The Impact of Level of Education on Vascular Events and Mortality in Patients with Type 2 Diabetes Mellitus: Results from the ADVANCE Study

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ABSTRACT

Aims: The relationship between educational level and the risk of all-cause mortality is well established, whereas the association with vascular events in individuals with type 2 diabetes is not well described. Any association may reflect a link with common cardiovascular or lifestyle-based risk factors.

Methods: The relationships between the highest level of educational attainment and major cardiovascular events, microvascular complications and all-cause mortality were explored in a cohort of 11,140 individuals with type 2 diabetes. Completion of formal education before the age of 16 was categorized as a low level of education. Regional differences between Asia, East Europe and Established Market Economies were also assessed.

Results: During a median of 5 years of follow up, 1,031 (9%) patients died, 1,147 (10%) experienced a major cardiovascular event and 1,136 (10%) a microvascular event. After adjustment for baseline characteristics and risk factors, individuals with lower education had an increased risk of cardiovascular events (hazard ratio (HR) 1.31, 95% CI 0.1.16–1.48, $p<0.0001$), microvascular events (HR 1.23, 95% CI 1.09–1.39, $p=0.0013$) and all-cause mortality (HR 1.34, 95% CI 1.18–1.51, $p<0.0001$). In regional analyses the increased risk of studied outcomes associated with lower education was weakest in Established Market Economies and strongest in East Europe.

Conclusions: A low level of education is associated with an increased risk of vascular events and death in patients with type 2 diabetes, independently of common lifestyle associated cardiovascular risk factors. The effect size varies between geographical regions.

Key words: type 2 diabetes, level of education, cardiovascular events, microvascular events

1. Introduction

Lower levels of educational attainment are associated with a higher incidence of type 2 diabetes mellitus, especially in high income countries [1, 2]. Although the prevalence of type 2 diabetes in the US is rising among those of all educational backgrounds, this increase is greatest in those who fail to graduate from high school [3]. This is presumed to be due to a less healthy lifestyle, in particular a higher prevalence of obesity and physical inactivity. In the general population, lower levels of education are also associated with an increased mortality and a greater risk of cardiovascular events [4]. The relationship between educational level and outcome in a large cohort of patients with type 2 diabetes, and the nature of any such association, has not been well described, although some evidence point out a possible association [5].

In general populations education is one of the most widely used markers of socioeconomic status and is inversely related to cardiovascular disease, cancer and death [6]. However, the mechanisms whereby a lower educational level is associated with an increased risk of cardiovascular death is not entirely clear. Several common cardiovascular risk factors tend to follow a socioeconomic gradient, risk factors being more prevalent [7] and unhealthy behaviour more common [8] with increasing social deprivation [9]. For all-cause mortality, alcohol-related deaths seem to cover the majority of the increased mortality in lower socioeconomic groups [10]. Additionally, geographical differences have been observed such that a lower educational attainment in Asia has been associated with a higher excess risk of cardiovascular disease and premature mortality than in the Western populations of Australasia [11].

The association between educational level and mortality has been well described whereas associations with major cardiovascular events and especially microvascular complications are poorly recognized in type 2 diabetes populations. The aims of this study are to assess whether, in individuals with type 2 diabetes, educational level is associated with vascular outcomes and mortality, whether the association varies with geographical region, and how much common cardiovascular risk markers and lifestyle factors explain the associations.

