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Diabetes and Leisure Time Physical Activity in Relation to Cardiovascular Disease Risk and Mortality

Prospective data from the HUNT Study, Norway

Thesis for the degree of Philosophiae Doctor

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Summary

This thesis consists of three prospective studies, examining whether leisure time physical activity may compensate for the adverse association between diabetes and risk of death from cardiovascular disease and risk of acute myocardial infarction (AMI). We have used data from the HUNT Study, linked with the Cause of Death Registry as well as hospital admissions due to acute myocardial infarction at the two hospitals in Nord-Trøndelag County.

Diabetes was associated with almost threefold higher risk of death from cardiovascular disease among the physically inactive. People with diabetes who reported ≥ 3 hours of light physical activity had similar risk as inactive people without diabetes. We also found that the favourable effect of physical activity were largest among those with most severe diabetes, measured as medical treatment status. Finally, we found an increased risk of first acute myocardial infarction among people with diabetes, and that this excess risk was cancelled out among those who reported a high physical activity level. Moreover, a normal body weight was associated with lower risk of first AMI, especially when combined with a moderate or high level of physical activity.

Our results suggests that the favourable effect of physical activity should be within reach for most people with diabetes and should be more strongly encouraged as a therapeutic measure additional to medical treatment.

Norwegian summary

Denne avhandlingen består av tre prospektive studier som undersøker hvorvidt fysisk aktivitet kan kompensere for den uheldige sammenhengen mellom diabetes og risiko for kardiovaskulær død og risiko for hjerteinfarkt. Vi har benyttet data fra Helseundersøkelsen i Nord-Trøndelag koblet til Dødsårsaksregisteret, samt informasjon om sykehusinnleggelser grunnet hjerteinfarkt ved de to sykehusene i Nord-Trøndelag.

Diabetes var assosiert med nesten tre ganger så høy risiko for å dø av kardiovaskulær sykdom hos de fysisk inaktive. Personer med diabetes som rapporterte ≥ 3 timer med lett fysisk aktivitet per uke, hadde tilsvarende risiko som inaktive personer uten diabetes. Videre fant vi at den gunstige effekten av fysisk aktivitet var størst for de med alvorligst grad av diabetes, målt som medikamentell behandling. Vi fant også en økt risiko for hjerteinfarkt blant personer med diabetes, og at denne forhøyete risikoen ble kansellert blant de som rapporterte et høyt fysisk aktivitetsnivå. En normal kroppsvekt var også assosiert med lavere risiko for hjerteinfarkt, særlig i kombinasjon med fysisk aktivitet.

Våre resultater tyder på at den gunstige effekten av fysisk aktivitet er innen rekkevidde for de fleste med diabetes og i enda større grad bør vektlegges som et ledd i behandlingen av personer med diabetes, i tillegg til medisinering.

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Content

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List of papers

This thesis is based on the following papers:

Paper I: Moe B, Eilertsen E, Nilsen TIL. (2013). The combined effect of leisure time physical activity and diabetes on cardiovascular mortality: the HUNT cohort study, Norway. *Diabetes Care*, 36(3):690-695.

Paper II: Moe B, Augestad LB, Nilsen TIL. (2013). Diabetes severity and the role of leisure time physical activity on cardiovascular mortality: the Nord-Trøndelag Health study (HUNT), Norway. *Cardiovascular Diabetology*, 6;12;83.

Paper III: Moe B, Augestad LB, Flanders WD, Dalen H, Nilsen TIL. (2014). The adverse association of diabetes on first acute myocardial infarction is modified by physical activity and body mass index. Prospective data from the HUNT Study, Norway. *Diabetologia*, accepted for publication.

1 Introduction

The incidence of diabetes has increased during the past decades (1-3). Worldwide, it has been estimated that 347 million people had diabetes in 2011 (4) and that the prevalence will increase to 439 million by 2030 (5). In Norway approximately 90,000–120,000 individuals were diagnosed with diabetes in 2004 and it is expected that almost as many have undiagnosed diabetes (6).

Diabetes increases the risk of cardiovascular disease (7), whereas leisure time physical activity is found to reduce the risk of cardiovascular disease in both people with and without diabetes (8-11). However, whether physical activity could reduce the excess risk of cardiovascular disease associated with diabetes is not known.

Increased knowledge of effective means for primary prevention of cardiovascular disease among people with diabetes is therefore important (12).

1.1 Pathology of diabetes

Diabetes is a chronic metabolic disease characterized by hyperglycemia that is caused by either insufficient insulin production, insufficient insulin action, or both (13). The disease is diagnosed by demonstrating any of the following glucose criteria according to the World Health Organization (WHO) and the International Diabetes Federation (IDF): a fasting plasma glucose level at or above 7.0 mmol/L, a plasma glucose level at or above 11.1 mmol/L two hours after a 75 g oral glucose load in a glucose tolerance test, or symptoms of hyperglycemia and a casual plasma glucose level at or above 11.1 mmol/L (14).

Type 1 diabetes (previously known as insulin dependent diabetes or juvenile diabetes), accounts for approximately 5–10 % of the diabetes cases (15), and occurs most commonly in childhood and early adulthood (16; 17). The pathophysiology of the disease is characterized by the autoimmune destruction of the insulin-producing beta cells of the islets of Langerhans in the pancreas, leading to insulin deficiency (18). Although, some individuals may retain sufficient beta cell functioning for years, individuals with type 1 diabetes will usually be dependent on exogenous insulin to survive (19). The reason why people develop type 1 is not entirely understood, but it is believed that both genetic factors and environmental triggers are involved (13; 20-22).

Type 2 diabetes (previously known as noninsulin-dependent diabetes or adult onset diabetes) is responsible for about 90–95 % of the cases (15), and occurs most commonly in middle-aged persons (16). The pathophysiology of the disease is characterized by insulin resistance and usually a relative insulin deficiency, in contrast with the more absolute insulin deficiency in type 1 diabetes (23; 24). The disease develops gradually, beginning with insulin resistance; a condition in which the muscle, fat and liver cells have a diminished ability to respond to the normal actions of insulin (25). Subsequently, the beta cells increase the production of insulin to overcome the insulin resistance. Over time, the beta cells are unable to produce the required amount of insulin to overcome the insulin resistance, resulting in hyperglycemia (26). Chronic hyperglycemia increases inflammatory chemicals which impairs and possibly destroys beta cells, leading to a vicious cycle where more inflammation results in more insulin resistance and vice versa (27). This process occurs gradually and with few initial symptoms. Therefore, type 2 diabetes is often undiagnosed for several years, and for some it may remain undiagnosed throughout life (15). The precise cause of type 2

diabetes is unknown, but it is believed that it is caused by a combination of genetic predispositions, obesity, physical inactivity, and increasing age (13; 20; 28-30). Research also indicates that the risk of diabetes is increased in people with hypertension and dyslipidemia (31).

People with diabetes are advised to achieve adequate glycemic control. According to the recommendations by The American Diabetes Association, this corresponds to a glycated hemoglobin level (HbA_{1C}) < 7 % (19). HbA_{1C} reflects the average blood glucose over the preceding two to three months. Some individuals may achieve this goal with weight reduction, physical activity, and/or glucose lowering agents, while others require exogenous insulin in addition (32). However, glycemic control usually worsens over time due to a progressive loss in beta cells, so a gradual progression to more intensive treatment is common (33; 34).

For both types of diabetes, elevated levels of plasma glucose is associated with microvascular complications (diabetic nephropathy, neuropathy, and retinopathy) and macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) (35). Therefore, glycemic control is important to avoid or delay complications associated with the disease (35-37). Because the onset of diabetes usually occurs several years prior to the clinical diagnosis, micro- and macrovascular complications are often present at the time when diabetes is diagnosed (38-40).

1.2 Diabetes and cardiovascular disease

Nearly 80% of people with diabetes die from cardiovascular disease (41). This represents a substantial burden to the individuals with diabetes and their families, as

well as to the society (42). Several prospective cohort studies have found a 2-4 fold higher risk of death from cardiovascular disease in people with diabetes, compared to people without diabetes (43-47). Previous studies also indicate that diabetes might be more detrimental for women than men (48-50). In people with diabetes, studies have reported increased cardiovascular mortality associated with hyperglycaemi, hypertension , dyslipidaemia and overweight (9; 44; 51; 52). These modifiable risk factors tend to accelerate the progression of atherosclerosis, and should be targets for lowering the risk of cardiovascular disease in people with diabetes (53). A higher risk of death from cardiovascular disease is also found in those treated with oral hypoglycemic drugs or insulin (54; 55) and in those with longer duration of diabetes (56-59). Longer duration of diabetes implies a longer exposure to hyperglycemia and is also found to be associated with increased prevalence of classical cardiovascular risk factors (e.g. hypertension and dyslipidaemia) (60). The combination of insulin treatment and longer duration of diabetes has been associated with a particular high risk of death from cardiovascular disease (61). These findings suggest that diabetes treatment and duration are important markers for diabetes severity.

Although a broad-based treatment of the mentioned risk factors may reduce the risk of cardiovascular complications, the knowledge of effective means for primary prevention of myocardial infarction and cardiovascular death among people with diabetes is still sparse (41).

1.3 Diabetes, cardiovascular disease and the role of physical activity

Regular physical activity in persons with diabetes may improve glycaemic control and several cardiovascular risk factors (62-65). Previous studies have shown that increasing levels of physical activity are associated with lower risk of cardiovascular death in both the general population (10; 11) and among people with diabetes (8; 9).

According to international recommendations (66), the general population is advised to perform at least 150 minutes of moderate-intensity aerobic physical activity, or at least 75 minutes of vigorous intensity aerobic physical activity per week. Moderate intensity should noticeably accelerate the heart rate such as during a brisk walk, whereas vigorous intensity should substantially increase the heart rate and cause rapid breathing. Different combinations of moderate and vigorous intensity physical activity can be performed to meet the recommendations. For additional benefit, people are advised to increase moderate intensity activity to 300 minutes, or their vigorous activity to 150 minutes per week. Additionally, activities that maintain or increase muscular strength and endurance in the major muscle groups should be performed two days each week. These recommendations have been adopted by the Norwegian guidelines, which was recently updated to incorporate advise on reducing sedentary time (67). Current guidelines for people with diabetes are equivalent to those of the general population, but highlight the dose-response relation between physical activity and health and suggest that a larger amount of physical activity (7 hours of moderate or vigorous aerobic activity) may be helpful (41; 68-70). Because physical activity can result in acute improvements in systemic insulin action lasting from 2 to 72 hours, people with diabetes are advised to spread out their physical activity over at least three days during the week.

Previous studies have shown that physical activity may compensate for the adverse effect of obesity on cardiovascular disease (71; 72), although the current evidence is conflicting (10; 71-73). Similar studies have also been conducted on the risk of diabetes (74; 75). Although physical activity is recommended for people with diabetes, it is unknown whether physical activity modifies the adverse association between diabetes and cardiovascular disease; i.e. whether being physically active may compensate for the adverse association between diabetes and cardiovascular mortality and myocardial infarction.

2 Objective

Based on The HUNT Study, the objective was to investigate the prospective association of diabetes on risk of death from cardiovascular disease and risk of acute myocardial infarction, and further, to assess how leisure time physical activity influence these associations. More specifically, the aims were:

I. To examine whether leisure time physical activity could cancel out the adverse effect of diabetes on risk of death from cardiovascular disease.

II. To examine whether diabetes severity, measured as medical treatment status and disease duration, influence the role of leisure time physical exercise on cardiovascular mortality.

III. To examine whether physical activity and body mass index could modify the association between diabetes and risk of first acute myocardial infarction among people without known cardiovascular disease.

3 Material and methods

3.1 Study population

The HUNT Study is a comprehensive population based study in the Nord-Trøndelag County in Norway including three consecutive health surveys of the adult population, HUNT1 in 1984-86, HUNT2 in 1995-97, and HUNT3 in 2006-08. The county is located in the central part of Norway and included approximately 127,500 residents in 1995. The population is stable (0.3% emigration per year (1996-2000)), homogenous (less than 3% non-Caucasians) and considered to be fairly representative for the Norwegian population (76). In this thesis we have used data from HUNT1 and HUNT2 and will therefore focus on these two surveys.

HUNT1 was conducted between January 1984 and March 1986. All inhabitants aged 20 years or older were invited to participate and a total of 77,216 attended (89.4% of those invited) (77). HUNT2 was conducted between August 1995 and June 1997. As in HUNT1, all inhabitants aged 20 years or older were invited to participate and a total of 65,237 attended (67.5% of those invited) (77).

Participants in both HUNT1 and HUNT 2 responded to a questionnaire that was sent with the invitation and returned this when they attended the clinical examination. At the clinical examination the participants were given a second questionnaire that they were asked to fill in at home and return in a pre-stamped envelope. People who reported diabetes in the first questionnaire were also given a third questionnaire to fill in and return from home.

Both HUNT1 and HUNT2 have been described in more detail elsewhere (76; 78), and information on questionnaires and procedures can also be found on

www.ntnu.edu/hunt. The self-reported information and clinical measurements that we used in the studies forming this thesis are described in section 3.2.

All participants in the HUNT Study gave a written informed consent upon participation and the Survey was recommended by the Regional Committee for Ethics in Medical Research, and approved by the Norwegian Data Inspectorate. The three present sub studies in this thesis were approved separately by the Regional Committee for Ethics in Medical Research (4.2009.911).

