The adverse association of diabetes with risk of first acute myocardial infarction is modified by physical activity and body mass index: prospective data from the HUNT Study, Norway

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Abstract

Aims/hypothesis Diabetes increases the risk of acute myocardial infarction (AMI) and effective means for primary prevention are warranted. We prospectively examined the joint association of diabetes and leisure-time physical activity, as well as of diabetes and BMI, with the risk of AMI.

Methods A total of 55,534 men and women in the Norwegian HUNT Study were followed-up for first AMI by hospital admission registries and the Cause of Death Registry. Cox proportional adjusted HRs with 95% CIs were estimated.

Results Overall, 1,887 incident AMIs occurred during 12.3 years. Compared with inactive people without diabetes, inactive people with diabetes had an HR of 2.37 (95% CI 1.58,

3.57), whereas the HR among highly active persons with diabetes was 1.04 (95% CI 0.62, 1.74). Normal-weight (BMI 18.5–25 kg/m²) persons with diabetes had an HR of 1.60 (95% CI 1.05, 2.44) and obese (BMI >30 kg/m²) persons with diabetes had an HR of 2.55 (95% CI 1.97, 3.29) compared with normal-weight persons without diabetes. The data suggest biological interaction between diabetes and physical activity, with a relative excess risk of inactivity and diabetes of 1.43 (95% CI 0.08, 2.78). For obesity and diabetes, the excess risk due to interaction was smaller (0.67; 95% CI −0.24, 1.58).

Conclusions/interpretation Body weight and, in particular, physical activity modified the association between diabetes and risk of first AMI. This highlights the potential importance of physical activity and weight maintenance in primary prevention of AMI among people with diabetes.

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Keywords Acute myocardial infarction · Diabetes mellitus ·
Epidemiology · Physical activity

Abbreviations

AMI Acute myocardial infarction
CK Creatine kinase
GADA Autoantibodies to glutamate decarboxylase
RERI Relative excess risk due to interaction

Introduction

Diabetes induces vascular dysfunction that predisposes to atherosclerosis [1, 2] and is associated with about a twofold increased risk of acute myocardial infarction (AMI) [3–5]. Although a broad-based treatment may improve survival in people with diabetes with existing cardiovascular disease,

knowledge of effective means for primary prevention of AMI among people with diabetes is still sparse [6].

People with diabetes are recommended to be physically active for at least 150 min per week and to reduce or maintain their body weight [7, 8]. Physical activity can improve glycaemic control and insulin sensitivity as well as conventional cardiovascular risk factors such as blood pressure and blood lipids [9–12]. Correspondingly, people with a BMI < 25 kg/m² have better glycaemic control, insulin sensitivity, blood pressure and lipid profile than their overweight or obese counterparts [13–16]. This may indicate that being physically active and being normal weight are two interrelated factors that could counteract atherosclerotic processes and reduce the excess risk of AMI seen among people with diabetes.

The objective of this large population-based cohort study was therefore to prospectively examine whether physical activity and BMI could modify the association between diabetes and risk of AMI among people without existing cardiovascular disease.

Methods

Participants The HUNT Study is a large population-based health survey in Nord-Trøndelag County in Norway. Between 1995 and 1997, all inhabitants aged 20 years or older (94,194) were invited to participate in the second wave of the study (HUNT2) and a total of 64,961 (70%) accepted the invitation, completed questionnaires and attended a clinical examination. All participants in the HUNT Study gave written informed consent upon participation and the study was approved by the Regional Committee for Ethics in Medical Research.

For the purpose of the present study, a total of 9,427 participants were excluded at baseline: 2,443 with prior AMI; 40 without information on diabetes status; 6,357 without information on leisure-time physical activity; 342 without information on BMI and 245 without information on potentially confounding factors (i.e. systolic blood pressure or total serum cholesterol). After these exclusions, 55,534 participants (26,229 men and 29,305 women) were available for statistical analyses.

