


## RESEARCH: EPIDEMIOLOGY

# Type 1 diabetes, cognitive ability and incidence of cardiovascular disease and death over 60 years of follow-up time in men

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## Abstract

**Aims:** There are few cohorts of type 1 diabetes that follow individuals over more than half a century in terms of health outcomes. The aim of this study was to examine associations between type 1 diabetes, diagnosed before age 18, and long-term morbidity and mortality, and to investigate whether cognitive ability plays a role in long-term morbidity and mortality risk.

**Methods:** In a Swedish cohort, 120 men with type 1 diabetes and 469 without type 1 diabetes were followed between 18 and 77 years of age as regards morbidity and mortality outcomes, and impact of cognitive ability at military conscription for the outcomes. In Cox regression analyses and Kaplan-Meier analyses with log-rank tests, associations between diabetes and cognitive ability respectively, and outcomes (mortality, cardiovascular morbidity and diabetes complications) were investigated.

**Results:** Men with type 1 diabetes suffered from dramatically higher mortality (HR 4.62, 95% CI: 3.56–5.60), cardiovascular mortality (HR 5.60, 95% CI: 3.27–9.57), and cardiovascular events (HR 3.97, 95% CI: 2.79–5.64) compared to men without diabetes. Higher cognitive ability at military conscription was associated with lower mortality in men without diabetes, but was not associated with any outcome in men with diabetes.

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**Conclusions:** In this historical cohort study with 60 years of follow-up time and a less effective treatment of diabetes than today, mortality rates and cardiovascular outcomes were high for men with type 1 diabetes. Morbidity or mortality did not differ between those that had low to normal or high cognitive ability among men with type 1 diabetes.

**KEYWORDS**

cardiovascular events, cognition, diabetes mellitus type 1, epidemiology, mortality, prognosis

## 1 | INTRODUCTION

Despite prognostic improvements during the past century, type 1 diabetes is still associated with premature mortality and risk of cardiovascular disease.<sup>1,2</sup> To identify risk factors of poor prognosis, it is of value to follow cohorts over long periods of time. Few studies have however had a follow-up period of more than 50 years, and studies with a long follow-up period have so far focused on certain patient groups of long-term survivors, such as the Golden years Cohort<sup>3</sup> from the U.K. and the Medalist Study<sup>4</sup> from the U.S.

Furthermore, there is little data on prognostic outcomes such as mortality and cardiovascular morbidity from before the 1970s worldwide. In one of the earliest reliable studies covering the period 1897–1961 in Massachusetts, U.S., the greatest prognostic improvement was seen during 1922–1940.<sup>5</sup> In Europe, a study from the U.K. showed that mortality rates decreased on average by 32% per decade between 1940 and 1991.<sup>6</sup> In Scandinavia, a Danish study showed that mortality increased during 1933–1965, after which it decreased.<sup>7</sup> A Finish study from 1965 to 1994 showed low mortality rates compared to a Japanese population during the same time period.<sup>8</sup> Apart from these studies there is little data from the corresponding time periods in Europe and Scandinavia respectively. In Sweden, there are few studies dating before 1996 when the National Diabetes Registry (NDR)<sup>9</sup> was established, but two older studies include one from Linköping (1961–2000<sup>10</sup>), and one on nationwide hospital mortality 1965–1983.<sup>11</sup> As the incidence rate of type 1 diabetes in Sweden is the second highest in the world,<sup>12</sup> more data on disease prognosis during the past decades would be of value.

One factor that is less well studied in type 1 diabetes, but that could potentially affect health outcomes later in life, is cognitive ability early in life.<sup>13,14</sup> Studies on the general population have shown that higher intelligence can protect against mortality<sup>15,16</sup> and coronary heart disease,<sup>17,18</sup> independently of socio-economic status. Childhood cognition has also been linked to glycaemic status later in life.<sup>19,20</sup> As it has been shown that type 1 diabetes can

### What's new

- There is little data from Scandinavia on the long-term prognosis of type 1 diabetes before 1970, and no studies that investigate cognitive ability early in life as a predictor of long-term morbidity and mortality in type 1 diabetes.
- Men with type 1 diabetes followed for 60 years had a 4.6 times higher risk of all-cause mortality than men without diabetes. Cognitive ability at 18 years significantly predicted mortality in men without, but not with, type 1 diabetes.
- The results add to the literature describing the prognosis of type 1 diabetes in Scandinavia during the time period from 1934 until today.

affect cognitive ability negatively in childhood,<sup>21</sup> it would be of value to study the possible impact of this on future complications.

