men appears to increase levels of estrogens and decreases levels of SHBG, and may also decrease testosterone [3, 41]. Although the dogma for several decades has been that androgens increase prostate cancer risk [42], the epidemiologic evidence has often failed to support that contention [43]. Several recently published large and well-designed cohort studies have found that a high androgenic environment (high testosterone and/or low estradiol/testosterone ratio) is associated with reduced risk of high-grade prostate cancer, while a high estrogenic environment is associated with a decreased risk that is perhaps specific to low-grade disease [44–46]. These associations are consistent with our findings of an increased cancer risk associated with physical activity in obese men, because increased levels of SHBG would reduce levels of free estrogens and counteracts estrogen's protective effect on obesity. We cannot, however, explain how increased SHBG (and perhaps lower testosterone) among normal-weight men would decrease risk. We speculate that among lean men, other mechanisms related to physical activity, such as decreased levels of insulin and insulin like growth factors or enhancement of immune function, could explain the lower prostate cancer risk [2, 3, 11].

Strengths of our study include assessment of duration, frequency, type and intensity of recreational physical activity in the 10 years before baseline, as well as frequency of recreational activity at earlier ages (18, 30, and 45) using a questionnaire with good measurement properties [23]. However, our physical activity assessment was limited to recreational activity, and we could have misclassified men who were very active at their jobs but who did little recreational or household activity. Occupational activity was relatively low in this cohort. During the 10 years before baseline, only 6% of men ever had jobs with strenuous activity (median duration of 3 years), and 16% had ever had jobs with moderate activity (median duration 8 years). Another limitation of our physical activity assessment is that we only collected information on intensity of activity for walking, while we assumed that other activities were done at a moderate intensity and assigned a MET-code accordingly (e.g., we assigned a MET of 8.0 for those who reported running/jogging), which likely led to non-differential misclassification as men may have exercised at a higher or lower intensity. Nevertheless, due to the prospective design of this study, any measurement error in the assessment of physical activity should not have been differential between men who developed prostate cancer during follow-up and men who did not. Finally, participants in the current study were self-selected and predominantly Caucasian and middle-class. These factors could affect the generalizability of our findings.

The current study adds to the growing number of studies that suggest that it is unlikely that physical activity plays a strong role in reducing prostate cancer risk. Certainly, a possible reason for the equivocal results is our limited ability to collect accurate information on the various aspects of physical activity in population-based studies [47, 48]. On the other hand, our study suggests that higher levels of physical activity may decrease prostate cancer risk in normal weight men, possibly because higher levels of activity in normal weight men have a hormonal effect that reduces prostate cancer risk whereas the hormonal milieu in obese men may result in the opposite effects. Our study also suggests that physical activity may be differentially associated with different types of tumors and underscores the importance of analyzing results separately by tumor grade and stage. Replication of these subgroup findings and a better understanding of the potential mechanisms are needed. In particular, studies that examine associations among steroid hormone concentrations, physical activity and obesity with prostate cancer risk will help us to better understand these conflicting findings.

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	ヒト	動物	地　域	欧米	研究の種類	縦断研究
対象	一般健常者	空白		( )		コホート研究
性別	男性	( )		( )		( )
年齢	50-76歳	[redacted]		( )		前向き研究
対象数	10000以上			( )		( )
調査の方法	質問紙	( )				
アウトカム 予防	なし	なし	ガン予防	なし	( )	( )
アウトカム 維持・改善	なし	なし	なし	なし	( )	( )

図　表

Table 2 Adjusted* hazard ratio (HR) of prostate cancer for 10-year average recreational physical activity measures and stair climbing

