# Physical-Activity and Incidence of Non-Insulin-Dependent Diabetes-Mellitus in Women

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# Physical activity and incidence of non-insulin-dependent diabetes mellitus in women

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The potential role of physical activity in the primary prevention of non-insulin-dependent diabetes mellitus (NIDDM) is largely unknown. We examined the association between regular vigorous exercise and the subsequent incidence of NIDDM in a prospective cohort of 87 253 US women aged 34–59 years and free of diagnosed diabetes, cardiovascular disease, and cancer in 1980.

During 8 years of follow-up, we confirmed 1303 cases of NIDDM. Women who engaged in vigorous exercise at least once per week had an age-adjusted relative risk (RR) of NIDDM of 0·67 ($p<0·0001$) compared with women who did not exercise weekly. After adjustment for body-mass index, the reduction in risk was attenuated but remained statistically significant (RR = 0·84, $p=0·005$). When analysis was restricted to the first 2 years after ascertainment of physical activity level and to symptomatic NIDDM as the outcome, age-adjusted RR of those who exercised was 0·5, and age and body-mass index adjusted RR was 0·69. Among women who exercised at least once per week, there was no clear dose-response gradient according to frequency of exercise. Family history of diabetes did not modify the effect of exercise, and risk reduction with exercise was evident among both obese and nonobese women. Multivariate adjustments for age, body-mass index, family history of diabetes, and other variables did not alter the reduced risk found with exercise.

Our results indicate that physical activity may be a promising approach to the primary prevention of NIDDM.

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## Introduction

The potential role of physical activity in preventing non-insulin-dependent diabetes mellitus (NIDDM) has not been widely investigated. Laboratory and clinical studies provide a rationale for a possible benefit of exercise in reducing risk of NIDDM, because physical training, even in the absence of weight loss, can increase insulin sensitivity and improve glucose tolerance.[1–7] Exercise can improve glycaemic control and insulin sensitivity in patients with pre-existing NIDDM and in nondiabetic individuals, an effect that can persist for up to 72 h after cessation of exercise.[2–4] Furthermore, studies in nondiabetic individuals suggest that the addition of exercise to diet therapy will facilitate, and assist in the maintenance of, weight loss, particularly of adipose tissue.[8]

Despite the biologic plausibility of a benefit of physical activity in preventing NIDDM, epidemiologic evidence is limited. Indirect evidence is provided by descriptive comparisons of the prevalence of NIDDM in active rural and inactive urban populations.[9,10] Support for a benefit of exercise also comes from cross-sectional studies, which showed the prevalence of diabetes or abnormal glucose tolerance to be greater among sedentary individuals than among their more active counterparts, independent of age and body-mass index.[11–13] However, in other studies, physical activity was not independently associated with 2 h post-load plasma glucose concentrations.[14,15] A retrospective longitudinal study suggested that women who participated regularly in sports as college students had reduced risks of subsequent diabetes,[16] and a recent prospective study in men also suggested a protective role of exercise in relation to NIDDM.[17]

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NIDDM, which affects 12 million people in the USA and is pandemic in several other populations, is a major cause of cardiovascular morbidity and mortality, particularly among women. Although obesity is a dominant determinant of NIDDM, efforts to prevent obesity through diet therapy have been disappointing.[7] Family history of diabetes, the other major known risk factor for NIDDM is, of course, not modifiable. The role of physical acivity in prevention of NIDDM deserves closer examination. We have examined prospectively the association between physical activity and subsequent incidence of clinical NIDDM among 87 253 women aged 34 to 59 years who were followed for up to 8 years in the Nurses' Health Study.

## Subjects and methods

### Subjects

The Nurses' Health Study cohort was established in 1976 when 121 700 female registered nurses aged 30 to 55 years and residing in one of eleven US states responded to mailed questionnaires regarding their medical history and health practices; details have been published elsewhere.[18] The subjects for the present investigation were 87 253 women from this cohort who were free from diagnosed diabetes mellitus, coronary heart disease, stroke, and cancer, and completed questions about exercise frequency in 1980. Based on a subsample of 249 subjects, we estimate that 98% of the cohort is white.

### Risk factors

Questionnaires mailed in 1976 asked about a previous diagnosis of diabetes mellitus and other major illnesses, and about age, height, and weight. Biennial follow-up questionnaires from 1976 to 1988 provided updated information on weight and diagnoses of diabetes mellitus and other conditions. On the 1982 questionnaire, we inquired about a family history of diabetes in the mother, father, sisters or brothers of participants.