The *primary aim* of this observational cohort study is to investigate associations between type 1 diabetes diagnosed before 18 years of age and long-term morbidity and mortality in men, over a time period of 60 years. A *secondary aim* is to examine whether cognitive ability plays a role in the prediction of long-term morbidity and mortality among men with and without type 1 diabetes.

## 2 | METHODS

### 2.1 | Participants

#### 2.1.1 | Men with diabetes

A group of 154 men with type 1 diabetes born 1934–1943 were identified in hospital registers in the region of Scania, Southern Sweden. Out of these, 139 were also identified in military registers (see flow chart in [Figure 1](#)). The final study group consisted of 120 of these men that were also

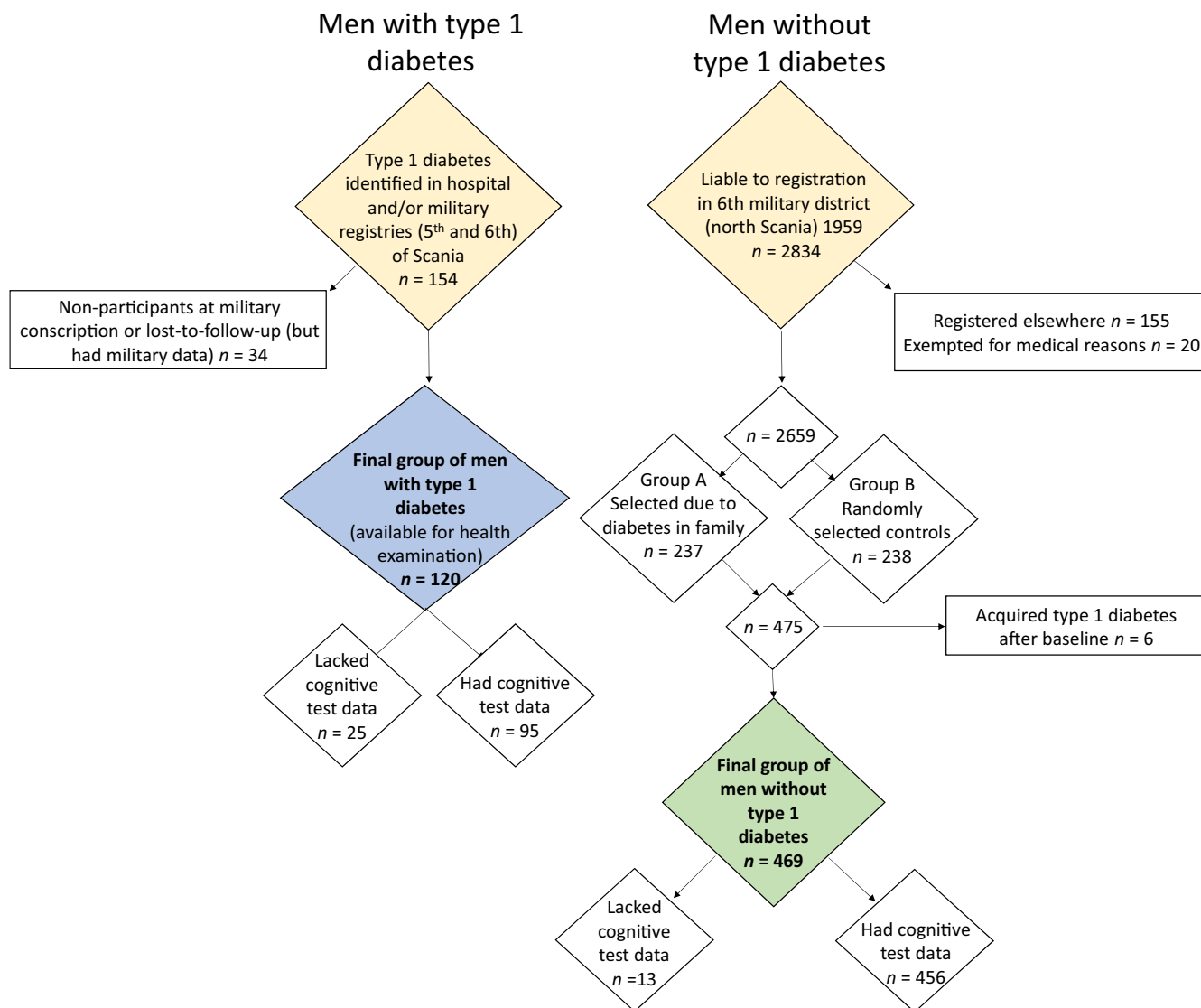


FIGURE 1 Study flow-chart

able to attend a physical health examination 6 months later, representing approximately 80% of men with type 1 diabetes of the same age in the area. The remaining 34 men were not included due to a time delay between the data collection and subsequent health examinations, and their personal registration numbers were thus not available for collection of follow-up data. There was however available information on their mean g-factor, weight and height at conscription.<sup>22</sup>