Follow-up From the date of participation in HUNT2 (1995–1997), the participants were followed-up until a diagnosed first AMI or until the end of follow-up (31 December 2008). AMIs were primarily identified through medical records from the two hospitals in Nord-Trøndelag County, but also through a linkage with the National Cause of Death Registry. The mandatory reporting of death to the Cause of Death Registry at Statistics Norway constitutes the basis for the coding of underlying cause of death. Deaths were classified according to the ICD-9 ([www.icd9data.com/2007/Volume1/240-279/250-](http://www.icd9data.com/2007/Volume1/240-279/250-259/250/default.htm)

[259/250/default.htm](http://www.icd9data.com/2007/Volume1/240-279/250-259/250/default.htm)) and ICD-10 (www.who.int/classifications/icd/en/). AMI was defined by ICD-9 code 410 and ICD-10 code I21, when identified through the Cause of Death Registry. The diagnosis of myocardial infarction followed international recommendations (first definition of myocardial infarction [17] and second universal definition of myocardial infarction [18]). Central to the diagnosis is the rise and fall of cardiac biomarkers above the 99th percentile of detection. Troponin I and T was included in the two hospitals from 1998 and from 2001 creatine kinase (CK) and the CK-MB test have been excluded from the routine diagnostic kit. In addition to the myocardial cell death detected by the biomarkers, at least one of the following was necessary: ischaemic symptoms (mostly chest discomfort or dyspnoea) or changes in the ECG indicative of ischaemia (development of pathological Q-waves, dynamic ST-segment changes, T-wave inversions or left bundle branch block). The cardiac units at the two hospitals validated most of the infarctions, and only about 5% of the infarctions were validated at departments outside a cardiac unit (i.e. internal medicine or surgery).

Study variables A detailed description of selection procedures, questionnaires and measurements can be found at www.ntnu.edu/hunt and in a report by Holmen and colleagues [19]. Briefly, information was collected on a range of lifestyle- and health-related factors, including medical history, physical activity, smoking status, alcohol consumption and educational attainment. At the clinical examination, standard anthropometric measures were obtained in standing shoeless participants (height to the nearest centimetre, weight to the nearest half kilogram and waist and hip circumference to the nearest centimetre). BMI was calculated as weight (kg) divided by the squared value of height (m). For the purpose of the statistical analysis individuals were defined as being normal weight (<25.0 kg/m²), overweight (25–29.9 kg/m²) or obese (≥30 kg/m²). In the normal-weight group, 2.5% had a BMI < 18.5 kg/m² and were excluded from the analysis of BMI due to possible bias by pre-existing conditions. Blood pressure was measured three times using a Dinamap 845XT (Critikon, Tampa, USA), and the mean of the second and third measure was calculated. A non-fasting whole-blood sample was drawn from all participants at the screening site. Blood was separated by centrifugation and serum samples were transported in a cooler to the Central Laboratory at Levanger Hospital and analysed on a Hitachi 911 Auto-analyzer (Hitachi, Mito, Japan). Glucose was measured using an enzymatic hexokinase method and total cholesterol using an enzymatic colorimetric cholesterol esterase method. All exposures were measured once, at baseline, without any updated information throughout the follow-up period.

Diabetes Diabetes status was defined by two methods. First, participants who answered ‘Yes’ to the question ‘Do you have

or have you had diabetes?’ were defined as having diabetes ($n=1,200$). Second, persons who answered ‘No’ to this question but who presented with a non-fasting glucose level of ≥ 11 mmol/l at the examination were classified as having newly diagnosed diabetes ($n=166$). A similar procedure has also been used in previous studies [20–22]. Ideally this criterion should be accompanied by information on symptoms of diabetes (e.g. polyuria) [22] but this information was not available. Those confirming diabetes in the questionnaire were invited to a follow-up investigation. A total of 926 individuals (77% of those invited) took part in these investigations, where blood glucose, serum C-peptide and autoantibodies to glutamate decarboxylase (GADA) were measured in a fasting state. In addition, GADA was analysed in individuals who declared having diabetes but who did not attend the follow-up and from whom serum was available from a non-fasting state ($n=228$). Among those attending the follow-up visit, those with a GADA level >8.0 or with a GADA level <8.0 plus a C-peptide level <150 pmol/l were classified as having type 1 diabetes. Among those not attending the follow-up, only the former diagnostic criteria (GADA level >8.0) was used to classify type 1 diabetes. This resulted in a total of 185 people being classified as having type 1 diabetes.