The HUNT Study is a collaboration between the HUNT Research Centre, Faculty of Medicine, Norwegian University of Science and Technology, Levanger, Norway, The National Institute of Public Health, the National Health Screening Service of Norway, and the Nord-Trøndelag County Council.

3.2 Study variables

3.2.1 Diabetes

Information on diabetes diagnosis was obtained from the first questionnaire that the participants were given in both HUNT1 and HUNT2. Participants who answered 'Yes' to the question 'Do you have or have you had diabetes?' were defined as having diabetes.

In HUNT2, a non-fasting whole blood sample was drawn from all participants at the screening site. Blood was separated by centrifuging before the 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

cholesterolesterase method. Participants who answered 'No' to the diabetes question above, but had a non-fasting glucose level ≥11mmol/l at the examination in HUNT2, were classified as having newly diagnosed diabetes in paper I and possible diabetes in paper III.

In HUNT1, a third questionnaire was given only to persons with known diabetes and contained the following questions: 'Do you take tablets for your diabetes?', 'Do you take insulin injections?', and 'When were you first diagnosed with diabetes?'. The answers to these questions provided information on use of diabetes medication and diabetes duration that was used in paper II.

Those who confirmed to have diabetes in the questionnaire in HUNT2 were invited to a follow-up investigation, where blood glucose, serum C-peptide and glutamic acid decarboxylase antibodies (GADA) were measured in a fasting state. In addition, GADA was analyzed in cases declaring diabetes who did not attend the follow-up and who had serum available from a non-fasting state. Among those attending the follow-up information, those with an anti-GAD level $\geq$ 8,0 or an anti-GAD < 8,0 and/or C-peptide < 150 pmol/l were classified as having type 1 diabetes. Among those not attending the follow-up, only the former diagnostic criteria (anti-GAD level $\geq$ 8,0) was used to classify type 1 diabetes. This information was used in paper III.

3.2.2 Leisure time physical activity

Information on leisure time physical activity was obtained from the second questionnaire in HUNT1 and the first questionnaire in HUNT2. The questions about leisure time physical activity were different in HUNT1 and HUNT2.

In HUNT1, participants were asked ‘how often do you exercise (weekly average for the year)?’, with five response options 1) *Never*, 2) *Less than once a week*, 3) *Once a week*, 4) *2-3 times per week*, or 5) *Nearly every day*. In the questionnaire, exercise was defined as ‘going for walks, skiing, swimming and working out/sports.’ Those who reported exercising once a week or more were also asked ‘for how long do you exercise each time (weekly average for the year)?’, with four mutually exclusive response options 1) *Less than 15 min*, 2) *16-30 min*, 3) *30 minutes – 1 hour* or 4) *More than 1 hour*. For the purpose of the statistical analysis in paper II, we used the information of both frequency and duration of exercise to calculate ‘hours of leisure time physical activity per week’.The frequency response option 2–3 times per week was counted as 2.5 times and ≥4 per week counted as five times, whereas the duration response options <15, 15–30, 31–60, >60 min were counted as 10, 25, 45 and 75 minutes, respectively. We categorized this variable into the following three categories: inactive, 0.1-1.9 hours, and ≥ 2.0 hours of leisure time physical activity per week.

In HUNT2, participants were asked ‘How much of your leisure time have you been physically active during the last year? (Think of a weekly average for the year. Your commute to work counts as leisure time).’ The participants were given four response options for light activity 1) *None*, 2) *Less than 1 hour*, 2) *1-2 hours*, or 3) *≥ 3 hours*), and the same response options for hard activity. In the questionnaire, light activity was defined as ‘no sweating/being out of breath’, whereas hard activity was defined as ‘sweating/out of breath’. For the purpose of the statistical analysis in paper I and III, a new variable was constructed based on the information on hours of both light and hard activity during a week, providing information on total leisure time activity. The participants were classified into the following four categories; inactive (no light or

hard activity), low (<3 hours light and/or <1 hour hard activity), medium (≥3 hours light and/or <1 hour hard activity), and high (any light and >1 hour hard activity). To increase statistical power in paper III, those with a low and medium level of physical activity were collapsed into one group ('low/medium').

3.2.3 Other factors

Blood pressure was measured two times in HUNT1 using a mercury manometer and three times in HUNT2 using a Dinamap 845XT (Critikon, Tampa, USA). From HUNT1 we used the mean value of the first and second measurement, whereas from HUNT2 we used the mean value of the second and third measurement.

Height and weight were measured in standing subjects with without shoes and outdoor clothing: height to the nearest centimetre and weight to the nearest half kilogram. Body mass index (BMI) was calculated as weight (kg) divided by the square value of height (m). For the purpose of the statistical analysis in paper III, people were defined as normal weight (<25.0 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥30 kg/m^2).

Information on smoking status was obtained from the second questionnaire in HUNT1 and the first questionnaire in HUNT2. The participants were asked about current daily smoking, previous smoking, smoking cessation, amount of smoking, etc. Based on this information, we classified the participants in four categories of smoking; never, former, current, and unknown.

Information on alcohol consumption was obtained from the second questionnaire in HUNT1 and the first questionnaire in HUNT2, with somewhat different questions. In HUNT1, the participants were asked 'how often did you drink alcohol (beer, wine or

spirits) during the last 14 days?', with five response options: 1) *I did not drink alcohol, though I am not a non-drinker*, 2) *1-4 times*, 3) *5-10 times*, 4) ≥ *10 times*, or 5) *I am a non-drinker, I never drink alcohol*. In HUNT2, the participants were asked 'how many times a month do you normally drink alcohol?'. They could also specify if they were a non-drinker of alcohol. For the purpose of the statistical analyses in paper I and III we classified participants in HUNT2 in five categories of alcohol consumption: never, not the last 4 weeks, 1-3 units the last 4 weeks, more than 4 units the last 4 weeks, and unknown.

Information on education was obtained from the second questionnaire in HUNT1 and the first questionnaire in HUNT 2. In HUNT1, the participants were asked 'What is your educational background? (only specify highest level achieved)', with eight response options: 1) *7 years primary school or less*, 2) *middle school*, 3) *9 years compulsory primary and lower secondary school*, 4) *10 years primary and lower secondary school*, 5) *one or two years at upper secondary school*, 6) *general Certificate of Education, commercial college or sixth form college*, 7) *college or university, less than 4 years*, or, 8) *college or university, 4 years or more*. In HUNT 2, the participant were asked 'What is your highest level of education?', with five response options: 1) *primary school 7-10 years, continuation school, folk high school*, 2) *high school, intermediate school, vocational school, 1-2 years high school*, 3) *university qualifying examination, junior college, A levels*, 4) *university or other post-secondary education, less than 4 years*, or, 5) *university/college, 4 years or more*. In the analyses we classified the participants in four categories of education; <10 years, 10-12 years, >13 years, and unknown.

3.3 Follow up

Every Norwegian citizen has a unique 11-digit personal identification number which enables linkage between the HUNT database and other health and disease registries.

The mandatory reporting of death to the Cause of Death Registry in Norway constitutes the basis for the coding of underlying cause of death. Deaths were classified according to the International Classification of Disease (ICD-9 and ICD-10). Cardiovascular disease was defined by ICD-9: 390-459 and ICD-10: I00-I99, and ischemic heart disease by ICD-9: 410-414 and ICD-10: 120-125. In paper I and II we calculated individual person time at risk of death from the date of participation in HUNT1 (1984-86) or HUNT2 (1995-97) until the date of death or until the end of follow-up (31st December 2008), whichever occurred first.

The myocardial infarctions were either identified through medical records from the two hospitals in Nord-Trøndelag County, or for those who never reached the hospital, a linkage with the Cause of Death Registry. Myocardial infarction was defined by ICD-9 code 410 and ICD-10 code I21, when identified through the Cause of Death Registry. When myocardial infarctions were identified through medical records, the definition included certain symptoms according to case history information, specified changes in blood levels of cardiac enzymes, and specified ECG changes. In paper III we calculated individual person time at risk from the date of participation in HUNT 2 (1995-97) until a diagnosed first acute myocardial infarction or until the end of follow-up (31st December 2008), whichever occurred first.

3.4 Statistical analyses

We used Cox proportional hazard models to estimate adjusted hazard ratios (HRs) of death from cardiovascular disease or from fist acute myocardial infarction, according to diabetes and leisure time physical activity.

In paper I, we estimated HRs of death from cardiovascular disease associated with diabetes, and in separate analyses, assessed the combined association of diabetes and leisure time physical activity on risk of death from cardiovascular disease.

In paper II, we estimated HRs of death from cardiovascular disease and ischaemic heart disease associated with diabetes treatment (with or without oral hypoglycemic drugs or insulin) and disease duration, and in a separate analysis, assessed the combined association of leisure time physical exercise and diabetes treatment with risk of death.

In paper III, we estimated HRs of first acute myocardial infarction associated with diabetes, and in separate analyses, assessed the combined association of leisure time physical activity and diabetes, as well as body mass index and diabetes, with the risk of acute myocardial infarction. We also combined information on body mass index and leisure time physical activity to examine risk of acute myocardial infarction among people with diabetes.

Precision of the estimated hazard ratios was assessed by a 95% confidence interval (CI). Departure from the proportional hazards assumption was evaluated by Schoenfeld residuals and graphical procedures (log-log plots). All estimated associations were adjusted for age (as the time scale) and other possible confounding factors. In the analyses of the combined associations of diabetes and physical activity, we adjusted for sex in a pooled sample to increase statistical power. We used a

likelihood ratio test to assess statistical interaction (i.e. departure from a multiplicative effect) between diabetes and sex, and between diabetes and physical activity. The association between physical activity and risk of death from cardiovascular disease or risk of acute myocardial infarction was assessed in analyses stratified by diabetes status.

In paper I, a test for linear trend across categories of physical activity was conducted by treating the categories as an ordinal variable in the regression model. In paper III, we estimated the relative excess risk due to interaction (RERI) between physical activity and diabetes, as wells as between body mass index and diabetes. Additional sensitivity and subgroup analyses were conducted when appropriate. All statistical tests were two-sided.

The data in paper I were analysed using Stata for Windows, version 10.0 and the data in paper II and III were analysed using Stata for Windows, version 11.2 (StataCorp, Texas, USA).

4 Main results

4.1 Paper I: The combined effect of leisure time physical activity and diabetes on cardiovascular mortality: the HUNT cohort study, Norway.

We examined whether leisure time physical activity could cancel out the adverse effect of diabetes on the risk of death from cardiovascular disease.

Data on 53,587 participants in the HUNT 2 Study (1995-97) were linked with the Cause of Death Registry. During a median follow-up of 12.0 years, 1,716 people died from a cardiovascular disease. Both men and women with diabetes (N = 1,195) had a higher risk of death from cardiovascular disease than people without diabetes. The adjusted HR was 1.72 (95% CI: 1.37, 2.16) in men and 1.96 (95% CI: 1.55, 2.50) in women. Compared to the reference group of physically inactive people without diabetes, inactive people with diabetes had an adjusted HR of 2.81 (95% CI: 1.93, 4.07). Persons with diabetes who reported 1-2 hours per week of light activity had approximately similar risk as the reference group (HR, 1.07; 95% CI: 0.63, 1.81), and the risk was further reduced among persons with diabetes who reported ≥3 hours of light activity (HR, 0.89; 95% CI: 0.48, 1.63). The HR among persons without diabetes who reported ≥3 hours per week of light activity was 0.78 (95% CI: 0.63, 0.96). There was statistical evidence for a dose-response effect of light physical activity, both among persons with (P_{trend}, <0.001) and without (P_{trend}, 0.007) diabetes. Analyses stratified by total activity level showed a gradually reduced association of diabetes with mortality with increasing activity level ($P_{interaction}$ = 0.003). In sensitivity analyses, we excluded the first five years of follow up, and then also people who reported a moderate or high degree of movement disability. Both analyses gave largely similar results as those presented above.

4.2 Paper II: Diabetes severity and the role of leisure time physical activity on cardiovascular mortality: the Nord-Trøndelag Health study (HUNT), Norway.

We examined whether diabetes severity, measured as medical treatment status and disease duration, influence the role of leisure time physical exercise on cardiovascular mortality.

Data on 56,170 participants in the HUNT 1 Study (1984-86) were linked with the Cause of Death Registry. During a median follow-up of 23.8 years, 7,723 people died from a cardiovascular disease. Both men and women with diabetes (N = 1,105) had a higher risk of death from cardiovascular disease than people without diabetes. Compared to people without diabetes, the adjusted HR for cardiovascular death was 1.59 (95% CI: 1.29, 1.96) among men with diabetes who received no medical treatment, and 2.16 (95% CI: 1.80, 2.60) for men with diabetes who used medication. The adjusted HR for cardiovascular death was 1.64 (95% CI: 1.34, 2.00) in diabetic women without medication and 2.85 (95% CI: 2.43, 3.34) for those who used medication. In people with diabetes who did not use medication, the adjusted HR for cardiovascular death was 1.65 (95% CI: 1.34, 2.03) for inactive people and 0.99 (95% CI: 0.68, 1.45) for those who reported ≥ 2.0 hours of leisure time physical exercise per week. Among people with more severe diabetes (i.e. those who used medication), the adjusted HR for cardiovascular death was 2.46 (95% CI: 2.08, 2.92) in people who were inactive and 1.58 (95% CI: 1.21, 2.05) for those who reported ≥ 2.0 hours of leisure time physical exercise per week. People with diabetes who exercised 0.1-1.9 hours per week had approximately similar HRs as those who were inactive. A similar pattern was observed for death from ischaemic heart disease, although the difference in HRs between inactive

people and the most active were somewhat larger. The results remained similar in sensitivity analyses were we excluded the first five years of follow up, and also after excluding people who reported a moderate or high degree of movement disability.