### 2.1.2 | Men without diabetes

A group of men without diabetes was selected at baseline, and was referred to as a control group in the original study without follow-up. Out of 2834 men liable to registration in the military district 6 in the region of Scania, 20 did

not attend for health reasons and 155 were registered elsewhere. The group originally consisted of two groups, one with and one without a family history of diabetes, because investigating hereditary factors in diabetes was the original aim of the study. Participants in the group with a family background of diabetes ( $n = 237$ ) were selected through responding to a written inquiry sent to all men in the same school year within the military district. The group without a family background of diabetes ( $n = 238$ ) consisted of randomly selected men from the same military district in 1959. The majority were born in 1941 and were thus 18 at military conscription, but 23 men were born during 1939–1940 or 1942–1943 due to completing their education at different times. In this study, we analyse the control group as a whole, with the exception of six participants that acquired type 1 diabetes after baseline, leaving 469 participants in the group.

## 2.2 | Baseline data

Baseline data was collected during 1959–1961.<sup>22</sup> Intelligence test results from military conscription were obtained for 95 of the men with type 1 diabetes and 456 of the men without type 1 diabetes. The tests during 1953–1959 were based on the American ‘Army General Classification Test’<sup>23</sup> and previous versions of the general intelligence test used for conscription in Sweden.<sup>24</sup> These included sub-tests on logic/general intelligence; verbal tests of synonym detection; tests of visuospatial/geometric perception; and technical/mechanical skills with mathematical/physics problems. The outcome of each test was ranked 1–9 (9 = highest score). These values were transformed into a new standard-nine (stanine) scale as a measure of general ability (g-factor). Weight and height were measured during the health examination and information on socio-demographic factors was obtained. Education was classified as elementary school (7 years); secondary school or folk high school (8–11 years); or higher education ( $\geq 11$  years). Socio-economic status was defined by the occupation of the father and was classified into three social groups (3 = highest status).

## 2.3 | Follow-up data

All participants were identified in national registers administered by the National Board of Health and Welfare through their Swedish personal registration numbers. We hereby obtained data on morbidity and mortality during a 60-year follow-up period. As there were differences in year of birth between men with and without diabetes we used age as a time scale and followed all participants until they reached a maximum of 77 years of age, as the majority were born in 1941 and thus were maximally 77 years old at the end of the study (2018).

Mortality data were obtained from the Swedish Cause of Death Registry from the start of the register in 1961 until December 31st 2018. Data on medical diagnoses were obtained from the Swedish National Patient Register (NPR) from the start of the register in 1964 until December 31st 2016. The register had full national coverage from 1987 and onwards.<sup>25</sup> The validity of diagnoses in both registers is over 90%.<sup>26,27</sup> The diagnoses (codes specified in Table S1) were classified according to the International Statistical Classification of Diseases (ICD) established by the World Health Organization (WHO), versions 7–10. The outcomes were mortality, cardiovascular mortality, cardiovascular events, heart failure and complications of diabetes. A cardiovascular event was defined as the first occurrence of acute myocardial infarction or stroke. Diabetes complications included diabetic eye complications, diabetic kidney

disease, peripheral arterial disease, neuropathy, and hypo- and hyperglycaemic emergencies.

## 2.4 | Ethics

The study was approved by the Regional Ethical Committee in Linköping (Dnr 2011/15-31) and in Gothenburg (Dnr 2017/461-32). Written informed consent was obtained from all participants. The reported investigations have been carried out in accordance with the principles of the Declaration of Helsinki as revised in 2008.

## 2.5 | Statistical analyses

Statistical analyses were performed using IBM SPSS version 25 for MacOSX. A  $p$ -value of  $<0.05$  was considered significant.

First, means and standard deviations of continuous variables as well as proportions of categorical variables were calculated. Differences between men with and without type 1 diabetes were calculated through logistic regression analyses with type 1 diabetes as dependent variable.

