over. Available at:*https://www.elsa-project.ac.uk/uploads/elsa/docs_w4/project_instructions_nurse.pdf* [accessed on 23 November 2016].

301. Pierce MB, Zaninotto P, Steel N, Mindell J. Undiagnosed diabetes—data from the English longitudinal study of ageing. *Diabetic Medicine 2009*; **26**(7):679-85.

302. Gilleard C, Hyde M, Higgs P. The impact of age, place, aging in place, and attachment to place on the well-being of the over 50s in England. *Research on Aging 2007*; **29**(6):590-605.

303. Yee JL, Niemeier D. Advantages and disadvantages: Longitudinal vs. repeated cross-section surveys. *Project Battelle 1996*; **94**(16).

304. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. *Journal of psychosomatic research 2002*; **53**(4):897-902.

305. Mosovich SA, Boone RT, Reichenberg A, Bansilal S, Shaffer J, Dahlman K, Harvey PD, Farkouh ME. New insights into the link between cardiovascular disease and depression. *International Journal of Clinical Practice 2008;***62**(3): 423-432.

306. Hackett ML, Yapa C, Parag V, Anderson CS. Frequency of depression after stroke a systematic review of observational studies. *Stroke 2005*; **36**(6):1330-40.

307. Gainotti G, Azzoni A, Marra C. Frequency, phenomenology and anatomical-clinical correlates of major post-stroke depression. *The British Journal of Psychiatry 1999*; **175**(2):163-7.

308. Krishnan KR, McDonald WM, Doraiswamy PM, Tupler LA, Husain M, Boyko OB, Figiel GS, Ellinwood Jr EH. Neuroanatomical substrates of depression in the elderly. *European archives of psychiatry and clinical neuroscience 1993*; **243**(1):41-6.

309. Santos M, Kövari E, Gold G, Bozikas VP, Hof PR, Bouras C, Giannakopoulos P. The neuroanatomical model of post-stroke depression: towards a change of focus? *Journal of the neurological sciences 2009*; **283**(1):158-62.

310. Miller GE, Blackwell E. Turning up the heat inflammation as a mechanism linking chronic stress, depression, and heart disease. *Current Directions in Psychological Science 2006*; **15**(6):269-72.

311. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation 2002*; **105**(9):1135-43.

312. Liuzzo G, Biasucci LM. *Markers of inflammation, in Acute Coronary Syndromes: A Companion to Braunwald's Heart Disease.* Edited by Théroux P. Philadelphia, WB Saunders, 2003, pp 209–225

313. Lespérance F, Frasure-Smith N, Théroux P, Irwin M.The association between major depression and levels of soluble intercellular adhesion molecule 1, interleukin-6, and C-reactive protein in patients with recent acute coronary syndromes. *American Journal of Psychiatry 2004*; **161**(2):271-7.

314. Anisman H, Merali Z. Cytokines, stress, and depressive illness. *Brain, behavior, and immunity 2002*; **16**(5):513-24.

315. Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, McCorkle R, Seligman DA, Schmidt K. The relationship of depression and stressors to immunological assays: a meta-analytic review. *Brain, behavior, and immunity 2001*;**15**(3):199-226.

316. Miller GE, Stetler CA, Carney RM, Freedland KE, Banks WA. Clinical depression and inflammatory risk markers for coronary heart disease. *The American journal of cardiology 2002*; **90**(12):1279-83.

317. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of general psychiatry 2005*; **62**(6):593-602.

318. Legato MJ, Gelzer A, Goland R, Ebner SA, Rajan S, Villagra V, Kosowski M. Gender-specific care of the patient with diabetes: review and recommendations. *Gender Medicine 2006*; **3**(2):131-58.

319. Dalen H, Thorstensen A, Vatten LJ, Aase SA, Stoylen A. Reference values and distribution of conventional echocardiographic Doppler measures and longitudinal tissue Doppler velocities in a population free from cardiovascular disease. *Circulation: Cardiovascular Imaging 2010;***3***:*614–622.

320. Shah AJ, Veledar E, Hong Y, Bremner JD, Vaccarino V. Depression and history of attempted suicide as risk factors for heart disease mortality in young individuals. *Archives of general psychiatry 2011*; **68**(11):1135-42.

321. Fuller JH, Keen H, Jarrett RJ, Omer T, Meade TW, Chakrabarti R, North WR, Stirling Y. Haemostatic variables associated with diabetes and its complications. *BMJ 1979*; **2**(6196):964-6.

322. Lam CS, Little WC.Sex and cardiovascular risk: are women advantaged or men disadvantaged? *Circulation 2012;* **126***:*913–915.

323. Smulyan H, Marchais SJ, Pannier B, Guerin AP, Safar ME, London GM. Influence of body height on pulsatile arterial hemodynamic data. *Journal of the American College of Cardiology 1998*; 31:1103–1109

324. Pickett KE, Wilkinson RG. Income inequality and health: a causal review. *Social Science & Medicine 2015*; **128**:316-26.

325. Doyal L. Sex, gender, and health: the need for a new approach. *BMJ 2001*; **323**(7320):1061.

326. Lorant V, Deliège D, Eaton W, Robert A, Philippot P, Ansseau M. Socioeconomic inequalities in depression: a meta-analysis. *American journal of epidemiology 2003*; **157**(2):98-112.

327. Czaja SJ, Lee C. The Impact of the Internet. *Impact of technology on successful aging 2003*: 113.

328. Melenhorst AS, Rogers WA, Caylor EC. The use of communication technologies by older adults: exploring the benefits from the user's perspective. In: *Proceedings of the Human Factors and Ergonomics Society Annual Meeting 2001*; **45**(3):221-225. Sage CA: Los Angeles, CA: SAGE Publications.

329. Kurniawan S. Older people and mobile phones: A multi-method investigation. *International Journal of Human-Computer Studies 2008*; **66**(12):889-901.

330. Eastman JK, Iyer R. The elderly's uses and attitudes towards the Internet. *Journal of Consumer Marketing 2004*; *21*(3):208-20.

331. Osman Z, Poulson D, Nicolle C. Introducing computers and the Internet to older users: findings from the Care OnLine project. *Universal Access in the Information Society 2005*; **4**(1):16-23.

332. Kondo M, Koyama Y, Nakamura Y, Shimada S. A novel 5HT3 receptor–IGF1 mechanism distinct from SSRI-induced antidepressant effects. Molecular Psychiatry 2017 Apr 25.

333. Banks J, Muriel A, Smith JP. Attrition and health in ageing studies: evidence from ELSA and HRS. *Longitudinal and life course studies 2011*; **2**(2).

334. Weissman MM, Sholomskas D, Pottenger M, Prusoff BA, Locke BZ. Assessing depressive symptoms in five psychiatric populations: a validation study. *American journal of Epidemiology 1977*; **106**(3), 203-14.

335. Boyd JH, Weissman MM, Thompson WD, Myers JK. Screening for depression in a community sample: understanding the discrepancies between depression symptom and diagnostic scales. *Archives of General Psychiatry 1982*; **39**(10), 1195.

336. Greenland S, Robins JM. Identifiability, exchangeability, and epidemiological confounding. *International journal of epidemiology 1986*; **15**(3):413-9.

337. Morabia A. Poppers, Kaposi′ s-Sarcoma, and HIV-Infection: Empirical Example of a Strong Confounding Effect?. *Preventive medicine 1995*; **24**(1):90-5.

338. Phillips AN, Smith GD. Bias in relative odds estimation owing to imprecise measurement of correlated exposures. *Statistics in medicine 1992 ;* **11**(7):953-61.

339. Shrive FM, Stuart H, Quan H, Ghali WA. Dealing with missing data in a multi-question depression scale: a comparison of imputation methods. *BMC medical research methodology 2006*; **6**(1), 1.

340. Taylor R, Conway L, Calderwood L, Lessof C, Cheshire H, Cox K and Scholes S. Health, wealth and lifestyles of the older population in England: The 2002 English Longitudinal Study of Ageing Technical Report. Available at: https://www.ifs.org.uk/elsa/report03/w1_tech.pdf [accessed 21 August 2017].

341. Baraldi AN, Enders CK. An introduction to modern missing data analyses. *Journal of school psychology 2010*; **48**(1):5-37

Appendix 1 : Peer reviewed article 'Chigogora S, Zaninotto P, Kivimaki M, Steptoe A, Batty GD. Insulin-like growth factor 1 and risk of depression in older people: the English Longitudinal Study of Ageing. Translational psychiatry 2016 Sep 1;6(9):e898.'

