Diabetes and Cardiovascular Mortality: The Role of Physical Activity

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Abstract

Background An increased level of physical activity may reduce the risk of death from cardiovascular diseases (CVD), whilst diabetes increases risk of CVD mortality. However, whether physical activity may compensate for the adverse effects of diabetes remains to be investigated. Hence, the aim of this study is to assess the independent effect of diabetes and leisure time physical activity on CVD mortality, and also to examine the combined effect of leisure time physical activity and diabetes on risk of death from cardiovascular disease.

Methods The HUNT 2 study is the second wave of a large, population-based, longitudinal health study in the county of Nord-Trøndelag, Norway. A total of 59193 participants aged 20 years and older, without known cardiovascular diseases (CVD), were followed through a linkage with the Cause of Death Registry from baseline in 1995-1997 until the date of death, or until the end of follow-up December 31, 2005. 1537 individuals were defined as having diabetes at baseline. Hazard ratios (HRs) of death from CVD and ischemic heart disease (IHD) were estimated from Cox proportional hazard analysis with adjustment for potential confounding factors.

Results The HR of CVD death associated with diabetes was 1.94 (95% confidence interval (CI), 1.53-2.45) for men and 1.72 (95% CI, 1.33-2.22) for women. The corresponding risk of death from IHD was approximately two-fold, both in men and women. Participants who reported at least four hours of total physical activity each week had half the risk of CVD deaths compared to the least active. A similar effect was found for IHD mortality. In analysis of the combined effect, the least active persons with diabetes had more than twice the risk of death from CVD and IHD compared to the reference group of non-diabetic persons with the lowest activity level. On the other hand, individuals with diabetes who attended at least four hours of physical activity each week had a HR of 0.81 (95% CI, 0.41-1.63) for CVD mortality and 0.95 (95% CI, 0.35-2.59) for IHD mortality compared to the reference group.

Conclusion Persons with diabetes had approximately twice the risk for death from CVD and IHD compared to persons without diabetes. However, highly active people with diabetes had a risk of death that was equal to or even lower than the least active persons without diabetes, suggesting that high levels of physical activity may compensate for the risk-increasing effect of diabetes on cardiovascular mortality.

Keywords Diabetes ĀCardiovascular disease ĀIschemic heart disease ĀMortality ĀPhysical activity ĀFollow-up

Contents

Introduction

The World Health Organization (WHO) estimates that more than 220 million people worldwide have diabetes (1). Diabetes is associated with increased risk of fatal cardiovascular events. A large cohort study suggests that between five and eight percent of all cardiovascular deaths in the second half of the 20th century could be attributed to diabetes (2). Cardiovascular diseases (CVD) are a group disorders in the heart and blood vessels, including ischemic heart disease (IHD) (3). Recent studies have shown that individuals with diabetes have a two- to four-fold higher risk of dying from IHD compared with individuals without diabetes (4, 5). Worldwide, 17.1 million people died from CVD in 2004, and makes it the number one cause of death in a global perspective, accounting for almost one third of all deaths (3).

Diabetes is a chronic disease that occurs when the pancreas is unable to produce enough insulin (i.e., type 1 diabetes), or alternatively, when the body is unable to effectively use the available insulin (i.e., type 2 diabetes) (1, 6). Uncontrolled diabetes leads to hyperglycemia which over time may cause damage to many systems in the human body (7). Hyperglycemia promotes atherosclerosis through three major mechanisms; accumulation of advanced glycosylation end products (8, 9), oxidative stress and protein kinase C activation (8). Atherosclerosis is a process that leads to a group of diseases characterized by a thickening of artery walls, which limits blood supply (3, 10, 11). Atherosclerosis causes many deaths from heart attacks and accounts for nearly 75 percent of all deaths from CVD (10).

Physical activity (PA) seems to be of major importance with respect to enhancing and maintaining health (12). Physical activity has been associated with a reduced incidence of type 2 diabetes (13) and has been inversely associated with cardiovascular morbidity (14) and mortality (15). Despite the numerous health benefits of physical activity, at least 60% of the worldôs population fails to reach the recommended amount of activity (16)

Among individuals with already established diabetes, a moderate or high level of PA is associated with decreased all-cause and CVD mortality (17). Research suggests that among people with type 2 diabetes, glycemic control, insulin sensitivity, and CVD risk factors improves with increased levels of physical activity (18, 19). Moreover, a recent study in Norway found that people with clustering of cardiovascular risk factors who were highly active had the same risk of death from ischemic heart disease and stroke as healthy individuals who reported no physical activity (20).