We then investigated the impact of type 1 diabetes on risk of future cardiovascular outcomes, diabetes complications and mortality, through univariate Cox regression analyses with age as time scale and type 1 diabetes as predictor of outcomes. The results were presented as hazard ratios and 95% confidence intervals. The proportional hazards assumption was verified by plotting incidence of mortality and cardiovascular disease over time for different categories of risk factors.

As the next step, we explored the impact of cognitive ability at military conscription on the associations by including cognitive ability as an interaction term in the analyses previously carried out. In these multivariable Cox regression analyses the covariates were thus type 1 diabetes (1 = diabetes), g-factor (1 = higher cognitive ability scores 6–9) and an interaction term of type 1 diabetes \* g-factor. In analyses for which the interaction term was significantly associated with the outcome, we stratified for type 1 diabetes in a separate analysis. In this way we examined the impact of cognitive ability within each group on the outcomes.

To visualize survival or time to first event of the same cardiovascular outcomes as above for those with diabetes and those without, we also created Kaplan-Meier curves using log-rank tests, with age as a time scale. We then carried out the corresponding analyses for categories of men with and without type 1 diabetes, sub-grouped into high or low to normal cognitive ability for prediction of the outcomes.

In order to control for potential socio-economic differences between groups, we performed a multiple imputation followed by a propensity score adjusted analysis. Data were imputed for the variables education, socio-economic status, height and weight using a

multiple imputation method (fully conditional specification) with five consecutive imputations. A propensity score was created out of these variables using logistic regression with diabetes status as dependent variable. (Age was not included for the reason that we instead

**TABLE 1** Baseline characteristics, incidence of outcomes and comparisons between men with and without type 1 diabetes

Baseline data at age 18	Total study sample (N = 589)	Men without type 1 diabetes (n = 469)	Men with type 1 diabetes (n = 120)	p for difference between groups (valid data)
g-factor (1–9) <sup>a</sup>	4.63 (1.82)	4.51 (1.76)	5.24 (1.97)	<0.001
g-factor (binary) <sup>a</sup>				
1–5	384 (70)	332 (73)	52 (55)	0.001
6–9	167 (30)	124 (27)	43 (45)	
Duration of diabetes (years) <sup>b</sup>			5.81 (5.66)	
Education				
Missing data	25 (4.2)	14 (3.0)	11 (9.2)	
0–7 years	376 (64)	305 (65)	71 (59)	
8–13 years	112 (19)	89 (19)	23 (19)	0.770
>13 years	76 (13)	61 (13)	15 (13)	
Socio-economic status				
Missing data	308 (52)	270 (58)	11 (9.2)	
Low	214 (36)	130 (28)	84 (70)	
Medium	74 (13)	56 (12)	18 (15)	0.101
High	20 (3.4)	13 (2.8)	7 (5.8)	
Outcomes during follow-up				
All-cause mortality	242 (41)	146 (31)	96 (80)	
Age at death	70.0 (13)	72.9 (10)	58.5 (17)	
Death before age 50	61 (10)	23 (4.9)	38 (32)	
Cardiovascular mortality	55 (9.3)	31 (6.6)	24 (20)	
Cardiovascular events (Acute myocardial infarction or stroke)	144 (24)	97 (21)	47 (39)	
Acute myocardial infarction	96 (16)	63 (13)	33 (28)	
Stroke	70 (12)	47 (10)	23 (19)	
Heart failure	75 (13)	47 (10)	28 (23)	
Diabetes complications (all below)			84 (70)	
Diabetic eye disease			68 (57)	
Diabetic kidney disease			40 (33)	
Peripheral arterial disease			30 (25)	
Neuropathy			39 (33)	
Hypo- or hyperglycaemic emergencies			34 (28)	

Note: g-factor, age at death and duration of diabetes are presented as mean (SD). All other data are presented as n (%).

<sup>a</sup>Valid data on g-factor: n = 551, (n = 456 for the group without diabetes and n = 95 for diabetes group).

<sup>b</sup>Valid data on diabetes duration: n = 117 (diabetes group).

used age as time scale in the Cox regression analyses due to all birth years not being represented in both groups). After excluding the top and bottom 2.5% of values to exclude outliers, quintile groups of propensity scores were created. Logistic regression analyses were used to compare covariates between men with and without diabetes across propensity score quintile groups. Additional Cox regression analyses equivalent of those above, but adjusted for propensity score (in five categories), were then carried out.

### 3 | RESULTS

Characteristics of the study sample and prevalence of outcomes are presented in Table 1 and Table S2. Average cognitive ability at baseline was higher in the group with type 1 diabetes compared to the group without (mean g-factor 5.24 compared to 4.51,  $p < 0.001$ ), but there were no significant differences in educational level or socio-economic status between the groups.