2. Materials and methods

The Action in Diabetes and Vascular Disease: Preterax and Diamicron modified release Controlled Evaluation (ADVANCE) study (ClinicalTrials.gov number NCT00145925) was a factorial, randomized, controlled trial conducted in 20 countries which recruited 11,140 patients with type 2 diabetes [12]. Participants were eligible for the study if they were ≥55 years old, had been diagnosed with type 2 diabetes after the age of 30 years and had a minimum of one major macro or micro-vascular diabetic complication or at least one additional cardiovascular risk factor. The study made two randomized comparisons: a double-blind assessment of the efficacy of a fixed combination perindopril-indapamide (2mg/0.625mg for 3 months increasing, if tolerated, to 4mg/1.25mg) versus placebo, and an open-label evaluation of an intensive glucose lowering regimen using modified release gliclazide, with a target HbA1c of ≤6.5% (48 mmol/mol), versus standard guideline based glycemic control. The study outcomes included all-cause mortality, major cardiovascular events (defined as death from cardiovascular disease, non-fatal stroke or non-fatal myocardial infarction) and microvascular events (defined as new or worsening renal disease or diabetic eye disease). All participants of the study provided written informed consent and approval was obtained from the local ethics committee in all participating centers. Detailed study eligibility criteria and study methods [12] as well as the main results [13, 14], have been previously reported.

The age of participants at the completion of their highest level of education was self-reported at baseline. Due to differences of schooling systems between the participant countries, education was included in the analyses as a dichotomized variable. Patients, who had completed their education before the age of 16, were considered to have a low level of education. Studied lifestyle variables included current smoking, physical activity by the number of sessions of activity of ≥15 minutes duration per week [15] and alcohol use (any regular alcohol consumption versus no alcohol consumption) [16]. Lipid lowering medication included any medication indicated for dyslipidemia. All medications for hypertension were recorded and beta-blockers were enquired separately.

The effects of education level on outcomes in participants from different regions of the world were also examined using the following, pre-set geographic and economic partition: Asia (China, India, Malaysia, and the Philippines), eastern Europe (Czech Republic, Estonia, Hungary, Lithuania, Poland, Russia, and Slovakia), and established market economies (Australia, Canada, France, Germany, Ireland, Italy, The Netherlands, New Zealand, and the United Kingdom) [17].

2.1 Statistical analyses

The associations between educational attainment and the study outcomes were explored first in Spearman correlation coefficients and thereafter in Cox proportional hazard models to assess the relationship in more detail. The first model fitted included non-modifiable variables such as age, sex, ADVANCE study glycemic control arm, ADVANCE study blood pressure treatment arm and duration of diabetes and prior cardiovascular disease. Into the second model we added the modifiable risk factors of body-mass index, HbA1c, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, creatinine clearance, systolic blood pressure, heart rate, blood pressure medication, lipid lowering medication and use of acetyl salicylic acid or thienopyridines. The final model assessed the impact of lifestyle factors and included all previous variables added with lifestyle factors of physical activity, smoking and alcohol use. To detect regional differences the final models for each outcome were tested in 3 geographic and economic partitions and tested for heterogeneity by fitting a model including regional interaction terms. SAS version 9.3 (SAS Institute Inc, Cary, North Carolina) was used for all analyses.

3. Results

The age at completion of the highest level of education was available from all 11,140 participants (table 1). The mean age at completion of the highest level of education was 18.4 years and the median age was 17.0 years. Four thousand and twenty-four (36%) individuals had completed their highest level of education before the age of 16 years and formed the low education group. Individuals with lower educational attainment had lower levels of cholesterols, smoked less but had higher body mass index, systolic blood pressure and HbA1c, whereas no differences were observed in history of cardiovascular disease or in the duration of diabetes. Among cardiovascular medications, only lipid lowering medication differed between the groups and was higher in the group with lower educational attainment (Table 1).

During a median of 5 years of follow up 1,147 (10%) participants experienced a major cardiovascular event, 1,136 (10%) experienced a microvascular complication and 1,031 (9%) patients died.