Physical activity also seems to compensate for the adverse effects of being overweight or obese. It has been shown that obese men who were classified as fit had a lower risk of all cause and CVD mortality than did their lean but unfit counterparts (21). Similar findings have been found among individuals with diabetes; persons within the highest third of the BMI scale who attended a high or moderate level of physical activity had a lower risk of total and cardiovascular mortality compared with the most sedentary, yet leanest group (17). Moreover, a large prospective study found that overweight individuals with a high level of physical activity had a lower risk of hypertension than did normal weight individuals with a low level of physical activity (22). However, whether PA may cancel out the adverse effect of diabetes has not been previously studied.

The aim of this prospective follow-up study is to examine the association between diabetes and mortality from IHD and CVD, and also to study the effect of leisure time physical activity on mortality. Finally, we will investigate the combined effect of leisure time physical activity and diabetes with respect to cardiovascular mortality.

Material and methods

Study population

The county of Nord-Trøndelag is located in the middle of Norway. The county is sparsely populated, and the largest town has a population of only 21000 people. Average income, prevalence of higher education, and prevalence of smokers are a little lower than the remainder of Norway. However, the county is fairly representative to Norway considering economy, geography, industry, sources of income, morbidity and mortality. The countyôs population of 127 000 is fairly homogenous, with less than 3% having a non-Caucasian origin, making it suitable for epidemiologic studies (23).

Invitation letter and questionnaires

Between 1995 and 1997, all residents in the county of Nord-Trøndelag aged 20 years and older were invited to participate in the second wave of the Nord-Trøndelag Health Study (HUNT 2). The study consisted of several questionnaires, clinical examination, and collection of blood and urine samples. Invitation was sent by mail along with a three page questionnaire and an information folder. The participants returned the completed questionnaires at the screening site, and received a second questionnaire to fill in at home and return in a pre-stamped envelope. Measurements on the participantsô health status along with lifestyle-related topics were collected from the questionnaires. The clinical examinations consisted of measurements on blood pressure, heart rate, height, weight, and hip and waist circumference. Blood sampling was done whenever subjects attended the examination, i.e., in non-fasting or ñrandomò state. The HUNT 2 Study has been described in detail elsewhere (23).

Participation

In total, 94194 individuals were invited to participate in HUNT 2 (23). We received data on 64945 (69%) persons who chose to participate. Of these, we excluded a total of 5194 individuals who reported prevalent CVD (i.e., angina, myocardial infarction, and/or stroke). We also excluded 37 persons with missing information on the questionnaires relevant to CVD. Additional exclusions were made in the following stepwise manner:

32 individuals with missing data on the diabetes variable.

121 individuals with missing data on the glucose variable.

312 individuals with missing data on the BMI variable.

56 individuals with missing data on the systolic blood pressure variable.

After these exclusions 59193 individuals were available for statistical analysis.

Follow-up

Individual person time at risk of death was calculated from the date of participation in the HUNT 2 study (1995-97) until the date of death or until the end of follow-up 31 December 2005, whichever occurred first. The mandatory reporting of death to 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. Ischemic heart disease was defined by ICD-9: 410-414 and ICD-10: I20-I25.

Study variables

Diabetes

Individuals who answered óyesô to the question óDo you have or have you had diabetes?ô were defined as having diabetes. Individuals who had a non-fasting glucose level Ó11mmol/l were also classified as diabetic, even if their answer to the diabetes-question was óNoô. The same cut-off point has been used in other studies (24, 25).

Physical activity

The questionnaire contained two different questions on leisure time physical activity. One tried to establish how many hours a week during the last year the participants had performed light physical activity. The second question was óHow many hours a week the last year have you been participating in vigorous physical activityô, activity that should result in sweating and heavy breathing. The values on both variables were ónoneô, óless than one hourô, ó1-2 hoursô or ó3 hours or moreô. The question on vigorous physical activity was exemplified as activities that would result in sweating or heavy breathing, whereas light PA would not.

The American College of Sports Medicine (ACSM) and the American Heart Association (AHA) recommends that healthy adults participate in a minimum of 30 minutes of moderate aerobic physical activity five days a week, or a minimum of 20 minutes vigorous aerobic physical activity three days each week in order to promote and maintain health (12). I.e., to obtain a similar health improving effect, vigorous physical activity would be 2.5 times less time-consuming than moderate physical activity.