For the 34 men with diabetes that were excluded at baseline due to non-participation in the health examination, the mean g-factor was 5.24, which was the same as for the included group. The average height in the excluded group was 0.6 cm shorter and weight 2.0 kg lower than in the included group (see Table S2 for mean values for the included group). The 25 men with type 1 diabetes that were excluded for health reasons during the conscription testing sessions and therefore lacked cognitive data, had on average 1.6 years longer diabetes duration (see Table S3 for comparison of those with and without cognitive data).

The incidence of all-cause and cardiovascular mortality and morbidity was dramatically higher in the group with type 1 diabetes. As shown in Table 1, 80% of the men with diabetes type 1 had died at the end of the follow-up period, compared to 31% of the control group. Out of the diabetes group, 32% were deceased before 50 years of age, compared to 5% in the control group.

The diabetes group had a high incidence of cardiovascular outcomes, 39% with cardiovascular events compared to 21% of men without diabetes, and, correspondingly 23% with heart failure compared to 10% within the group without diabetes. Incidence rates over time of all outcomes were also high in the type 1 diabetes group, as shown in Table 2. See also Kaplan-Meier curves in Figure 2.

In Table 3, an interaction model is presented where we examine the impact of cognitive ability on morbidity and mortality. There was a significant effect of cognitive ability in the whole study group on all-cause mortality (HR 0.59, 95% CI 0.39–0.91), but not on the other outcomes. There

TABLE 2 Univariate Cox Proportional Hazards Modelling of years from birth to first event with type 1 diabetes as predictor of the events

Total cohort (N = 589)	HR (95% CI)	p
All-cause mortality	4.62 (3.56–5.60)	<b>&lt;0.001</b>
Cardiovascular mortality	5.60 (3.27–9.57)	<b>&lt;0.001</b>
Cardiovascular events (Acute myocardial infarction or stroke)	3.97 (2.79–5.64)	<b>&lt;0.001</b>
Acute myocardial infarction	4.17 (2.72–6.37)	<b>&lt;0.001</b>
Stroke	3.68 (2.22–6.09)	<b>&lt;0.001</b>
Heart failure	4.98 (3.11–7.98)	<b>&lt;0.001</b>

p-values less than 0.05 are highlighted in bold text.