4.3 Paper III: The adverse association of diabetes on first acute myocardial infarction is modified by physical activity and body mass index. Prospective data from the HUNT Study, Norway.

We examined whether physical activity and body mass index could modify the association between diabetes and risk of first acute myocardial infarction among people without existing cardiovascular disease.

Data on 55,534 participants in the HUNT 2 Study (1995-97) were linked with hospital admission registries and the Cause of Death Registry. During a median follow-up of 12.3 years, 1,887 persons had been diagnosed with a first acute myocardial infarction. Both men and women with diabetes had a higher risk of acute 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. People with diabetes who were classified as highly active (i.e. at least 1 hour of hard activity) had similar risk (HR: 1.04; 95% CI: 0.62, 1.73) 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). Total physical activity was inversely and dose-dependently associated with risk of acute myocardial infarction in both people with diabetes (P_{trend} =0.019) and in people without diabetes (P_{trend} = 0.010). Sensitivity analyses were we first excluded 185 persons who were likely to have diabetes type 1 and second, excluded the first three years of follow up to avoid possible bias by pre-clinical disease,

gave largely similar results to those presented above. 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). Compared to normal weight people (< 25 kg/m^2) without diabetes, normal weight people (BMI <25 kg/m^2) with diabetes had a HR of 1.61 (95% CI: 1.06-2.45) and obese people (BMI >30 kg/m^2) with diabetes had a HR of 2.57 (95% CI: 1.99, 3.31). For obesity and diabetes, the excess risk due to interaction was smaller (0.67; 95% CI: -0.24-1.58).

5 Discussion

In the studies included in this thesis we have attempted to use epidemiologically sound methods to achieve accurate estimates of how leisure time physical activity influence the adverse association of diabetes and risk of cardiovascular death, and on risk of a first acute myocardial infarction. Briefly, the main findings were:

- Even modest physical activity may cancel out the adverse association of diabetes on cardiovascular mortality.
- The favorable effect of exercise in people with diabetes is especially strong among people with diabetes using medical treatment compared to those without medical treatment.
- Body weight, and in particular physical activity, modified the association between diabetes and risk of first acute myocardial infarction.

When interpreting the results of our studies, it should be noted that they could be distorted by random error, which reduces the precision of the associations, or by systematic error which interferes with the validity of the results (79). These topics are further discussed below.

5.1 Random error (lack of precision)

Random error is the fluctuation in the observed value from the true value due to any factors caused by chance (80). We have used a relatively large study population, which should reduce the impact of random error. This is indicated by the narrow confidence intervals around the point estimates in most of the analyses. However, some of the more infrequent exposure categories had relatively few cases, leading to less precise estimates

for some of the comparisons. For this reason, we performed analyses of the joint association of diabetes and physical activity on a pooled sample of men and women, adjusting for sex in the regression model. Thus, possible effect modification by sex could not be adequately inferred in these data.

5.2 Systematic error (lack of validity)

Systematic errors in estimates could have several sources, such as how the subjects were selected, how the study variables were measured, and by incomplete control of confounding factors (80).

5.2.1 The role of selection bias

Selection bias would influence the validity of our result if the observed associations were different for the participants of the study and the theoretically eligible non-participants. In HUNT 1, the participation rate was 89.4 %, whereas the participation rate in HUNT 2 was 67.5 %. The high participation rates indicate that the study cohort is fairly representative for the underlying population, and reduce the likelihood of selection bias. However, studies of the non-responders in both HUNT 1 and HUNT 2 have shown that non-responders had lower socio-economic status, higher mortality and were more likely to have diabetes and cardiovascular disease than participants (76; 81). Although, possible selection bias cannot be ruled out, it has been argued that representativeness is not a prerequisite for valid results (82).

5.2.2 The role of information bias

Information bias (or misclassification) would influence the validity of our result if the variables under study have been measured randomly or systematically wrong. The assessment of diabetes status, leisure time physical activity, cardiovascular deaths and acute myocardial infarctions are all prone to measurement error.

The self-reported diagnosis of diabetes in the HUNT Study was validated in a separate study (83), showing that 96.4 % of the self-reported diabetes could be verified in medical files. Other studies have also verified the diagnosis in 97% of the cases (56; 84). Participants who answered 'No' to the question of having diabetes, but had a non-fasting glucose level ≥11mmol/l at the examination in HUNT2 were classified as having newly diagnosed diabetes in paper I and III. A similar procedure has also been used in previous studies (13; 85; 86). Ideally, this criterion should be accompanied by information on symptoms of diabetes (e.g. polyuria) (13), but this information was not available. Still, unknown diabetes could have underestimated the association between diabetes and cardiovascular disease. In the self-reported assessment of diabetes treatment and disease duration, misclassification could not be ruled out.

The questions about leisure time physical activity were validated in separate studies of young adult men by comparison with more objective measures of fitness and activity, such as VO2max and ActiReg (87; 88). The questions in HUNT1 were reported to have good repeatability and provide a useful measure of leisure time physical exercise (87). In HUNT2, the question about hard activity was found to have acceptable repeatability and provide a valid measure of vigorous activity, shown by moderate correlations with VO2max, whereas light activity showed no correlation and had poor reproducibility (88). Although not sufficient to increase cardiorespiratory

fitness, light activity could elicit other biological mechanisms that are beneficial for cardiovascular health (e.g. improved glycaemic control). In both HUNT1 and HUNT2, possible subjective interpretation of the questions and perception of the activity can be influenced by factors such as age, social context, and seasonal variation (89), and in our studies, by diabetes status, duration, and treatment. However, it is unlikely that an over reporting of the activity level would overestimate the effect of physical activity, as indicated in a previous study with measures of both fitness and activity (90). Non-differential measurement error of physical activity between people with and without diabetes would most likely cause bias towards the null value, thereby leading to underestimation of the associations. On the other hand, if people with diabetes classified their physical activity differently than people without diabetes, the results may be biased. Nevertheless, validation studies have shown that questionnaires are valid for large epidemiological studies attempting to classify individuals into broad categories of physical activity (e.g., low, moderate, and high activity) (91).

There may also be errors in the classifications of death from cardiovascular disease. Older people, and in particular those with diabetes, could be prone to this misclassification. This would overestimate the association between diabetes and death from cardiovascular disease. The overall validity of the Cause of Death Registry has not been assessed, but meticulous coding systems has been implemented to facilitate high data quality (92).

Diabetes status and leisure time physical activity was only assessed at baseline, and does therefore not take into account individual changes over time. Studies have shown that the prevalence of diabetes has gradually increased in the population (2; 93). Thus, people who were diagnosed with diabetes during the follow-up may have inflated

the risk in the reference group of people without diabetes at baseline, attenuating the association between diabetes and cardiovascular disease. It is also possible that the people who were diagnosed with diabetes at baseline would change their level of physical activity as a result. However, a sensitivity analysis in paper I were we excluded people with newly diagnosed diabetes gave similar results to those observed for the total diabetes group.

5.2.3 The role of confounding

Confounding would influence the validity of our results if the observed associations between diabetes, physical activity and cardiovascular disease are totally or partly due to some other extraneous factor(s) not completely controlled for in the analyses.

Selection of possible confounders was done based on a priori knowledge about factors that could be related both to diabetes and cardiovascular disease.

Both diabetes and cardiovascular disease is strongly associated with increasing age. Therefore, we adjusted for attained age (as the time scale) in all analyses. In paper II and III, we additionally adjusted for birth cohort (5 year strata) to take into account that possible secular trends in diagnoses and treatment of diabetes could influence the observed associations.

We found a stronger association between diabetes and cardiovascular death and acute myocardial infarction in women than in men. However, the sex specific analyses of the combined association of diabetes and physical activity had low statistical power (e.g. no women with diabetes and a high level of physical activity had acute myocardial infarction in paper III). Thus, the main results are based on the pooled sample, adjusting

for sex. As mentioned previously, this implies that the role of physical activity may be somewhat different between men and women.

We also considered smoking, alcohol consumption, education, body mass index, systolic blood pressure and total serum cholesterol as possibly confounding variables and adjusted for them in the analyses. However, in paper II we did not have information about total serum choleterol from HUNT1, so this variable could not be controlled for. Also, residual confounding due to unknown, unmeasured, or poorly measured (misclassified) factors cannot be ruled out.

Some of the factors that we adjusted for could be on the causal pathway between physical activity and cardiovascular disease (e.g. body mass index and systolic blood pressure). Adjusting for such mediators could underestimate the true effect. However, the small difference between age and multivariably adjusted estimates suggests that this is not likely.

Diabetes, or survival until onset of diabetes, 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 (94).

5.3 Appraisal of the principal findings

In paper I, we found an approximately two-fold increase in risk of death from cardiovascular disease among persons with diabetes. This is in accordance with previous prospective cohort studies, including The Reykjavik Study (43), the NHANES 1 study (46), the Framingham Heart Study (47), and studies from the first HUNT survey (44; 49), reporting a 2-4 fold increased risk of cardiovascular death in people with

diabetes. The results from paper II, are also in agreement with previous prospective studies, showing that people with diabetes treated with oral hypoglycemic drugs or insulin have a higher risk of death from cardiovascular disease than those without medication (54; 55). Several studies have reported a positive association between diabetes duration and cardiovascular mortality (56-59; 61), but we did not find any strong effect of diabetes duration on cardiovascular mortality when diabetes treatment was taken into account. Furthermore, similar to the results in paper III, previous studies have showed that diabetes increase the risk of acute myocardial infarction (95-97). In all three papers, the associations between diabetes and the outcome were stronger among women than men. This is in accordance with other studies (48; 49; 96; 97), suggesting that treatment of cardiovascular risk factors could favour men more than women, and that women with diabetes have more adverse cardiovascular risk profiles (48).

To our knowledge, paper I is first to show that even modest physical activity may cancel out the adverse association between diabetes and cardiovascular mortality, paper II is first to show a differential effect of physical exercise on cardiovascular mortality by diabetes severity, and paper III is first to show that physical activity and body mass index modifies the association between diabetes and risk of a first acute myocardial infarction among people with diabetes. Similar to our studies, previous studies have shown that increasing levels of physical activity are associated with lower risk of cardiovascular death among people with diabetes (8; 9) and in the general population (10; 11). Comparisons between studies are difficult due to different methods of assessing physical activity. Nevertheless, it has been shown that the most physically active persons with diabetes have approximately half the risk compared to inactive diabetics (8; 9). Also, people with diabetes and a low body mass index have been

reported to have lower risk of death from cardiovascular disease, than obese people with diabetes (51).

There are several possible mechanisms that could explain how physical activity reduces the risk of cardiovascular death among persons with diabetes. Physical activity may improve glycaemic control, insulin sensitivity, blood pressure, lipid profile, and body composition in people with diabetes (62-65). Prospective studies have shown a weak independent association between hyperglycaemia and risk of cardiovascular disease in persons with diabetes (44; 98). High cholesterol levels increase the risk of cardiovascular disease, both in persons with (14, 39) and without (9; 98; 99) diabetes, as do high blood pressure and body mass index (9). Also, people with a normal body mass index have better glycemic control, insulin sensitivity, blood pressure and lipid profile than their obese counterparts (3; 100-102). This indicates that physical activity and maintaining a normal body mass index are two interrelated and modifiable risk factors that deserve increased attention in diabetes management. Thus it is likely, that the beneficial effect of physical activity may be explained by the sum of improvements in several conventional cardiovascular disease risk factors.

5.4 Conclusion and implications

We found that inactive persons with diabetes had almost three-fold higher risk of cardiovascular death compared with those without diabetes. The excess risk was reduced with increasing amount of leisure time physical activity and the results suggest that 1-2 hours of non-vigorous activity may be sufficient to obtain a favourable effect. We also found a more beneficial effect of physical exercise on risk of death from cardiovascular disease in people with more severe diabetes, measured as medical treatment status. Finally, we found that the excess risk of acute myocardial infarction associated with diabetes was cancelled out among those 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.

Our results highlight the importance of leisure time physical activity and weight maintenance as effective means for primary prevention of risk of death from cardiovascular disease and risk of acute myocardial infarction among people with diabetes. Furthermore, our results suggest that the favourable effect of physical activity should be within reach for most people with diabetes and should be more strongly encouraged as effective means of primary prevention additional to medical treatment.

6 References

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Paper I

The Combined Effect of Leisure Time Physical Activity and Diabetes on Cardiovascular Mortality

The Nord-Trøndelag Health (HUNT) cohort study, Norway

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OBJECTIVE—To examine if leisure time physical activity could cancel out the adverse effect of diabetes on cardiovascular mortality.

RESEARCH DESIGN AND METHODS—This study prospectively examined the combined effect of clinical diabetes and reported leisure time physical activity on cardiovascular mortality. Data on 53,587 Norwegian men and women participating in the population-based Nord-Trøndelag Health (HUNT) Study (1995–1997) were linked with the Cause of Death Registry at Statistics Norway.