Leisure-time physical activity Information on leisure-time physical activity was obtained from the first questionnaire. Participants were asked to report their usual number of hours per week of light and/or hard leisure-time physical activity during the past year, with four response options (0, <1 , 1–2, and ≥ 3 h) for light activity and the same response options for hard activity. In the questionnaire, light activity was defined as ‘not sweating/being out of breath’, whereas hard activity was defined as ‘sweating/out of breath’. For the purpose of the statistical analysis, a new variable was constructed based on the number of hours of both light and hard activity undertaken during a week, providing information on the level of total leisure-time physical activity. The participants were classified into the following four categories of leisure-time physical activity: inactive (no light or hard activity); low (<3 h light activity and/or <1 h hard activity per week); medium (≥ 3 h light activity and/or <1 h hard activity per week) and high (any light activity and ≥ 1 h hard activity per week). To increase the statistical power, participants with a low and medium level of physical activity were collapsed into one group (‘low/medium’).

Statistical analyses Cox proportional hazard model was used to estimate adjusted HRs of first AMI associated with diabetes and, in separate analyses, to assess the combined association of physical activity and diabetes, and BMI and diabetes, with the risk of AMI. We also combined the information on BMI and physical activity to examine risk of AMI among people with diabetes. The precision of the estimated HRs was

assessed by a 95% CI. All estimated associations were adjusted for possible confounding by attained age (as the time scale) and birth cohort (5 years strata). In multivariable models we adjusted for smoking status (never, former, current, unknown), alcohol consumption (never, not the last 4 weeks, one to three units in the last 4 weeks, more than four units in the last 4 weeks, unknown), education (<10 years, 10–12 years, ≥ 13 years, unknown), BMI (kg/m^2), systolic blood pressure (mmHg) and total serum cholesterol (mmol/l). Additionally, we controlled for leisure-time physical activity level (inactive, low, medium, high) when estimating the associations between diabetes and risk of AMI. The analyses of the combined associations of diabetes and physical activity were conducted sex-specific and in the pooled sample adjusting for sex in the regression model. We used a likelihood ratio test of a product term in the model to assess statistical interaction (i.e. departure from a multiplicative effect) between diabetes and sex and between diabetes and physical activity. Additionally, the association between leisure-time physical activity level and risk of AMI was assessed in analyses stratified by diabetes status. In this analysis, among people with diabetes, we adjusted for diabetes duration (<5 years, 5–10 years, 10–15 years, >15 years, unknown) and reporting of ulcers on feet that had taken more than 3 weeks to heal (yes, no, unknown) in addition to the factors mentioned above. Finally, in an additive model we estimated the relative excess risk due to interaction (RERI) between physical activity and diabetes, as well as between BMI and diabetes. We used a method described by Andersson et al [23] to calculate 95% CIs around the RERI estimate. A RERI larger than zero may suggest biological interaction between two or more risk factors.

Departure from the proportional hazards assumption was evaluated by Schoenfeld residuals and graphical procedures (log–log plots). All statistical tests were two-sided, and all analyses were conducted using Stata for Windows, version 11.2 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics of the study population according to diabetes severity are presented in Table 1. During a median follow-up of 12.3 years (654,928 person-years), 1,887 persons had been diagnosed with a myocardial infarction (1,237 men and 650 women). There was no evidence of departure from the proportional hazards assumption for any of the exposure variables under study. Compared with the 7,029 participants who were excluded due to missing values on central variables, the 55,534 included in the analyses were on average younger (mean age, 47.9 vs 65.0 years), with a lower prevalence of diabetes (2.4% vs 7.1%), a lower BMI (mean BMI 26.3 vs 27.2 kg/m^2) and a lower risk of death from cardiovascular disease (age- and sex-adjusted HR 0.79, 95% CI 0.72, 0.86).