Physical activity measure	Cases		Cohort		Incidence (per 10^4)	HR* (95% CI)
	N	%*	N	%*		
Recreational physical activity						
None	83	14.4	5,225	15.0	73.7	1.0
Some	493	85.6	29,532	85.0	75.0	0.92 (0.72–1.2)
MET-hours/week (kcal/kg-hours × week)						
None	83	14.4	5,225	15.0	73.7	1.0 [b]
>0–3.9	120	20.8	7,392	21.2	76.1	0.95 (0.71–1.3)
4.0–10.4	123	21.3	7,266	20.9	79.0	0.96 (0.72–1.3)
10.5–21.0	121	20.9	7,503	21.6	74.9	0.84 (0.63–1.1)
21.1–157.25	131	22.7	7,363	21.2	81.9	0.93 (0.70–1.2)
Intensity of physical activity						
MET-hours/week of high- and moderate-intensity activity[c]						
None	283	49.0	17,046	49.1	57.4	1.0 [b]
>0–8.1	139	24.1	8,763	25.2	73.7	1.0 (0.84–1.3)
>8.1	156	27.0	8,928	25.7	80.9	1.1 (0.89–1.4)
MET-hours/week of high-intensity activity[c]						
None	437	75.6	24,374	71.3	62.2	1.0 [b]
>7.6	70	12.1	4,929	14.2	65.9	0.93 (0.71–1.2)
>7.6	71	12.3	5,054	14.5	64.8	0.95 (0.73–1.2)
Pace of walking (per 5 MET-h/week)						
Slow walking (1.50 mile/week)	50	8.6	3,363	10.2	–	0.78 (0.52–1.2)
Moderate walking (3.00 mile/week)	226	39.3	13,022	37.5	–	0.94 (0.83–1.1)
Fast walking (7.5 mile/week)	141	24.2	7,036	20.0	–	1.0 (0.83–1.1)
Type of other physical activities (per 5 MET-h/week)						
Jogging/running (33 mile/week)[d]	59	10.1	5,098	14.5	–	1.0 (0.93–1.1)
Swimming (40 mile/week)[d]	27	4.6	1,810	5.1	–	1.0 (0.83–1.3)
Slow cycling or stair machine (60 mile/week)[d]	46	7.9	3,222	9.1	–	0.82 (0.58–1.2)
Fast cycling or stair machine (98 mile/week)[d]	42	7.2	3,275	9.3	–	0.99 (0.67–1.5)
Stair climbing (flights/day)[e]						
0–1	194	33.6	10,799	30.5	83.8	1.0 [b]
2–4	169	29.3	9,230	26.4	84.4	1.2 (0.94–1.5)
5–9	123	21.3	7,832	22.4	73.7	0.97 (0.76–1.2)
10+	92	15.9	7,143	20.4	59.2	0.87 (0.67–1.1)

Numbers presented are those with non-missing values for covariates

*Adjusted for family history of prostate cancer and BMI, and stratified on latitude (categorical, with a category for missing latitude) and PSA in 2 years before baseline

[a]Also adjusted for MET-hours/week from other activities

[b]p for trend > 0.2

[c]8.1 and 7.6 MET-h/week were the median values for the respective categories

[d]For intensity of physical activity, pace of walking, and types of other physical activities, the percentage refers to the proportion of people reporting doing any of that type of activity

図表掲載箇所	P836, 表2
概　要 (800字まで)	本研究は，余暇における身体活動と前立腺癌発症リスクとの関連について検討することを目的とした大規模なコホート研究(the VITamins And Lifestyle(VITAL))である．34757名の男性を対象とし，10年間追跡された．余暇身体活動は過去10年間における，ウォーキング，ウエイトリフティング，ヨガ，ゴルフ，ジョギングなどの身体活動を実施した頻度と時間，期間について調査され，週あたりのメッツ・時に換算された．余暇の身体活動と前立腺癌発症リスクとの関連について検討した結果，余暇活動を実施しない者と比較して，週0.1-3.9メッツ・時の者の調整ハザード比は0.95(95%CI:0.71-1.3)，4-10.4メッツ・時/週の者は0.96(0.72-1.3)，10.5-21.0メッツ・時/週の者は0.84(0.63-1.1)，21.1-157.25メッツ・時/週の者は0.93(0.70-1.2)となり，統計上有意な関連性は認められなかった．活動強度別に分けて，4メッツ以上の中高強度活動，6メッツ以上の高強度活動のみにおいても同様に解析したが，関連性は認められなかった．さらに，歩行速度や18，30，45歳時の運動頻度ついても検討したが，関連性はなかった．
結　論 (200字まで)	余暇における身体活動は，前立腺癌発症リスクと間に関連性は認められなかった．
エキスパートによるコメント (200字まで)	本研究において余暇時間における身体活動量と前立腺癌との間に関連性は認められなかった．これまでの研究において，身体活動と前立腺癌との関連については議論が様々である．これまでの研究の身体活動評価は，質問紙法によるものであるため，客観性や信頼性に乏しい．今後，更なる検討を要するだろう．

