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1 **Excess mortality and cardiovascular disease in type 1**  
2 **diabetes in relation to age at onset: a nationwide**  
3 **study of 27,195 young adults with diabetes**

4  
5 Araz Rawshani<sup>1\*</sup>, Professor Naveed Sattar<sup>2\*</sup>, Stefan Franzén<sup>3</sup>, Aidin Rawshani<sup>4</sup>,  
6 Professor Andrew T Hattersley, Ann-Marie Svensson<sup>3</sup>, Professor Björn Eliasson<sup>5</sup>,  
7 Professor Soffia Gudbjörnsdottir<sup>2,3</sup>  
8

9 <sup>1</sup>Department of Molecular and Clinical Medicine, Institute of Medicine, University of Gothenburg,  
10 Gothenburg, Sweden

11 <sup>2</sup>Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK

12 <sup>3</sup>The Swedish National Diabetes Register, Västra Götalandsregionen, Gothenburg, Sweden

13 <sup>4</sup>The Sahlgrenska University Hospital, Gothenburg, Sweden

14 Institute of Biomedical & Clinical Science, University of Exeter Medical School, Exeter, UK

15 <sup>5</sup>Department of Internal Medicine, Institute of Medicine, University of Gothenburg, Gothenburg,  
16 Sweden

17  
18 \* Joint first authors

19  
20 **Corresponding authors:**

21 [Araz.rawshani@gu.se](mailto:Araz.rawshani@gu.se)

22 [Naveed.Sattar@glasgow.ac.uk](mailto:Naveed.Sattar@glasgow.ac.uk)

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27 **Evidence before this study**

28 People with type 1 diabetes are at 2- to 5-fold increased risk of death and 3- to 7-fold increased risk  
29 of coronary heart disease. Several risk factors, notably glycemic control, affect survival in type 1  
30 diabetes. The importance of age at disease onset, however, remains weakly studied. Guidelines do  
31 not articulate any specific recommendations in relation to age at disease onset, only duration. We  
32 did a systematic search in PubMed for articles published between Jan 1, 1960, and April 15, 2018.  
33 Our search terms included “type 1 diabetes”, “age at diagnosis”, “age at disease onset”, “childhood  
34 onset”, “late onset”, “debut age”, “mortality”, “cardiovascular disease”, “coronary artery disease”,  
35 “myocardial infarction”. We searched articles by title and abstract to identify relevant studies.  
36 Studies were also sought within reference lists of eligible studies. We considered studies that  
37 evaluated association between age at onset/diagnosis of type 1 diabetes and cardiovascular disease  
38 and survival. Studies using diabetes free controls as comparator were of primary interest, as such  
39 studies addresses the excess risk conferred by diabetes.

40

41 **Added value of this study**

42 By studying 27,195 individuals with type 1 diabetes and 135,178 matched controls, we demonstrate  
43 a ubiquitous inverse association between age at diagnosis and risk of mortality and cardiovascular  
44 disease, independent of diabetes duration. Patients with type 1 diabetes with disease onset before  
45 10 years of age experienced a 30-fold increased risk of CHD and AMI. Women with onset of type 1  
46 diabetes before 10 years of age displayed a 60- and 90-fold increased risk of CHD and AMI,  
47 respectively. The difference in risk levels between those with onset at age 0–10 years and 25–30  
48 years was up to 5-fold (AMI and CHD). Although absolute risks were low in this young cohort,  
49 developing T1D before 10 years of age resulted in a loss of 17.7 and 14.2 life years for women and  
50 men, respectively, whereas years of life lost were around 9-10 years with later age at diagnosis.

51

52 **Implications of all the available evidence**

53 Age at disease onset appears an important determinant of survival and, in particular of,  
54 cardiovascular disease in type 1 diabetes. These findings suggest that more patients with earlier  
55 onset type 1 diabetes be offered cardioprotective medications (statins, BP medications) sooner than  
56 currently practiced. A greater effort towards improved glycaemia control in such individual would  
57 also be beneficial.

58

59

60

## 61 Abstract

### 62 Background

63 We compared individuals with type 1 diabetes (T1D) to matched controls in order to  
64 examine how age at diagnosis of T1D relates to excess mortality and cardiovascular  
65 (CV) risk.