3.1 Educational level and associations with outcomes

In the first multivariable Cox proportional hazard analyses, with adjustment for the non-modifiable variables, low education was associated with increased risk of major cardiovascular (hazard ratio (HR) 1.35, 95% CI 1.20-1.52, $p<0.0001$) and microvascular outcomes (HR 1.26, 95 % CI 1.12-1.42, $p=0.0002$) and all-cause mortality (HR 1.38, 95% CI 1.22-1.56, $p<0.0001$). In the second model with included modifiable risk markers apart from lifestyle variables, the corresponding numbers indicated similar risk for major cardiovascular (HR 1.31, 95% CI 1.16-1.48, $p<0.0001$), for microvascular outcomes (HR 1.23, 95 % CI 1.08-1.39, $p=0.0013$) and all-cause mortality (HR 1.34, 95% CI 1.18-1.53, $p<0.0001$). Finally, comparable levels of associations were observed in the fully adjusted model included with lifestyle variables of smoking, physical activity and alcohol use (Figure 1).

3.2 Geographic variation and analyses of heterogeneity

The effects of educational attainment on outcomes varied across geographic and economic partition where associations between low levels of education and cardiovascular outcomes and all-cause mortality were strongest in East Europe and weakest in EMEs (Figure 2). All outcomes in the 3 different regions were tested for heterogeneity between educational level and region. For major cardiovascular events heterogeneity was found in EME ($p=0.025$) and in East Europe ($p=0.0035$) but not for Asia ($p=0.97$). For microvascular complications no heterogeneity was observed but instead for all-cause mortality heterogeneity was found in EME ($p=0.013$) and in East Europe ($p=0.043$) but not for Asia ($p=0.39$).

4. Discussion

The current study demonstrates that, among individuals with type 2 diabetes from an internationally representative trial, lower formal educational attainment is associated with a higher incidence of cardiovascular events and mortality. In addition, lower educational attainment is also associated with an increased risk of microvascular complications: a relationship that has been presumed but lacking robust confirmation.

The associations between lower educational attainment and worse outcomes were consistent despite adjustment for a variety of non-modifiable as well as modifiable cardiovascular risk factors and lifestyle factors, suggesting that any effects of educational status are largely independent of these influences. However, the extent of the observed risks appears to vary between geographic and economic regions such that the associations between educational attainment and outcome were less evident in EME and most apparent in East European countries.

4.1 Education, cardiovascular and microvascular events and mortality

The relationships between educational level and premature mortality and cardiovascular disease are well described in the general population, where individuals with a lower educational level are at increased risk of premature death [18] and cardiovascular disease is the major contributor to life-years lost [19]. Indeed, cardiovascular disease is reported to account for 35% of the life-years lost before the age of 75 in persons who failed to complete high-school, whereas diabetes accounted for approximately 4% [19]. Nevertheless, there is a paucity of data relating to type 2 diabetes and to our knowledge, no prior studies have reported the association between educational level and major cardiovascular and microvascular outcomes specifically in a large patient cohort with type 2 diabetes.

Data on all-cause mortality based on follow up of over 2 million participants in the American Cancer Society cohorts from 1959–1972 and 1982–1996 confirmed a relationship between a lower level of educational attainment and increased death rates among those with diabetes, based on death certificate records [20]. The association between low educational level and the microvascular complications of type 2 diabetes is a novel finding. This is in keeping with other data from this cohort which demonstrate an association between microvascular complications and lifestyle factors, such as physical inactivity and moderate alcohol consumption [15, 16]. It seems likely that these associations are mediated through similar complex mechanisms to those that determine the relationship between educational level and major cardiovascular events and mortality.

4.2 Regional differences

In spite of widespread improvements in the treatment of cardiovascular disease and related risk factors such as diabetes, the incidence of cardiovascular complications differs significantly between geographical regions [21]. In addition, there are clear geographical differences in the prevalence of microvascular complications, even in newly diagnosed patients with diabetes. For example, the prevalence of retinopathy in newly diagnosed diabetes ranges from 1.5 % to 31% between different countries [22]. Potential explanations may include variation in the level of treatment [23] but it seems likely that the time between the onset of diabetes and diagnosis is also a factor.

Although participation in the ADVANCE trial may partially mitigate any treatment related differences it is still likely that there will have been, pre-existing, geographical variations in the access to diagnostic services and medical care, especially to medications [23], and that these may play a role in reducing the impact of educational factors in higher income countries.