### Assessment of physical activity

The 1980 questionnaire included the questions: "At least once a week, do you engage in any regular activity similar to brisk walking, jogging, bicycling, etc, long enough to work up a sweat?" "If yes, how many times per week?" "What activity is this?". These questions about vigorous exercise have been validated as a measure of physical activity.[19-22] Activity level assessed from questions about sweat-inducing episodes per week is strongly correlated with scores from the Harvard Alumni Activity Survey,[23] and also correlates with resting heart rate,[21] obesity,[21,22] and high-density lipoprotein cholesterol level.[22]

### Diagnosis of diabetes

We mailed a supplementary questionnaire regarding symptoms, diagnostic tests, and hypoglycaemic therapy to women who responded positively on any follow-up questionnaire to the question, "Have you had diabetes mellitus diagnosed?". The supplementary questionnaire was mailed in 1984 to women reporting diabetes between 1976 and 1984, and subsequently in 1986 and 1988 to women reporting diabetes on the biennial questionnaire in those years. Women reporting a diagnosis of diabetes before 1980 (n = 2263) were excluded from these analyses. A case of diabetes was considered confirmed if at least one of the following was reported on the supplementary questionnaire: (1) one or more classic symptoms (thirst, polyuria, weight loss, hunger, pruritis) plus fasting plasma glucose at least 140 mg/dl (7·8 mol/l) or random plasma glucose at least 200 mg/dl (11·1 mmol/l); (2) at least two elevated plasma glucose concentrations on different occasions (fasting at least 140 mg/dl and/or random at least 200 mg/dl and/or concentration at least 200 mg/dl after 2 h or more on oral glucose tolerance testing) in the absence of symptoms; or (3) treatment with hypoglycaemic medication (insulin or oral hypoglycaemic agent). All women with diabetes in these analyses were at least 34 years old at the time of diagnosis. We excluded 63 cases of insulin-dependent (type 1) diabetes, and also excluded 7 women classified as having gestational diabetes only. The remaining women (n = 1303) were classified as having NIDDM and included in the present analyses. Because of potential associations between weight and physical activity, no weight criteria were used in the classification of type of diabetes for these analyses. Our criteria for diabetes classification are consistent with those proposed by the National Diabetes Data Group.[24]

To document the validity of the confirmation of diabetes by the supplementary questionnaire, we examined medical records in a random sample of 84 participants classified as having NIDDM. 71 of these women gave permission for their medical records to be reviewed and records were available for 62. An endocrinologist (J. E. M.), blinded to the information reported on the supplementary questionnaire, reviewed the records according to recommended criteria.[24] The diagnosis of NIDDM was confirmed in 61 of the 62 women.

TABLE I—DISTRIBUTION OF BASELINE VARIABLES IN 1980 ACCORDING TO PHYSICAL ACTIVITY LEVEL

| Frequency of vigorous exercise per week | No of subjects | Mean (SD) age (yr) | Mean (SD) body-mass index | % with family history of diabetes* |
|---|---|---|---|---|
| 0 | 48 539 | 46·5 (7·1) | 24·7 (4·7) | 18·9 |
| 1 | 8291 | 45·3 (7·2) | 24·1 (4·1) | 17·8 |
| 2 | 9688 | 45·5 (7·3) | 23·9 (3·9) | 18·2 |
| 3 | 8236 | 45·6 (7·2) | 23·8 (3·9) | 18·0 |
| 4+ | 12 499 | 46·1 (7·3) | 23·7 (4·0) | 17·6 |
| Total | 87 253 | 46·1 (7·2) | 24·3 (4·4) | 18·4 |

*Ascertained on the 1982 questionnaire

### Statistical analysis

Incidence rates for NIDDM between 1980 and 1988 were computed according to physical activity level at baseline in 1980, with the follow-up period extending from the date of return of the 1980 questionnaire to the date of diagnosis of diabetes or June 1, 1988, whichever came first. Participants were classified as engaging in vigorous exercise less than once per week or at least once per week; they were also classified into one of five categories for frequency of vigorous exercise: 0 (less than once per week), 1, 2, 3, and 4 or more times per week. Women reporting diabetes mellitus, coronary heart disease, stroke, or cancer before 1980 were excluded from the analysis, and those with such reports during the 1980–1988 interval contributed to the follow-up only until the time of diagnosis. Rates of NIDDM were obtained by dividing number of cases by person-years in each category of physical activity. Follow-up rate was 92% of total potential person-years of follow-up. Rate ratios (referred to hereafter as relative risks [RRs]) were computed as the rate of occurrence of NIDDM in a specific category of physical activity divided by the incidence rate in the lowest category (less than once per week), after adjustment for age (5-year categories) and body-mass index (weight in kg divided by the square of the height in metres) categorised by deciles. Body-mass index was updated every 2 years in these analyses. We also examined the modifying effect of family history of diabetes. Proportional hazards models were used in a multivariate analysis to evaluate simultaneously the effects of physical activity, age, body-mass index, and family history of diabetes, and cigarette smoking, alcohol consumption, history of hypertension, high serum cholesterol, and parental history of myocardial infarction before age 60. We calculated the 95% CI for each RR[25] and all p values are two-tailed.