66

### 67 Methods

68 We studied 27,195 persons with T1D in the Swedish National Diabetes Registry, and  
69 135,178 matched controls from the general population. Using Cox regression, and  
70 with adjustment for diabetes duration, we estimated excess risk of all-cause  
71 mortality, CV mortality, non-CV mortality, acute myocardial infarction (AMI), stroke,  
72 CVD (AMI and stroke), coronary heart disease (CHD), heart failure (HF) and atrial  
73 fibrillation (AF). Individuals with T1D were categorized into five groups, according to  
74 age at diagnosis: 0–9, 10–14, 15–19, 20–24 and 25–30 years.

75

### 76 Findings

77 A total of 27,195 persons with T1D and 135,178 controls were included; 924 persons  
78 with T1D and 1,405 controls died during follow-up, of which median was 10 years.  
79 Patients who developed T1D at 0–10 years of age displayed hazard ratios (95% CI) of  
80 4.11 (3.24–5.22) for death, 7.38 (3.65–14.94) for CV death, 11.44 (7.95–16.44) for  
81 CVD, 30.50 (19.98–46.57) for CHD, 30.95 (17.59–54.45) for AMI, 6.45 (4.04–10.31) for  
82 stroke, 12.90 (7.30–22.51) for HF and 1.17 (0.62–2.20) for AF. Corresponding figures  
83 for those who developed T1D in the age-range 26–30 were 2.83 (2.38–3.37) for  
84 death, 3.64 (2.34–5.66) for CV death, 3.85 (3.05–4.87) for CVD, 6.08 (4.71–7.84) for  
85 CHD, 5.77 (4.08–8.16) for AMI, 3.22 (2.35–4.42) for stroke and 5.07 (3.55–7.22) for  
86 HF; hence excess risk differed up to 5-fold across the diagnosis age. The highest  
87 overall incidence rate, noted for all-cause mortality, was 1.9 (95% CI 1.71 to 2.11) per  
88 100,000 person-years for patients with T1D. Developing T1D before 10 years of age  
89 resulted in a loss of 17.7 and 14.2 life years for women and men, respectively,  
90 whereas years lost were 10.1 and 9.4 in those diagnosed between 26-30 years of age.

91

### 92 Interpretation

93 Age at onset of type 1 diabetes is an important determinant of survival, as well as all  
94 cardiovascular outcomes, with highest excess risk in females. Greater focus on  
95 cardioprotection maybe warranted in those with early onset T1D.

96

### 97 Funding

98 Swedish Heart and Lung Foundation

## 99 Introduction

100 Type 1 diabetes is the second most common chronic disease of childhood, although  
101 the disorder may develop throughout the life span.<sup>1</sup> Remarkable improvements in  
102 management and survival has been observed during the past century. A recent study  
103 demonstrated that the relative risk of death declined by 29% over a 10-year period.  
104 Yet, mortality in type 1 diabetes is still increased two- to eightfold,<sup>2,3</sup> which is  
105 reflected by a loss of life expectancy at age 20 years of approximately 12 years.<sup>4</sup>  
106 Cardiovascular disease is the main driver of morbidity and mortality in people with  
107 type 1 diabetes. Guidelines therefore recommend aggressive management of  
108 cardiovascular risk factors in type 1 diabetes, especially once beyond 40 years of age  
109 or with evidence of microvascular complications.<sup>5</sup> Yet, guidelines are not well  
110 adhered to in type 1 diabetes and even with risk factors at target, people with type 1  
111 diabetes are at elevated risk of mortality and cardiovascular disease.<sup>6</sup> No current  
112 guideline considers age of onset as an important risk stratifier.

113  
114 Age at diagnosis may be important in type 1 diabetes. It may carry information on–  
115 *and thus act as a proxy for*–several important factors, such as total glycemic load,  
116 varying autoimmune mechanisms, age-related variations in clinical care, differences  
117 in ability to cope with the disease *etc.* Accordingly, recent studies have demonstrated  
118 that age at diagnosis can contribute to identifying subtypes of type 2 diabetes in  
119 adults,<sup>7</sup> as well as predict risk factor trajectories.<sup>8</sup> Furthermore, other evidence  
120 supports younger onset type 2 diabetes being more harmful than diabetes diagnosed  
121 in later life.<sup>8,9</sup>

122  
123 By contrast, such data in type 1 diabetes are less evident.<sup>10-14</sup> No study has examined  
124 how age at diagnosis relates to excess risk of death and cardiovascular outcomes,  
125 while accounting for duration of diabetes, and using such granular age categories. We  
126 studied 27,195 individuals with T1D and 135,178 matched controls to answer this  
127 research question.