RESULTS—Overall, 1,716 people died of cardiovascular disease during follow-up through 2008. Compared with the reference group of 3,077 physically inactive people without diabetes, 121 inactive people with diabetes had an adjusted hazard ratio (HR) of 2.81 (95% CI 1.93–4.07). The HR (95% CI) among people who reported ≥3 h of light activity per week was 0.89 (0.48–1.63) if they had diabetes (n = 403) and 0.78 (0.63–0.96) if they did not (n = 17,714). Analyses stratified by total activity level showed a gradually weaker association of diabetes with mortality with increasing activity level (Pinteraction = 0.003).

CONCLUSION—The data suggest that even modest physical activity may cancel out the adverse impact of diabetes on cardiovascular mortality.

Many studies have shown that the incidence of diabetes has increased during the past decades (1–3), in parallel to the increase in obesity that is observed in most developed countries (4,5). Several studies have shown that diabetes approximately doubles the risk of death from cardiovascular disease (6–11).

There is less evidence that physical activity has favorable effects on cardiovascular disease risk and mortality among people with diabetes (12,13), but physical activity has been shown to improve glycemic control and several cardiovascular risk factors in people with diabetes (14–17). Current guidelines recommend an even higher level of physical activity for people with diabetes than for the general population (18,19). However, it is unknown whether physical activity could reduce the excess cardiovascular mortality in people with diabetes beyond the effect observed among those without diabetes. A few previous studies have shown that physical activity may compensate for the adverse effects of other cardiovascular risk factors, such as obesity (20) and hypertension (21).

A recent report indicated that people with a clustering of cardiovascular risk factors who were highly physically active had the same risk of death from ischemic heart disease and stroke as healthy individuals who reported no physical activity (22). The aim of this prospective study was therefore to investigate the combined effect of leisure time physical activity and diabetes with respect to cardiovascular mortality and to assess if physical activity could cancel out the adverse effect of diabetes.

RESEARCH DESIGN AND METHODS

RESEARCH DESIGN AND METHODS—The Nord-Trøndelag Health (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 were invited to participate in the second wave of the study (HUNT 2). Among 94,194 eligible participants, 65,361 (70%) accepted this invitation, completed questionnaires, and attended a clinical examination (34,786 women and 30,575 men). From this original cohort, 11,774 participants were excluded at baseline: 5,186 who reported prevalent cardiovascular disease (angina, myocardial infarction, and/or stroke), 6,060 without information on physical activity, 32 without information on diabetes status, and 496 without information on potentially confounding factors. After these exclusions, 53,587 participants (25,159 men and 28,428 women) were available for follow-up on cause of death. The HUNT Study is a collaboration between the HUNT Research Centre, Faculty of Medicine, Norwegian University of Science and Technology, Verdal, Norway, The National Institute of Public Health, the National Health Screening Service of Norway, and the Nord-Trøndelag County Council.

A detailed description of selection procedures, questionnaires, and measurements can be found at http://www.ntnu.edu/hunt and in Holmen et al. (23). 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 subjects without shoes (height

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to the nearest centimeter, weight to the nearest half kilogram, and waist and hip circumference to the nearest centimeter). Blood pressure was measured three times using a Dinamap 845XT (Critikon, Tampa, FL), and the mean of the second and third measure was calculated. A nonfasting whole-blood sample was drawn from all participants at the screening site. Blood was separated by centrifuging before the serum samples were transported in a cooler to the Central Laboratory at Levanger Hospital and analyzed 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.

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. The self-reported diagnosis of diabetes in HUNT was validated in a separate study (24), showing that 96.4% of the self-reported diabetes could be verified in medical files. People who answered "No" to the diabetes question, but who presented with a nonfasting glucose level ≥11 mmol/L at the examination, were classified as having newly diagnosed diabetes. A similar procedure has been used in previous studies (25–27). Ideally, this criterion should be accompanied by information on symptoms of diabetes (e.g., polyuria) (27), but this information was not available.

Information on leisure-time physical activity was obtained from the standard questionnaire. Participants were asked to report their usual weekly hours 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. The questionnaire defined light activity as "not sweating/being out of breath," whereas hard activity was defined as "sweating/out of breath." We did not have information about metabolic equivalent of task (MET), therefore the terms light and hard physical activity should not be interpreted as categories conventionally defined by METs.

For the purpose of the statistical analysis, a new variable was constructed based on the information on hours of light and hard activity during a week, providing information on total leisure time activity. The participants were classified into four categories: inactive (no light or hard activity), low (<3 h light and/or <1 h hard activity), medium (≥3 h light and/or <1 h hard activity), and high (any light and >1 h hard activity).

Individual person-time at risk for death was calculated from the date of participation in the HUNT 2 study (1995–1997) until the date of death or until the end of follow-up (31 December 2008), whichever occurred first. The mandatory reporting of death to 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 and ICD-10. Cardiovascular disease was defined by ICD-9 codes 390–459 and ICD-10 codes I00–I99.

Statistical analysis

A Cox proportional hazard model was used to estimate adjusted hazard ratios (HRs) of death from cardiovascular disease associated with diabetes, and in a separate analysis, to assess the combined effect of physical activity and diabetes on risk of death from cardiovascular disease. Precision of the estimated HRs was assessed by a 95% CI. All estimated associations were adjusted for the potential confounding effect of age (as the time scale), smoking status (never, former, current, unknown), alcohol consumption (never, not the last 4 weeks, 1–3 units the last 4 weeks, >4 units the last 4 weeks), education (<10, 10–12, >13 years, unknown), BMI (kg/m^2), systolic blood pressure (mmHg), and total serum cholesterol (mmol/L).

In addition, we controlled for total physical activity level (inactive, low, medium, high) when analyzing the independent effect of diabetes. The latter analyses were conducted separately for men and women, whereas in analyses of the combined effect, we adjusted for sex in a pooled sample necessary for statistical power. This pooling was justified by log-likelihood tests of interaction between diabetes and sex (P = 0.17). Although physical activity and sex showed weak evidence of interaction (P = 0.08), the associations were not largely different in men and women. A test for linear trend across categories of physical activity was conducted by treating the categories as an ordinal variable in the regression model. To examine if physical activity could modify the association between diabetes and cardiovascular mortality, we conducted stratified analyses and tested statistical interaction (departure from a multiplicative effect) between diabetes and physical activity in a likelihood ratio test. Furthermore, we conducted a competing-risks analysis according to the method of Fine and Gray (28) to explore whether our results could be biased by deaths from causes other than cardiovascular disease.

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 10.0 software (StataCorp, College Station, TX).

The study was approved by the Regional Committee for Ethics in Medical Research, and all HUNT 2 Study participants gave a written consent.

RESULTS—Table 1 reports baseline characteristics of the study population. During a median follow-up of 12.0 years (642,888 person-years), 1,716 people

Table 1—*Baseline characteristics of the study population*

	Men		Women	
Characteristics	Diabetes n = 636	No diabetes n = 24,523	Diabetes n = 559	No diabetes n = 27,869
Age at study entry (mean [SD] years)	59.0 (14.7)	46.2 (15.3)	61.8 (15.2)	46.1 (15.7)
BMI (mean [SD] kg/m^2)	28.1 (4.3)	26.3 (3.4)	29.8 (5.7)	25.9 (4.4)
Systolic blood pressure (mean [SD] mmHg)	150.1 (21.8)	138.4 (17.7)	154.0 (25.7)	132.1 (21.6)
Total cholesterol (mean [SD] mmol/L)	5.83 (1.20)	5.76 (1.15)	6.35 (1.31)	5.81 (1.29)
High physical activity level[a] (%)	22.8	34.4	10.7	22.8
BMI ≥ 30 kg/m^2 (%)	28.9	13.1	43.2	16.2
Current smoker (%)	26.9	29.2	15.6	31.1
High alcohol consumption[b] (%)	14.5	18.0	3.9	7.9

[a]At least "1–2 h or more" of vigorous physical activity each week. [b]Four times or more during the last month.

died of a cardiovascular disease (956 men and 760 women). Compared with the 6,588 participants who were excluded due to missing values on central variables, the 53,587 responders were, on average, younger (mean age, 46.5 vs. 64.5 years) and were less likely to die of cardiovascular disease (age- and sex-adjusted HR 0.74 [95% CI 0.68–0.80]). There was no evidence of departure from the proportional hazards assumption for any of the exposure variables under study.

The men and women with diabetes (N = 1,195) had a higher risk of death from cardiovascular disease than those without diabetes (Table 2). The adjusted HR (95% CI) was 1.72 (1.37–2.16) in men and 1.96 (1.55–2.50) in women. In a sensitivity analysis, we excluded the 201 people with newly diagnosed diabetes based on a nonfasting glucose >11.0 mmol/L, but the HRs (95% CIs) remained largely similar to those observed for the total diabetes group: 1.76 (1.38–2.25) in men and 2.01 (1.57–2.57) in women (data not shown).

Table 3 reports the combined effect of diabetes and physical activity on cardiovascular mortality using the 3,077 inactive people without diabetes as the reference group for all comparisons. First, we analyzed the effect of diabetes in combination with light physical activity (i.e., no sweating/not being out of breath) among people who reported no hard activity (i.e., sweating/being out of breath) per week. Compared with the reference group, inactive people with diabetes had a HR (95% CI) of 2.81 (1.93–4.07). People with diabetes who reported 1–2 h per week of light activity had approximately similar risk as the reference group (1.07 [0.63–1.81]), and the risk was further reduced among people with diabetes who reported ≥3 h of light activity (0.89 [0.48–1.63]). Among people without diabetes who reported ≥3 h per week of light activity, the HR (95% CI) was 0.78 (0.63–0.96). There was statistical evidence for a dose–response effect of light physical activity among people with ($P_{trend} < 0.001$) and without (P_{trend} = 0.007) diabetes.

Second, we analyzed a total physical activity variable that incorporated light and hard activity. Compared with the reference group, people with diabetes who were classified as highly active (i.e., at least 1 h of hard activity) had a HR (95% CI) of 0.91 (0.51–1.60), whereas among highly active people without diabetes this was 0.66 (0.53–0.81). Total physical activity also showed a dose-response relation to cardiovascular mortality ($P_{trend} < 0.001$ in both groups). Age- and sex-adjusted estimates were largely similar to the multivariably adjusted results, indicating little confounding and/or low mediating effects of these variables. Because few people reported that they only engaged in hard activity (i.e., no light activity), the data did not allow us to assess the separate effect of hard activity.

There was statistical evidence of interaction between diabetes and total physical activity level (P = 0.03), suggesting that the adverse effect of diabetes on cardiovascular mortality was smaller among active than among inactive people. This was also suggested from analyses stratified by total physical activity level: diabetes was associated with a HR (95% CI) of 2.76 (1.88–4.07) among inactive persons and 1.88 (1.47–2.39), 1.43 (1.02–2.00), and 1.34 (0.75–2.39) among people with low, medium, and high activity levels, respectively (data not shown).

It is conceivable that our results could be biased by severity of disease (i.e., those who are least active may have poorly controlled diabetes). To explore this we conducted a supplementary stratified analysis excluding the first 5 years of follow-up. The results did not substantially deviate from the results presented above: diabetes was associated with a HR (95% CI) of 3.24 (1.94–5.43) among inactive persons and 1.75 (1.29–2.38), 1.29 (0.85–1.97), and 1.22 (0.61–2.46) among people with low, medium, and high activity level, respectively (data not shown).

We also did a stratified analysis excluding people reporting a moderate or high degree of movement disability. In this analysis, diabetes was associated with a HR (95% CI) of 2.61 (1.65–4.14) among inactive people and 1.70 (1.30–2.23), 1.40 (0.96–2.04), and 1.26 (0.67–2.37) among people with low, medium, and high activity levels, respectively (data not shown). Corresponding analyses accounting for potential competing risk from other causes of death than cardiovascular disease gave largely similar associations. The HR (95% CI) among inactive people was 2.72 (1.91–3.87) and 1.90 (1.40–2.42), 1.44 (1.02–2.04), and 1.55 (0.89–2.71) among those with low, medium, and high activity levels, respectively (data not shown).

DISCUSSION—In this large population-based cohort study, people with diabetes had a nearly twofold higher risk of death from cardiovascular disease than people without diabetes, with a slightly stronger association among women than among men. Diabetes was associated with a nearly threefold higher risk among people who reported being physically inactive. The risk of death from cardiovascular disease among people with diabetes who reported a moderate to high physical activity level was similar to inactive people without diabetes.

The strengths of this study include the population-based sample, the prospective design, the large number of participants, and ascertainment of total and cardiovascular death through the Cause of Death Registry at Statistics Norway. The latter allows for a complete

Table 2—*HRs for death from cardiovascular disease associated with diabetes*

	Men					Women				
Diabetes status	Person-years	Deaths *N*	HR[a]	HR[b]	95% CI	Person-years	Deaths *N*	HR[a]	HR[b]	95% CI
No diabetes	292,792	873	1.00	1.00	Reference	337,509	681	1.00	1.00	Reference
Diabetes	6,668	83	1.67	1.72	1.37–2.16	5,908	79	2.04	1.96	1.55–2.50

[a]Adjusted for age (as the time scale). [b]Adjusted for age (as the time scale), physical activity level each week (inactive, low, medium, high), smoking status (never, former, current, unknown), alcohol consumption (never, not the last 4 weeks, 1–3 units the last 4 weeks, >4 units the last 4 weeks), education (<10, 10–12, >13 years, unknown), BMI (kg/m^2), systolic blood pressure (mmHg), and total serum cholesterol (mmol/L).