Table 1 Baseline characteristics of the study population

Characteristic	Men		Women	
	Diabetes	No diabetes	Diabetes	No diabetes
No. of participants	726	25,503	640	28,665
Mean age at study entry (SD), years	60.4 (14.6)	47.0 (15.7)	63.4 (14.9)	46.8 (16.1)
Mean BMI (SD), kg/m ²	28.2 (4.3)	26.3 (3.4)	30.0 (5.5)	26.0 (4.4)
Mean systolic blood pressure (SD), mmHg	151 (22)	138 (18)	155 (25)	133 (22)
Mean total cholesterol (SD), mmol/l	5.9 (1.2)	5.8 (1.2)	6.4 (1.3)	5.8 (1.3)
Physical activity level ^a , <i>n</i> (%)				
Inactive	62 (8.5)	1,623 (6.4)	91 (14.2)	1,678 (5.9)
Low/medium	507 (69.8)	15,290 (60.0)	489 (76.4)	20,578 (71.8)
High	157 (21.6)	8,590 (33.7)	60 (9.4)	6,409 (22.4)
BMI, <i>n</i> (%)				
Normal weight (<25.0 kg/m ²)	168 (23.1)	9,371 (36.7)	128 (20.0)	13,635 (47.6)
Overweight (25–29.9 kg/m ²)	337 (46.4)	12,746 (50.0)	230 (35.9)	10,321 (36.0)
Obese (≥30 kg/m ²)	221 (30.4)	3,386 (13.3)	282 (44.1)	4,709 (16.4)
Current smoker, <i>n</i> (%)	184 (25.3)	7,382 (29.0)	104 (16.3)	8,804 (30.7)
High alcohol consumption ^b , %	101 (13.9)	4,527 (17.8)	25 (3.9)	2,224 (7.8)

^a Activity level defined as inactive (no light or hard activity), low (<3 h light activity and/or <1 h hard activity per week), medium (≥3 h light activity and/or <1 h hard activity per week) and high (any light activity and >1 h hard activity per week)

^b Alcohol consumed four times or more during the last month

Both men and women with diabetes ($n=1,366$) had a higher risk of myocardial infarction than people without diabetes. The adjusted HR was 1.49 (95% CI 1.20, 1.86) in men and 2.76 (95% CI 2.17, 3.51) in women. In a sensitivity analysis, we excluded the 164 people with newly diagnosed diabetes based on a non-fasting glucose level of >11.0 mmol/l, but the HRs remained largely similar to those observed for the total diabetes group: 1.57 (95% CI 1.24, 1.98) in men and 2.79 (95% CI 2.18, 3.57) in women. There was statistical interaction between diabetes and sex ($p<0.001$), with a stronger association among women than among men. However, the sex-specific analyses of the combined association of diabetes and physical activity had lower statistical power, due to there being few cases of AMI in some of the categories of physical activity (e.g. no women with diabetes and a high level of physical activity). Thus, the main results are based on the pooled sample.

Figure 1a (and electronic supplementary material [ESM] Table 1) shows the combined associations of diabetes and leisure-time physical activity level on risk of AMI, using inactive people without diabetes as the reference group for all comparisons. People with diabetes who were classified as highly active (i.e. at least 1 h of hard activity per week) had similar risk (HR 1.04; 95% CI 0.62, 1.74) as the reference group of inactive people without diabetes. The corresponding HR among persons without diabetes who were highly active was 0.77 (95% CI 0.64, 0.94). Leisure-time physical activity level was inversely and dose-dependently associated with risk

of AMI in people with and without diabetes ($p_{trend}=0.019$ and 0.010, respectively). ESM Table 2 shows the combined association of diabetes and light leisure-time physical activity (i.e. no sweating/not being out of breath) among people who reported no hard activity per week. Compared with the reference group of inactive persons without diabetes, inactive persons with diabetes had an HR for first AMI of 2.37 (95% CI 1.58, 3.57), whereas people with diabetes who reported undertaking ≥3 h of light physical activity per week had an HR of 1.50 (95% CI 0.94, 2.39). Correspondingly, the HR among persons without diabetes who also reported ≥3 h of light physical activity was 0.78 (95% CI 0.63, 0.97). Few cases of AMI among people who reported only hard activity prevented separate analyses on this variable (e.g. only two cases of AMI among people with diabetes who reported doing ≥3 h of hard physical activity per week).