128

## 129 Methods

### 130 Data sources and study population

131 The Swedish National Diabetes Register (NDR),<sup>2,6,15</sup> includes longitudinal data  
132 regarding risk factors, complications, treatment and management for virtually all  
133 individuals with type 1 diabetes aged 18 years and older. Virtually all Swedes ≥18  
134 years of age with type 1 diabetes are enrolled in the registry. Type 1 diabetes is

135 defined for the NDR on the basis of epidemiological data: treatment only with insulin  
136 and a diagnosis at  $\leq 30$  years of age, which has been validated as accurate in 97% of  
137 cases. Validation was done by comparing the concordance between the  
138 epidemiological classification and the physician's classification of diabetes type.<sup>16,17</sup>  
139 We included patients with at least 1 registration between January 1, 1998, and  
140 December 31, 2012. For the baseline (i.e the first registration in the NDR) each  
141 patient was matched for age, sex, and county with 5 controls (without diabetes  
142 mellitus) randomly selected from the Swedish population, as previously done.<sup>2,15,18</sup>  
143 Matching on county aimed at reducing geographical differences in characteristics.

144 We excluded patients with type 1 diabetes, along with their controls, if the former  
145 had severe congenital disorders or syndromes that may bias the association between  
146 diabetes and outcomes. A complete list of these disorders is provided at the end of  
147 the supplementary appendix. If any individual in the matched set (consisting of 1  
148 individual with type 1 diabetes and 5 matched controls) had such conditions, the  
149 entire matched set was excluded. This led to exclusion of 0.6% of the originally  
150 eligible individuals. We also excluded individuals with inconsistent vital data (i.e the  
151 registration in the NDR was dated after time of death), which resulted in exclusion of  
152 255 patients with type 1 diabetes, along with their controls. Finally, we excluded  
153 individuals with more than 20 years duration of diabetes, the reason for which is  
154 explained below. Finally, 27,195 persons with type 1 diabetes and 135,178 matched  
155 controls were studied. Supplementary Tables 1 and 2 presents the number of  
156 individuals excluded due to congenital disorders and inconsistent vital data.

157

## 158 **Covariates, coexisting conditions and causes of death**

159 Information on socioeconomic data, coexisting conditions, dates and causes of death  
160 was retrieved by linking data to Statistics Sweden, the Swedish Inpatient Registry and  
161 the Cause of Death Register, respectively. Data linkage is seamless since all Swedish  
162 citizens are assigned to a personal identification number which is used in these  
163 registries.

164

165 Statistics Sweden includes information regarding annual income, country of birth,  
166 marital status and education. The Inpatient Register includes all hospital admissions  
167 since 1987. Primary and secondary discharge diagnoses are coded according to the  
168 International Classification of Diseases (ICD). We assessed ICD-9 and ICD-10 codes to  
169 define the following coexisting conditions: coronary heart disease: 410-414 (ICD-9),

170 I20-I25 (ICD-10); acute myocardial infarction: 410 (ICD-9), I21 (ICD-10); stroke: 431-  
171 434, 436 (ICD-9), I61-I64 (ICD-10); hospitalization for heart failure: 428 (ICD-9), I50  
172 (ICD-10); atrial fibrillation: 427D (ICD-9), I48 (ICD-10); cancer: 140-208 (ID-9), C00-C97  
173 (ICD-10). For each outcome, only the first recorded event in the Inpatient Register  
174 was assessed. The validity and reliability of these diagnoses in the Inpatient Register  
175 has been examined in detail.<sup>19</sup>

176

### 177 **Outcomes and exposures**

178 We estimated the excess risk of all-cause mortality, cardiovascular (CV) mortality,  
179 non-cardiovascular mortality, acute myocardial infarction (AMI), stroke, CVD  
180 (composite of AMI and stroke), coronary heart disease (CHD), heart failure (HF) and  
181 atrial fibrillation (AFib). Individuals with type 1 diabetes were categorized into five  
182 groups, according to age at diagnosis: 0 to 10 years, 11 to 15 years, 16 to 20 years, 21  
183 to 25 years and 26 to 30 years.