Unfortunately, the HUNT data did not include information on time spent on moderate PA, but we expect that at least some of the light PA reported in the HUNT questionnaire could be equivalent to ACSMs moderate PA. Thus, to obtain a measure of total physical activity, we multiplied hours of vigorous physical activity with 2.5 to make the time spent on vigorous activity comparable with time spent on light activity. The two variables were then summarized into one variable, representing total hours of (light) physical activity per week. People were then classified into four groups of total activity; 0.0-0.9 hours, 1.0-1.9 hours, 2.0-3.9 hours and more than 4 hours each week. To increase statistical power in analysis of the combined effect of diabetes and physical activity, the two middle categories (1.0-1.9 and 2.0-3.9 hours) were collapsed into a group of 1.0-3.9 hours of physical activity each week.

Statistical analysis

A Cox proportional hazard model was used to estimate adjusted hazard ratios (HR) of death from CVD and IHD among people with and without diabetes, between different categories of physical activity, and to assess the combined effect of physical activity and diabetes on risk of death from CVD and IHD. A 95% confidence interval (CI) was calculated to evaluate the precision of the estimated hazard ratios. All estimated associations were adjusted for age (continuous), and in additional multivariable adjusted analysis we controlled for the potential confounding effect of diabetes (yes/no), smoking status (never, former, current, unknown), alcohol consumption (never, not the last 4 weeks, 1-2 units the last 4 weeks, 3-4 units the last 4 weeks, Ó5 units the last 4 weeks), BMI (kg/m^2), systolic blood pressure (mmHg), and education (compulsory school, high school, university/college). Moreover, light physical activity was adjusted for hard activity and vice versa. All statistical analyses of the independent effect of diabetes and PA were conducted sex specifically. However, to increase the statistical power in the analyses of the combined effect of diabetes and PA, men and women were analyzed together, with sex as a potential confounder in the regression model. Finally, we evaluated potential interaction between PA and diabetes by entering a product term of these factors in the model.

All statistical tests were two-sided, and all analyses were conducted using SPSS for Windows (version 16.0 SPSS Inc., Chicago, IL, USA).

Ethics

The study is approved by the regional committee for ethics in medical research and by the Norwegian Data Inspectorate. All participants signed a written consent upon participation at the HUNT 2 Study.

Results

Individuals with diabetes were older, had higher diastolic and systolic blood pressure, used more blood pressure medication, had higher BMI, and were less likely to have a higher level of education compared with individuals without diabetes. A higher percentage of individuals without diabetes were current smokers compared to individuals with diabetes (*Table 1)*.

Table 1. Baseline characteristics of study population

	Without DM	With DM
Participants	57656	1537
Male/Female	26419/31237	747/790
Deaths caused by CVD	1188	148
Deaths caused by IDH	495	67
Age at study-entry	47.9 [16.3]	62.9 [14.9]
Age at death from CVD (years)	74.5 [10.3]	75.2 [8.2]
Age at death from IHD (years)	73.3 [10.8]	74.2 [8.2]
Follow up period (range)	7.3 (0.0-8.4)	6.7 (0.1-8.4)
Systolic blood pressure (mmHg)	136.4 [21.1]	154.0 [24.1]
Diastolic blood pressure (mmHg)	79.9 [12.1]	85.6 [13.1]
Blood pressure medication [a] (% current)	7.9	33.3
Weight (kg)	76.2 [13.9]	82.1 [15.4]
BMI (kg/m^2)	26.2 [4.0]	29.1 [5.1]
Current smokers (%)	29.5	19.3
Higher education [b c] (%)	20.2	10.4

All data are presented as means, [SD], Abbreviations: DM = diabetes mellitus, CVD = cardiovascular disease, IHD = ischemic heart disease, BMI = body mass index,
[a] system missing = 108, [b] University/college, [c] missing without DM = 4.3%, missing with DM 11.9%.

Diabetes and cardiovascular mortality

Men with diabetes were more likely to die from CVD (multiadjusted HR, 1.94; 95% CI, 1.53-2.45) compared with men without diabetes. A similar association was found in women (multiadjusted HR, 1.72; 95% CI, 1.33-2.22) (*Table 2*).