OPEN

Citation: Transl Psychiatry (2016) **6**, e898; doi:10.1038/tp.2016.167
www.nature.com/tp

ORIGINAL ARTICLE

Insulin-like growth factor 1 and risk of depression in older people: the English Longitudinal Study of Ageing

S Chigogora[1], P Zaninotto[1], M Kivimaki[1], A Steptoe[1] and GD Batty[1,2]

Depressive disorders are a leading cause of disability in older age. Although the role of psychosocial and behavioural predictors has been well examined, little is known about the biological origins of depression. Findings from animal studies have implicated insulin-like growth factor 1 (IGF-1) in the aetiology of this disorder. A total of 6017 older adults (mean age of 65.7 years; 55% women) from the English Longitudinal Study of Ageing provided serum levels of IGF-1 (mean = 15.9 nmol l^{-1}, s.d. 5.7) during a nurse visit in 2008. Depression symptoms were assessed in the same year and again in 2012 using the eight-item Center for Epidemiologic Studies Depression Scale. Self-reports of a physician-diagnosis of depression were also collected at both time points. In separate analyses for men and women, the results from both the cross-sectional and longitudinal analyses revealed a 'U'-shaped pattern of association, such that lower and higher levels of IGF-1 were associated with a slightly elevated risk of depression, whereas the lowest risk was seen around the median levels. Thus, in men, with the lowest quintile of IGF-1 as the referent, the age-adjusted odds ratios (95% confidence interval) of developing depression symptoms after 4 years of follow-up, for increasing quintiles of IGF-1, were: 0.51 (0.28–0.91), 0.50 (0.27–0.92), 0.63 (0.35–1.15) and 0.63 (0.35–1.13) (*P*-value for quadratic association 0.002). Some attenuation of these effects was apparent after adjustment for co-morbidity, socioeconomic status and health behaviours. In conclusion, in the present study of older adults, there was some evidence that moderate levels of IGF-1 levels conferred a reduced risk of depression.

Translational Psychiatry (2016) **6,** e898; doi:10.1038/tp.2016.167; published online 20 September 2016

INTRODUCTION

Depression, a major public health problem, has profound effects on the economy and on individuals. According to the World Health Organization, it is the leading cause of disability worldwide,[1] responsible for 65 million disability-adjusted life years in 2008.[2] In addition to being an important disease in its own right, depression is also associated with an increased risk of suicide,[3,4] cardiovascular disease,[5–7] some cancers[8] and premature mortality.[9–11] Although effective treatments for depression are available, the majority of cases among older people remain undiagnosed; prevention of the disorder is therefore crucial.[12,13] A series of studies have identified a range of behavioural (heavy alcohol use, some dietary characteristics) and social (loneliness, socioeconomic disadvantage, bereavement) predictors of depression in later life.[14,15] Although the aetiological role of weight, height, genetic factors and several plasma markers has been examined,[16–18] relatively less attention has been paid to biological risk factors.

Insulin-like growth factor 1 (IGF-1) is a complex peptide hormone produced in multiple tissue sites whose main function is to mediate cell growth, differentiation and transformation by promoting mitosis and inhibiting apoptosis.[19] Evidence from laboratory studies suggests that expression and function of IGF-1 is similar in humans and rodents.[20,21] In humans, elevated IGF-1 levels are associated with increased skeletal muscle and tissue growth,[22,23] bone mineral density,[24] risk of selected malignancies[25] and cardiovascular disease.[26,27] IGF-1 has also been implicated in psychological functioning of both animals and humans. Thus, rodents whose circulating IGF-1 levels were experimentally perturbed displayed marked changes in mood. For instance, the application of a viral vector to drastically reduce circulating IGF-1 levels resulted in mice showing signs of depression as assessed using the forced swim and tail suspension tests.[28] Elsewhere, rodents given IGF-1 infusions experienced a reduction in depression symptoms relative to a no treatment group.[29,30] In laboratory-based experimental studies of humans, through a range of mechanisms such as altered neuroprotection, modulation of neuronal excitability, brain angiogenesis, hippocampal neurogenesis and neuroplasticity,[31–33] alterations of IGF-1 levels have been linked to hippocampal dysfunction, which in turn have been associated with mood disorders.[34,35] IGF-1 expression in the hippocampus has also been found to be reduced in sufferers of depression, and enhanced by the administration of antidepressants.[36]

Of the two general population-based studies of which we are aware, one showed that low IGF-1 in women, but high levels in men, were predictive of depressive disorder.[37] In another, relative to moderate levels, women with high IGF-1 values experienced an elevated risk of minor depression.[38] In both the studies, incident depression was rare resulting in low statistical power, and in one,[38] the measurement of depression was made using a non-standard scale of unknown validity. Accordingly, against this background of study paucity, discordant findings and methodological concerns, we examined the cross-sectional and longitudinal association between IGF-1 and depression symptoms in a large, well-established general population-based study of older adults in England (UK).

[1]Department of Epidemiology and Public Health, University College London, London, UK and [2]Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK. Correspondence: S Chigogora, Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London WC1E 6BT, UK.
E-mail: s.chigogora.11@ucl.ac.uk
Received 1 June 2016; accepted 18 July 2016

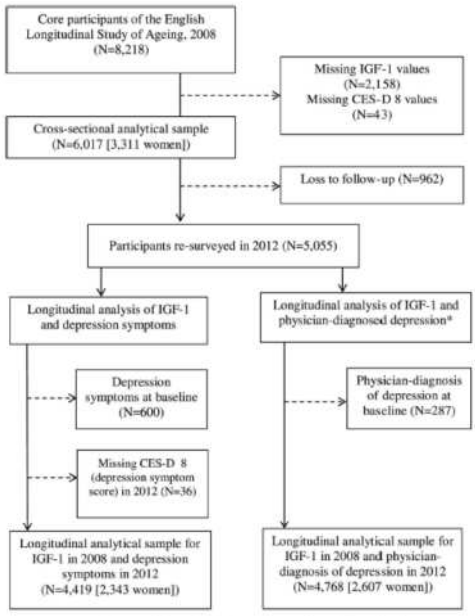


Figure 1. Derivation of the analytical sample for cross-sectional (2008) and longitudinal (2012) analyses of the association between serum IGF-1 and depression: the English Longitudinal Study of Ageing. CES-D, Center for Epidemiologic Studies Depressive scale; IGF-1, insulin-like growth factor 1.

MATERIALS AND METHODS

Study population

The English Longitudinal Study of Ageing is an ongoing prospective cohort study of adults aged 50 years and over who, when recruited, lived in private households in the United Kingdom. Initiated in 2002/3, the original sample was drawn from participants in the Health Surveys for England, a collection of population-based cross-sectional studies. With data collection occurring every 2 years, as of 2012, there have been a total of six waves. As IGF-1 levels were first measured in 2008 (wave 4), this represents our study 'baseline' for the purposes of the present analyses. Ethical approval for all data collection was granted by the National Research and Ethics Committee,[39] and the participants provided written consent.

Measurement of IGF-1

Study members were requested not to eat, smoke, drink alcohol or engage in vigorous exercise for 30 min before blood being drawn. The whole-blood samples were transported to a single laboratory (Royal Victoria Infirmary, Newcastle, UK), where the serum was separated, frozen at 40 °C and batch-assayed (completed in 2008) using the DPC Immulite 2000 method. The inter-assay coefficient of variation for IGF-1 across a range of levels was ⩽3.7%, and the intra-assay coefficient of variation was ⩽5.3%. The IGF-1 values are reported as whole numbers (range: 3–200 nmol l^{-1}).[40]

Depressive symptoms and physician-diagnosis of depression

Depression symptoms were ascertained during a computer-assisted personal interview using the eight-item Center for Epidemiologic Studies Depressive (CES-D8) scale.[41] Each item requires a dichotomous (yes/no) response, and scores range between 0 and 8 (higher score denotes more severe symptoms). Consistent with other analyses, we defined 'caseness' as anyone scoring 4 or above.[42] The CES-D has been widely used in population-based studies of older groups[43,44] and has been validated against clinician-assessed depression.[45] Notably, the shortened CES-D8 has good internal consistency (Cronbach's $\alpha = 0.78$) and similar psychometric properties to the full 20-item CES-D.[46] The participants also had an opportunity to self-report a physician-diagnosis of depression. During the main English Longitudinal Study of Ageing interview, the participants first reported whether they had ever been diagnosed with any emotional, nervous or psychiatric problems. This was followed by the identification of the actual condition as selected from a list of ailments common to this group, of which depression was one.[47] The assessment of depression in this manner has been shown to be valid in a separate study using the Structured Clinical Interview for DSM-IV Axis I Disorders as the gold standard.[48] Both these measurements of depression were made in 2008 and 2012.

Measurement of covariates

We grouped covariates, including potential confounders and mediators, according to theme. Anthropometric measures comprised height and weight, which were measured during the nurse visit; body mass index (kg/m^2) calculated by dividing each individual's measured weight by height squared. Psychosocial factors were level of education (no qualification, completed secondary (high school) education, educated beyond secondary education but below degree level, and educated beyond degree level); quintiles of net non-pension wealth (derived from an estimation of financial wealth and physical assets reported by study participants and their partners, excluding pension savings and net of debts such as credit cards and loans);[49] and marital status (currently living with a partner or not). Health-related behaviours comprised smoking status (current, ex-smoker and never), frequency of alcohol consumption in the past year (less than daily/daily, with consumption on at least 5 days of the week being classed as daily consumption) and leisure time physical activity (low/sedentary, moderate or high activity of exercises such as jogging, cycling, gardening, walking). Co-morbidities were self-reported physician-diagnosis of cancer, diabetes or cardiovascular disease (heart murmur, ischaemic heart disease, abnormal heart rhythm, stroke, valvular heart disease or any other reported heart disease).

Statistical analysis

In Figure 1, we illustrate the flow of participants through the study. Of the 8218 participants at baseline in 2008 who had received a nurse visit, we excluded those who had missing values for IGF-1 ($N = 2158$) comprising people who declined to give blood (771), unsuitability or loss of a blood sample (395), or failure to obtain blood sample (992). We also excluded participants with missing values for depression symptoms (43), although none had missing data for physician-diagnosed depression at baseline. The cross-sectional sample therefore comprised 6017 study members from data collection in 2008. We also carried out the longitudinal analyses, again using IGF-1 values from 2008 but relating to new (incident) cases of depression at resurvey in 2012. In deriving new cases of depression, we excluded participants who were classed as depression cases in 2008, resulting in samples of 4419 for the analysis of depression symptoms and 4768 for physician-diagnosed depression.