4.3 Potential mechanisms

The current results suggest that the mechanisms for the observed higher risk associated with lower educational level are not clearly mediated by current lifestyle or other cardiovascular risk factors. Nevertheless, there are reports associating lower levels of education with higher rates of smoking, higher body mass index, lower levels of physical activity and increased alcohol consumption [24]. Moreover, these may be accompanied with other, often inter-related, factors that may be important determinants of health outcomes; including lower income levels, poorer living conditions in childhood, consumption of a less healthy diet, higher prevalence of cardiovascular risk factors and psychosocial stressors [4]. A unifying determinant of all of these is socioeconomic status which is closely linked to educational attainment [6] and is associated with the prevalence of diabetes [25].

Socioeconomic status may act independently of, or in combination, with lifestyle risk factors in influencing trajectories of health during life time [26, 27]. Three models have been proposed to explain how socioeconomic position may influence health. The *latent effects model* [28, 29] suggests low childhood socioeconomic position may provoke biological and behavioural changes that place individuals at higher risk, irrespective of their risk burden in adulthood, whereas in the *pathway model* [30] childhood conditions may trigger social circumstances and health behaviour affecting the risk trajectory. The third model, *cumulative burden model,* suggests the risk in adulthood is attributable to psychosocial, physiological and environmental factors not only in childhood but throughout life [30]. Based on our findings, the cumulative burden model would be the most likely of these to explain the disparity in risks, although it is presumably a mixture of all three.

4.4 Strengths and limitations

The current study is, as far as we are aware, the first to explore the relationship between educational level and outcomes in a large cohort of type 2 diabetes. Nonetheless, it has limitations. The age at the completion of highest level of education was recorded, but this is a crude indicator of educational attainment and we have no details regarding the schooling systems, which vary between the countries represented, or the receipt of informal education and training. The level of education is likely to influence the average income and social class of patients and this in turn may affect many other factors, including their access to healthcare. This is a potential confounding factor that we cannot assess. Similarly we can’t exclude the possibility that our adjustments don’t control the effects of the assessed lifestyle factors on the various risks, albeit done in best available detail, which could explain the observation at least in part. Finally, we acknowledge that the ADVANCE trial participants represent educational attainment gained mainly from 1950’s to 1970’s, with several socio-economic factors influencing on it, as well as the educational system itself have changed considerably since then. Therefore we can’t exclude a secular effect on the discovered associations.

5. Conclusions

This study shows that a higher level of education is associated with a reduced risk of major cardiovascular and microvascular complications and lower risk of all-cause mortality in patients with type 2 diabetes. These differences do not appear to be explained solely by lifestyle factors such as the level of physical activity, smoking and alcohol consumption. The effects of educational level on cardiovascular risk and mortality appear to be less important in high income countries.

Conflict of Interest

J.C. has received research grants from Servier, administered through the University of Sydney. J.C, A.P, B.N, MW and S.Z. have received honoraria from Servier for speaking at scientific meetings. B.N. holds a Senior Research Fellowship from the National Health and Medical Research Council of Australia. M.W. holds a Principal Research Fellowship from that Council. J.I.B. is employed by AstraZeneca R&D. No other potential conflicts of interest to this article were reported.

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Author contributions

J.I.B, G.S.H. S.Z. and M.W. designed this sub study, undertook the statistical analyses, and wrote the initial drafts of the paper. J.C, N.P, B.W, S.H, M.M. and B.N. collected the data. All authors revised and approved the paper for scientific content.