Table 3—*The combined effect of diabetes and physical activity on risk of death from cardiovascular disease*

	No diabetes				Diabetes			
Physical activity	Person-years	Deaths *N*	HR (95% CI)[a]	P_{trend}[b]	Person-years	Deaths *N*	HR (95% CI)[a]	P_{trend}[b]
Inactive	35,056	215	1.00 (Reference)	—	1,102	33	2.81 (1.93–4.07)	—
Light activity								
<1 h	48,182	153	1.04 (0.84–1.28)	—	997	19	2.81 (1.75– 4.51)	—
1–2 h	62,459	192	0.86 (0.71–1.05)	—	1,438	15	1.07 (0.63– 1.81)	—
≥3 h	36,220	172	0.78 (0.63–0.96)	0.007	1,055	11	0.89 (0.48– 1.63)	<0.001
Total activity[c]								
Low	200,260	648	0.92 (0.78–1.07)	—	2,212	78	1.77 (1.36– 2.30)	—
Medium	213,450	507	0.74 (0.63–0.87)	—	4,796	38	1.04 (0.73– 1.47)	—
High	181,546	184	0.66 (0.53–0.81)	<0.001	2,387	13	0.91 (0.51– 1.60)	<0.001

[a]Adjusted for age (as the time scale), sex (man, woman), smoking status (never, former, current, unknown), alcohol consumption (0, 1, 2–3, ≥4 times last month, total abstainer, unknown), education (<10, 10–12, >13 years, unknown), BMI (kg/m^2), systolic blood pressure (mmHg), and total serum cholesterol (mmol/L). [b]Test for linear trend across categories of physical activity. [c]Total activity level defined as inactive (no light or hard activity, 2), low (<3 h light and/or <1 h hard activity), medium (≥3 h light and/or <1 h hard activity), and high (any light and >1 h hard activity).

measure of outcome and practically no dropouts throughout the median 12-year follow-up period. An additional strength is the large number of potential confounding factors that were available.

Limitations of the study include the somewhat low precision of effect estimates in some of the categories in the combined analysis due to few deaths (32% of all deaths) from cardiovascular disease. Also, leisure-time physical activity was self-reported and only assessed at baseline, without follow-up information. Possible subjective interpretation of the questions and perception of the activity can be influenced by factors such as age, social context, and seasonal variation (29), and in the current study, by known diabetes status, duration, and severity. However, it is unlikely that an overreporting of the activity level would overestimate the effect of physical activity, as indicated in a previous study with measures of both fitness and activity (30). The physical activity questions in the current study did not distinguish between different types of leisure-time physical activity. Consequently, the specific effect of aerobic versus resistance training could not be estimated.

The activity questions have been validated in a separate study of young adult men by comparison with VO_{2max}, ActiReg, and with the International Physical Activity Questionnaire. Hard activity was found to correlate well with VO_{2max} (Pearson correlation coefficient = 0.46), whereas light activity showed no correlation (−0.03) (31). Although not sufficient to increase cardiorespiratory fitness, light activity could elicit other adaptions. However, the validation study showed only a weak correlation between reported light activity and energy expenditure measured with ActiReg (0.21) (31). Nevertheless, validation studies have shown that questionnaires are most practical for large epidemiological studies attempting to classify individuals into categories of physical activity (e.g., low, moderate, and high activity) (32).

Furthermore, it is curious that the prevalence of diabetes has increased only slightly during the 12-year follow-up (33). It is possible that unknown diabetes could over- or underestimate the association between diabetes and cardiovascular mortality. Unfortunately, updated information on diabetes status and physical activity level was not available. Also, some people without known diabetes at baseline were probably not identified due to the absence of a postchallenge glucose test (23). In Norway it is likely that being diagnosed with diabetes could vary by population subgroups that had differential use of health care services and health literacy. As in all observational studies, residual confounding due to unknown or unmeasured factors cannot be ruled out. Several of the factors that we adjusted for could be on the causal pathway between physical activity and cardiovascular mortality, such that overadjusting could have occurred. However, the small difference between age and multivariably adjusted estimates suggests that this is not likely.

Several previous prospective cohorts, including The Reykjavik Study (6), the National Health and Nutrition Examination Survey 1 study (34), the Framingham Heart Study (35), and studies from the first HUNT survey (7,11) found a two- to fourfold higher cardiovascular mortality among people with diabetes. Our results showed an approximately twofold increase in risk of death from cardiovascular disease among people with diabetes, with a somewhat stronger association among women than among men. This is in accordance with other studies that reported the association of diabetes with cardiovascular mortality to be higher among women (11,36). Treatment of cardiovascular risk factors could favor men more than women, such that women with diabetes have more adverse cardiovascular risk profiles (36).

Previous studies have also shown that increasing levels of physical activity are associated with lower risk of cardiovascular death among people with diabetes (12,13) and in the general population (37,38). Comparisons between studies are difficult due to different methods of assessing physical activity. Nevertheless, the most physically active people with diabetes have been shown to have approximately half the risk compared with inactive patients with diabetes (12,13), similar to our results.

Several possible mechanisms may explain how physical activity reduces the risk of cardiovascular death among people with diabetes. Recent studies have reported that regular physical activity improves glycemic control, insulin sensitivity, blood pressure, lipid profile, and body composition in people with diabetes (14–17). Prospective studies have shown a weak independent association between hyperglycemia and risk of

cardiovascular disease in people with diabetes (7,39). High cholesterol levels increase the risk of cardiovascular disease, both in people with (14,39) and without diabetes (13,39,40), as do high blood pressure and BMI (13). Thus, the protective effect of physical activity observed in our study may likely be explained by the sum of improvements in conventional cardiovascular disease risk factors. People with diabetes in the current study who reported only 1–2 h of light physical activity per week had a significantly lower mortality than those who reported no activity. If confirmed, this suggests that the favorable effect of physical activity should be within reach for most people.

In conclusion, the results from this prospective cohort study show that inactive people with diabetes had almost threefold higher risk of cardiovascular death compared with those without diabetes. The excess risk was reduced with increasing amount of leisure-time physical activity. Thus physical activity may, to a large extent, cancel out the detrimental effect of diabetes on cardiovascular death, at least among those healthy enough to do physical exercise. Furthermore, the results suggest that 1–2 h of nonvigorous activity may be sufficient to obtain a favorable effect.

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B.M. and E.E. prepared and analyzed the data, interpreted the results, drafted the manuscript, and contributed to the final version of the manuscript. T.I.L.N. initiated the study, interpreted the results, and contributed to the final version of the manuscript. T.I.L.N. is guarantor of this work, and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Paper II

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Diabetes severity and the role of leisure time physical exercise on cardiovascular mortality: the Nord-Trøndelag Health study (HUNT), Norway

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Abstract

Background: Physical activity has been associated with lower cardiovascular mortality in people with diabetes, but how diabetes severity influence this association has not been extensively studied.

Methods: We prospectively examined the joint association of diabetes severity, measured as medical treatment status and disease duration, and physical exercise with cardiovascular mortality. A total of 56,170 people were followed up for 24 years through the Norwegian Cause of Death Registry. Cox proportional adjusted hazard ratios (HRs) with 95% confidence intervals (CI) were estimated.

Results: Overall, 7,723 people died from cardiovascular disease during the follow-up. Compared to the reference group of inactive people without diabetes, people with diabetes who reported no medical treatment had a hazard ratio (HR) of 1.65 (95% CI: 1.34, 2.03) if they were inactive and a HR of 0.99 (95% CI: 0.68, 1.45) if they reported ≥2.0 hours physical exercise per week. Among people who received oral hypoglycemic drugs or insulin, the corresponding comparison gave HRs of 2.46 (95% CI: 2.08-2.92) and 1.58 (95% CI: 1.21, 2.05), respectively.

Conclusions: The data suggest a more favourable effect of exercise in people with diabetes who used medication than in those who did not, suggesting that physical exercise should be encouraged as a therapeutic measure additional to medical treatment.

Keywords: Diabetes severity, Leisure time physical exercise, Cardiovascular mortality, Epidemiology

Background

Among people with diabetes, the highest risk of death from cardiovascular disease is found in those treated with oral hypoglycemic drugs or insulin [1,2] and in those with longer duration of diabetes [3-6]. The combination of insulin treatment and longer duration of diabetes has been associated with a particular high risk of death from cardiovascular disease [7]. These findings imply that diabetes treatment and duration are important markers for diabetes severity.

Regular physical activity may improve glycaemic control, insulin sensitivity, and cardiovascular risk factors (e.g., blood pressure, lipid profile, and body composition) in people with diabetes [8-11]. It has been reported that the most physically active people with diabetes have approximately half the risk of death from cardiovascular disease, compared to physically inactive people with diabetes, [12,13]. In a recent study, people with diabetes who reported a moderate to high level of leisure time physical exercise had the same risk of death from cardiovascular disease as inactive people without diabetes [14]. However, if the beneficial effect of leisure time physical exercise on cardiovascular mortality among people with diabetes is modified by diabetes severity is not known.

The aim of this prospective follow-up study was therefore to assess whether diabetes severity, measured as medical treatment status and disease duration, influence the role of leisure time physical exercise on cardiovascular mortality.

Methods

Subjects

The HUNT Study is a large population-based health survey in Nord-Trøndelag County in Norway. Between

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1984 and 1986, all inhabitants aged 20 years or older (85,100) were invited to participate in the first wave of the study (HUNT 1) and a total of 77,216 (90.7%) accepted the invitation, filled in a questionnaire and attended a clinical examination. The participants were given a second questionnaire at the clinical examination to complete at home and return in a pre-stamped envelope. All participants in the HUNT Study gave a 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 21,046 participants were excluded at baseline; 4,413 who reported prevalent cardiovascular disease (i.e. angina, myocardial infarction, and/or stroke), 1,003 without sufficient information on diabetes (diagnosis, treatment or duration), 15,227 without information on leisure time physical exercise and 403 without information on potentially confounding factors (i.e. systolic blood pressure, body mass index). After these exclusions, 56,170 participants (27,321 men (mean age= 47.4 years old) and 28,852 women (mean age= 48.5 years old)) were available for follow up on cause of death.

Follow-up

Individual person time at risk of death was calculated from the date of participation in the HUNT 1 study (1984–86) until the date of death or until the end of follow-up 31st December 2008, whichever occurred first. The mandatory reporting of death to the Cause of Death Registry in Norway constitutes the basis for the coding of underlying cause of death. Deaths were classified according to the International Classification of Disease (ICD-9 and ICD-10). Cardiovascular disease was defined by ICD-9: 390–459 and ICD-10: I00-I99, and ischemic heart disease by ICD-9: 410–414 and ICD-10: 120–125.

Study variables

A detailed description of selection procedures, questionnaires, and measurements can be found at http://www.ntnu.edu/hunt and in a report by Holmen and colleagues [15]. Briefly, information was collected on a range of lifestyle and health related factors, including medical history, leisure time physical exercise, smoking status, alcohol consumption and education. Height was measured to the nearest centimetre and weight to the nearest half kilogram, and body mass index (BMI) was calculated as weight (kg) divided by the square value of height (m). Blood pressure was measured two times using a mercury manometer and the mean of the two measures was used.

Diabetes

Participants who answered 'Yes' to the question 'Do you have or have you had diabetes?' in the first questionnaire, were defined as having diabetes (N=1,105).

The second questionnaire included additional questions to those with known diabetes. People who responded 'No' to the questions 'Do you take tablets for your diabetes?' and 'Do you take insulin injections?' were categorized as people without medication, while people who responded 'Yes' to one of the questions were categorized as people with medication. We did not have sufficient power in the statistical analyses to assess the two questions separately. The question 'When were you first diagnosed with diabetes?', provided information on diabetes duration.

Leisure time physical exercise

Information on leisure-time physical exercise was obtained from the second questionnaire. The participants were asked 'How often do you exercise (on the average)?, By exercise we mean going for walks, skiing, swimming and working out/sports' with five mutually exclusive response options: 0, <1, 1, 2–3, ≥4 times per week. Those who reported exercising once a week or more were also asked 'for how long do you exercise each time (average)?', with four mutually exclusive response options: <15, 15–30, 31–60, >60 min. Based on the information of both frequency and duration of exercise we calculated 'hours of leisure time physical exercise per week'. The frequency response option 2–3 times per week was counted as 2.5 times and ≥4 per week counted as five times, whereas the duration response options <15, 15–30, 31–60, >60 min were counted as 10, 25, 45 and 75 min, respectively. For the purpose of the statistical analysis, we categorized this variable into three groups. This resulted in 22,885 physically inactive participants, 24,140 participants performing 0.1-1.9 hours of leisure time physical exercise per week and 8,040 participants performing ≥2.0 hours of leisure time physical exercise per week.

Statistical analyses

A Cox proportional hazard model was used to estimate adjusted hazard ratios (HRs) of death from cardiovascular disease and ischemic heart disease associated with diabetes treatment (with or without oral hypoglycemic drugs or insulin) and duration, and in a separate analysis, to assess the combined association of leisure time physical exercise and diabetes treatment with risk of death. Precision of the estimated hazard ratios was assessed by a 95% confidence interval (CI). All estimated associations were adjusted for possible confounding by attained age (as the time scale) and birth cohort (five years strata). In multivariable models we adjusted for smoking status (never, former, current, unknown), alcohol consumption (0, 1–4, ≥ 5 times last 14 days, total abstainer, unknown), education (<10 years, 10–12 years, >13 years, unknown), body mass index (kg/m^2) and systolic blood pressure (mmHg).