Multivariable logistic regression analyses were used to summarize the association of IGF-1 levels with both depression outcomes. The lowest quintile of IGF-1 was used as the referent. There is existing evidence of differential IGF-1-depression relationships in men and women,[39,40,50] so we present gender-specific analyses here also. We adjusted effect estimates for known covariates in a stepwise manner. In our analyses, depression symptoms were our primary outcome, with physician-diagnosed depression used to test convergence of evidence. All the analyses were carried out using Stata12SE software.[51]

RESULTS

IGF-1 and baseline characteristics: cross-sectional analyses

In Table 1 (women) and Table 2 (men), we present baseline study participant characteristics according to IGF-1 quintiles. As expected, mean IGF-1 values were higher in men (16.5 nmol l^{-1}) than women (15.2 nmol l^{-1}). In men and women, IGF-1 was inversely associated with age and directly related to height and

Table 1. Baseline characteristics of study participants according to quintiles of serum IGF-1 (nmol l^{-1}): 3311 women in the English Longitudinal Study of Ageing, 2008

	IGF-1 quintile (range)						*P-value for difference*
	1	*2*	*3*	*4*	*5*	*All*	
	(2–11 nmol l^{-1})	*(12–14 nmol l^{-1})*	*(15–16 nmol l^{-1})*	*(17–20 nmol l^{-1})*	*(21–65 nmol l^{-1})*		
Subject numbers	861	813	479	681	477		
IGF-1, nmol l^{-1}, mean (s.e.)	9.2 (0.06)	13.0 (0.03)	15.5 (0.02)	18.3 (0.04)	25.2 (0.22)	15.2 (0.10)	<0.001
Age, years, mean (s.e.)	68.7 (0.4)	66.2 (0.3)	65.1 (0.4)	64.4 (0.3)	63.2 (0.4)	65.9 (0.2)	<0.001
Anthropometry mean (s.e.)							
Height, cm	158.8 (0.3)	159.9 (0.2)	160.4 (0.3)	160.6 (0.2)	160.9 (0.3)	160.0 (0.1)	<0.001
BMI, kg/m^2	28.7 (0.2)	28.4 (0.2)	27.6 (0.2)	27.7 (0.2)	27.6 (0.2)	28.1 (0.1)	<0.001
Co-morbidities, % (s.e.)							
Diabetes	8.5 (0.9)	6.0 (0.8)	6.9 (1.2)	5.9 (0.9)	7.8 (1.2)	7.0 (0.4)	0.213
Cancer	6.6 (0.8)	4.5 (0.7)	4.6 (1.0)	3.2 (0.7)	6.1 (1.1)	5.0 (0.4)	0.029
Cardiovascular disease	26.6 (1.5)	24.4 (1.5)	21.5 (1.9)	18.6 (1.5)	23.9 (2.0)	23.3 (0.7)	0.005
Psychosocial factors, % (s.e.)							
Lowest wealth quintile	23.1 (1.4)	16.0 (1.3)	11.7 (1.5)	15.0 (1.4)	14.5 (1.6)	16.8 (0.7)	<0.001
No educational qualifications	34.1 (1.6)	30.3 (1.6)	29.0 (2.1)	27.2 (1.7)	23.1 (1.9)	29.4 (0.8)	0.001
Lives alone	43.1 (1.7)	37.5 (1.7)	28.4 (2.1)	32.8 (1.8)	36.3 (2.2)	36.5 (0.8)	<0.001
Behavioural factors, % (s.e.)							
Sedentary or low physical activity	39.4 (1.7)	30.0 (1.6)	26.5 (2.0)	25.8 (1.7)	30.2 (2.1)	31.1 (0.8)	<0.001
Current smoking	12.2 (1.1)	13.3 (1.2)	12.7 (1.5)	13.5 (1.3)	16.1 (1.7)	13.4 (0.6)	0.663
Daily alcohol intake	15.2 (1.2)	16.0 (1.3)	16.5 (1.7)	15.9 (1.4)	16.8 (1.7)	16.0 (0.6)	0.902
Depression							
CES-D score, mean (s.e.)	1.8 (0.07)	1.6 (0.07)	1.3 (0.08)	1.5 (0.07)	1.6 (0.09)	1.6 (0.03)	<0.001
High depression symptoms, % (s.e.)	20.6 (1.3)	15.9 (1.3)	14.4 (1.6)	14.2 (1.3)	17.8 (1.5)	16.8 (0.7)	0.005
Physician-diagnosed depression, % (s.e.)	7.1 (0.9)	6.4 (0.9)	5.4 (1.0)	6.5 (0.9)	6.7 (1.1)	6.5 (0.4)	0.837

Abbreviations: BMI, body mass index; CES-D, Center for Epidemiologic Studies Depressive scale; IGF-1, insulin-like growth factor 1.

socioeconomic position. Psychosocial factors, which included social position and cohabiting with a partner, typically occurred at more favourable levels in men and women with higher IGF-1 values. A total of 776 participants (12.9%) had CES-D8 scores of 4 and above at baseline and were therefore denoted as 'cases' (71.8% were female); 344 (5.7%) participants reported physician-diagnosis of depression. As for some of the somatic conditions such as cancer, there was a suggestion that the greatest proportions of both men and women who reported high depression symptoms and self-declared physician-diagnosed depression were seen in the lowest and highest quintiles of IGF-1, although the differences across groups were not considerable.

IGF-1 and depression: cross-sectional analyses

In Table 3, the computation of odds ratios for the cross-sectional association between IGF-1 and depression symptoms supports earlier evidence of a somewhat higher risk of depression symptoms at opposite ends of the IGF-1 continuum in men and women in this study. Although a similar 'U'-shaped pattern was apparent for physician-diagnosed depression (see Supplementary Table 1), statistical significance at conventional levels was rarely apparent for individual point estimates in these analyses. Adjustment for an array of covariates had little impact on this pattern of association, although taking into account all covariates simultaneously led to some flattening of the IGF-1–depression relationship.

IGF-1 and depression: prospective analyses

In Table 4, we depict the association between IGF-1 and depression symptoms after 4 years of follow-up in participants initially free of depression symptoms at baseline (longitudinal analyses). A 'U'-shaped pattern of risk was again observed for the IGF-1–depression association in both genders based on symptomatology. Similar results were apparent for physician-diagnosis of depression but only among women (Supplementary Table 2). Statistical significance was, again, rarely apparent for individual point estimates. In none of our analyses was there strong statistical evidence that gender modified the IGF-1–depression association (*P*-values for interaction for the multiply adjusted odds of developing depression symptoms and physician-diagnosed depression in longitudinal analyses are 0.531 and 0.275, respectively).

DISCUSSION

The main finding of this study of older people was that having IGF-1 levels at opposing ends of the continuum was associated with a slightly higher risk of depression symptoms. Similar results were apparent for physician-diagnosis of depression.

Comparison with existing studies

Our results partially accord with the two population studies on IGF-1 and depression of which we are aware. When compared with data from the Study of Health in Pomerania in Germany,[38]

Table 2. Baseline characteristics of study participants according to quintiles of serum IGF-1 (nmol l^{-1}): 2706 men in the English Longitudinal Study of Ageing, 2008

	IGF-1 quintile (range)						*P-value for difference*
	1	*2*	*3*	*4*	*5*	*All*	
	(2–11 nmol l^{-1})	*(12–14 nmol l^{-1})*	*(15–16 nmol l^{-1})*	*(17–20 nmol l^{-1})*	*(21–65 nmol l^{-1})*		
Subject number	483	615	384	667	557		
IGF-I, nmol l^{-1} (s.e.)	9.3 (0.08)	13.1 (0.03)	15.5 (0.03)	18.4 (0.04)	25.1 (0.22)	16.5 (0.11)	<0.001
Age, years, mean (s.e.)	68.7 (0.5)	65.3 (0.4)	65.0 (0.5)	64.4 (0.3)	64.0 (0.3)	65.4 (0.2)	<0.001
Anthropometry, mean (s.e.)							
Height, cm	171.7 (0.3)	172.8(0.3)	173.8 (0.4)	173.8 (0.3)	174.2 (0.3)	173.3 (0.1)	<0.001
BMI, kg/m^2	28.6 (0.2)	27.8 (0.2)	27.9 (0.2)	28.0 (0.2)	27.9 (0.2)	28.0 (0.1)	0.078
Co-morbidities, % (s.e.)							
Diabetes	12.6 (1.5)	6.8 (1.0)	6.3 (1.2)	10.6 (1.2)	11.1 (1.3)	9.6 (5.7)	0.001
Cancer	4.8 (1.0)	5.4 (1.0)	4.4 (1.1)	5.2 (0.9)	4.3 (0.9)	4.9 (4.1)	0.897
Cardiovascular disease	31.5 (2.1)	24.6 (1.7)	25.7 (2.2)	26.3 (1.7)	27.2 (1.9)	26.9 (0.9)	0.121
Psychosocial factors, % (s.e.)							
Lowest wealth quintile	18.0 (1.8)	13.3 (1.4)	14.3 (1.8)	12.0 (1.3)	13.1 (1.4)	13.9 (0.7)	0.167
No educational qualifications	25.9 (2.0)	20.0 (1.6)	23.4 (2.1)	17.3 (1.5)	16.3 (1.6)	20.1 (0.8)	0.056
Lives alone	26.7 (2.0)	20.7 (1.6)	20.8 (2.1)	21.4 (1.6)	16.7 (1.6)	21.1 (0.8)	0.003
Behavioural factors, % (s.e.)							
Sedentary or low physical activity	26.9 (2.0)	18.4 (1.6)	22.1 (2.1)	17.4 (1.5)	21.9 (1.8)	20.9 (0.8)	0.005
Current smoking	13.7 (1.6)	12.7 (1.3)	12.8 (1.7)	11.8 (1.3)	14.0 (1.5)	12.9 (0.6)	0.306
Daily alcohol intake	28.6 (2.2)	24.7 (1.7)	27.6 (2.2)	26.4 (1.7)	24.1 (1.8)	26.1 (0.8)	<0.001
Depression							
CES-D8 score, mean (s.e.)	1.0 (0.08)	0.9 (0.06)	0.8 (0.07)	0.9 (0.06)	1.1 (0.07)	0.9 (0.03)	0.07
High depression symptoms, % (s.e.)	9.3 (1.3)	7.5 (1.1)	5.7 (1.0)	6.7 (1.0)	11.0 (1.3)	8.1 (0.5)	0.018
Physician-diagnosed depression, % (s.e.)	5.2 (1.0)	4.2 (0.8)	4.2 (1.0)	3.9 (0.7)	6.5 (1.0)	4.8 (0.4)	0.238