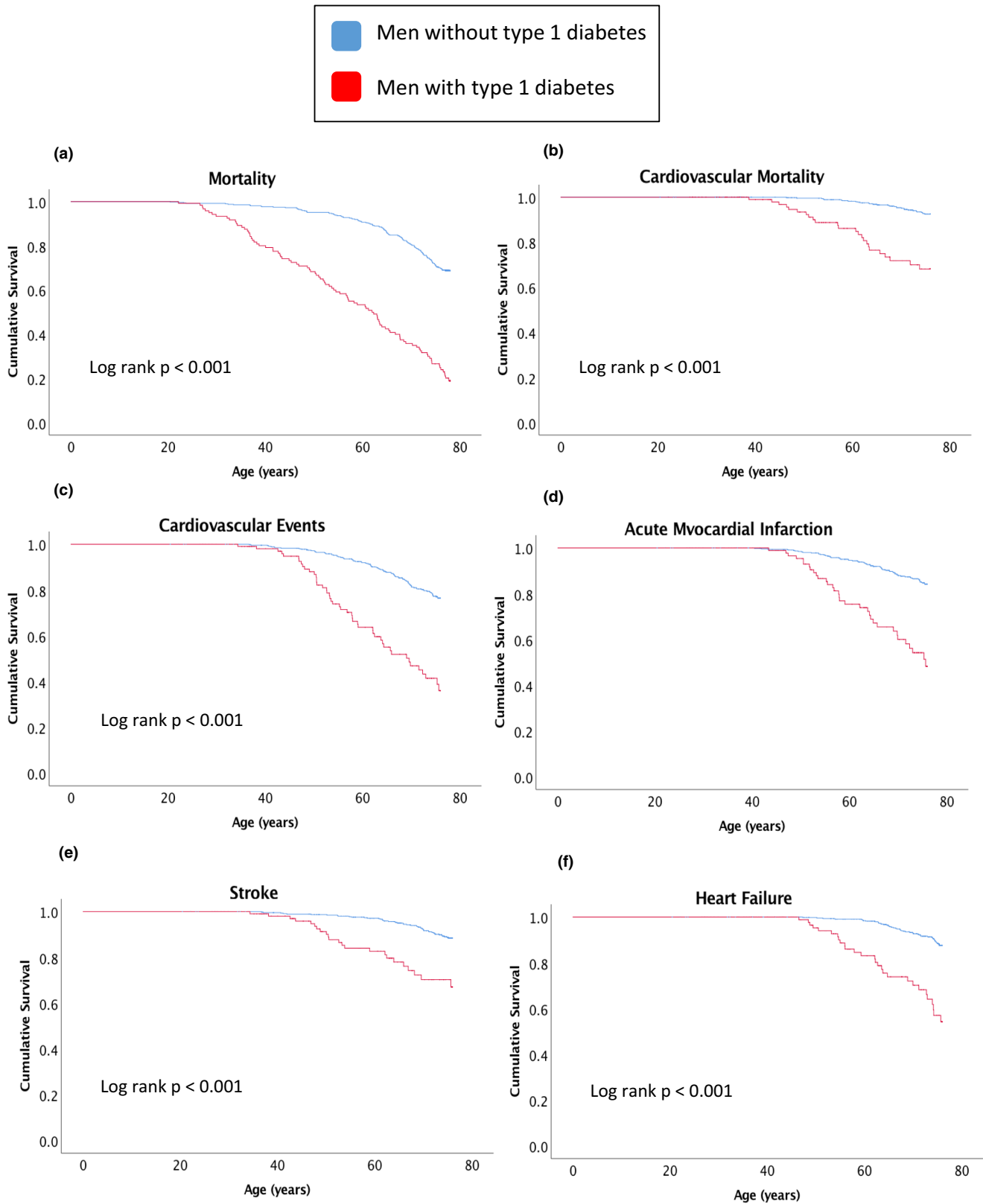
was also a significant interaction between type 1 diabetes and g-factor in relation to this outcome ( $p = 0.015$ ). When we stratified for type 1 diabetes in a further Cox regression analysis of cognitive ability as a predictor of all-cause mortality, higher cognitive ability was significantly associated with a lower risk of mortality within the control group (HR 0.59, 95% CI: 0.39–0.90), but not within the group with type 1 diabetes (HR 1.19, 95% CI: 0.76–1.86). See also Kaplan-Meier curves in Figure 3 for visualization of incidence rates of outcomes for groups of type 1 diabetes and no type 1 diabetes, further grouped into low to normal or high cognitive ability.

Additional analyses where we control for potential socioeconomic differences between the groups are presented in Table S4–S6. The distribution of education, socioeconomic status, height and weight in men with and without type 1 diabetes is presented in Table S4, for different levels of propensity score (see above). The relationships between diabetes, g-factor and incidence of events were very similar in the propensity score adjusted analyses, (Tables S5 and S6).

### 4 | DISCUSSION

In this historical cohort with 60 years of follow-up time, men with type 1 diabetes had a 4.6 times higher risk of all-cause mortality, a 5.6 times higher risk of cardiovascular mortality and a 4.0 times higher risk of cardiovascular events compared to those without. Higher cognitive ability at conscription was associated with lower mortality in men without diabetes, but was not associated with any of the outcomes in men with type 1 diabetes.

The substantially increased risk in these individuals could be explained by the less than optimal treatment profile of type 1 diabetes 60 years ago, based on the use of non-human insulin preparations that were given only once daily in most cases. Besides, no effective treatment



**FIGURE 2** Kaplan-Meier curves of (a) mortality, (b) cardiovascular mortality, (c) cardiovascular events, (d) acute myocardial infarction, (e) stroke and (f) heart failure among men with and without type 1 diabetes

**TABLE 3** Multivariable Cox Proportional Hazards Modelling of years from birth to first event with type 1 diabetes, cognitive ability at 18 years of age (g-factor), and interaction between diabetes and g-factor as predictors of the events

Total cohort (N = 551)	HR (95% CI)	P
All-cause mortality		
Diabetes	3.79 (2.63–5.47)	<b>&lt;0.001</b>
g-factor	0.59 (0.39–0.91)	<b>0.015</b>
Diabetes × g-factor		<b>0.023</b>
Cardiovascular mortality		
Diabetes	3.66 (1.65–8.13)	<b>&lt;0.001</b>
g-factor	0.40 (0.14–1.14)	0.086
Diabetes × g-factor		0.800
Cardiovascular events <sup>a</sup>		
Diabetes	3.89 (2.41–6.29)	<b>&lt;0.001</b>
g-factor	0.72 (0.45–1.17)	0.186
Diabetes × g-factor		0.788
Acute myocardial infarction		
Diabetes	3.41 (1.88–6.19)	<b>&lt;0.001</b>
g-factor	0.69 (0.38–1.24)	0.213
Diabetes × g-factor		0.325
Stroke		
Diabetes	4.72 (2.48–8.99)	<b>&lt;0.001</b>
g-factor	0.81 (0.41–1.60)	0.547
Diabetes × g-factor		0.349
Heart failure		
Diabetes	5.07 (2.72–9.46)	<b>&lt;0.001</b>
g-factor	0.71 (0.35–1.43)	0.334
Diabetes × g-factor		0.879
Diabetes complications <sup>b</sup>		
g-factor	1.11 (0.75–1.65)	0.590