Analyses of the independent association of diabetes treatment were stratified by sex, whereas analyses of the combined association were adjusted for sex in a pooled sample to increase statistical power. The latter was justified by likelihood ratio tests of interaction with sex in the independent analyses of diabetes treatment (P = 0.11) and in the analyses combining diabetes treatment and leisure time physical exercise (P = 0.37).

Additional to the analyses combining leisure time physical exercise and diabetes treatment, we conducted analyses of physical activity stratified by diabetes treatment and tested for possible statistical interaction between the two variables in a likelihood ratio test. Moreover, a likelihood ratio test was used to assess whether the results were modified by age at baseline (< 70 years and ≥ 70 years).

We also conducted three sensitivity analyses; first, people with probable type 1 diabetes (i.e. who were diagnosed with diabetes before 40 years of age and reported insulin injections); second, we excluded the first five years of follow up to evaluate possible bias that could arise if people with the most severe diabetes were unable to be physically active; third, we excluded people who reported a moderate or high degree of movement disability.

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 LP, Texas 77845, USA).

Results

Baseline characteristics of the study population according to diabetes severity are presented in Table 1. During a median follow-up of 23.8 years (1,145,786 person-years), a total of 17,383 people died. Of these, 7,723 people died from cardiovascular disease and 3,518 from ischaemic heart disease. Compared to the 16,633 people who were excluded due to missing data on central variables, the 56,170 included study participants were similar in age (mean age, 49.7 versus 49.1 years), but were less likely to

Table 1 Baseline characteristics of the study population

	No diabetes	Diabetes	
Characteristics		**Without medication***	**With medication***
Men (n=27,318)			
No. of participants	26,815	202	301
Mean age at study entry (SD), years	47.0 (16.7)	65.9 (12.3)	62.2 (17.0)
Mean duration of diabetes (SD), years		6.1 (6.7)	11.9 (10.7)
Mean body mass index (SD), kg/m^2	25.2 (3.2)	26.3 (3.7)	26.2 (3.8)
Mean SBP (SD), mmHg	138.7 (19.7)	155.5 (25.1)	151.1 (25.4)
Hours of leisure time physical exercise per week, %			
Inactive	42.5	47.0	38.2
0.1-1.9 hours	40.5	33.2	35.9
≥ 2.0 hours	17.0	19.8	25.9
Current smoker, %	35.3	31.7	21.0
Alcohol consumption ≥ 5 times last 14 days, %	8.6	7.9	5.3
Women (n=28,852)			
No. of participants	28,250	239	363
Mean age at study entry (SD), years	48.1 (17.0)	67.7 (12.5)	66.7 (13.3)
Mean duration of diabetes (SD), years		5.1 (6.0)	10.5 (8.5)
Mean body mass index (SD), kg/m^2	24.9 (4.4)	28.5 (5.1)	28.5 (5.4)
Mean SBP (SD), mmHg	135.1 (24.9)	163.0 (28.0)	160.2 (26.4)
Hours of leisure time physical exercise per week, %			
None	40.7	43.5	49.0
0.1-1.9 hours	47.0	43.9	34.2
≥ 2.0 hours	12.3	12.6	16.8
Current smoker, %	31.5	13.8	9.1
Alcohol consumption ≥ 5 times last 14 days, %	3.2	1.0	2.2

Abbreviations: *SBP* Systolic blood pressure.
*Medication refers to oral hypoglycemic drugs or insulin.

die from cardiovascular disease (age and sex adjusted HR 0.85, 95% CI: 0.81, 0.88). There was no evidence of departure from the proportional hazards assumption for any of the exposure variables under study.

Table 2 presents the independent association between diabetes treatment, measured as medical treatment status and duration, with risk of death from cardiovascular disease and ischemic heart disease. Compared to people without diabetes, the adjusted HR for cardiovascular death was 1.59 (95% CI: 1.29, 1.96) among men with diabetes who received no medical treatment, and 2.16 (95% CI: 1.80, 2.60) for men with diabetes who used medication. These associations were slightly stronger in women, although no statistical significant interaction with sex was observed (P=0.11). The adjusted HR for cardiovascular death was 1.64 (95% CI: 1.34, 2.00) in diabetic women without medication and 2.85 (95% CI: 2.43, 3.34) for those who used medication. Overall, the corresponding analyses of death from ischaemic heart disease gave slightly stronger associations in both men and women.

In a sensitivity analysis we excluded 113 participants (39 men and 74 women) with possible type 1 diabetes, but the results remained largely unchanged. The HRs for people with diabetes who used medication was 2.23 (95% CI: 1.83, 2.71) in men and and 2.82 (95% CI: 2.36, 3.37) in women (data not shown). Moreover, tests of interaction suggest a possible modifying effect of age ($P_{\text{interaction}}$ = 0.01 in men and 0.03 in women), with a slightly weaker association in the oldest age groups (≥70 years). However, stratified analyses showed that all associations between diabetes treatment status and mortality remained statistically significant in both age groups (data not shown).

The association between diabetes duration and mortality are also presented in Table 2, displaying the HRs after subdividing each of the medical treatment categories into two categories of disease duration. Overall, disease duration was not strongly related to mortality from cardiovascular disease, although the HRs were generally slightly stronger in the subgroup of longer duration (i.e. ≥5 years for persons without medical treatment, and ≥10 years for those

Table 2 Hazard ratios (HRs) for death from cardiovascular disease associated with diabetes treatment and disease duration

		Death from cardiovascular disease			Death from ischaemic heart disease		
Mortality	**No. of person-years**	**No. of deaths**	**HR***	**HR† (95% CI)**	**No. of deaths**	**HR***	**HR† (95% CI)**
Men							
No diabetes	545,005	3,802	1.00	1.00 (reference)	1,980	1.00	1.00 (reference)
Diabetes without medication‡	2,553	91	1.67	1.59 (1.29-1.96)	49	1.85	1.73 (1.30-2.31)
Diabetes with medication‡	3,739	120	2.09	2.16 (1.80-2.60)	70	2.47	2.53 (1.99-3.22)
No diabetes	545,005	3,802	1.00	1.00 (reference)	1,980	1.00	1.00 (reference)
Diabetes without medication‡							
<5 years	1,354	49	1.59	1.54 (1.16-2.05)	29	2.03	1.91 (1.32-2.77)
≥5 years	1,199	42	1.78	1.66 (1.22-2.26)	20	1.65	1.53 (0.98-2.38)
Diabetes with medication‡							
<10 years	1,967	71	2.01	2.01 (1.59-2.55)	42	2.40	2.39 (1.76-3.26)
≥10 years	1,772	49	2.22	2.42 (1.82-3.22)	28	2.57	2.77 (1.90-4.04)
Women							
No diabetes	597,934	3,442	1.00	1.00 (reference)	1,297	1.00	1.00 (reference)
Diabetes without medication‡	3,327	100	1.88	1.64 (1.34-2.00)	41	2.00	1.65 (1.21-2.26)
Diabetes with medication‡	4,228	168	3.12	2.85 (2.43-3.34)	81	3.78	3.44 (2.73-4.33)
No diabetes	597,934	3,442	1.00	1.00 (reference)	1,297	1.00	1.00 (reference)
Diabetes without medication‡							
<5 years	2,087	60	1.75	1.61 (1.25-2.09)	23	1.75	1.55 (1.03-2.35)
≥5 years	1,240	40	2.12	1.67 (1.22-2.29)	18	2.45	1.80 (1.12-2.87)
Diabetes with medication‡							
<10 years	2,371	104	3.00	2.74 (2.25-3.35)	45	3.26	2.98 (2.20-4.04)
≥10 years	1,857	64	3.36	3.04 (2.37-3.91)	36	4.71	4.25 (3.03-5.95)

Abbreviations: *CI* confidence interval, *HR* hazard ratio.

* Adjusted for age (as the time scale) and birth cohort (5 years strata).

† Adjusted for age (as the time scale) and birth cohort (5 years strata), smoking (never, former, current, unknown), education (<10 years, 10–12 years, >13 years, unknown), alcohol (0, 1–4, ≥ 5 times last 14 days, total abstainer, unknown), systolic blood pressure, body mass index and hours of leisure time physical exercise per week (inactive, 0.1-1.9 hours, ≥ 2.0 hours).

‡Medication refers to oral hypoglycemic drugs or insulin.

with medical treatment). The slightly stronger associations with longer duration were somewhat more evident in the analyses of ischemic heart disease.

There was statistical evidence of interaction between diabetes treatment and hours of leisure time physical exercise per week (P <0.001), suggesting that the favorable effect of physical activity were larger in people with more severe diabetes. Table 3 shows the combined association of diabetes treatment and hours of leisure time physical exercise per week with death from cardiovascular disease and ischemic heart disease, using inactive people without diabetes as the reference group for all comparisons. In people with diabetes who did not use medication, the adjusted HR for cardiovascular death was 1.65 (95% CI: 1.34, 2.03) for inactive people and 0.99 (95% CI: 0.68, 1.45) for those who reported ≥ 2.0 hours of leisure time physical exercise per week. Among people with more severe diabetes (i.e. those who used medication), the adjusted HR for cardiovascular death was 2.46 (95% CI: 2.08, 2.92) in people who were inactive and 1.58 (95% CI: 1.21, 2.05) for those who reported ≥ 2.0 hours of leisure time physical exercise per week. People with diabetes who exercised 0.1-1.9 hours per week had approximately similar HRs as those who were inactive. A similar pattern was observed for death from ischaemic heart disease, although the difference in HRs between inactive people and the most active were somewhat larger.

These combined effects were further explored in analyses of leisure time physical exercise stratified by diabetes status and treatment. Compared to being inactive, ≥2.0 hours of physical activity per week was associated with an adjusted HR of 0.84 (0.89-0.89) in people without diabetes, a HR of 0.79 (95% CI: 0.56, 1.11) in people with diabetes who received no medical treatment, and a HR of 0.49 (95% CI: 0.56, 1.11) in people with diabetes who were medically treated (data not shown).

In sensitivity analyses, we excluded the first five years of follow up, and then also people who reported a moderate or high degree of movement disability. Both analyses gave largely similar results as those presented above (data not shown).

Discussion

In this large population based cohort study, less severe diabetes that was not medically treated was associated with a 60 per cent increased risk of death from cardiovascular disease, whereas more severe diabetes treated with oral agents or insulin was associated with a two-fold increased risk in men and a nearly three-fold higher risk in women. Within each category of treatment status, disease duration was not strongly associated with mortality. Leisure time physical exercise reduced the risk of death from cardiovascular disease in both categories of diabetes severity, but there was evidence of a stronger association in people with more severe diabetes. Corresponding analyses of death from ischaemic heart disease gave slightly stronger associations, although the precision of the estimated associations were lower.

The results of the present study are in agreement with previous prospective studies, showing that people with

Table 3 Hazard ratios (HRs) for death from cardiovascular disease and ischaemic heart disease associated with diabetes treatment and leisure time physical exercise

		Death from cardiovascular disease			Death from ischaemic heart disease		
Hours of leisure time physical exercise per week	No. of person-years	No. of deaths	HR*	HR† (95% CI)	No. of deaths	HR*	HR† (95% CI)
Without diabetes							
Inactive	468,436	3,108	1.00	1.00 (reference)	1,391	1.00	1.00 (reference)
0.1-1.9 hours	514,603	2,759	0.78	0.83 (0.79-0.87)	1,256	0.79	0.86 (0.80-0.93)
≥ 2.0 hours	159,901	1,377	0.77	0.84 (0.79-0.89)	630	0.80	0.88 (0.80-0.97)
Diabetes without medication‡							
Inactive	2,359	95	1.74	1.65 (1.34-2.03)	48	2.04	1.90 (1.42-2.54)
0.1-1.9 hours	2,514	69	1.45	1.44 (1.13-1.83)	30	1.50	1.48 (1.03-2.13)
≥ 2.0 hours	1,008	27	1.06	0.99 (0.68-1.45)	12	1.08	1.02 (0.58-1.80)
Diabetes with medication‡							
Inactive	3,151	140	2.49	2.46 (2.08-2.92)	70	2.91	2.92 (2.29-3.72)
0.1-1.9 hours	3,233	91	2.48	2.64 (2.14-3.25)	57	3.41	3.67 (2.81-4.79)
≥ 2.0 hours	1,583	57	1.49	1.58 (1.21-2.05)	24	1.39	1.49 (0.99-2.23)

Abbreviations: *CI* confidence interval, *HR* hazard ratio.
*Adjusted for age (as the time scale) and birth cohort (5 years strata), sex (male, female).
†Adjusted for age (as the time scale) and birth cohort (5 years strata), sex (male, female), smoking (never, former, current, unknown), education (<10 years, 10–12 years, >13 years, unknown), alcohol (0, 1–4, ≥ 5 times last 14 days, total abstainer, unknown), systolic blood pressure, body mass index.
‡Medication refers to oral hypoglycemic drugs or insulin.

diabetes treated with oral hypoglycemic drugs or insulin have a higher risk of death from cardiovascular disease than those without medication [1,2]. Several studies have reported a positive association between diabetes duration and cardiovascular mortality [3-7], but we did not find any strong effect of diabetes duration on cardiovascular mortality when diabetes treatment was taken into account. Although there was no statistically significant interaction between sex and diabetes treatment in the present study, the association between diabetes treatment and cardiovascular mortality was somewhat stronger in women than in men. Previous studies have also reported a stronger association of diabetes with cardiovascular mortality in women than in men [16,17].