Abbreviations: BMI, body mass index; CES-D, Center for Epidemiologic Studies Depressive scale; IGF-1, insulin-like growth factor 1.

our results were in agreement with the finding that having a low IGF-1 level was associated with higher risk of developing depression symptoms among women. However, we also found a similar association for men. Our results are also in agreement with the second existent study, which used data from The Longitudinal Aging Study Amsterdam,[39] where associations were found between median levels of IGF-1 and lower risk of both prevalent and incident depression symptoms. Once again, the main difference with this present study is that we identified this association among both men and women. The 'U'-shaped relationship that we identified between IGF-1 and depression symptoms is supported by observations of increased reports of lifetime affective disorders in individuals with lower (pituitary dwarfism) and higher (acromegaly) levels of this growth hormone.[52–54] It may be that this apparent differential result for men and women in these existing studies is due to statistical instability.

To directly compare our findings with some of those already published, we re-categorized IGF-1 levels in our own analyses. In these new analyses, we still found evidence for increased odds of depression symptoms among those with very low and very high IGF-1. Our results after initial re-categorization of IGF-1 levels[38] showed that, after 4 years of follow-up, the age-adjusted odds ratios (95% confidence interval) of depression symptoms for the lowest and highest tenth percentiles of IGF-1 among men were 2.26 (1.25, 4.09) and 1.51 (0.86, 2.68), respectively when compared with those with intermediate levels; whereas the corresponding results in women were 1.38 (0.93, 2.07) and 1.27 (0.77, 2.10). Following further re-categorization,[39] when compared with the middle tertile, the odds ratios (95% confidence interval) of depression for the lowest and highest tertiles of IGF-1 among men were 1.14 (0.72, 1.80) and 0.89 (0.55, 1.43), respectively, and corresponding results for women were 1.08 (0.79, 1.49) and 1.14 (0.79, 1.65).

Our findings, however, contrast with the results from the handful of case–control studies where IGF-1 levels were found to be elevated in depressed patients compared with healthy controls.[55,56] This may be owing to specific consequences of previous use of anti-depressant medications, such as where they have been seen to improve expression of IGF-1 and other neutrophic and growth factors in the hippocampus.[31] Furthermore, there may yet be other unknown biological mechanisms related to the state of being depressed, which cause serum IGF-1 levels to increase, implying reverse causation in the reported case–control studies, where the depression in the cases had, in fact, caused the IGF-1 levels to increase. In this study, we attempted to circumvent the problem of reverse causality by utilizing depression incidence as our outcome in the longitudinal analyses; that is, new cases of depression in participants who, at baseline, were symptom-free and had not previously reported being diagnosed with the condition by a physician.

Table 3. Odds ratio (95% confidence interval) for the cross-sectional association between serum IGF-1 and depression symptoms: the English Longitudinal Study of Ageing, 2008

	IGF-1 quintile (range)[a]					*P-value for linearity*	*P-value for quadratic*
	1 (2–11)	*2 (12–14)*	*3 (15–16)*	*4 (17–20)*	*5 (21–65)*		
Women (analytical sample)							
Adjustments							
Age (3311)	1 (ref)	0.76 (0.58, 0.97)	0.69 (0.50, 0.93)	0.68 (0.52, 0.90)	0.91 (0.68, 1.22)	0.027	0.009
Age, anthropometric measures[b] (3181)	1	0.79 (0.61, 1.02)	0.74 (0.54, 1.01)	0.72 (0.54, 0.95)	0.96 (0.71, 1.30)	0.061	0.037
Age, co-morbidities[c] (3308)	1	0.75 (0.58, 0.96)	0.68 (0.50, 0.92)	0.69 (0.52, 0.91)	0.89 (0.66, 1.19)	0.031	0.012
Age, psychosocial factors[d] (3162)	1	0.81 (0.62, 1.06)	0.79 (0.57, 1.09)	0.73 (0.55, 0.98)	0.96 (0.70, 1.30)	0.494	0.026
Age, behavioural factors[e] (2920)	1	0.77 (0.58, 1.02)	0.76 (0.55, 1.06)	0.76 (0.56, 1.02)	0.91 (0.66, 1.25)	0.08	0.078
Multiply adjusted (2691)	1	0.86 (0.63, 1.16)	0.9 (0.63, 1.29)	0.85 (0.62, 1.29)	1 (0.71, 1.41)	0.756	0.199
Men (analytical sample)							
Adjustments							
Age (2706)	1 (ref)	0.75 (0.49, 1.16)	0.56 (0.33, 0.95)	0.66 (0.43, 1.02)	1.12 (0.74, 1.69)	0.008	0.004
Age, anthropometric measures[b] (2627)	1	0.85 (0.54, 1.34)	0.62 (0.35, 1.09)	0.79 (0.50, 1.25)	1.26 (0.81, 1.96)	0.037	0.011
Age, co-morbidities[c] (2696)	1	0.76 (0.49, 1.18)	0.58 (0.34, 0.98)	0.64 (0.41, 0.99)	1.11 (0.73, 1.68)	0.009	0.003
Age, psychosocial factors[d] (2592)	1	0.85 (0.54, 1.34)	0.61 (0.35, 1.06)	0.75 (0.47, 1.19)	1.3 (0.90, 2.16)	0.015	0.045
Age, behavioural factors[e] (2377)	1	0.68 (0.40, 1.16)	0.57 (0.31, 1.06)	0.71 (0.43, 1.18)	1.32 (0.83, 2.12)	<0.001	0.052
Multiply adjusted (2277)	1	0.84 (0.47, 1.50)	0.63 (0.32, 1.24)	0.84 (0.48, 1.47)	1.54 (0.90, 2.64)	0.006	0.153

Abbreviations: BMI, body mass index; IGF-1, insulin-like growth factor 1. [a]IGF-1 units are nmol l^{-1}. [b]BMI, height. [c]Cancer, diabetes, cardiovascular disease. [d]Own wealth quintile per benefit unit (unit is a couple or single person along with their dependent children), education level. [e]Alcohol consumption, smoking, physical activity.

Table 4. Odds ratio (95% confidence interval) for the longitudinal association between serum IGF-1 in 2008 and new depression symptoms in 2012: the English Longitudinal Study of Ageing

	IGF-1 quintile (range)[a]					*P-value for linearity*	*P-value for quadratic*
	1 (2–11)	*2 (12–14)*	*3 (15–16)*	*4 (17–20)*	*5 (21–65)*		
Women (analytical sample)							
Adjustments							
Age (2343)	1 (ref)	0.88 (0.60, 1.29)	0.77 (0.51, 1.16)	0.84 (0.53, 1.35)	0.95 (0.60, 1.50)	0.647	0.027
Age, anthropometric measures[b] (2276)	1	0.84 (0.57, 1.25)	0.76 (0.50, 1.16)	0.84 (0.52, 1.36)	0.93 (0.58, 1.48)	0.652	0.033
Age, co-morbidities[c] (2342)	1	0.86 (0.58, 1.26)	0.77 (0.51, 1.16)	0.84 (0.53, 1.35)	0.94 (0.60, 1.49)	0.649	0.014
Age, psychosocial factors[d] (2243)	1	0.9 (0.60, 1.34)	0.86 (0.56, 1.30)	0.9 (0.55, 1.45)	1.06 (0.66, 1.69)	0.816	0.026
Age, behavioural factors[e] (2116)	1	0.91 (0.61, 1.35)	0.76 (0.49, 1.17)	0.86 (0.52, 1.40)	0.93 (0.58, 1.51)	0.915	0.029
Multiply adjusted (1969)	1	0.86 (0.56, 1.31)	0.78 (0.50, 1.23)	0.87 (0.52, 1.46)	0.94 (0.56, 1.57)	0.922	0.008
Men (analytical sample)							
Adjustments							
Age (2076)	1 (ref)	0.51 (0.28, 0.91)	0.5 (0.27, 0.92)	0.63 (0.35, 1.15)	0.63 (0.35, 1.13)	0.126	0.002
Age, anthropometric measures[b] (2042)	1	0.51 (0.28, 0.94)	0.5 (0.27, 0.93)	0.66 (0.36, 1.20)	0.63 (0.34, 1.14)	0.142	0.002
Age, co-morbidities[c] (2070)	1	0.52 (0.29, 0.94)	0.56 (0.24, 0.85)	0.64 (0.35, 1.16)	0.65 (0.36, 1.16)	0.098	0.002
Age, psychosocial factors[d] (2031)	1	0.53 (0.29, 0.97)	0.54 (0.29, 0.99)	0.62 (0.33, 1.17)	0.68 (0.37, 1.24)	0.173	0.001
Age, behavioural factors[e] (2076)	1	0.52 (0.27, 0.99)	0.49 (0.25, 0.96)	0.67 (0.35, 1.30)	0.58 (0.30, 1.11)	0.165	0.001
Multiply adjusted (1765)	1	0.51 (0.25, 1.02)	0.5 (0.22, 0.95)	0.67 (0.33, 1.33)	0.6 (0.30, 1.19)	0.072	0.003

Abbreviations: BMI, body mass index; IGF-1, insulin-like growth factor 1. [a]IGF-1 units are nmol l^{-1}. [b]BMI, height. [c]Cancer, diabetes, cardiovascular disease. [d]Own wealth quintile per benefit unit (unit is a couple or single person along with their dependent children), education level. [e]Alcohol consumption, smoking, physical activity.