担当者　川上諒子

A Prospective Study of Exercise and Incidence of Diabetes Among US Male Physicians

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Objective.—To examine prospectively the association between regular exercise and the subsequent development of non–insulin-dependent diabetes mellitus (NIDDM).

Design.—Prospective cohort study including 5 years of follow-up.

Participants.—21 271 US male physicians participating in the Physicians' Health Study, aged 40 to 84 years and free of diagnosed diabetes mellitus, myocardial infarction, cerebrovascular disease, and cancer at baseline. Morbidity follow-up was 99.7% complete.

Main Outcome Measure.—Incidence of NIDDM.

Results.—At baseline, information was obtained about frequency of vigorous exercise and other risk indicators. During 105 141 person-years of follow-up, 285 new cases of NIDDM were reported. The age-adjusted incidence of NIDDM ranged from 369 cases per 100 000 person-years in men who engaged in vigorous exercise less than once weekly to 214 cases per 100 000 person-years in those exercising at least five times per week (*P*, trend, <.001). Men who exercised at least once per week had an age-adjusted relative risk (RR) of NIDDM of 0.64 (95% CI, 0.51 to 0.82; *P*=.0003) compared with those who exercised less frequently. The age-adjusted RR of NIDDM decreased with increasing frequency of exercise: 0.77 for once weekly, 0.62 for two to four times per week, and 0.58 for five or more times per week (*P*, trend, .0002). A significant reduction in risk of NIDDM persisted after adjustment for both age and body-mass index: RR, 0.71 (95% CI, 0.56 to 0.91; *P*=.006) for at least once per week compared with less than once weekly, and *P*, trend, .009, for increasing frequency of exercise. Further control for smoking, hypertension, and other coronary risk factors did not materially alter these associations. The inverse relation of exercise to risk of NIDDM was particularly pronounced among overweight men.

Conclusions.—Exercise appears to reduce the development of NIDDM even after adjusting for body-mass index. Increased physical activity may be a promising approach to the primary prevention of NIDDM.

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NON–INSULIN-dependent diabetes mellitus (NIDDM) affects more than 12 million individuals in the United States and is a major cause of cardiovascular disease, renal failure, and blindness.[1] The potential influence of exercise in preventing NIDDM is relatively unexplored. Although laboratory and clinical studies have suggested which physical training, even in the absence of weight loss, can increase insulin sensitivity and improve glucose tolerance,[2-10] the epidemiologic literature on exercise and risk of NIDDM has been limited. Indirect evidence for a protective role of physical activity derives from ecological studies demonstrating a lower prevalence of NIDDM in active rural populations than in sedentary urban populations.[11,12] Support for a benefit of exercise is also provided by several cross-sectional studies, in which the prevalence of diabetes or abnormal glucose tolerance was greater among sedentary than active individuals,[13-17] and by a retrospective study in college alumnae.[18]

Only two previous prospective studies of physical activity and incidence of NIDDM have been reported, to our knowledge. Helmrich and colleagues[19] recently published their findings that leisure-time physical activity was inversely related to the development of NIDDM among 5990 male alumni of the University of Pennsylvania. Our research group has recently reported results from the Nurses' Health Study, in which a reduced incidence of NIDDM was also observed among women who engaged in regular exercise.[20]

In the present report, we provide prospective data on regular vigorous exercise and the incidence of NIDDM among 21 271 US male physicians in the Physicians' Health Study. Participants were 40 to 84 years of age at entry and were followed up for an average of 5 years.