Note: g-factor (1 = higher cognitive ability).

<sup>a</sup> Cardiovascular events = Acute myocardial infarction or stroke.

<sup>b</sup> Complications only analysed within diabetes group.

p-values less than 0.05 are highlighted in bold text.

for lipid disturbances was available and smoking habits were widespread among young men.

The mortality risk in this study during 60 years of follow-up time was relatively comparable to other European data. For instance, relative risk of mortality rates during 60 years of time in our study of 4.6 can be compared to 5.8 in Europe during 1940–1970.<sup>28</sup> Compared to US studies, our mortality rates were lower. For example, mortality rates before 50 years of age during the late 1980's were equivalent to mortality rates during the early 2000s in Pittsburgh, USA.<sup>29</sup>

In our study, men with type 1 diabetes had higher cognitive ability on average than those without at baseline. The underlying assumption of intelligence quotient is

that the scores are normally distributed in the population. However, in the control group, a relatively higher proportion of scores was in the lower range, whereas the distribution in the type 1 diabetes group was normal. Differences in geographical coverage could possibly be one reason for this (control group living mainly in rural areas, diabetes group living in rural and urban areas), as educational level and socio-economic status is lower in rural areas. Controlling for socio-economic status did however not change the results.

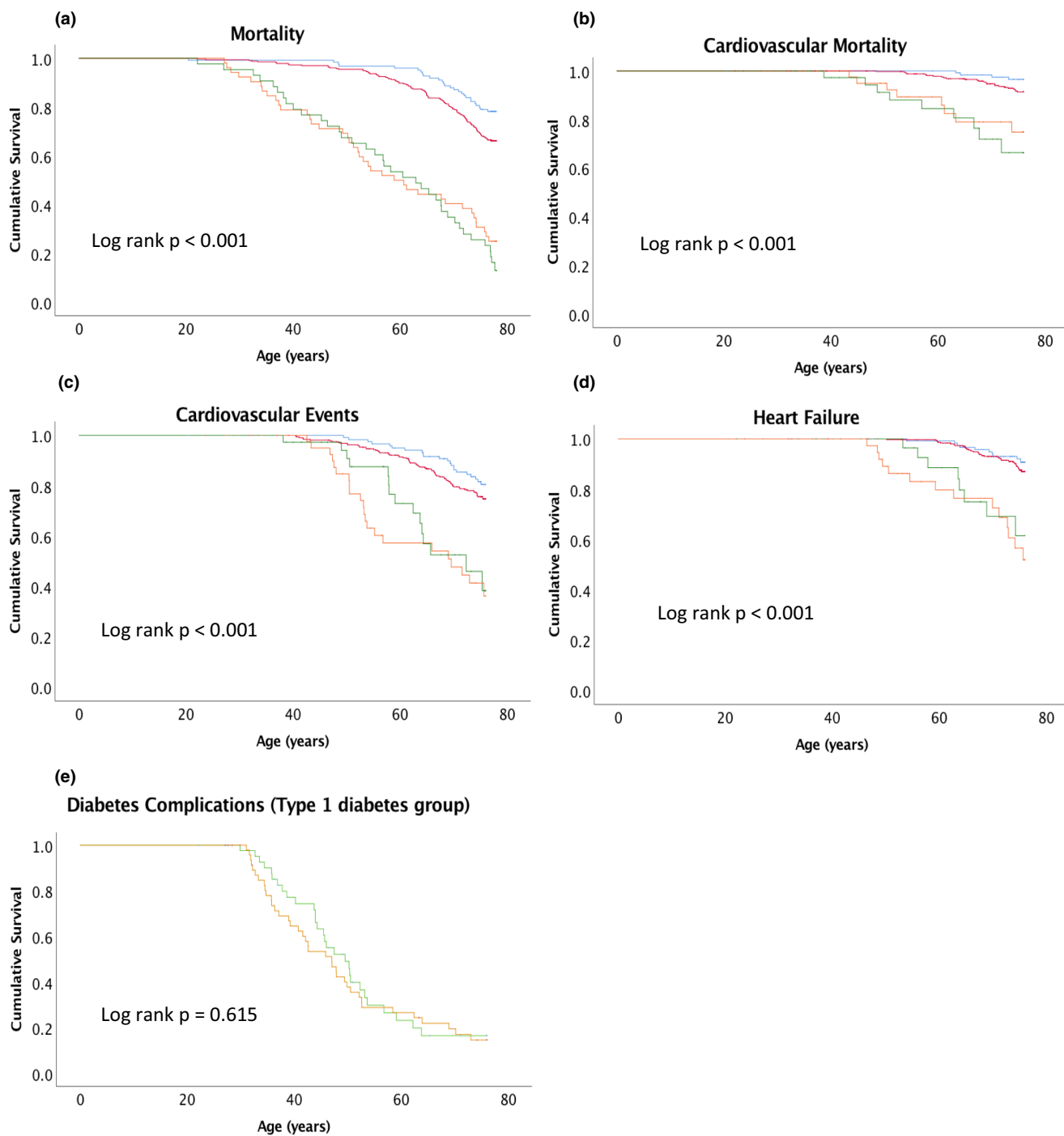
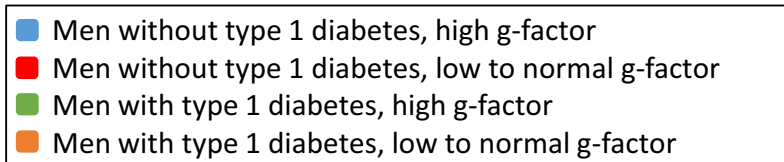
In the group with type 1 diabetes, higher cognitive ability did not protect from mortality, cardiovascular disease or specific diabetes complications later as we had hypothesized, based on other studies on the general population<sup>15,16,19</sup> and on type 2 diabetes.<sup>20</sup> The reason, apart from possible lack of statistical power, could be that effects of suboptimal treatment and risk factor control during the period outweighed the effects of cognitive ability on the prognosis.