## Results

Table I shows mean age, body-mass index, and proportion of women with a family history of diabetes according to category of physical activity at baseline in 1980. Women with high levels of physical activity were leaner than sedentary

TABLE II—PHYSICAL ACTIVITY AND RR OF NIDDM

| Weekly vigorous exercise | Total person years | No cases of NIDDM | Age-adjusted RR (95% CI) | Age and body-mass index adjusted RR (95% CI) | Multivariate RR* (95% CI) |
|---|---|---|---|---|---|
| *1980–88* | | | | | |
| No | 362 784 | 844 | 1·0 | 1·0 | 1·0 |
| Yes | 307 613 | 459 | 0·67 (0·6–0·75)† | 0 84 (0·75–0·95)‡ | 0·83 (0·74–0·93)§ |
| Total | 670 397 | 1303 | .. | .. | .. |
| *1980–82*‖ | | | | | |
| No | 99 895 | 155 | 1·0 | 1·0 | .. |
| Yes | 84 428 | 71 | 0 57 (0·43–0·75)¶ | 0 76 (0·57–1 0)** | .. |
| Total | 184 323 | 226 | .. | .. | .. |
| *1980–82*‖ | | | | | |
| *(Symptomatic cases of diabetes)* | | | | | |
| No | 99 895 | 98 | 1·0 | 1·0 | .. |
| Yes | 84 428 | 41 | 0·50 (0·35–0·71)¶ | 0·69 (0·48–1·0)** | .. |
| Total | 184 323 | 139 | .. | .. | .. |

*Variables included in the multivariate model were age (5-year categories), body-mass index (deciles), family history of diabetes (yes, no), and time period (1980–82, 1982–84, 1984–86, and 1986–88)
†p < 0 0001, ‡p = 0·005, §p = 0·002, ¶p < 0 001, **p = 0 05
‖Person-years are equal in these two analyses because the same cohort of individuals at risk of NIDDM are being considered in each case

women. Validation studies in our cohort show that self-reported weights were highly correlated with measured values (Spearman r = 0·96), although the self-reported weights averaged 1·5 kg less.[26,27] This difference is compatible with that between a random casual weight measured with clothing and a morning weight measured without clothing and after urination. Age and family history of diabetes did not differ appreciably by level of activity.

During 670 397 person-years of follow-up between 1980 and 1988, we confirmed 1303 cases of NIDDM. Compared with sedentary women (vigorous exercise less than once per week), age-adjusted RR of NIDDM among women exercising at least once per week was 0·67 (95% CI = 0·6–0·75, p < 0·001) (table II). After adjusting for age and body-mass index, RR for women who had weekly vigorous exercise was attenuated but remained statistically significantly reduced (RR = 0·84, 95% CI = 0·75–0·95, p = 0·005). In a multivariate analysis including simultaneous control for age, body-mass index, family history of diabetes, and time period, RR was not materially altered (RR = 0·83, 95% CI = 0·74–0·93, p = 0·002) (table II); further adjustment for cigarette smoking, alcohol consumption, history of hypertension, high serum cholesterol, and parental history of myocardial infarction before age 60 also did not alter the associations (RR = 0·84, 95% CI = 0·75–0·94, p = 0·003).

Because of the potential for misclassification caused by not having updated data on physical activity throughout the follow-up period, we examined the association of physical activity and risk of NIDDM between 1980 and 1982, the period immediately after collection of data on physical activity. Physical activity was associated with a greater reduction in risk of NIDDM during this period for women exercising at least once per week compared with sedentary women (table II); however, the small number of endpoints (n = 226) in this short period of follow-up limits the statistical power of these analyses.

To address the possibility that surveillance for diabetes varied according to physical activity, we did an analysis restricted to symptomatic cases of NIDDM (report of at least one symptom at diagnosis). 910 of the 1303 cases of NIDDM (70%) were symptomatic at diagnosis. Results for this subgroup were not appreciably different from those for the entire cohort between 1980 and 1988 (age-adjusted RR = 0·69, 95% CI = 0·6–0·78; and age and body-mass index adjusted RR = 0·85, 95% CI = 0·74–0·98), or for the period restricted to 1980 to 1982 (table II).