METHODS

Study Population

The Physicians' Health Study[21,22] is a randomized, double-blind, placebo-controlled trial designed to test whether low-dose aspirin reduces risks of cardiovascular disease and whether β-carotene decreases the incidence of cancer and cardiovascular disease. A detailed description of the subjects and methods has been previously published.[22] Briefly, 22 071 US male physicians aged 40 to 84 years at entry in 1982 and free from prior myocardial infarction, stroke, and transient cerebral ischemia were assigned at random using a 2×2 factorial design to aspirin, β-carotene, both active agents, or both placebos.

Questionnaires

Information was collected at baseline about previously diagnosed medical conditions, including diabetes mellitus, as well as about parental history of myocardial infarction, height and weight, history of hypertension, frequency of vigorous exercise, cigarette smoking, alcohol use, and other health variables. Information about family history of diabetes was not ascertained. The specific question about physical activity on the baseline questionnaire was: "How often do you exercise vigorously enough to work up a sweat?" Response options included "daily," "5-6 times/week," "2-4 times/week," "once/week," "1-3 times/month," and "rarely/never." Such questions about vigorous exercise have been validated as a measure of physical activity in several previous studies.[24-26] Activity levels assessed from questions about sweat-inducing episodes per week have a strong correlation with scores from the Harvard Alumni Activity Survey (r=.39 to .62),[24-27] as well as correlations with resting heart rate,[25] obesity,[25,26] and high-density lipoprotein cholesterol level.[26]

Follow-up

Every 6 months for the first year and annually thereafter, the participants were mailed brief questionnaires asking about their compliance with the randomized treatment assignment (aspirin [or its placebo] and β-carotene [or its placebo] on alternate days) and the occurrence of new medical diagnoses, including diabetes. Because the participants were physicians, medical records were not requested to confirm the self-reports of diagnosed diabetes. Due to the age structure of the study population, all incident cases of diabetes were diagnosed after the age of 40 years and were thus classified as NIDDM. The aspirin component of the study was terminated early (January 25, 1988) due primarily to the emergence of a statistically extreme 44% reduction in the risk of a first myocardial infarction among physicians in the aspirin group.[21,22] By this date, participants had been followed up for an average of 60.2 months (range, 45.8 to 77.0 months). Vital status was known for all physicians, and follow-up data on morbidity were 99.7% complete.

Table 1.—Distribution of Baseline Variables in 1982 According to Physical Activity Level in a Cohort of US Male Physicians 40 to 84 Years of Age

Vigorous Exercise,* Times/wk	No. of Participants	Mean (SD) Age, y	Mean (SD) Body-Mass Index†
0	5826	53.7 (9.5)	25.3 (3.3)
1	3931	52.5 (9.0)	25.2 (2.9)
2-4	8035	52.6 (9.3)	24.8 (2.9)
≥5	3479	53.3 (10.1)	24.2 (2.7)
Total	21 271	53.1 (9.4)	24.9 (3.0)

*Physical activity long enough to work up a sweat.
†Weight in kilograms divided by the square of height in meters.

Statistical Analyses

Incident cases of NIDDM were allocated to the physical activity level defined at baseline, with the follow-up period dating from return of these forms to the date of diagnosis of diabetes or to January 25, 1988, whichever came first. Participants were classified at baseline into a category of vigorous exercise either less than once weekly or at least once weekly, as well as into one of four categories for frequency of vigorous exercise: less than one, one, two to four, and five or more times per week. Men reporting diabetes mellitus, myocardial infarction, cerebrovascular disease, or cancer before entry were excluded from the analyses. Incidence rates of NIDDM were obtained by dividing incident cases by person-years in each category of physical activity, after adjustment for age. Relative risks were computed as the rate of occurrence of NIDDM in a specific category of physical activity divided by the corresponding rate in the lowest category (less than once per week), after adjustment for age (1-year categories), and after further adjustment for body-mass index (BMI) (weight in kilograms divided by the square of the height in meters [categorized by quartiles and deciles]).