Strengths and limitations

The main strength of this study is that it has a large, nationally representative sample of people aged 50 years plus in whom there were high rates of follow-up when two standard measures of depression were administered. Our study is not of course without its limitations. The observational nature of our study indicates that we are not able to make any assertions about cause and effect. Although suggestions for mechanisms of action have been posited, it remains possible that IGF-1 levels are a proxy for other factors that are causally related to depression (residual confounding). Although our study was very well characterized, we are not able to control for all possible confounders. Furthermore, although the CES-D8 is a widely used questionnaire in observational studies, it does not provide a diagnosis of depression. Conversely, although self-reported physician-diagnosis of depression does, in principle, do this, many people with depression do not seek medical intervention. The use of anti-depressant medication, which also has some utility in identifying study members with a depression diagnosis, was not gathered in English Longitudinal Study of Ageing. It is also the case, however, that administration of such therapy does not necessarily imply a diagnosis of depression: anti-depressant medication can be used in the treatment of, among other conditions, anxiety and chronic pain disorders. The occurrence of missing data is inevitable in any large-scale study, and about 10% of participants had missing data for one or more of the covariates. However, sensitivity analysis comparing results across the cases with complete information and those with some missing covariates made little difference to outcomes, suggesting that major bias is unlikely. Finally, severe liver and kidney disease may influence IGF-I levels, but we had no such data on these morbidities herein.

In conclusion, taken together, in the present study of older adults, having IGF-1 values at opposite ends of the continuum was associated with a somewhat increased risk of depression symptoms and physician-diagnosis of depression. Further studies are needed to examine whether the observed association is likely to be causal before meaningful discussions about normalizing IGF-1 levels with drugs could be useful in the prevention of depressive symptoms in older people.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

This work was supported by an ESRC-MRC studentship to SC. GDB is a member of The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative. Funding from the Biotechnology and Biological Sciences Research Council and Medical Research Council is acknowledged. MK is supported by the Medical Research Council (MR/K013351), the National Heart, Lung and Blood Institute (HL36310), the National Institute of Aging (AG034454), NordForsk, the Nordic Programme of Health and Welfare and an ESRC professorial fellowship (ES/J023299/1). Andrew Steptoe is a British Heart Foundation Professor of Psychology.

REFERENCES

1 World Health Organization. Depression, Fact sheet No. 369, October 2012. Available at http://www.who.int/mediacentre/factsheets/fs369/en/ [accessed 23 January 2015].
2 World Health Organization. *The Global Burden of Disease: 2004 Update*. World Health Organization: Geneva, Switzerland, 2008.
3 Isometsä E, Henriksson M, Marttunen M, Heikkinen M, Aro H, Kuoppasalmi K *et al.* Mental disorders in young and middle aged men who commit suicide. *BMJ* 1995; **310**: 1366–1367.
4 Bell S, Russ TC, Kivimäki M, Stamatakis E, Batty GD. Dose-response association between psychological distress and risk of completed suicide in the general population. *JAMA Psychiatry* 2015; **11**: 1–3.
5 Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. *JAMA* 2011; **306**: 1241–1249.
6 Daskalopoulou M, George J, Walters K, Osborn DP, Batty GD, Stogiannis D *et al.* Depression as a risk factor for the initial presentation of twelve cardiac, cerebrovascular, and peripheral arterial diseases: data linkage study of 1.9 million women and men. *PLoS One* 2016; **11**: e0153838.
7 Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J* 2006; **27**: 2763–2774.
8 Currier MB, Nemeroff CB. Depression as a risk factor for cancer: from pathophysiological advances to treatment implications. *Annu Rev Med* 2014; **65**: 203–221.
9 Davidson IA, Dewey ME, Copeland JRM. The relationship between mortality and mental disorder: evidence from the Liverpool Longitudinal Study. *Int J Geriatr Psychiatry* 1988; **3**: 95–98.
10 Russ TC, Stamatakis E, Hamer M, Starr JM, Kivimaki M, Batty GD. Association between psychological distress and mortality: individual participant pooled analysis of 10 prospective cohort studies. *BMJ* 2012; **345**: e4933.
11 Schulz R, Beach SR, Ives DG, Martire LM, Ariyo AA, Kop WJ. Association between depression and mortality in older adults: the Cardiovascular Health Study. *Arch Intern Med* 2000; **160**: 1761–1768.
12 Rodda J, Walker Z, Carter J. Depression in older adults. *BMJ* 2011; **343**: d5219.
13 Volkert J, Schulz H, Härter M, Wlodarczyk O, Andreas S. The prevalence of mental disorders in older people in Western countries—a meta-analyiss. *Ageing Res Rev* 2013; **12**: 339–353.
14 Cole MG, Dendukuri N. Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. *Am J Psychiatry* 2003; **160**: 1147–1156.
15 Djernes JK. Prevalence and predictors of depression in populations of elderly: a review. *Acta Psychiatr Scand* 2006; **113**: 372–387.
16 Blumberger DM, Daskalakis ZJ, Mulsant BH. Biomarkers in geriatric psychiatry: searching for the holy grail? *Curr Opin Psychiatry* 2008; **21**: 533–539.
17 Blazer DG, Hybels CF. Origins of depression in later life. *Psychol Med* 2005; **35**: 1241–1252.
18 Kalia M, Costa E Silva J. Biomarkers of psychiatric diseases: current status and future prospects. *Metabolism* 2015; **64** (3, Supplement 1): S11–S15.
19 Le Roith D. Seminars in medicine of the Beth Israel Deaconess Medical Center. Insulin-like growth factors. *N Engl J Med* 1997; **336**: 633–640.
20 Humbel RE. Insulin-like growth factors I and II. *Eur J Biochem* 1990; **190**: 445–462.
21 Junnila RK, List EO, Berryman DE, Murrey JW, Kopchick JJ. The GH/IGF-1 axis in ageing and longevity. *Nat Rev Endocrinol* 2013; **9**: 366–376.
22 Philippou A, Maridaki M, Halapas A, Koutsilieris M. The role of the insulin-like growth factor 1 (IGF-1) in skeletal muscle physiology. *In Vivo* 2007; **21**: 45–54.
23 Wit JM, Walenkamp MJ. Role of insulin-like growth factors in growth, development and feeding. *World Rev Nutr Diet* 2013; **106**: 60–65.
24 Rosen CJ. Insulin-like growth factor I and bone mineral density: experience from animal models and human observational studies. *Best Pract Res Clin Endocrinol Metab* 2004; **18**: 423–435.
25 Chhabra Y, Waters MJ, Brooks AJ. Role of the growth hormone-IGF-1 axis in cancer. *Expert Rev Endocrinol Metab* 2011; **6**: 71–84.
26 Delafontaine P, Song YH, Li Y. Expression, regulation, and function of IGF-1, IGF-1R, and IGF-1 binding proteins in blood vessels. *Arterioscler Thromb Vasc Biol* 2004; **24**: 435–444.
27 Higashi Y, Quevedo HC, Tiwari S, Sukhanov S, Shai SY, Anwar A *et al.* The interaction between IGF-1, atherosclerosis and vascular aging. *Front Horm Res* 2014; **43**: 107–124.
28 Mitschelen M, Yan H, Farley JA, Warrington JP, Han S, Hereñú CB *et al.* Long-term deficiency of circulating and hippocampal insulin-like growth factor I induces depressive behavior in adult mice: a potential model of geriatric depression. *Neuroscience* 2011; **185**: 50–60.
29 Duman CH, Schlesinger L, Terwilliger R, Russell DS, Newton SS, Duman RS. Peripheral insulin-like growth factor-I produces antidepressant-like behavior and contributes to the effect of exercise. *Behav Brain Res* 2009; **198**: 366–371.
30 Hoshaw BA, Malberg JE, Lucki I. Central administration of IGF-I and BDNF leads to long-lasting antidepressant-like effects. *Brain Res* 2005; **1037**: 204–208.
31 Bondy CA, Cheng CM. Signaling by insulin-like growth factor 1 in brain. *Eur J Pharmacol* 2004; **490**: 25–31.
32 Szczesny E, Slusarczyk J, Glombik K, Budziszewska B, Kubera M, Lason W *et al.* Possible contribution of IGF-1 to depressive disorder. *Pharmacol Rep* 2013; **65**: 1622–1631.
33 van Dam PS, Aleman A, de Vries WR, Deijen JB, van der Veen EA, de Haan EHF *et al.* Growth hormone, insulin-like growth factor I and cognitive function in adults. *Growth Horm IGF Res* 2000; **10**(Suppl B): S69–S73.
34 Schneider HJ, Pagotto U, Stalla GK. Central effects of the somatotropic system. *Eur J Endocrinol* 2003; **149**: 377–392.