184

185 For each matched set (the patient with T1D and the matched controls), follow-up  
186 started on the date of the patient's first registration in the NDR, and ended on date of  
187 event, death, emigration or end of follow-up (2014-12-31).

188

### 189 **Statistical methods**

190 Cox regression was used to study the association between age at diagnosis of  
191 diabetes and risk of the outcomes, compared with controls. Age was used as the  
192 underlying time-scale, allowing the baseline hazard to capture the increase in hazard  
193 due to aging. For individuals with type 1 diabetes, we centralized duration around its  
194 grand mean. Controls were modelled as individuals not yet diagnosed with diabetes,  
195 meaning that their duration of diabetes was set to zero; this allows us to account for  
196 duration without assigning an effect of duration to controls. The resulting hazard  
197 ratios represent the hazard ratio for each group after the average duration of  
198 diabetes, which was 13 years. In order to compute reliable estimates, we had to  
199 exclude patients with duration above 20 years. Limiting duration to 20 years allowed  
200 for computation of simple models, without the need for relaxing assumptions of  
201 linearity in duration and it also yielded the best overlap in distribution of duration  
202 between the diabetes groups. Moreover, limiting duration to 20 years also allows us  
203 to study a more contemporary cohort, which better reflects modern diabetes  
204 management.

205 In all models, we adjusted for age (using it as time scale), sex, marital status, income,  
206 educational level, region of birth, duration of diabetes, previous histories of AMI,

207 stroke, CVD, CHD, atrial fibrillation and heart failure.

208 This was done in the entire cohort (i.e including people with >20 years duration of  
209 diabetes). The life years lost was estimated as the difference between the predicted  
210 conditional median survival post 18 years of age in the 0-10 years and 10-15 years  
211 group and post the upper age interval for the other groups. The predicted conditional  
212 survival functions were derived from a Cox regression model with T1DM vs controls  
213 as the only independent variable. Age was used as the time scale, with left censoring  
214 at age of inclusion. The conditional median survival was estimated from the upper  
215 limit of each age interval.

216 The ethics committee of the University of Gothenburg, Sweden, approved the study.  
217 All patients with diabetes have provided informed consent before inclusion in the  
218 cohort. The funder had no role in any part of the study.

219

## 220 Results

221 A total of 27,195 persons with type 1 diabetes and 135,178 controls were included.  
222 Median follow-up was 10 years; 924 patients with type 1 diabetes and 1,405 controls  
223 died during follow-up. Follow-up time and number of deaths in each age category is  
224 presented in Supplementary Tables 3 and 4.

225

### 226 **Baseline characteristics**

227

#### 228 *Patients vs. controls*

229 Mean age among patients with T1D and controls was roughly 29 years and 56% were  
230 males (Table 1). There were only small differences in educational attainment and  
231 marital status between controls and patients. Controls earned 4700 SEK more per  
232 year (approximately 550 USD or 405 GBP). All coexisting conditions, with the  
233 exception of atrial fibrillation, were more common in patients with diabetes.  
234 Coronary artery disease at baseline was 9 times as common in patients with type 1  
235 diabetes.

236

#### 237 *Patients with diabetes*

238 Mean ages in the five age-groups were 23.5, 25.7, 27.6, 32.2 and 37.9 years (Table 2).  
239 HbA1c values were higher in patients with younger age at onset. Use of  
240 antihypertensives and statins were lowest in those with low age at onset of type 1



241 diabetes. Blood pressure, triglycerides, BMI, LDL cholesterol and prevalence of  
242 smoking increased with age at diagnosis. There were only small differences in  
243 physical activity and prevalence of micro- and macroalbuminuria.