In sensitivity analyses, after excluding 185 persons who were likely to have diabetes type 1 (ESM Table 3) and excluding the first 3 years of follow-up (1,185 people, of these 419 cases of AMI) to avoid possible bias by pre-clinical disease (ESM Table 4), the results were similar to those presented above.

Although, there was no statistical evidence of multiplicative interaction between diabetes and leisure-time physical activity level ($p=0.19$), the data suggest biological interaction between diabetes and physical activity, with a relative excess risk of inactivity and diabetes of 1.43 (95% CI 0.08, 2.78). This implies a synergetic effect of diabetes and inactivity on

Fig. 1 (a) The combined association of diabetes and leisure-time physical activity level on risk of first AMI compared with inactive people without diabetes. (b) The combined association of diabetes and BMI on risk of first AMI compared with normal-weight people without diabetes. Black bars, diabetes; white bars, no diabetes. Data in (a) were adjusted for age (as the time scale) and birth cohort (5 year strata), sex (man, woman), smoking status (never, former, current, unknown), alcohol consumption (0, 1, 2 or 3, ≥ 4 times last month, total abstainer, unknown), duration of education (<10 years, 10–12 years, ≥ 13 years, unknown), BMI (kg/m²), systolic blood pressure (mmHg) and total serum cholesterol (mmol/l). Data in (b) were adjusted for age (as the time scale) and birth cohort (5 year strata), sex (man, woman), smoking status (never, former, current, unknown), alcohol consumption (0, 1, 2 or 3, ≥ 4 times last month, total abstainer, unknown), duration of education (<10 years, 10–12 years, ≥ 13 years, unknown), systolic blood pressure (mmHg), total serum cholesterol (mmol/l) and leisure-time physical activity level each week (inactive, low/medium, high). * $p < 0.05$ from subgroup analysis stratified by diabetes status, using inactive (a) and BMI 18.5–24.9 kg/m² (b) as reference groups

risk of AMI. In an attempt to assess the direct effect of leisure-time physical activity level with the risk of AMI we did a supplementary analysis stratifying on diabetes status (ESM Table 5). In people without diabetes, the HR was 0.83 (95% CI 0.71, 0.97) among those with a low/medium physical activity level and 0.78 (95% CI 0.64, 0.94) among those with a high physical activity level. In people with diabetes, the corresponding HRs were 0.65 (95% CI 0.41, 1.01) and 0.46 (95% CI 0.24, 0.90), respectively. The associations were similar without stratifying on diabetes.

Figure 1b and ESM Table 6 present the joint associations of diabetes and BMI with the risk of first AMI, using normal-weight people (18.5–25 kg/m²) without diabetes as the reference group for all comparisons. In people without diabetes the HR was 1.12 (95% CI 1.00, 1.25) for those who were overweight (BMI 25–29.9 kg/m²) and 1.28 (95% CI 1.11, 1.47) for those who were obese (BMI ≥ 30 kg/m²). In people with

diabetes, the HR was 1.60 (95% CI 1.05, 2.44), 2.18 (95% CI 1.71, 2.77) and 2.55 (95% CI 1.97, 3.29) for those who were normal weight, overweight and obese, respectively. The relative excess risk for AMI due to interaction between diabetes and obesity was 0.67 (95% CI –0.24 1.58). When treating BMI as continuous variable in the model, one unit increase in BMI was associated with an HR of 1.01 (95% CI 0.98, 1.04) among people with diabetes and an HR of 1.02 (95% CI 1.01, 1.04) in those without diabetes.