35 Jacobs BL, van Praag H, Gage FH. Adult brain neurogenesis and psychiatry: a novel theory of depression. *Mol Psychiatry* 2000; **5**: 262–269.
36 Torres Aleman I. Role of insulin-like growth factors in neuronal plasticity and neuroprotection. *Adv Exp Med Biol* 2005; **567**: 243–258.
37 Sievers C, Auer MK, Klotsche J, Athanasoulia AP, Schneider HJ, Nauck M *et al.* IGF-I levels and depressive disorders: results from the Study of Health in Pomerania (SHIP). *Eur Neuropsychopharmacol* 2014; **24**: 890–896.
38 van Varsseveld NC, van Bunderen, Sohl E, Comijs HC, Penninx BWJH, Lips P *et al.* Serum insulin-like growth factor 1 and late-life depression: a population-based study. *Psychoneuroendocrinology* 2015; **54**: 31–40.
39 NatCen Social Research. English Longitudinal Study of Ageing (ELSA): Wave One to Wave Five—User Guide to the datasets. Available from http://www.ifs.org.uk/elsa/user_guides/waves_1_5_datasets_user_guide.pdf [accessed on 16 February 2015].
40 Freeman Laboratories Newcastle (2012). DPC Immulite 2000—IGF-1. (Laboratory summary of methods used up to 02 February 2012, available from laboratory on request).
41 Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1977; **1**: 385.
42 Steffick DE. *Documentation of Affective Functioning Measures in the Health and Retirement Study. HRS*. Survey Research Center University of Michigan: Ann Arbor, MI, USA, 2000.
43 Karim J, Weisz R, Bibi Z, ur Rehman S. Validation of the eight-item Center for Epidemiologic Studies Depression Scale (CES-D) among older adults. *Curr Psychol* 2014; 1–20.
44 Blake H, Mo P, Malik S, Thomas S. How effective are physical activity interventions for alleviating depressive symptoms in older people? A systematic review. *Clin Rehab* 2009; **23**: 873–887.
45 Reinecke MA, Schultz TM. Comparison of self–report and clinician ratings of depression among outpatient adolescents. *Depression* 1995; **3**: 139–145.
46 Turvey CL, Wallace RB, Herzog R. A revised CES-D measure of depressive symptoms and a DSM-based measure of major depressive episodes in the elderly. *Int Psychogeriatr* 1999; **11**: 139–148.
47 UK Data Archive Study Number 5050—English Longitudinal Study of Ageing (2009). English Longitudinal Study of Ageing Wave Four Interview Questionnaire —2008-2009 Draft Version 1.0. Available from http://www.elsa-project.ac.uk/uploads/elsa/docs_w4/questionnaire_main.pdf [accessed on 3 May 2015].
48 Sanchez-Villegas A, Schlatter J, Ortuno F, Lahortiga F, Pla J, Benito S *et al.* Validity of a self-reported diagnosis of depression among participants in a cohort study using the Structured Clinical Interview for DSM-IV (SCID-I). *BMC Psychiatry* 2008; **8**: 43.
49 Banks J, Breeze E, Crawford R, Demakakos P, de Oliveira C, Gjonça E *et al. Financial Circumstances, Health and Well-Being of the Older Population in England: The 2008 English Longitudinal Study of Ageing (wave 4)*. Institute of Fiscal Studies: London, UK, 2010.
50 Goodman-Gruen D, Barrett-Connor E. Epidemiology of insulin-like growth factor-I in elderly men and women: the Rancho Bernardo Study. *Am J Epidemiol* 1997; **145**: 970–976.
51 StataCorp LP. Stata 12 . StataCorp: College Station, TX, USA, 2011.
52 Sievers C, Dimopoulou C, Pfister H, Lieb R, Steffin B, Roemmler J *et al.* Prevalence of mental disorders in acromegaly: a cross-sectional study in 81 acromegalic patients. *Clin Endocrinol (Oxf)* 2009; **71**: 691–701.
53 McGauley GA, Cuneo RC, Salomon F, Sonksen PH. Psychological well-being before and after growth hormone treatment in adults with growth hormone deficiency. *Horm Res* 1990; **33**(Suppl 4): 52–54.
54 Wexler T, Gunnell L, Omer Z, Kuhlthau K, Beauregard C, Graham G *et al.* Hormone deficiency is associated with decreased quality of life in patients with prior acromegaly. *J Clin Endocrinol Metab* 2009; **94**: 2471–2477.
55 Deuschle M, Blum WF, Strasburger CJ, Schweiger U, Weber B, Korner A *et al.* Insulin-like growth factor-I (IGF-I) plasma concentrations are increased in depressed patients. *Psychoneuroendocrinology* 1997; **22**: 493–503.
56 Franz B, Buysse DJ, Cherry CR, Gray NS, Grochocinski VJ, Frank E *et al.* Insulin-like growth factor 1 and growth hormone binding protein in depression: a preliminary communication. *J Psychiatr Res* 1999; **33**: 121–127.

Supplementary Information accompanies the paper on the Translational Psychiatry website (http://www.nature.com/tp)

Appendix 3: Abstract for presentation of IGF-1 – depression findings at the Wellcome Trust Scientific Conference 'Longitudinal Studies: Maximising their value for Ageing Research', August 2015

Insulin-like Growth Factor 1 and risk of later depression in older people: follow-up of participants in the English Longitudinal Study of Ageing

Sungano Chigogora[1], Paola Zaninotto[1], G David Batty[1, 2, 3]

[1]Department of Epidemiology & Public Health, University College London, London, UK
[2]Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK
[3]Alzheimer Scotland Dementia Research Centre, University of Edinburgh, Edinburgh, UK

Depressive disorders are a leading cause of mortality and morbidity in older age. While the role of psychosocial and behavioural predictors has been well-examined, little is known about the biological origins of depression. In the present study, we examined the association of Insulin-like Growth Factor 1 (IGF-1) with both self-reported depression symptoms and physician diagnosis of depression. In 6,017 adults (mean age of 65.66; min=50, max=99 years) from the English Longitudinal Study of Ageing, serum levels of IGF-1 were based on samples taken during a nurse visit in 2008. Depression symptoms were assessed in 2008 and 2012 using the eight item Center for Epidemiological Studies Depression Scale (CES-D).

We show that after a 4 year follow-up period, low levels of IGF-1 were predictive of depression symptoms. Having IGF-1 levels immediately above the lowest fifth was associated with reduced risk of depression symptoms for both men (Odds Ratio (OR) 0.51; CI 0.26, 1.05) and women (OR 0.86; CI 0.56, 1.32). A similar reduction of risk was observed for physician diagnosed depression for women only (OR 0.39; CI 0.17, 0.90). A mild inflection of risk was observed above the 3rd quintile of IGF-1, such that high levels were also associated with increased odds of depression symptoms. The association between IGF-1 and depression symptoms was observed to be U-shaped in some analyses and reverse J-shaped in others, indicating that the lowest risk of having depression symptoms was among those with median IGF-1 levels. Analyses of the cross-sectional data supported the cohort analyses.

Appendix 4: Presentation of IGF-1 – depression findings at the Wellcome Trust Scientific Conference 'Longitudinal Studies: Maximising their value for Ageing Research', August 2015

Insulin-like Growth Factor 1 and risk of later depression in older people: follow-up of participants in the English Longitudinal Study of Ageing

Sungano Chigogora*, Paola Zaninotto, Andrew Steptoe, Mika Kivimaki, G David Batty

Department of Epidemiology and Public Health, University College London, London, UK

Summary

- Depressive disorders are a leading cause of disability in older age
- Findings from animal studies suggest a link between Insulin-Like Growth Factor 1 (IGF-1) and depression
- For the first time using a validated measure of depression symptoms, we tested this association in a large population study of humans
- A total of 6,017 adults (mean age 65.7 years [SD 9.3); range 50-99) from the English Longitudinal Study of Ageing (ELSA) provided serum levels of IGF-1 (mean 15.9 nanomoles per litre (SD 5.7)) during a nurse visit in 2008.
- Depression symptoms were assessed in 2008 and again in 2012. Self-report of physician diagnosed depression was used to test convergence of results
- In cross-sectional and longitudinal analyses, a 'U' -shaped pattern of association was apparent such that lower and higher levels of IGF-1 were associated with an increased risk of depression while the lowest risk was seen around the median levels.