Men with diabetes had a more than twofold higher risk (multiadjusted HR, 2.12; 95% CI, 1.52-2.95) of dying from IHD than did men without diabetes. Women with diabetes had 92% higher risk (multiadjusted HR, 1.92; 95% CI, 1.26-2.92) of dying from IHD compared with women without diabetes (*Table 2*).

Table 2. Hazard ratios (HRs) for death from cardiovascular disease (CVD) and ischemic heart disease (IHD) associated with diabetes

		CVD			IHD		
Diabetes	Person-years	Deaths	HR[a]	HR[b] (95% CI)	Deaths	HR[a]	HR[b] (95% CI)
Men							
No	192350	647	1.00	1.00 (Reference)	310	1.00	1.00 (Reference)
Yes	4940	80	1.91	1.94 (1.53-2.45)	41	2.07	2.12 (1.52-2.95)
Women							
No	229456	541	1.00	1.00 (Reference)	185	1.00	1.00 (Reference)
Yes	5383	68	1.75	1.72 (1.33-2.22)	26	1.99	1.92 (1.26-2.92)

[a]Adjusted for age. [b]Adjusted for age, hours total physical activity each week (0.0-0.9, 1.0-1.9, 2.0-3.9, >4), smoking status (never, former, current, unknown), alcohol consumption (never, not the last 4 weeks, 1-2 units the last 4 weeks, 3-4 units the last 4 weeks, ≥5 units the last 4 weeks), BMI (kg/m^2), systolic blood pressure (mmHg), and education (compulsory school, high school, university/college). CI denotes confidence interval.

Physical activity and cardiovascular mortality

Men who performed three hours or more of light physical activity each week had a decreased risk of CVD mortality (multiadjusted HR, 0.61; 95% CI, 0.48-0.77) and IHD mortality (multiadjusted HR, 0.73; 95% CI, 0.52-1.03) than did men with no physical activity. For women, the corresponding multiadjusted HRs were 0.60 (95% CI, 0.45-0.80) and 0.61 (95% CI, 0.37-0.99) (*Table 3*).

Men who reported three hours or more of hard physical activity had a 31% lower risk (multiadjusted HR, 0.69; 95% CI, 0.48-0.98) of CVD mortality and a 10% lower risk (multiadjusted HR, 0.90; 95% CI, 0.56-1.44) of IHD deaths compared with men who did not perform any physical activity. For women, the equivalent HRs were 0.31 (95% CI, 0.08-1.24) and 0.47 (95% CI, 0.06-3.37) (*Table 3*).

Men with more than four hours of total physical activity each week had a lower risk of death from both CVD (multiadjusted HR, 0.48; 95% CI, 0.37-0.69) and IHD (multiadjusted HR, 0.72; 95% CI, 0.50-1.04) compared with the least active men (< 1 hour each week). The corresponding HRs for women were 0.57 (95% CI, 0.36-0.91) for CVD mortality and 0.66 (95% CI, 0.32-1.36) for IHD mortality (*Table 3*).

Table 3. Physical activity (PA) in men and women and hazard ratios (HRs) of death from cardiovascular disease (CVD) and ischemic heart disease (IHD)