The association between frequency of vigorous exercise and subsequent incidence of NIDDM is shown in table III. Among women who exercised at least once per week, there was no clear dose-response gradient according to frequency of exercise. There was no notable modifying effect of family history of diabetes on the association between physical activity and NIDDM (table IV)—reductions in risk of NIDDM were seen among women who exercised irrespective of family history of diabetes. In addition, age did not materially change the associations (data not shown). To assess whether exercise would

TABLE III—PHYSICAL ACTIVITY LEVEL AND RR OF NIDDM DURING 8 YEARS OF FOLLOW-UP

| Frequency of vigorous exercise (per week) | Total person-years | No cases of NIDDM | Age-adjusted RR (95% CI) | Age and body-mass index adjusted RR (95% CI) |
|---|---|---|---|---|
| 0 | 362 784 | 844 | 1·0 | 1·0 |
| 1 | 62 740 | 100 | 0·74 (0 6–0·91) | 0·89 (0·72–1 11) |
| 2 | 73 242 | 88 | 0·55 (0·44–0·68) | 0 71 (0·56–0·89) |
| 3 | 62 139 | 100 | 0·73 (0·59–0·9) | 0·93 (0·75–1·16) |
| 4+ | 94 290 | 135 | 0·63 (0·53–0·75) | 0·86 (0·71–1·04) |
| Total | 655 195 | 1267 | .. | .. |

Differences in numbers of person-years and cases from table II are due to exclusion of women with missing information on frequency of exercise

TABLE IV—PHYSICAL ACTIVITY, FAMILY HISTORY OF DIABETES, OBESITY, AND RR OF NIDDM DURING 8 YEARS OF FOLLOW-UP

| — | Weekly vigorous exercise | |
|---|---|---|
| | No | Yes |
| *Family history of diabetes* | | |
| Person-years | 67 943 | 54 470 |
| No cases of NIDDM | 320 | 183 |
| Age-adjusted RR (95% CI) | 1·0 | 0·74 (0·61–0 88)* |
| *No family history of diabetes* | | |
| Person-years | 294 841 | 253 143 |
| No cases of NIDDM | 524 | 276 |
| Age-adjusted RR (95% CI) | 1·0 | 0·64 (0·56–0·74)† |
| *Nonobese women* | | |
| Person-years | 277 309 | 251 203 |
| No cases of NIDDM | 241 | 150 |
| Age-adjusted RR (95% CI) | 1·0 | 0 73 (0·59–0·89)* |
| *Obese women* | | |
| Person-years | 85 475 | 56 410 |
| No cases NIDDM | 603 | 309 |
| Age-adjusted RR (95% CI) | 1·0 | 0·79 (0·69–0·9)* |

*p < 0 01, †p < 0 001

reduce the risk of NIDDM for both nonobese (body-mass index less than 27) and obese (body-mass index 27 or greater) women we analysed physical activity and incidence of NIDDM separately for the two groups (table IV). A reduction in risk among women who exercised regularly was observed for nonobese and obese women.

## Discussion

We observed a reduced incidence of NIDDM among women who exercised regularly compared with their sedentary peers. The full benefit of exercise is best seen in analyses not adjusted for obesity, but a significantly reduced risk of NIDDM persisted after adjustment for age and body-mass index, and after adjustment for family history of diabetes and other variables. Benefits of exercise were observed for obese and nonobese women.

The prospective design of this study minimises the possibility that the reporting of physical activity was biased by diagnosis of diabetes. It is possible, however, that women at increased risk of diabetes due to subclinical glucose intolerance may have increased their physical activity to reduce subsequent risk of NIDDM. This would have led to an underestimation of the benefits of exercise in relation to NIDDM. The follow-up rate of our cohort was high and comparable across categories of physical activity; thus, study results are unlikely to be biased by losses to follow-up. Information relating to diabetes diagnosis, although based on self-report by a questionnaire, was corroborated by review of medical records in a random sample of participants. To assess a potential surveillance bias for diabetes screening according to level of physical activity, a separate analysis was done restricted to the 910 women with at least one symptom at the time of diabetes diagnosis. The absence of any notable change in results suggests that potential variations in medical surveillance are unlikely to have introduced any serious bias in these analyses.