244

#### 245 **Absolute risk estimates**

246 Supplementary Tables 5 and 6 present incidence rates for all outcomes. Incidence  
247 rates were low, mostly below 2 events per 100.000 person-years. Rates increased  
248 with age-group. The highest overall incidence rate was noted for all-cause mortality,  
249 being 1.9 (95% CI 1.71 to 2.11) per 100.000 person-years for patients with type 1  
250 diabetes and 0.6 (95% CI 0.56 to 0.66) for corresponding controls. In the highest age-  
251 group, incidence rates for CVD and CHD were 1.53 (95% CI 1.35 to 1.73) and 1.8 (95%  
252 CI 1.61 to 2.01) per 100.000 person-years, respectively, for patients, and 0.45 (95% CI  
253 0.41 to 0.5) 0.46 (95% CI 0.41 to 0.5) for controls. Corresponding rates for those who  
254 developed diabetes below 10 years of age were 0.48 (0.38, 0.58) and 0.5 (0.41, 0.61)  
255 per 100.000 person-years.

256

#### 257 **Life years lost**

258 There were marked differences in life years lost. Refer to Figure 1 and Supplementary  
259 Tables 7 through 9. Overall, being diagnosed with type 1 diabetes before 10 years of  
260 age resulted in loss of 16.0 (95% CI 15.7, 16.4) life-years. Men who were diagnosed  
261 before 10 years of age lost 14.2 (95% CI 14.4, 15.8) life-years. Females who were  
262 diagnosed at the same age lost 17.7 (95% CI 17.1, 17.8) life-years. Patients diagnosed  
263 after 20 years of age loss approximately 10 life-years.

264

#### 265 **Hazard ratios for mortality and cardiovascular outcomes**

266 All following hazard ratios represent the risk in people with type 1 diabetes,  
267 according to age at diagnosis, compared with controls. Overall hazard ratios refer to  
268 estimates for men and women collectively. Sex-specific hazard ratios are also  
269 provided.

270

#### 271 *General patterns*

272 Patients with diabetes displayed an excess risk of eight of nine outcomes, with atrial  
273 fibrillation being the only exception. There was a ubiquitous inverse association  
274 between age at diagnosis and risk of the outcomes. Excess risks were particularly  
275 pronounced in women; the greatest risks were noted for coronary artery disease and  
276 myocardial infarction, for which women with type 1 diabetes displayed a 60- and 90-  
277 fold increased risk, respectively.

278

279 **Mortality**

280 Figure 2 presents overall hazard ratios (men and women collectively). Hazard ratios  
281 (95% CI) for all-cause mortality were as follows: 4.11 (3.24 – 5.22), 3.21 (2.58 – 4.00),  
282 3.02 (2.44 – 3.73), 2.90 (2.41 – 3.50) and 2.83 (2.38 – 3.37), going from the youngest  
283 age-group to the oldest. CV mortality displayed a similar trend. The lowest hazard  
284 ratio for CV mortality, noted for those with diabetes onset at age 26–30 years, was  
285 3.64 (2.34 – 5.66). The highest hazard ratio was 7.38 (3.65 – 14.94) and noted for  
286 those with disease onset at age 0–10 years. Excess risk of non-CV mortality was  
287 consistently elevated with an incremental increase (albeit less marked than for CVD)  
288 with younger age at onset of T1D. Hazard ratio for patients diagnosed in the age  
289 range 26–30 years was 2.78 (2.29–3.38). For those diagnosed in the age-range 0–10  
290 years the hazard ratio was 3.96 (3.06–5.11).

291  
292 Figure 3 presents hazard ratios according to sex. There were no material differences  
293 between males and females (with type 1 diabetes) in the age-range 20 to 30 years.  
294 However, women displayed greater hazard ratios when developing diabetes before  
295 20 years of age. For those developing type 1 diabetes before 10 years of age, women  
296 displayed a 6-fold increased mortality risk, as compared with a 3-fold risk noted in  
297 males with type 1 diabetes.

298  
299 **Cardiovascular outcomes**

300 Cardiovascular risks were considerably higher and strongly related to age at disease  
301 onset. Several strong associations were noted.