			CVD			IHD		
		Person-years	Deaths	HR[a]	HR[b] (95% CI)	Deaths	HR[a]	HR[b] (95% CI)
Men								
Light PA	None	32324	120	1.00	1.00 (Reference)	53	1.00	1.00 (Reference)
	< 1 hour	31758	101	1.08	1.02 (0.78-1.34)	49	1.17	1.15 (0.77-1.72)
	1-2 hours	59383	137	0.63	0.65 (0.50-0.83)	66	0.68	0.71 (0.49-1.03)
	≥ 3 hours	60614	177	0.57	0.61 (0.48-0.77)	94	0.69	0.73 (0.52-1.03)
Hard PA	None	78329	397	1.00	1.00 (Reference)	181	1.00	1.00 (Reference)
	< 1 hour	42120	62	0.72	0.83 (0.63-1.10)	33	0.83	0.95 (0.65-1.40)
	1-2 hours	36479	40	0.57	0.67 (0.48-0.94)	27	0.83	0.99 (0.65-1.51)
	≥ 3 hours	27152	36	0.63	0.69 (0.48-0.98)	21	0.79	0.90 (0.56-1.44)
Total PA	0.0-0.9 hours	33372	178	1.00	1.00 (Reference)	72	1.00	1.00 (Reference)
	1.0-1.9 hours	38004	125	0.64	0.68 (0.54-0.86)	67	0.84	0.90 (0.64-1.26)
	2.0-3.9 hours	43271	141	0.52	0.55 (0.44-0.69)	68	0.62	0.67 (0.48-0.93)
	≥ 4 hours	69434	91	0.42	0.48 (0.37-0.69)	55	0.62	0.72 (0.50-1.04)
Women								
Light PA	None	24258	121	1.00	1.00 (Reference)	41	1.00	1.00 (Reference)
	< 1 hour	34207	74	0.83	0.84 (0.63-1.13)	33	1.05	1.06 (0.66-1.68)
	1-2 hours	79787	107	0.70	0.73 (0.56-0.96)	40	0.72	0.76 (0.48-1.20)
	≥ 3 hours	71073	89	0.54	0.60 (0.45-0.80)	31	0.53	0.61 (0.37-0.99)
Hard PA	None	120313	359	1.00	1.00 (Reference)	130	1.00	1.00 (Reference)
	< 1 hour	41222	17	0.60	0.69 (0.42-1.13)	10	0.92	1.11 (0.58-2.15)
	1-2 hours	34614	13	0.78	0.96 (0.55-1.69)	4	0.60	0.83 (0.30-2.29)
	≥ 3 hours	13177	2	0.25	0.31 (0.08-1.24)	1	0.33	0.47 (0.06-3.337)
Total PA	0.0-0.9 hours	40902	187	1.00	1.00 (Reference)	70	1.00	1.00 (Reference)
	1.0-1.9 hours	54765	105	0.78	0.81 (0.64-1.04)	40	0.75	0.81 (0.55-1.21)
	2.0-3.9 hours	55530	78	0.56	0.59 (0.45-0.77)	26	0.47	0.53 (0.33-0.83)
	≥ 4 hours	58127	21	0.49	0.57 (0.36-0.91)	9	0.51	0.66 (0.32-1.36)

[a]Adjusted for age. [b]Adjusted for age, diabetes, smoking status (never, former, current, unknown), alcohol consumption (never, not the last 4 weeks, 1-2 units the last 4 weeks, 3-4 units the last 4 weeks, ≥5 units the last 4 weeks), BMI (kg/m^2), systolic blood pressure (mmHg), and education (compulsory school, high school, university/college). In analysis on light PA, adjustments for hard PA have been done, and vice versa. CI denotes confidence interval.

Combined effect of diabetes and physical activity

Among the least active, individuals with diabetes had a more than twofold higher risk (multiadjusted HR, 2.12; 95% CI, 1.56-2.89) of death from CVD compared with those without diabetes. On the other hand, people with diabetes who were highly active had a HR of 0.81 (95% CI, 0.41-1.63) for CVD mortality compared with the reference group of non-diabetic people with a low level of physical activity. Highly active persons without diabetes had a HR of 0.51 (95% CI, 0.41-0.65).

The risk of death from IHD among the least active was more than two times higher (multiadjusted HR, 2.26; 95% CI, 1.39-3.68) in individuals with diabetes compared to individuals without diabetes, whereas highly active persons with diabetes had a HR of 0.95 (95% CI, 0.35-2.59) for IHD mortality compared with the reference group. Non-diabetic persons with a high level of physical activity had 27% lower risk (multiadjusted HR, 0.73; 95% CI, 0.52-1.00) of death from IHD.

The estimated hazard ratios presented in Table 4 suggest that the effect of physical activity on the risk of death might be larger among people with diabetes than among those without. However, there was no statistical evidence of effect modification. ($P_{interaction}$ 0.47 and 0.52 for deaths due to CVD and IHD, respectively).

Table 4. Combined effect of diabetes (DM) and total physical activity (PA) on risk of death from cardiovascular diseases (CVD) - and ischemic heart disease (IHD).