Findings from observational studies suggest that people with diabetes who are physically active have approximately half the relative risk of death from cardiovascular disease compared to inactive people with diabetes [12,13], although different methods for measuring physical activity make comparisons between studies difficult. The results from the present study suggest a differential effect of physical exercise on cardiovascular mortality by diabetes severity, showing that the favorable effect of exercise was relatively stronger in those who reported medical treatment than in those who did not. The beneficial effect of leisure time physical exercise on cardiovascular mortality in people with diabetes may be explained by the sum of improvements in cardiovascular disease risk factors. These risk factors may be more prevalent in medically treated diabetes. Studies have reported increased cardiovascular mortality associated with hyperglycaemia, hypertension, dyslipidaemia and overweight in people with diabetes [13,18-20], whereas regular physical exercise has been shown to improve the same risk factors [8-11,21]. Moreover, a recent review suggests that regular physical exercise could reduce the use of antidiabetic drugs in people with type 2 diabetes [22].

The strengths of the present study include the population-based sample, the prospective design, the large number of participants, the long follow-up period and the ascertainment of causes of death through the Cause of Death Registry at Statistics Norway.

Limitations of the study include the assessment of diabetes and leisure time physical exercise with a questionnaire at baseline. The self-reported diagnosis of diabetes in HUNT 1 was validated in a separate study [23], showing that 96.4% of the self-reported diabetes could be verified in medical files. Still, unknown diabetes could have underestimated the association between diabetes and cardiovascular mortality. It is also possible that the observed associations between diabetes treatment and cardiovascular mortality could depend on the type of diabetes. We had no information on type 1 or type 2 diabetes, but a sensitivity analysis excluding people who were diagnosed with diabetes before <40 years of age and who reported to use insulin injection suggest no large bias of the results. It should also be noted that diabetes treatment and duration is a rough estimate of diabetes severity. Unfortunately, we did not have information on glycaemic control. Nevertheless, the evidence of a dose-dependent association across diabetes treatment indicates that our classification is able to capture some of the variation in severity among people with diabetes. The physical activity questionnaire used in this study has been validated against more objective measures of fitness and activity, such as VO_2max and ActiReg, in a subsample of young men [24]. The questionnaire was reported to have good repeatability and provide a useful measure of leisure time physical exercise. It is possible that the reported exercise volume may be overestimated due to subjective interpretations. However, if the reported exercise volume is overestimated, the presented associations between exercise and mortality is likely to be underestimated. Also, the effects of exercise may be different in young and elderly people. In the present study, only information on frequency and duration was used to classify participants. We acknowledge that exercise intensity could be of importance for cardiovascular health, but analyses stratified according to exercise intensity were not possible due to limited statistical power. Leisure time physical exercise was only measured at baseline, and information on prior changes due to diabetes diagnosis or subsequent changes throughout the follow-up period was not available. Such changes in physical activity could both attenuate and strengthen the estimated association. Also, new cases of diabetes and more people with diabetes receiving medical treatment could result in an underestimated association with mortality. Finally, a substantial proportion of participants were excluded due to missing information on physical exercise and possible selection bias cannot be ruled out.

Conclusions

In conclusion, the results from this prospective cohort study show a positive association between diabetes severity, measured by treatment status, and mortality from cardiovascular disease and ischemic heart disease. Leisure time physical exercise was associated with reduced mortality, and this association was especially strong among people with diabetes who reported medical treatment compared to those who did not. This suggests that physical exercise should be encouraged as a therapeutic measure additional to medical treatment.

Competing interests

No potential conflicts of interest relevant to this article were reported.

Authors' contributions

BM prepared and analyzed the data, interpreted the results, drafted the manuscript, and contributed to the final version of the manuscript. LBA interpreted the results and contributed to the final version of the manuscript. TILN initiated the study, interpreted the results, and contributed

to the final version of the manuscript. TILN is guarantor of this work, and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Paper III

Full title

The adverse association of diabetes on first acute myocardial infarction is modified by physical activity and body mass index. Prospective data from the HUNT Study, Norway.

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Aim/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 body mass index (BMI), on 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 hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated.

Results Overall, 1,887 incident AMI occurred during 12.3 years. Compared to inactive people without diabetes, inactive people with diabetes had a 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, 1.73). Normal weight (BMI 18.5-25 kg/m^2) persons with diabetes had a HR of 1.60 (95% CI: 1.05-2.44) and obese (BMI >30 kg/m^2) persons with diabetes had a HR of 2.55 (95% CI: 1.97, 3.29) compared to 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.

Key words Acute myocardial infarction, Diabetes mellitus, Epidemiology, Physical activity

Abbreviations

AMI: acute myocardial infarction

HR: hazard ratio

Diabetes induce vascular dysfunction that predisposes to atherosclerosis [1, 2], and is associated with about a two-fold 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, the 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 at least 150 minutes per week and to reduce or maintain their body weight [7, 8]. Physical activity can improve glycemic control and insulin sensitivity, as well as conventional cardiovascular risk factors such as blood pressure and blood lipids [9-12]. Correspondingly, people with a body mass index <25 kg/m^2 have better glycemic 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 body mass index could modify the association between diabetes and risk of AMI among people without existing cardiovascular disease.

METHODS

Subjects

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 (HUNT 2) and a total of 64,961 (70%) accepted the invitation, completed questionnaires, and attended a clinical examination. All participants in the HUNT Study gave a 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 body mass index, 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 the HUNT 2 study (1995-97), the participants were followed-up until a diagnosed first AMI or until the end of follow-up 31st 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 and ICD-10. 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 (1st definition of myocardial infarction [17] and 2nd

universal definition of myocardial infarction [18]). Central in the diagnosis is the rice 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 CK and CK-MB 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: Ischemic symptoms (mostly chest discomfort or dyspnea)/ changes of the electrocardiogram (ECG) indicative of ischemia (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 approximately 5% of the infarctions are 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 http://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 subjects without shoes (height to the nearest centimetre, weight to the nearest half kilogram, and waist and hip circumference to the nearest centimetre). Body mass index was calculated as weight (kg) divided by the squared value of height (m). For the purpose of the statistical analysis people were defined as normal weight (<25.0 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥30 kg/m^2). In the former group, 2.5 % had a body mass index <18.5 kg/m^2, 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 centrifuging before the 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 cholesterolesterase 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). Persons who answered 'No' to the diabetes question above, but who presented with a non-fasting glucose level ≥11mmol/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 the invited) took part in these investigations, where blood glucose, serum C-peptide and GADA were measured in a fasting state. In addition, GADA was analyzed in cases declaring diabetes but not attending the follow-up and having serum available from a non-fasting state (*N* = 228). Among those attending the follow-up information, those with an anti-GAD level $\geq$ 8.0 or an anti-GAD < 8.0 and a C-peptid < 150 pmol/l were classified as having type 1 diabetes. Among those not attending the follow-up, only the former diagnostic criteria (anti-GAD level $\geq$ 8.0) was used to classify diabetes type 1. 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 weekly hours of light and/or hard leisure time physical activity during the past year, with four response options (0, <1, 1-2, and ≥3 hours) 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 information on hours of both light and hard activity during a week, providing information on total leisure time physical activity level. The participants were classified into the following four categories of leisure time physical activity; inactive (no light or hard activity), low (<3 hours light and/or <1 hour hard activity), medium (≥3 hours light and/or <1 hour hard activity), and high (any light and ≥1 hour hard activity). To increase statistical power, those with a low and medium level of physical activity was collapsed into one group ('low/medium').

Statistical analyses

A Cox proportional hazard model was used to estimate adjusted hazard ratios (HRs) of first AMI associated with diabetes, and in separate analyses, to assess the combined association of physical activity and diabetes, and body mass index and diabetes, with the risk of AMI. We also combined the information on body mass index and physical activity to examine risk of AMI among people with diabetes. Precision of the estimated hazard ratios was assessed by a 95% confidence interval (CI). All estimated associations were adjusted for possible confounding by attained age (as the time scale) and birth cohort (five years strata). In multivariable models we adjusted for smoking status (never, former, current, unknown),

alcohol consumption (never, not the last 4 weeks, 1-3 units the last 4 weeks, more than 4 units the last 4 weeks), education (<10 years, 10-12 years, >13 years, unknown), body mass index (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. Finally, in an additive model we estimated the relative excess risk due to interaction (RERI) between physical activity and diabetes, as wells as between body mass index and diabetes. We used a method described by Anderrson et al. 2005, to calculate 95% CIs around the RERI estimate[23]. 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 LP, Texas 77845, 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 to 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 versus 65.0 years) and had a lower risk of death from cardiovascular disease (age and sex adjusted HR: 0.79, 95% CI: 0.72, 0.86).

Table 2 presents the associations of diabetes with the risk of a first AMI among people without cardiovascular disease at baseline. Both men and women with diabetes (N = 1,366) had a higher risk of myocardial infarction than people without diabetes (Table 2). 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 >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 (data not shown). 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 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 Supplementary 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 hour of hard activity) 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

both people with and without diabetes (P_{trend} =0.019 and 0.010, respectively). Supplementary 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 to the reference group of inactive persons without diabetes, inactive persons with diabetes had a HR of 2.37 (95% CI: 1.58, 3.57), whereas people with diabetes who reported ≥ 3 hours of light physical activity per week had a HR of 1.50 (95% CI: 0.94, 2.39). Correspondingly, the HR among persons without diabetes who also reported ≥ 3 hours 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 ≥3 hours of hard physical activity).

Sensitivity analyses were we first excluded 185 persons who were likely to have diabetes type 1 (Supplementary table 3) and second, excluded the first three years of follow up to avoid possible bias by pre-clinical disease (Supplementary table 4) gave largely similar results 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 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 (Supplementary 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 0.64 (95% CI: 0.41, 1.00), 0.47 (95% CI: 0.24, 0.91), respectively. The associations were similar without stratifying on diabetes.

Figure 1b (and Supplementary table 6) presents the joint associations of diabetes and body mass index with the risk of first AMI, using normal weight people (18.5-25 kg/m^2) without diabetes as the reference group for all comparisons. In people without diabetes the HRs were 1.12 (95% CI: 1.00, 1.25) for those who were overweight (25-29.9 kg/m^2) and 1.28 (95% CI: 1.11, 1.47) for those who were obese (≥ 30 kg/m^2). In people with diabetes, the HRs were 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 a HR of 1.01 (95% CI: 1.02,1.04) among people with diabetes and a HR of 1.02 (95% CI: 1.01, 1.04) in those without diabetes.

In Table 3 we combined the information on body mass index and leisure time physical activity level to examine risk of AMI among people with diabetes. Compared to the reference group of participants with a body mass index ≥25 kg/m^2 and an inactive/low level of physical activity, people with a medium/high level of activity and a body mass index ≥25 kg/m^2 had a HR of 0.90 (95% CI: 0.64, 1.26). Among people with a body mass index between 18.5-25 kg/m^2, the HRs were 0.89 (95% CI: 0.48, 1.64) among those who had an inactive/low level of physical activity, and 0.51 (95% CI: 0.26, 0.99) among 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 on risk of AMI were modified by both leisure time physical activity and body mass

index. Diabetes was associated with more than two-fold increased risk among those who reported being physically inactive, whereas those reporting a high physical activity level had largely similar risk as inactive people without diabetes. Also among obese people, diabetes was associated with a more than two-fold increased risk of AMI, whereas this risk was substantially lower among normal weighted people. Among people with diabetes, the most physically active and with normal weight had half the risk of those who were least physically active and overweight or obese.

To our knowledge, the present study is the first study to show that physical activity and body mass index modifies the association between diabetes and risk of AMI among people without existing cardiovascular disease. Similar to the present study, previous studies have showed that diabetes increase the risk of AMI [3-5] with a stronger association among women than men [4, 5], and that the most physically active people with diabetes have approximately half the risk of cardiovascular death compared to 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 body mass index have been reported to have lower risk of death from cardiovascular disease, than obese people with diabetes [27]. The Look AHEAD Research Group recently reported that an intensive lifestyle intervention that promoted weight loss through caloric 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 five year period was associated with a considerably lower risk of cardiovascular disease than 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, either identified 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 HUNT 1 was validated in a separate study [23], 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 ≥11mmol/l as a cut-off for diabetes, although a similar procedure has been used in previous studies [20-22] People being diagnosed with diabetes during the follow-up could have underestimated the associations between diabetes and myocardial infarction. We did not have data on cardiorespiratory fitness, which have been suggested as a more important predictor for cardiovascular outcomes than both physical activity [30] and obesity [31]. Nevertheless, regularly performed physical activity have been shown to improve physical fitness in people with type 2 diabetes [32], suggesting that self-reported physical activity, at least to some degree, may reflect the participants physical fitness. The question about hard activity in the present study have been found to correlate well with VO_{2max} in a subsample of young men, while light activity showed no correlation [33]. Although light activity did not correlate with VO_{2max}, it may elicit other biological mechanisms that are beneficial for cardiovascular health (e.g. improved glycaemic control) [33]. A recent study which 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 [34]. It has also been reported that the most prevalent leisure time behaviour, television viewing, is associated with increased risk of cardiovascular disease, independently of total level of physical activity [35]. These studies suggest that light intensity physical activity and reduced sedentary behaviour may have beneficial effects without improved cardiorespiratory fitness. Also, because the questions did not distinguish between resistance and endurance training, differences associated with the two types of activity could not be estimated. Subjective interpretation of the activity questions could have influenced the results. 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 [36]. 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 [37]. Although it is possible that some people could have been hospitalized in another county (e.g. people living near the county border), and thus not registered with AMI in our data, this misclassification is not likely to be differential between people with and without diabetes.