302  
303 Overall hazard ratio for CVD (Figure 2) for patients diagnosed in the age-range 26–30  
304 years was 3.85 (3.05–4.87), whereas patients diagnosed in the age-range 0–10 years  
305 displayed a hazard ratio of 11.44 (7.95–16.44). There were notable differences  
306 between males and females, such that the latter displayed greater excess risk  
307 throughout (Figure 3). Women who developed type 1 diabetes before 10 years of age  
308 had a 13-fold increased risk of CVD.

309  
310 Overall hazard ratio for CHD was 30.50 (19.98–46.57) for those diagnosed in the age-  
311 range 0–10 years (Figure 2). The lowest hazard ratio for CHD was 6.08 (4.71–7.84),  
312 which was noted for those diagnosed in the age-range 26–30 years. There were  
313 differences between males and females with type 1 diabetes (Figure 3). Males with  
314 type 1 diabetes displayed a hazard ratio of 16.95 (10.03–28.67) and the  
315 corresponding figure for females was 58.73 (28.86–119.55).

316

317 Overall hazard ratio for AMI was 30.95 (17.59–54.45) for those diagnosed in the age-  
318 range 0–10 years (Figure 2). Women who developed type 1 diabetes before 10 years  
319 of age had a hazard ratio of 91.07 (32.72–253.47). The corresponding figure in males  
320 was 15.11 (7.53–30.33). These differences persisted further down the age span  
321 (Figure 3). The lowest hazard ratio for women with type 1 diabetes was 14.13 (7.75–  
322 25.76), which was noted for those with disease onset between age 26–30 years.

323  
324 Overall hazard ratio for stroke was 6.45 (4.04–10.31) for disease onset between 0–10  
325 years of age (Figure 2). This excess risk declined gradually with increasing age at  
326 onset, such that those with disease onset between 26–30 years had a hazard ratio of  
327 3.22 (2.35–4.00). There were no significant differences between men and women  
328 with type 1 diabetes (Figure 3).

329  
330 Hazard ratios for heart failure differed by a factor of two across the age-span. The  
331 lowest hazard ratio was 5.07 (3.55–7.22) and noted for the age-group 26–30 years  
332 (Figure 2). Being diagnosed with type 1 diabetes in the age-range 0–10 years resulted  
333 in a hazard ratio of 12.90 (7.39–22.51). There were no material differences between  
334 men and women with type 1 diabetes (Figure 3).

335  
336 With regards to atrial fibrillation, we did not note any excess risk for patients with  
337 diabetes, except from males with disease onset between age 21–25 years.

### 338 339 **Causes of death in relation to age at diagnosis**

340 Circulatory and endocrine causes represented roughly 70% of all primary causes of  
341 death in those with disease onset at age 0–10 years (Figure 4). The corresponding  
342 figure for those with age 26–30 was 61%. Other causes, especially neoplasms,  
343 became more common with later onset T1D.

344

## 345 **Discussion**

346 In this nationwide study of patients with type 1 diabetes we show that age at disease  
347 onset is an important determinant of survival and cardiovascular disease. The  
348 differences in hazard related to age of disease onset were in many cases extreme.  
349 Patients with type 1 diabetes with disease onset before 10 years of age experienced a  
350 30-fold increased risk of CHD and AMI in their early adult years. Women with onset of  
351 type 1 diabetes before 10 years of age displayed a 60- and 90-fold increased risk of  
352 CHD and AMI, respectively, in the same early adult period. Onset of type 1 diabetes

353 before 10 years of age was associated with 12-fold increased risk of heart failure over  
354 the same period and mortality risks, relative to age and sex matched controls,  
355 differed by 128%. It is important to note that although the relative risks were  
356 extremely high, absolute risks were low throughout. This is explained by the fact that  
357 we studied a relatively young cohort (mean age 29). However, our previous studies,  
358 in which the persons with T1D were approximately 8 years older than in the present  
359 study, we demonstrated that absolute risks were much higher.<sup>3</sup> Hence, if the relation  
360 between age at diagnosis and excess risks persist further into the future, it would in  
361 time translate to a very high absolute risk, as corroborated by our analysis of loss of  
362 life years; women who developed type 1 diabetes before 10 years of age lost almost  
363 18 life-years. A diagnosis at 26-30 was associated with around 10 years loss.

