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 ($P_{interaction}$ = 0.003).

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

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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

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 hazards 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 an 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 an 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 an 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 an 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 conducted a stratified analysis excluding people reporting a moderate or high degree of movement disability. In this analysis, diabetes was associated with an 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).

CONCLUSIONS—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 (male, female), 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), 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 $V_{O_{2max}}$, 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 the 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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