Results

- After 4 years of follow up, we found some evidence that the lowest and highest quintiles of IGF-1 were associated with increased odds of depression symptoms, with a dipping of effect being observed towards the median levels of IGF-1
- As such, we observed a 'U' -shaped pattern to the association between IGF-1 and depression symptoms
- Similar results were observed for physician-diagnosed depression, except after 4 years of follow-up among men, where no association was observed
- The 'U' –shaped pattern of association was also observed in cross-sectional results for both depression symptoms and physician-diagnosed depression
- Adjustment according to covariate groups had little impact on this pattern of association, although taking into account all covariates led to some flattening of the IGF-1-depression relationship

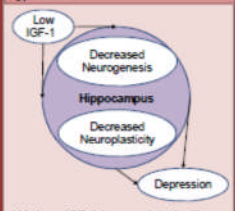
Background

- Depression is the leading cause of disability worldwide[1]
- Depressive disorders are a leading cause of morbidity in older age
- While the role of psychosocial and behavioural predictors has been well-examined, little is known about the biological origins of depression
- Insulin-like Growth Factor 1 (IGF-1) is a peptide hormone responsible for growth and development, whose circulating levels reduce with increasing age
- Evidence from rodent studies has shown that the dysregulation of IGF-1 results in marked changes in mood. Particularly, that low levels of IGF-1 are linked with higher depression symptoms. [2,3,4]
- Examination of the link between IGF-1 and depression in the general population is scarce

Aims

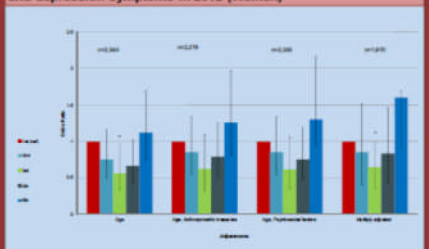
- To investigate the association between IGF-1 and depression symptoms in older people

Conceptual Framework and hypothesis



H1: Low IGF-1 is associated with higher depression symptoms in older people

Fig 1: Longitudinal association between quintiles of IGF-1 in 2008 and depression symptoms in 2012 (Women)



Methods

Study population:

- 6,017 participants (3,311 women) from ELSA, mean age 66 years
- ELSA is an ongoing prospective cohort study of adults aged 50 years and over who live in private households in England
- Initiated in 2002 - original sample recruited from people who had participated in the Health Survey for England (HSE) in one of the years from 1998 to 2001
- Subjective data on financial circumstances, health, well-being, behaviours, activities, biological markers and social networks collected

Exposure: IGF-1

Tested from serum samples and reported as whole number ranging from 3 to 200 nanomoles per litre (nmols/l)

Categorised in quintiles for these analyses, 1st quintile used as referent

Main outcome: Depression symptoms

- Assessed using an eight-item version of the Center for Epidemiologic Studies Depression Scale (CES-D)
- Cross-sectional and longitudinal analyses carried out, with longitudinal outcome being incident depression symptoms after 4 years of follow-up

Secondary outcome: Physician diagnosed depression

- Participants asked if they had been told by a doctor that they had depression
- Longitudinal outcome is incident depression after 4 years

Multivariable logistic regression was used to examine the association between IGF-1 and depression, adjusting for known confounders

Fig 2: Longitudinal association between quintiles of IGF-1 in 2008 and depression symptoms in 2012 (Men)

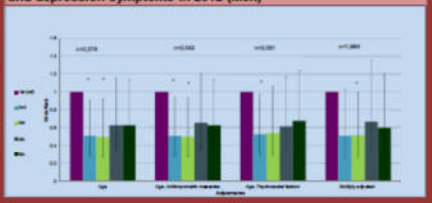
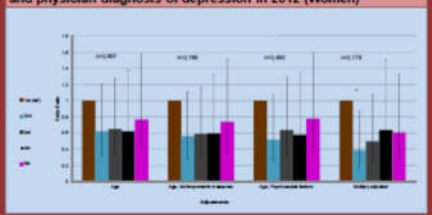


Fig 3: Longitudinal association between quintiles of IGF-1 in 2008 and physician diagnosis of depression in 2012 (Women)



Conclusions

- The main finding of this study was that, in older people, having IGF-1 levels in the lowest and highest quintiles was associated with higher risk of depression symptoms, which decreased towards the median levels of IGF-1, such that a 'U'-shaped relationship was observed on occasion.
- These results were generally consistent with those observed for the association between IGF-1 and physician-diagnosis of depression.
- Further studies are needed to examine if the observed association is likely to be causal and whether normalizing IGF-1 levels with drugs could be useful and safe in treating of depressive symptoms in older people.

References

1. World Health Organization (2012). Depression. Fact sheet No. 369. October 2012. http://www.who.int/mediacentre/factsheets/fs369/en/
2. Mitschelen M, et al. Long-term deficiency of circulating and hippocampal insulin-like growth factor I induces depressive behavior in adult mice: a potential model of geriatric depression. *Neuroscience 2011;* **185**(0): 50-60.
3. Duman CH, Schlesinger L, Terwilliger R, Russell DS, Newton SS, Duman RS. Peripheral insulin-like growth factor-I produces antidepressant-like behavior and contributes to the effect of exercise. *Behav Brain Res* **2009**; **198**(2): 366-371
4. Hoshaw BA, Malberg JE,Lucki I. Central administration of IGF-I and BDNF leads to long-lasting antidepressant-like effects. *Brain Res 2005;* **1037**(1-2): 204-208.

Image source: Vincent van Gogh, 1890. *Sorrowing Old Man ('At Eternity's Gate') At: imgur.com/gallery/7IbqzFh*

Correspondence to: s.chigogora.11@ucl.ac.uk

Funder: This work was supported by the a joint fund from the Medical Research Council (MRC) and the Economic and Social Research Council [grant number ES/J500185/1

Appendix 5: Presentation of findings of the relationship between Internet use future depression, ELSA Wave 7 Launch conference, 2016.

Internet use and risk of depression in older people: longitudinal and cross-sectional evidence from the English Longitudinal Study of Ageing

Sungano Chigogora, Paola Zaninotto, G David Batty
Department of Epidemiology and Public Health, University College London, London, UK

UCL

The Internet paradox: A social technology that reduces social involvement and increases risk of depression???

- Depression is the leading cause of disability worldwide (WHO, 2012)
- Depressive disorders are a leading cause of morbidity in older age
- Older people are spending more and more time on the Internet
- Evidence suggests that time spent on the Internet may lead to a reduction of time spent being active and socialising, leading to increased risk of depression
- Furthermore, social ties and relationships that are made or maintained on the internet are believed to be weaker than real life social ties
- High levels of Internet use have previously have been found to be associated with psychological distress (Kraut et al, 1998)

What is the role of the Internet in the development of depression symptoms in older people

- In 6,532 participants (3,710 women) from the English Longitudinal Study of Ageing who were free from depression at baseline, Internet use was measured as 'Yes' or 'No' in 2002 (Wave 1) and every other year until 2012 (Wave 6)
- 7,524 who took part in wave 6 also reported the frequency with which they accessed the Internet (infrequently, weekly, daily), and the activities they engaged in when they did so
- Subjective and objective covariate data on SES (wealth, education, cohabitation status), physical health and loneliness were also collected
- Depression symptoms were assessed using an eight-item version of the Center for Epidemiologic Studies Depression Scale
- Generalized Estimating Equations with an exchangeable correlation matrix were used to examine the association between Internet use and depression, adjusting above covariates, using all data from wave 1 to wave 6
- Cross sectional multivariable logistic regression analyses were used to examine the association between Internet use and depression symptoms at wave 6, also adjusting for above covariates

Internet use: A means of communication that reduces the risk of depression

- Compared with Internet users, participants that reported not using the Internet were 1.7 times (CI 1.6, 2.0) more likely to develop depression symptoms over the 10-year follow-up period of ELSA
- After accounting for all covariates, the odds of developing depression symptoms reduced to 1.3 (CI, 1.2, 1.5).
- The largest attenuation of effect was observed when loneliness was taken into account. Wealth and education also accounted for some of the effect of Internet use on depression
- **Relative to NO Internet use**:
  - Using the Internet daily was associated with the lowest odds of reporting depression symptoms (age and sex adjusted OR 0.35, CI 0.29, 0.58)
  - The odds of reporting depression symptoms reduced with each increase in frequency of use
  - Engaging in the median number of online activities (four to six) was associated with the lowest risk of reporting depression symptoms (OR 0.37, CI 0.31, 0.45). Low and high numbers of activities indicated marginal benefit; thus, a U shaped relationship was observed
- Significantly lower risk of reporting depression symptoms was observed when participants reported using the Internet for **communication via email** (age adjusted OR 0.33, CI 0.27, 0.39), and **social networking** (OR 0.65, CI 0.50, 0.84)

Conclusion:
- Among ELSA participants, using the Internet was associated with reduced risk of developing depression symptoms
- Cross sectional analyses showed that relative to non-users, participants who were least likely to report depression symptoms were those who used the Internet daily, for a moderate number of activities, and specifically for communication via email and social networking

Image source:
1. http://gawker.com/how-the-internet-causes-depression-1724491043
2. http://uk.complex.com/pop-culture/2013/10/why-do-old-people-hate-the-internet
3. http://www.fanpop.com/clubs/depression/images/34369241/title/internet-photo

Correspondence to: s.chigogora.11@ucl.ac.uk
Funder: This work was supported by the a joint fund from the Medical Research Council (MRC) and the Economic and Social Research Council [grant number ES/J500185/1]