	CVD		IHD	
	Without DM	With DM	Without DM	With DM
< 1 hour PA				
Person-years	72135	2138	72135	2138
Deaths	318	47	123	19
HR (95% CI)	1.00 (Reference)	2.12 (1.56-2.89)	1.00 (Reference)	2.26 (1.39-3.68)
1-4 hours PA				
Person-years	187266	4304	187266	4304
Deaths	408	41	182	19
HR (95% CI)	0.65 (0.56-0.75)	1.08 (0.78-1.49)	0.73 (0.58-0.93)	1.24 (0.76-2.02)
> 4 hours PA				
Person-years	125935	1626	125935	1626
Deaths	104	8	60	4
HR (95% CI)	0.51 (0.41-0.65)	0.81 (0.41-1.63)	0.73 (0.52-1.00)	0.95 (0.35-2.59)

Adjusted for age, sex, smoking status (never, former, current, unknown), alcohol consumption (never, not the last 4 weeks, 1-2 units the last 4 weeks, 3-4 units the last 4 weeks, ≥5 units the last 4 weeks), BMI (kg/m^2), systolic blood pressure (mmHg), and education (compulsory school, high school, university/college. CI denotes confidence interval and HR denotes hazard ratio.

Discussion

Major findings

In this large population based cohort study, we found that individuals with diabetes had approximately twice the risk of death from CVD and IHD as did individuals without diabetes. Overall, the risk of dying from cardiovascular diseases decreased with increasing amount of physical activity, whereas individuals with diabetes who participated in a high level of PA had a lower risk of dying from CVD and IHD compared to the least active individuals without diabetes.

Strengths and limitations

The strengths of this study include the population-based nature of the data, the prospective design, and the large number of participants. However, some of the categories, especially in the combined analysis, had limited number of persons, and consequently the results should be interpreted with caution. Additional strengths are the large number of potential confounding factors that were available, as well as the ascertainment of cause of death through the Cause of Death Registry. The latter allows for accurate measures of outcome and practically no drop-outs throughout the nearly ten years of follow-up.

Assessing the level of physical activity through questionnaires is the major limitation of this study. As for several other studies (14), the present study relied on questionnaire based information on physical activity level collected at baseline. We had no data on possible changes in physical activity level during the follow-up period. An over-reporting of the actual activity level may cause an underestimation of the effect of physical activity, as indicated by the results from a previous study with measures both on fitness and activity (26). Moreover, the questions on physical activity in HUNT 2 did not distinguish between aerobic (endurance) physical activity and strength training. Consequently, a differential effect of various activities could not be estimated.

Despite these limitations related to assessing physical activity from questionnaires, validation studies have shown that questionnaires is useful when classifying large number of subjects into broad categories of PA (i.e. light, moderate and vigorous PA) (27).

Diabetes status was collected at baseline. The prevalence of diabetes in the study population has slightly increased during the follow-up (28). This could underestimate the association between diabetes and CVD mortality. Only non-fasting glucose measures were available in

HUNT 2. A misclassification of individuals with diabetes could as a result occur. Furthermore, no data on type of drugs used for the treatment of diabetes were available. Another concern is that we did not have any information on whether the subjects in the survey had diabetes type 1 or 2. Most studies are investigating the effect of PA among individuals with diabetes type 2. However, estimates shows that type 2 diabetes comprises about 90% of individuals with diabetes worldwide (1). ACSM suggests that persons with type 2 diabetes often find endurance exercise to be uncomfortable (29). Consequently, individuals with the mildest form of diabetes may be more likely to participate in high levels of PA than do persons with a more severe form of diabetes. In one study, individuals with poorly controlled diabetes had a higher risk of CVD mortality that did individuals with better control of the disease (5). Unfortunately, we had no information on the severity of diabetes.

Comparison with existing literature

Diabetes and cardiovascular mortality

Several previous prospective cohorts, including The Reykjavik Study (30) , the NHANES 1 study (31), the Framingham Heart Study (32), and studies from the first HUNT survey (4, 5) found a 2-4 fold increase in risk of CVD mortality among persons with diabetes. Our results showed an approximately two-fold increase in risk of death from CVD and IHD. Different atherosclerotic processes may explain the increase in risk of CVD mortality among individuals with diabetes (8, 9).

Prospective cohorts, including the present study, rarely provide data on possible treatments during the follow-up period. Data is collected at baseline, and possible changes in behavior, diet and treatment is seldom accounted for.

Men with diabetes had a slightly higher risk of IHD mortality than did diabetic women, whereas several other studies have found the effect of diabetes to be highest among women (4, 33). It is suggested that treatment of risk factors for IHD favours men more so than women and that women with diabetes have more adverse cardiovascular risk profiles, including higher blood pressure, obesity and dyslipidemia (33).