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Table 1. Patient characteristics in general and by education groups

	Total	**Low education**	**Higher education**	**p**
No of individuals	**11,140**	**4,024**	**7,116**	
Age (years)	65.8 (6.4)	67.1 (6.3)	65.0 (6.3)	<0.0001
Female (%)	4.733(42.4)	2748 (49.3)	1985 (38.6)	<0.0001
Body mass index (kg/m2)	28.3 (5.2)	28.9 (5.4)	28.0 (5.0)	<0.0001
Current smoking (%)	1,550 (13.9)	491(12.2)	1,059(14.9)	<0.0001
Never smoked (%)	6,466 (58.0)	2,219 (55.1)	4,247 (59.7)	<0.0001
Alcohol use (%)	3,389 (30.4)	1,125 (30.2)	2,174 (30.6)	<0.0001
History of cardiovascular disease (%)	3,590 (32.2)	1,270 (31.6)	2,320 (32.6)	0.26
History of microvascular disease (%)	1,155 (10.4)	475 (11.8)	680 (9.6)	0.0002
History of stroke (%)	1,023 (9.2)	358 (8.9)	665 (9.3)	0.43
Age at completion of highest level of education (years)	18.4 (7.3)	12.9 (3.6)	21.5 (7.0)	<0.0001
Systolic blood pressure (mmHg)	145.0 (21.5)	146.4 (21.8)	144.2 (21.3)	<0.0001
Diastolic blood pressure (mmHg)	80.6 (10.9)	80.0 (10.9)	81.0 (11.0)	<0.0001
Heart rate (beats/minute)	74 (12)	74 (12)	74 (12)	0.20
Total cholesterol (mmol/l)	5.20 (1.19)	5.13 (1.17)	5.23 (1.20)	<0.0001
HDL-cholesterol (mmol/l)	1.26 (0.35)	1.25 (0.36)	1.26 (0.35)	0.033
LDL-cholesterol (mmol/l)	3.11 (1.03)	3.06 (1.03)	3.14 (1.03)	<0.0001
Triglycerides (mmol/l)	1.95 (1.29)	1.95 (1.24)	1.96 (1.31)	0.40
HbA1c (%)	7.51 (1.57)	7.60 (1.58)	7.47 (1.54)	<0.0001
Physical activity (times/week, 15 min. minimum/time)	8.8 (10.8)	8.0 (8.9)	9.3 (11.7)	<0.0001
Creatinine clearance (ml/min)	82.3 (28.6)	79.9(29.7)	83.6(27.8)	<0.0001
ACE/ARB medication (%)	5,311 (47.7)	1,963 (48.8)	3,348 (47.0)	0.079
Beta blocker (%)	2,729 (24.5)	930 (23.1)	1,799 (25.3)	0.011
Any blood pressure medications (%)	8,365 (75.1)	3,043 (75.6)	5,322 (74.8)	0.33
Lipid lowering medication (%)	3,934 (35.3)	1,519 (37.7)	2,415 (33.9)	<0.0001
Aspirin or thienopyridines (%)	5.199 (46.7)	1,868 (46.2)	3,331 (46.8)	0.69
Duration of diabetes (years)	7.9 (6.4)	8.0 (6.5)	7.9 (6.3)	0.63

Results shown as number (%) or mean (standard deviation). Completion of formal education before the age of 16 was categorized as a low level of education.

Figure legends

Figure 1. Hazard ratios for low education and outcomes.

Footnote: Adjusted for age, sex, body mass index, glucose and blood pressure treatment arms, systolic blood pressure, heart rate, HbA1c, creatinine clearance, duration of diabetes, HDL-cholesterol, LDL-cholesterol, triglycerides, lipid lowering medication, blood pressure medication, antithrombotic medication, history of cardiovascular disease, alcohol use, smoking, exercise and education.

Figure 2. Education and outcomes by geographic and economic regions.

Footnote: Asia = China, India, Malaysia, and the Philippines; Eastern Europe = The Czech Republic, Estonia, Hungary, Lithuania, Poland, Russia, and Slovakia; Established Market Economies = Australia, Canada, France, Germany, Ireland, Italy, The Netherlands, New Zealand, and the United Kingdom

Adjustments as in figure 1.