Appendix 6: Framingham model score allocation by risk factor and gender

Risk Factor	Sub-category	Points allocated if Female	Points allocated if Male
Age (years)	50–54	6	6
	55–59	8	8
	60–64	10	10
	65–69	12	11
	70–74	14	12
	75–79	16	13
Total Cholesterol (Age 50 – 59 years)	Less than 4.138mmol/l	0	0
	4.137 – 5.171mmol/l	2	2
	5.172 – 6.205mmol/l	4	3
	6.2064 – 7.2407mmol/l	5	4
	7.2408mmol/l and higher	7	5
(Age 60 – 69 years)	Less than 4.138mmol/l	0	0
	4.137 – 5.171mmol/l	1	1
	5.172 – 6.205mmol/l	2	1
	6.2064 – 7.2407mmol/l	3	2
	7.2408mmol/l and higher	4	3
(Age 50 – 59 years)	Less than 4.138mmol/l	0	0
	4.137 – 5.171mmol/l	1	0
	5.172 – 6.205mmol/l	1	0
	6.2064 – 7.2407mmol/l	2	1
	7.2408mmol/l and higher	2	1
Smoking: Non smoker		0	0
Smoking: Smoker	Aged 50 59 years	4	3
	Aged 60–69 years	2	1
	Aged 70–79 years	1	1
HDL cholesterol	1.552mmols/l or higher	-1	-1
	1.293 – 1.551mmols/l	0	0
	1.034 – 1.292mmols/l	1	1
	Less than 1.292mmols/l	2	2
Systolic Blood Pressure: Untreated	Under 120mmHg	0	0
	120 – 129mmHg	1	0
	130 – 139mmHg	2	1
	140 – 159mmHg	3	1
	160 or higher	4	2
Systolic Blood Pressure: Treated	Under 120mmHg	0	0
	120 – 129mmHg	3	1
	130 – 139mmHg	4	2
	140 – 159mmHg	5	2
	160 or higher	6	3
Highest possible score		35	26

Appendix 7: Allocation of 10-year percentage risk of fatal and non-fatal CVD according to Framingham scores

Percentage risk	Matching points for Females	Matching points for male
<1	<9	0
1%	9-12	1-4
2	13-14	5-6
3	15	7
4	16	8
5	17	9
6	18	10
8	19	11
10	-	12
11	20	
		13
14	21	
		14
17	22	
		15
22	23	
		16
27	24	
30+	25+	17+

Appendix 8: Image of QRISK2 Online Calculator

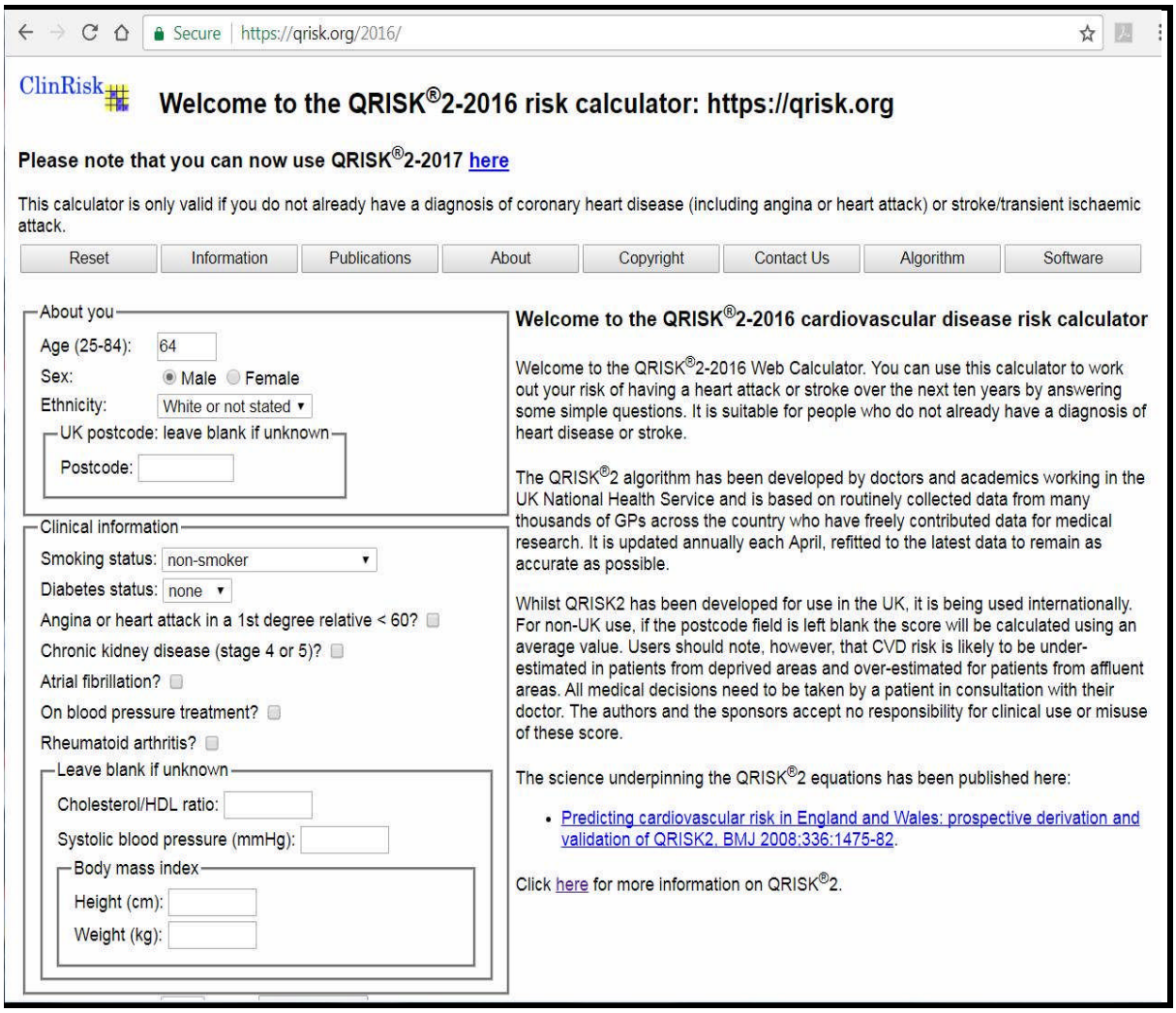


Image source: https://qrisk.org/2016/ (accessed on 25 July 2017)

Appendix 9: SCORE – European low risk chart: 10-year risk of fatal CVD in low risk regions of Europe by gender, age, systolic blood pressure total cholesterol and smoking status

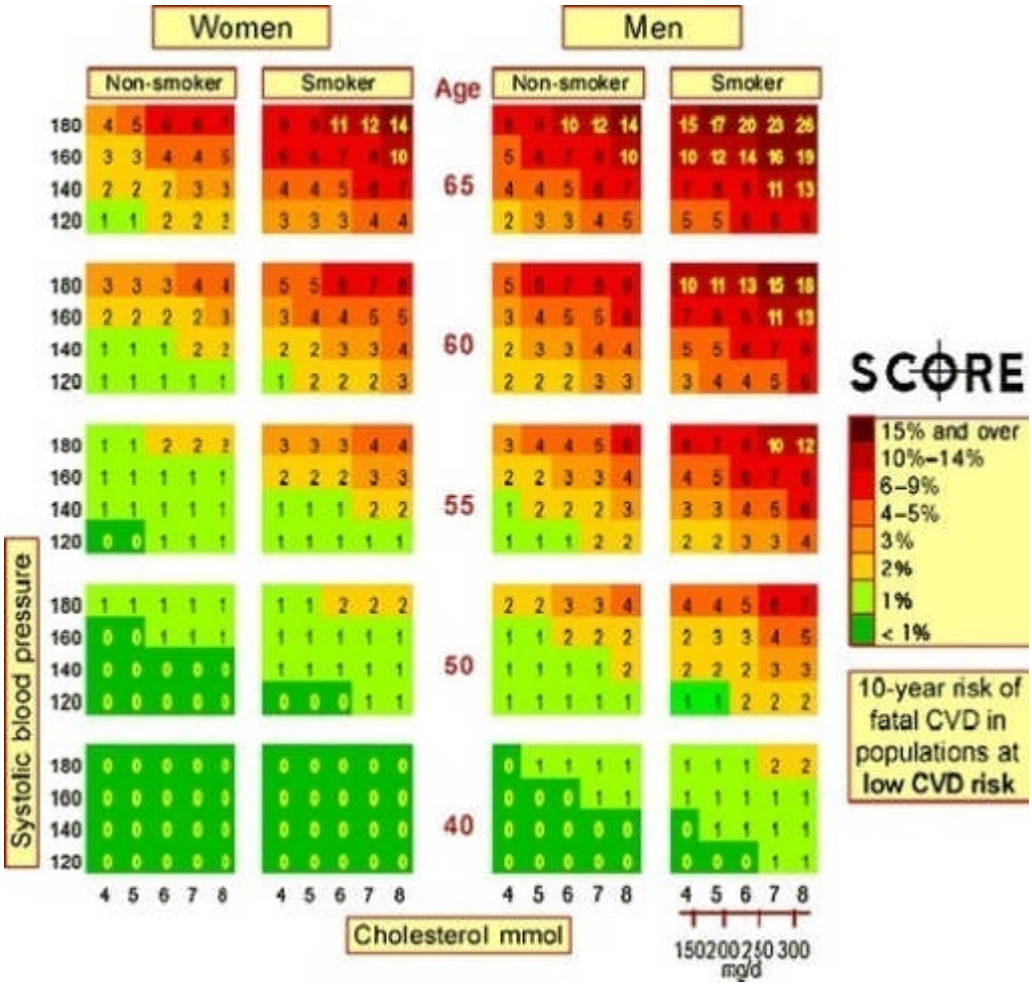


Image source:

https://openi.nlm.nih.gov/imgs/512/73/3405365/PMC3405365_13167_2011_66_Fig3_HTML.png