Physical activity and cardiovascular mortality

Consistent with our ýndings, other studies have shown that an increased level of physical activity is associated with lower risk of cardiovascular mortality (15, 20, 34, 35). Additionally, our results suggest a dose-response relationship between PA and CVD mortality. This is supported by three different studies based on data from the first HUNT survey (15, 20, 34) and a review article from 2001 (14). However, one study found that a single weekly bout of high intensity PA had a better risk reducing effect on cardiovascular mortality than the same amount of low intensity PA, whereas increasing frequency on PA did not give further reductions in risk (36). The majority of studies investigating the potential risk reducing effect of physical activity is done on men in prospective cohort studies (14).

According to ACSM, vigorous PA would be 2.5 times less time consuming than moderate PA to achieve the same health benefit (12). The HUNT questionnaire contains questions on light and vigorous physical activity, but no information on moderate activity. However, based on ACSMs description (12), we found it reasonable to assume that at least some of the activity classified as light PA in HUNT could be equivalent to ACSMs moderate physical activity. Thus, multiplying weekly hours of vigorous physical activity with 2.5 to make it comparable with light PA could be justified. On the other hand, this method would conceal the potentially larger health improving effect of vigorous PA compared to light PA (36). The results from the independent questions on light and hard PA in the current study may indicate that low and moderate levels of intensity (i.e. light PA) are even more beneficial in terms of cardiovascular disease risk as are high intensity physical activity (i.e. hard PA). However, the measure of intensity based on these questions may be considered rather crude.

Combined effect of diabetes and physical activity

To our knowledge, no other studies have previously investigated whether physical activity may cancel out the adverse effect diabetes have on cardiovascular mortality. However, the effect of PA among individuals with diabetes is thoroughly examined (19). A review of randomized controlled trials on the effects of exercise in persons with type 2 diabetes showed several favorable changes, i.e., improved insulin sensitivity, better glycemic control and improvements in other CVD risk factors (19). The positive effects of PA are further supported by others (29, 37). Our results showed that the most active persons without DM had half the risk of CVD death compared with the least active. The Insulin Resistance Atherosclerosis Study showed improvements in insulin sensitivity among adults who increased their levels of nonvigorous, overall and vigorous PA (38). Furthermore, low-to-moderate intensity PA is recommended for the majority of persons with type 2 diabetes (29), in contrast to moderate or vigorous intensity PA for healthy adults (12). However, we have no information on whether these recommendations have been used or followed in this population.

The combined effect of PA and other risk factors for cardiovascular death have been previously studied (17, 21, 22). A cohort study on more than 20 000 men found that obese men classified as fit had a lower risk of all cause and CVD mortality than lean and unfit men (21). Moreover, a Finnish study on adults with diabetes, found that active persons within the highest third of the BMI scale had a lower risk of both total and CVD mortality compared with inactive persons in the lowest third of the BMI scale (17). The protective effect of PA was also present among those with the highest blood pressure, highest total cholesterol level, and among current smokers. Another large prospective study found that overweight individuals with a high level of physical activity had a lower risk of hypertension than did normal weight individuals with a low level of physical activity (22).

A prospective study from the first HUNT survey investigated whether physical activity could weaken the positive association between a clustering of cardiovascular risk factors and cardiovascular mortality (20). The risk factors were a combination of the most used criteria for the metabolic syndrome, such as a BMI level Ó25 kg/m^2, systolic blood pressure Ó130mmHg and/or diastolic blood pressure Ó85mmHg, and a non-fasting glucose level Ó6mmol/l. The study showed that increasing levels of PA was associated with a decrease in risk of IHD mortality. Furthermore, individuals with a clustering of cardiovascular risk factors, who attended a high level of PA, had the same risk of IHD death as did the healthy, but inactive persons. These results are fairly consistent with ours.

Conclusions

This study shows that men and women with diabetes had about twice the risk of cardiovascular mortality than did those without the disease. Overall, an increase in leisure time physical activity was associated with a decrease in the risk of death from CVD and IHD. The risk reducing effect of physical activity found in this study is comparable with that of others. Furthermore, the analyses of the combined effect of diabetes and leisure time physical activity on the risk of cardiovascular mortality showed that the least active diabetic persons had the highest risk of death, whereas people with diabetes who were highly active had a risk that was similar to, and even lower, than people without diabetes who reported a low activity level. However, due to limited number of persons in some of the categories, results should be interpreted with caution. However, if the results from this study reflect a causal association, the beneficial role of physical activity for persons with diabetes should be clearly emphasized and communicated.

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