In men without type 1 diabetes, higher cognitive ability was associated with a 41% risk reduction of mortality compared to low to normal cognitive ability, in line with previous findings in Swedish military cohorts.<sup>15,16</sup> In contrast to another Swedish study,<sup>17</sup> our study did however not show protective effects of cognitive ability on coronary heart disease.

Limitations of this study include the small sample size, inclusion of only men and inability to follow up 34 participants with type 1 diabetes. Furthermore, there were no available health data on outcomes before the national registers were started (between age 18 to 30 of the participants), although the studied outcomes are unusual at this age. As regards possible health selection bias in the diabetes group, it is possible that some individuals could not be identified in hospital registries due to undiagnosed diabetes, but these are likely to have been few as hospital registries had a high coverage rate already during this period in Sweden. For the 34 individuals that were lost to follow-up there were no differences in mean g-factor and very small differences in height and weight compared to the study participants, implying that this group was comparable to the included cohort. However, the 25 men lacking cognitive data at conscription had longer diabetes duration, which could imply that these participants were less healthy, and could possibly have caused a small bias. The strengths of the study were the long follow-up time, the high coverage of men with type 1 diabetes of the same age in the area (80%) and the high validity of follow-up data.

Our study contributes new insights into the prognosis of type 1 diabetes in Sweden during 1934–2018. Data are also informative for clinicians working with patients surviving with the disease until today. Moreover, for younger





**FIGURE 3** Kaplan-Meier curves of (a) mortality, (b) cardiovascular mortality, (c) cardiovascular events, and (d) heart failure among men with and without type 1 diabetes, both groups divided further into sub-groups with low to normal or high cognitive ability (g-factor 1–5 or 6–9). In (e) diabetes complications (composite outcome equivalent to in Table 3) are visualized for the type 1 diabetes group, sub-grouped into low to normal or high cognitive ability

age groups, these findings provide perspective on how diabetes treatment and prognosis have developed and could therefore serve as motivating evidence of the benefits of today's treatment.

There is a need of studies on larger and later-born cohorts of type 1 diabetes to detect possible associations between early cognitive ability and prognosis later in life. The literature suggests a possibility of such associations although we could not confirm them in this cohort born during an era of suboptimal treatment alternatives as compared to today.

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## CONFLICTS OF INTEREST

None.

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## SUPPORTING INFORMATION

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