364

365 In the light of the fact that around half of type 1 diabetes cases are diagnosed before  
366 14 years of age,<sup>20</sup> this study highlights a need to consider age at diagnosis in  
367 guidelines. The magnitude of these risk estimates – with point estimates  
368 approaching 100 in the early adult years – appear at least as high as those conferred  
369 by familial hypercholesterolemia.<sup>21</sup>

370

371 Our risk estimates for the 0-10 years of age of onset subgroup are higher than figures  
372 presented in the most recent statement from the American Heart Association and  
373 American Diabetes Association, which noted that patients with T1D were at 3– (men)  
374 and 7–fold (women) increased risk of CHD. Notably, this statement did not consider  
375 age of onset as a risk stratifier, whereas our data suggest age of onset should now be  
376 considered in the management of CVD risk in T1DM.

377

378 Our data suggests that excess risks are generally greater in women developing T1D  
379 (with the exception of heart failure). This can, to some extent, be explained by the  
380 fact that women in the general population have a low risk of these events, as  
381 compared with men. Hence, higher excess risks in women with type 1 diabetes do  
382 not necessarily translate into higher absolute risks compared to their male  
383 counterparts.<sup>22</sup>

384

385 Our data add meaningfully to the limited information available on the long-term  
386 survival in type 1 diabetes in relation to age at disease onset. *Conway* and colleagues  
387 compared mortality in diabetes with onset in childhood (under 20 years of age,  
388 n=162) versus young adulthood (20 to 29, n=313); no marked differences in mortality  
389 or coronary artery disease were noted, although the small sample offered low  
390 power.<sup>14</sup> In a bigger study, *Harjutsalo* and colleagues examined CHD mortality in early

391 (0–14 years) and late onset (15–29) T1D. They reported that CHD mortality rate was  
392 2.8-fold greater in early onset type 1 diabetes compared with late onset type 1  
393 diabetes. *Harjutsalo* et al suggested that this higher risk may be explained by the  
394 longer duration of diabetes in those with early onset type 1 diabetes. Our study,  
395 which had the benefits of individual's controls, adjustment for duration, more age  
396 subgroups, as well as a range of CVD outcomes, demonstrates that mortality in T1D is  
397 uniformly and markedly elevated as compared with the general population.

398

399 Although the explanations for our findings are likely to be multifaceted, diabetes  
400 duration is likely to play a key role, since even though we adjusted for duration more  
401 robustly than other studies, complete adjustment is near impossible. Duration of  
402 diabetes is a component of total *glycemic load*. The latter—defined as the  
403 vasculatures cumulative exposure to glucose—is a function of duration of diabetes  
404 and glycemic variability. The longer the duration of diabetes, the greater the glycemic  
405 load and thus the damages (analogous to area under the curve for exposure to LDL  
406 cholesterol).<sup>23,24</sup> It is also clear from our data that the coronary arteries seem  
407 especially vulnerable to hyperglycemia, and more so when hyperglycaemia  
408 commences early in life (under 10-15 years).

409 One possible recent explanation for our findings is that patients with a younger age  
410 of onset have a more severe and rapid loss of beta-cells which contributes to higher  
411 glycaemia, as we noted. Recent studies of the pancreas of patients who die close to  
412 diagnosis of diabetes show that those diagnosed under 7 years have very severe loss  
413 of residual insulin-containing islets (ICIs) compared to those diagnosed over the age  
414 of 13 years who retain ~40% ICIs.<sup>25,26</sup> A different type of insulinitis is seen in these 2  
415 subgroups: in those diagnosed under 7 there is a high proportion of CD20 B  
416 lymphocytes (CD20Hi), in contrast to those diagnosed over 13 years who have a low  
417 proportion (CD20Lo).<sup>25</sup> This implies that the two forms of insulinitis are differentially  
418 aggressive and that the patients diagnosed under 7 years with a CD20Hi profile lose  
419 their  $\beta$ -cells at a more rapid rate.