In Table 2 we combined the information on BMI and leisure-time physical activity level to examine risk of AMI among people with diabetes. Compared with the reference group of participants with a BMI ≥ 25 kg/m² and an inactive/low level of physical activity, people with a medium/high level of activity and a BMI ≥ 25 kg/m² had an HR for first AMI of 0.90 (95% CI 0.64, 1.26). Among people with a BMI of 18.5–25 kg/m², the HR was 0.89 (95% CI 0.48, 1.65) in those who had an inactive/low level of physical activity and 0.51 (95% CI 0.26, 0.99) in those with a medium/high level of physical activity.

Discussion

In this large population-based cohort study, diabetes was associated with an increased risk of first AMI, with a stronger association among women than men. The adverse association of diabetes with risk of AMI was modified by both leisure-time physical activity and BMI. Diabetes was associated with a more than twofold increased risk among those who reported being physically inactive, whereas those reporting a high level of physical activity had a risk largely similar to that of inactive people without diabetes. Also, in obese people, diabetes was associated with a more than twofold increased risk of AMI, whereas this risk was substantially lower among people of normal weight. Among people with diabetes, those who were the most physically active and were of normal weight had half the risk of those who were least physically active and were overweight or obese. People with diabetes who were overweight and physically active had a similar risk to those who were normal weight and inactive.

To our knowledge, the present study is the first to show that physical activity and BMI modifies the association between diabetes and risk of AMI in people without existing cardiovascular disease. Similar to the present study, previous studies have shown that diabetes increases the risk of AMI [3–5], with a stronger association in women than in men [4, 5], and that the most physically active people with diabetes have approximately half the risk of cardiovascular death compared with inactive people with diabetes [24, 25]. Moreover, we have recently shown that physical activity modified the association between diabetes and mortality [26]. Also, people with diabetes and a low BMI have been reported to have a lower risk of death from cardiovascular disease when compared with obese

Table 2 The combined association of leisure-time physical activity level and BMI with risk of first AMI among people with diabetes

Physical activity level ^a	BMI ≥25 kg/m ²					BMI 18.5–24.9 kg/m ²				
	No. of person-years	No. of AMIs	HR ^b	HR ^c	95% CI	No. of person-years	No. of AMIs	HR ^b	HR ^c	95% CI
Inactive/low	5,519	84	1.00	1.00	Reference	1,174	13	0.86	0.89	0.48, 1.65
Medium/high	5,303	65	0.92	0.90	0.64, 1.26	1,778	10	0.53	0.51	0.26, 0.99

^a Activity level defined as inactive (no light or hard activity), low (<3 h light activity and/or <1 h hard activity per week), medium (≥3 h light activity and/or <1 h hard activity per week) and high (any light activity and >1 h hard activity per week)

^b Adjusted for age (as the time scale) and birth cohort (5 year strata), sex (man, woman)

^c Adjusted for age (as the time scale) and birth cohort (5 year strata), sex (man, woman), smoking status (never, former, current, unknown), alcohol consumption (consumed 0, 1, 2–3, ≥4 times last month, total abstainer, unknown), duration of education (<10 years, 10–12 years, >13 years, unknown), systolic blood pressure (mmHg) and total serum cholesterol (mmol/l)

people with diabetes [27]. The Look AHEAD Research Group recently reported that an intensive lifestyle intervention that promoted weight loss through modification of energy intake and increased physical activity did not reduce the rate of cardiovascular events in overweight or obese people with type 2 diabetes [28]. However, a large observational study found that increased physical activity during a 5 year period was associated with a considerably lower risk of cardiovascular disease when compared with the risk in people who remained at a low physical activity level [29].

The strengths of the present study include the population-based sample, the prospective design and the large number of participants. Additionally, the ascertainment of first AMI, identified either through medical records or through the National Cause of Death Registry, allows for a complete measure of outcome and practically no dropouts throughout the 12 year follow-up period. Improved survival from cardiovascular disease due to improved treatment suggests that using first AMI may be a more appropriate endpoint than mortality, which is more commonly used. The large number of potential confounding factors is another important strength, although residual confounding due to unknown or unmeasured factors cannot be ruled out.