There are several possible interrelated mechanisms that may explain how physical activity and maintaining a normal body weight could reduce risk of first AMI among 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 body mass index have

better glycemic 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 bodyweight 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 two-fold increased risk of a first AMI, compared to inactive people without diabetes. This excess risk was cancelled out among 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 acute myocardial infarction among people with diabetes.

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Duality of interest

The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement

All of the authors listed helped with the conception/design of the study as well as 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. Tom Ivar Lund Nilsen is the guarantor of this work.

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Table 1. Baseline characteristics of the study population

Characteristics	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 body mass index (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], n (%)				
Inactive	62 (8.5)	1,623 (6.3)	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)
Body mass index, n (%)				
Normal weight (<25.0 kg/m^2)	168 (23.0)	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, n(%)	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, 2), low (<3 hours light and/or <1 hour hard activity), medium (≥3 hours light and/or <1 hour hard activity), and high (any light and >1 hour hard activity).

[b]Four times or more during last month

Table 2. Hazard ratios (HRs) for first acute myocardial infarction associated with diabetes

	Men					Women				
Diabetes status	No. of person-years	No. of AMI	HR[a]	HR[b]	(95% CI)	No. of person-years	No. of AMI	HR[a]	HR[b]	(95% CI)
No diabetes	297,943	1,148	1.00	1.00	(reference)	343,191	567	1.00	1.00	(reference)
Diabetes	7,265	89	1.55	1.49	(1.20-1.86)	6,529	83	2.73	2.76	(2.17-3.51)

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; HR, hazard ratio

[a]Adjusted for age (as the time scale) and birth cohort (5 years strata).

[b]Adjusted for age (as the time scale) and birth cohort (5 years strata), smoking status (never, former, current, unknown), alcohol consumption (never, not the last 4 weeks, 1-3 units the last 4 weeks, more than 4 units the last 4 weeks), education (<10 years, 10-12 years, >13 years, unknown), total serum cholesterol (mmol/l), systolic blood pressure (mmHg), BMI (kg/m^2), and leisure time physical activity level each week (inactive, low / medium, high).

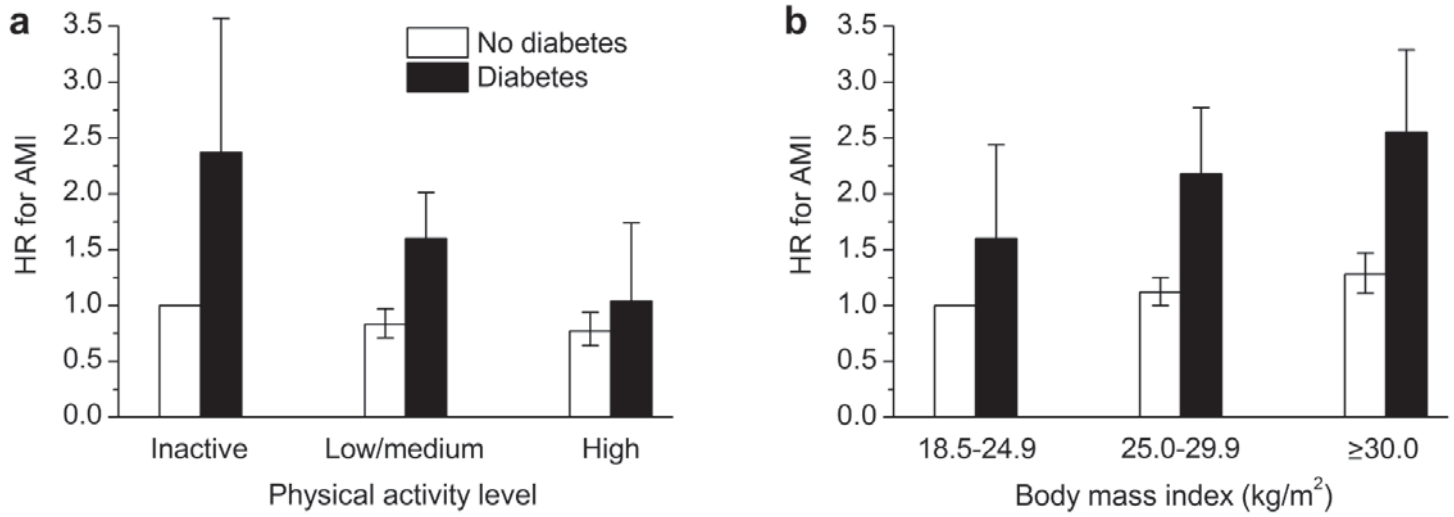

Fig. 1 The combined association of diabetes and leisure time physical activity level on risk of first acute myocardial infarction compared to inactive people without diabetes **(a)** and the combined association of diabetes and body mass index on risk of first acute myocardial infarction compared to normal weight people without diabetes **(b)**. Fig. 1a were adjusted for age (as the time scale) and birth cohort (5 years strata), sex (man, woman), smoking status (never, former, current, unknown), alcohol consumption (0, 1, 2-3, ≥4 times last month, total abstainer, unknown), education (<10 years, 10-12 years, >13 years, unknown), BMI (kg/m^2), systolic blood pressure (mmHg), and total serum cholesterol (mmol/l). Fig. 1b were adjusted for age (as the time scale) and birth cohort (5 years strata), sex (man, woman), smoking status (never, former, current, unknown), alcohol consumption (0, 1, 2-3, ≥4 times last month, total abstainer, unknown), 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).

Table 3. The combined association of diabetes and body mass index on risk of first acute myocardial infarction compared to overweight people without diabetes.

	Body mass index ≥25 kg/m^2					Body mass index 18.5-24.9 kg/m^2				
Physical activity level[a]	No. of person-years	No. of AMI	HR[b]	HR[c]	(95% CI)	No. of person-years	No. of AMI	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)

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; HR, hazard ratio;

[a]Activity level defined as inactive (no light or hard activity, 2), low (<3 hours light and/or <1 hour hard activity), medium (≥3 hours light and/or <1 hour hard activity), and high (any light and >1 hour hard activity).

[b]Adjusted for age (as the time scale) and birth cohort (5 years strata), sex (man, woman).

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

Supplementary table 1. The combined association of diabetes and leisure time physical activity level on risk of first acute myocardial infarction compared to inactive people without diabetes.

	No diabetes					Diabetes				
Physical activity level[a]	No. of person-years	No. of AMI	HR[b]	HR[c]	(95% CI)	No. of person-years	No. of AMI	HR[a]	HR[c]	(95% CI)
Inactive	36,263	182	1.00	1.00	(reference)	1,145	27	2.09	2.37	(1.58-3.57)
Low/medium	422,549	1,233	0.74	0.83	(0.71-0.97)	9,999	129	1.49	1.60	(1.28-2.01)
High	182,321	300	0.63	0.77	(0.64-0.94)	2,446	16	0.90	1.04	(0.62-1.74)

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; HR, hazard ratio;

[a]Activity level defined as inactive (no light or hard activity, 2), low (<3 hours light and/or <1 hour hard activity), medium (≥3 hours light and/or <1 hour hard activity), and high (any light and >1 hour hard activity).

[b]Adjusted for age (as the time scale) and birth cohort (5 years strata), sex (man, woman).

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

Supplementary table 2. The combined association of diabetes and light leisure time physical activity on risk of first acute myocardial infarction among people who reported no hard physical activity per week, compared to inactive people without diabetes

	No diabetes					Diabetes				
Light physical activity	No. of person-years	No. of AMI	HR[a]	HR[b]	(95% CI)	No. of person-years	No. of AMI	HR[a]	HR[b]	(95% CI)
Inactive	36,263	182	1.00	1.00	(reference)	1,145	27	2.09	2.37	(1.58-3.57)
<1 hour	49,072	141	0.81	0.92	(0.74-1.15)	1,095	17	2.02	2.14	(1.29-3.53)
1-2 hours	64,122	189	0.72	0.81	(0.66-1.00)	1,555	22	1.48	1.62	(1.03-2.53)
≥3 hours	37,836	158	0.64	0.78	(0.63-0.97)	1,102	20	1.46	1.50	(0.94-2.39)

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; HR, hazard ratio;

[a]Adjusted for age (as the time scale) and birth cohort (5 years strata), sex (man, woman).

[b]Adjusted for age (as the time scale) and birth cohort (5 years strata), sex (man, woman), smoking status (never, former, current, unknown), alcohol consumption (0, 1, 2-3, ≥4 times last month, total abstainer, unknown), education (<10 years, 10-12 years, >13 years, unknown), BMI (kg/m^2), systolic blood pressure (mmHg), and total serum cholesterol (mmol/l).

Supplementary table 3. The combined association of diabetes and leisure time physical activity level on risk of first acute myocardial infarction, excluding people who the 185 persons who were likely to have diabetes type 1, compared to inactive people without diabetes

	No diabetes					Diabetes				
Physical activity level[a]	No. of person-years	No. of AMI	HR[b]	HR[c]	(95% CI)	No. of person-years	No. of AMI	HR[a]	HR[c]	(95% CI)
Inactive	36,263	182	1.00	1.00	(reference)	1,203	27	2.17	2.41	(1.60-3.61)
Low/medium	422,549	1,233	0.74	0.83	(0.71-0.97)	8,605	115	1.47	1.57	(1.24-1.99)
High	182,321	300	0.63	0.78	(0.64-0.94)	1,937	13	0.88	0.97	(0.55-1.71)

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; HR, hazard ratio;

[a]Activity level defined as inactive (no light or hard activity, 2), low (<3 hours light and/or <1 hour hard activity), medium (≥3 hours light and/or <1 hour hard activity), and high (any light and >1 hour hard activity).

[b]Adjusted for age (as the time scale) and birth cohort (5 years strata), sex (man, woman).

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

Supplementary table 4. The combined association of diabetes and leisure time physical activity level on risk of first acute myocardial infarction, excluding the first three years of follow up to avoid possible bias by pre-clinical cardiovascular disease (supplementary table 3), compared to inactive people without diabetes

	No diabetes					Diabetes				
Physical activity level[a]	No. of person-years	No. of AMI	HR[b]	HR[c]	(95% CI)	No. of person-years	No. of AMI	HR[a]	HR[c]	(95% CI)
Inactive	26,601	136	1.00	1.00	(reference)	861	21	2.51	2.88	(1.81-4.58)
Low/medium	315,951	964	0.74	0.82	(0.69-0.99)	7,097	96	1.50	1.61	(1.24-2.10)
High	137,541	239	0.61	0.76	(0.61-0.94)	1,844	12	0.88	1.02	(0.56-1.84)

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; HR, hazard ratio;

[a]Activity level defined as inactive (no light or hard activity, 2), low (<3 hours light and/or <1 hour hard activity), medium (≥3 hours light and/or <1 hour hard activity), and high (any light and >1 hour hard activity).

[b]Adjusted for age (as the time scale) and birth cohort (5 years strata), sex (man, woman).

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

Supplementary table 5. The association of leisure time physical activity level on risk of first acute myocardial infarction among people with and without diabetes, compared to inactive people with and without diabetes respectively

	No diabetes					Diabetes				
Physical activity level[a]	No. of person-years	No. of AMI	HR[b]	HR[c]	(95% CI)	No. of person-years	No. of AMI	HR[b]	HR[c]	(95% CI)
Inactive	36,263	182	1.00	1.00	(reference)	1,145	27	1.00	1.00	(reference)
Low/medium	422,549	1,233	0.74	0.83	(0.71-0.97)	9,999	129	0.70	0.64	(0.41-1.00)
High	182,321	300	0.62	0.78	(0.64-0.94)	2,446	16	0.49	0.47	(0.24-0.91)

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; HR, hazard ratio;

[a]Activity level defined as inactive (no light or hard activity, 2), low (<3 hours light and/or <1 hour hard activity), medium (≥3 hours light and/or <1 hour hard activity), and high (any light and >1 hour hard activity).

[b]Adjusted for age (as the time scale) and birth cohort (5 years strata), sex (man, woman).

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

Supplementary table 6. The combined association of diabetes and body mass index on risk of first acute myocardial infarction compared to normal weight people without diabetes.

	No diabetes					Diabetes				
Body mass index[a]	No. of person-years	No. of AMI	HR[b]	HR[c]	(95% CI)	No. of person-years	No. of AMI	HR[b]	HR[c]	(95% CI)
Normal weight	269,995	494	1.00	1.00	(reference)	2,952	23	1.61	1.60	(1.05-2.44)
Overweight	272,397	859	1.14	1.12	(1.00-1.25)	5,658	80	2.18	2.18	(1.71-2.77)
Obese	94,295	356	1.36	1.28	(1.11-1.47)	5,164	69	2.63	2.55	(1.97-3.29)

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; HR, hazard ratio;

[a]Body mass index defined as obese (≥30 kg/m^2), overweight (25-29.9 kg/m^2) and normal weight (18.5-24.9 kg/m^2)

[b]Adjusted for age (as the time scale) and birth cohort (5 years strata), sex (man, woman).

[c]Adjusted for age (as the time scale) and birth cohort (5 years strata), sex (man, woman), smoking status (never, former, current, unknown), alcohol consumption (0, 1, 2-3, ≥4 times last month, total abstainer, unknown), 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).