420 Moreover, children and adolescents with type 1 diabetes exhibit subclinical CVD  
421 abnormalities already after 10 years diabetes duration. This has been demonstrated  
422 using numerous methodologies.<sup>27-31</sup>

423 Our data suggest a need to better target cardiovascular risk in those with childhood  
424 onset type 1 diabetes. There are readily available and effective means to mitigate the  
425 risk of coronary events, notably statins, blood pressure lowering, insulin pump,  
426 continuous glucose measurement etc. Trial data suggest CVD reductions in type 1

427 diabetes with statins are near identical in magnitude to those with type 2 diabetes,<sup>32</sup>  
428 whereas observational data suggest statin use markedly lower CVD risk in type 1  
429 diabetes.<sup>33-35</sup> More recent trials evidence from addIT trial support an effect of ACE  
430 inhibition to lessen microalbuminuria and statins to lower lipids when prescribed in  
431 adolescence, and to do so without any short term harm.<sup>36</sup>

432 We are **not** advocating giving children with type 1 diabetes statins or ACE inhibitors  
433 but our data in conjunction with prior observations might argue for greater  
434 consideration of statins once individuals with early onset type 1 diabetes reach 30 to  
435 40 years of age. From current data, plus prior work in Scotland,<sup>37</sup> only around 10-  
436 20% of individuals with type 1 diabetes appear to be on statin by 40 years of age, and  
437 more than half have SBP>120 mmHg. Some guidelines include long duration of  
438 diabetes (i.e. >20 years) as a reason to consider statins in 30-40 year old patients with  
439 type 1 diabetes.<sup>38</sup> However, that such patients - who would have been diagnosed  
440 when under 10 or 20 years of age - also have highest risks of AMI and lose most life  
441 years from their diabetes, is strongly advanced by our present findings. We believe  
442 physicians might need to reconsider more complete targeting of cholesterol, blood  
443 pressure and glycemia in their younger onset patients when they reach 30-40 years  
444 of age, if possible and as clinically indicated. We appreciate ACE inhibitors are  
445 teratogenic whereas, although yet no clear data for such risks, statins are also not  
446 recommended for women planning pregnancy. Thus, some caution in women with  
447 type 1 diabetes is needed but even so, better blood pressure control without ACE  
448 inhibitors in women, improved glycaemia control and smoking cessation in such  
449 groups could meaningfully extend life expectancy in those with younger onset  
450 diabetes. Such interventions given earlier in life, increase life expectancy most,<sup>38</sup> and  
451 some interventions (e.g. statins) have legacy effects.<sup>39</sup> In other words, whilst short  
452 term risks are low to modest, given young age of diabetes onset, lifetime risks will be  
453 high and thus gains from preventative therapies will be greatest when given earlier in  
454 life.

455 There are a number of limitations to the current study. The investigation is a register  
456 study, which has limitations related to such design and data. We lacked information  
457 on glycaemic control prior to enrolment in the registry. We used an epidemiological  
458 definition of type 1 diabetes, which implies that misclassification of diabetes type is  
459 possible. However, a validation study has demonstrated that the epidemiological  
460 classification is highly reliable.<sup>16</sup> Furthermore, we excluded patients with diabetes  
461 duration above 20 years in order to compute reliable regression models; this slightly  
462 restricts the permitted inferences but it does not affect the reliability of the  
463 estimates. Neither did this affect calculation of life years lost, since those analyses

464 included all patients (no restriction with regards to diabetes duration; i.e virtually all  
465 Swedes with type 1 diabetes).

466 To conclude, independent of diabetes duration, age at onset of type 1 diabetes  
467 appears an important determinant of survival, as well as all cardiovascular outcomes.  
468 Early onset type 1 diabetes is associated with up to 30 times increased risk of serious  
469 cardiovascular outcomes, with risk levels being 90 times higher for women with early  
470 onset diabetes, who also die around 18 years earlier than their diabetes free  
471 counterparts. These findings advance the arguments for wider and earlier use of  
472 cardioprotective agents.

473

#### 474 **Contributors**

475 Ar.R, N.S, Ai.R and SG contributed to study concept and design. S.F performed the  
476 statistical analyses. Ar.R, N.S had the primary responsibility for writing the paper. ATH  
477 added new data interpretation. All authors reviewed and revised subsequent versions  
478 of the manuscript. Ar.R, N.S, S.F, Ai.R and S.G vouch for the integrity of the analyses.

479

#### 480 **Declaration of interests**

481 NS has consulted for Boehringer Ingelheim, Novo Nordisk, Janssen and Eli Lilly, and  
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