Some limitatons of this study deserve comment. Our "nondiabetic" participants were not screened for glucose intolerance, and about 2% of women in the age groups represented in our cohort may have undiagnosed NIDDM.[28] However, the prevalence of undiagnosed diabetes is likely to be lower in this cohort of nurses with a high degree of access to, and contact with, medical facilities. Moreover, such misclassification would not produce any important alteration in RRs. Since our analysis was restricted to clinical diabetes mellitus, we were unable to assess a possible relation of physical activity with conditions involving lesser degrees of glucose intolerance, such as impaired glucose tolerance; but it is unlikely that the association between physical activity and subclinical glucose intolerance would differ materially from that for overt diabetes. The absence of any appreciable alteration in our findings when we restricted the analysis to symptomatic NIDDM cases suggests that surveillance bias is unlikely. A further limitation is the imprecise assessment of physical activity and the absence of updated data on exercise throughout the follow-up period. This imprecision may have contributed to the absence of a clear trend in risk reductions according to frequency of exercise. Although the exercise questions have been validated in previous studies, a more detailed assessment of physical activity, with regular updates, might have disclosed a stronger benefit of exercise in relation to NIDDM.

Several biological mechanisms could explain the benefit of physical activity in reducing risk of NIDDM. Skeletal muscle is a principal site of insulin resistance in NIDDM;[5] this resistance may be attenuated by exercise training.[6] In addition to the independent effects of exercise on insulin resistance, studies in nondiabetic individuals suggest that the addition of exercise to diet therapy will enhance weight loss, particularly of adipose tissue mass, and will assist in the maintenance of reduced body weight.[8] Efforts to prevent obesity through diet alone have been generally unsuccessful,[7] but exercise appears to confer benefits in achievement and maintenance of weight reduction. Our finding of a marked reduction of incidence of NIDDM among the physically active in age-adjusted analyses are consistent with such benefits.

Physical activity appears to have an important role in the prevention of NIDDM through its association with reduced body weight and through independent effects on insulin resistance and glucose tolerance. Further research is needed to assess the magnitude of the benefits of exercise and to determine the most effective exercise programmes for reducing the incidence of NIDDM.

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# Differential phenotypic expression by three mutant alleles in familial lecithin:cholesterol acyltransferase deficiency

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Familial deficiency of lecithin:cholesterol acyltransferase (LCAT) is an autosomal recessive disorder characterised by abnormalities of all plasma lipoprotein classes and by abnormal deposition of unesterified cholesterol in tissues. To elucidate the molecular basis of the disease, the LCAT genes of three unrelated Japanese patients were amplified by means of the polymerase chain reaction. Direct sequencing of the amplified fragments covering all exons and junctions showed that the patients are homozygotes for separate gene mutations. In one patient a 3 bp insertion, which should cause a substantial change in the enzyme structure, was found in exon 4; he had near absence of LCAT mass and activity. Two separate missense mutations were identified in exon 6 of the other two patients, who produced functionally defective enzymes that differed widely in specific activity. The replacement of asparagine$^{228}$ with positively charged lysine completely abolished enzyme activity, whereas the other, conservative, aminoacid substitution (methionine$^{293}$→isoleucine) gave rise to a partially defective enzyme. These results show that distinct mutations cause differences in plasma LCAT activity and LCAT mass, ultimately leading to differential phenotypic expression of familial LCAT deficiency.

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## Introduction

Lecithin:cholesterol acyltransferase (LCAT; EC 2.3.1.43) is a glycoprotein synthesised by hepatocytes and secreted into the plasma. It forms a complex with high density lipoprotein (HDL) particles that contain high amounts of unesterified free cholesterol derived from peripheral cell membranes. Within this complex, LCAT catalyses the transfer of a fatty acyl residue from lecithin to cholesterol to form most of the cholesteryl esters in plasma lipoproteins. This enzyme therefore brings about the maturation of the HDL particles; it mediates an essential step in the reverse cholesterol transport process which facilitates the net movement of cholesterol from peripheral tissues to the liver.[1]

Familial LCAT deficiency has been reported in at least 27 families.[2,3] Most of the cases have been from European countries, but three independent families have been discovered in Japan.[4–6] The patients have many plasma lipoprotein abnormalities affecting all lipoprotein classes, such as greatly reduced concentrations of plasma esterified cholesterol and HDL-cholesterol. The clinical manifestations include corneal opacities, haemolytic anaemia, proteinuria, and premature atherosclerosis, which all result from the detrimental accumulation of cholesterol in tissues.[3] Renal failure can be a life-threatening complication.

Although many findings from clinical and immunological studies have suggested heterogeneity of familial LCAT deficiency,[7] the molecular basis has not been fully elucidated. Cloning of cDNA[8] and genomic DNA[9] for human LCAT showed that the gene consists of six exons encoding a mature protein of 416 aminoacids. A missense mutation in exon 4 has been reported in an Italian patient.[10]

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