Limitations of the study include the classification of diabetes and leisure-time physical activity by self-report at baseline, and without follow-up information. The self-reported diagnosis of diabetes in the HUNT Study was validated in a separate study [30], showing that 96.4% of the self-reported diabetes could be verified in medical files. We are not aware of studies that have evaluated the reliability of using a non-fasting glucose level ≥11 mmol/l as a cut-off for diabetes, although a similar procedure has been used in previous studies [20–22]. Although it is conceivable that diabetes-related complications could have developed during the follow-up period, such information was not available. Also, diagnosis of diabetes during the follow-up period could have caused underestimation of the associations between diabetes and myocardial infarction. We did not have data on cardiorespiratory fitness, which has been suggested as a more important predictor for cardiovascular outcome than either physical activity [31] or obesity

[32]. Nevertheless, regularly performed physical activity has been shown to improve physical fitness in people with type 2 diabetes [33], suggesting that self-reported physical activity, at least to some degree, may reflect the participants' physical fitness. The findings regarding hard activity in the present study have been found to correlate well with reported maximal oxygen consumption ($\dot{V}O_{2\max}$) in a subsample of young men [34], while light activity showed no correlation. Although light activity did not correlate with $\dot{V}O_{2\max}$, it may elicit other biological mechanisms that are beneficial for cardiovascular health (e.g. improved glycaemic control) [34]. A recent study that objectively assessed ambulatory activity found that both baseline levels and changes in ambulatory activity displayed a graded inverse association with subsequent risk of cardiovascular events [35]. It has also been reported that the most prevalent leisure-time behaviour, television viewing, is associated with increased risk of cardiovascular disease, independently of the total level of physical activity [36]. These studies suggest that light-intensity physical activity and reduced sedentary behaviour may have beneficial effects without improved cardiorespiratory fitness. Also, because these studies did not distinguish between resistance and endurance training, differences associated with the two types of activity could not be estimated. Subjective interpretation of the questions regarding activity could have influenced the results in our study. If the interpretation of activity is related to diabetes status this could have over- or underestimated our results. On the other hand, if the interpretation of activity is unrelated to diabetes status, the associations would be attenuated towards the null. Individual changes in physical activity during the follow-up could both attenuate and strengthen the estimated association. Another possible limitation to the results of this and nearly every similar study is the possibility for collider bias [37]. Diabetes, or survival until onset, could be a collider (caused by two factors [e.g. physical activity and some other risk factor]) so that stratification may induce an association between physical activity and another risk factor, potentially biasing the association of physical activity with the outcome [38]. Although it is possible that some people could have been

hospitalised in another county (e.g. people living near the county border) and thus not been registered as having an AMI in our data, this misclassification is not likely to be differential between people with and without diabetes. We excluded 7,029 people (11%) with missing data on central variables and thus the results may not be representative of the whole cohort. Moreover, people with missing values for factors such as smoking status (2.9%) and alcohol consumption (3.6%) were included in the analyses as a separate category to increase the statistical precision of the associations. We cannot rule out that this may lead to residual confounding.

There are several possible interrelated mechanisms that may explain how physical activity and maintaining a normal body weight could reduce the risk of first AMI in people with diabetes. Physical activity may improve cardiovascular risk factors (e.g. blood pressure, lipid profile and body composition) [9–12] and people with a normal BMI have better glycaemic control, insulin sensitivity, blood pressure and lipid profile than their obese counterparts [13–16]. Thus, it is likely that the beneficial effects of physical activity and maintaining a normal body weight are explained by the sum of improvements in cardiovascular risk factors.

In conclusion, the results from this prospective cohort study showed that inactive people with diabetes had a more than twofold increased risk of a first AMI when compared with inactive people without diabetes. This excess risk was cancelled out in people with diabetes who reported a high physical activity level. Moreover, a normal body weight was also associated with lower risk of first AMI, especially when combined with a moderate or high level of physical activity. The data suggest that leisure-time physical activity and weight maintenance may be effective means for the primary prevention of AMI in people with diabetes.

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Contribution statement All of the authors listed helped with the conception/design of the study as well as with the analysis and/or interpretation of these data. All authors assisted in either drafting the article and/or revising it critically. All authors approved the final version of the manuscript for publication. TILN is the guarantor of this work.

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