Multiple logistic regression models were used to control simultaneously for age (1-year categories), BMI (deciles), aspirin and β-carotene treatment assignment, cigarette smoking (current, former, never), alcohol consumption (four categories), reported systolic and diastolic blood pressure (quartiles), history of hypertension, high serum cholesterol level, and parental history of myocardial infarction before age 60 years. The Mantel-extension test (χ^2 with 1 df) was used to assess the overall trend of increasing exercise level in data stratified by age as well as by both age and BMI.[28] To evaluate possible modifying effects of BMI, analyses were performed within quartiles of this variable (<23, 23 to 24.4, 24.5 to 26.4, and >26.4 kg/m^2). Multivariate analyses of BMI and history of hypertension as predictors of NIDDM were also performed. The population-attributable risk percentage for physical activity in relation to NIDDM was calculated as the difference between the incidence rate for NIDDM in the total population and that in the active population (vigorous exercise at least once weekly), divided by the incidence rate in the former (×100%).[29] We calculated the 95% confidence intervals (CIs) for each relative risk (RR),[30] and all P values are two-tailed.

RESULTS

The mean age and BMI of the 21 271 participants are presented in Table 1, according to their baseline category of physical activity. Physicians who had higher frequencies of vigorous exercise tended to be leaner than their more sedentary peers, but age did not differ appreciably.

During an average of 5 years of follow-up (105 141 person-years), a total of 285 incident cases of diabetes were reported. The incidence of NIDDM was inversely related to the frequency of vigorous exercise; incidence rates ranged from 369 cases per 100 000 person-years in men who exercised less than once weekly to 214 cases per 100 000 person-years in those who exercised at least five times per week (P, trend, <.001) (Fig 1). Compared with sedentary men (vigorous exercise less than once per week), the age-adjusted RR of NIDDM among men exercising at least once per week was 0.64 (95% CI, 0.51 to 0.82; P=.0003) (Table 2). After adjustment for both age and BMI

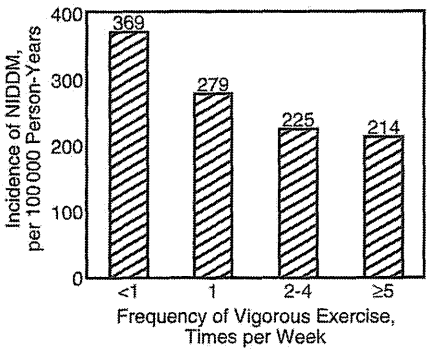

Fig 1.—Age-adjusted incidence rates of non–insulin-dependent diabetes mellitus (NIDDM) according to frequency of vigorous exercise (χ^2, trend [1 *df*] =13.1; *P*<.001).

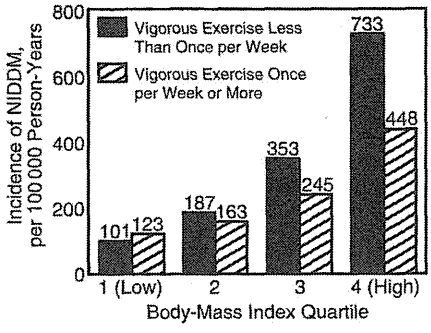

Fig 2.—Age-adjusted incidence rates of non–insulin-dependent diabetes mellitus (NIDDM) according to frequency of vigorous exercise (less than once per week vs at least once weekly), presented separately by quartile of body-mass index. Cut-points for the body-mass index quartiles are <23, 23 to 24.4, 24.5 to 26.4, and >26.4 kg/m².

(quartiles), these RRs were only slightly attenuated and remained substantially reduced (RR, 0.71; 95% CI, 0.56 to 0.91; *P*=.006). In a multivariate analysis including simultaneous control for age, BMI (categorized by deciles), aspirin and β-carotene treatment assignment, cigarette smoking, alcohol consumption, reported systolic and diastolic blood pressure, history of hypertension, history of high serum cholesterol level, and parental history of myocardial infarction before age 60 years, these results were not materially altered (RR, 0.71; 95% CI, 0.54 to 0.94; *P*=.015).

In Table 2 we also present the association between frequency of vigorous exercise and subsequent incidence of NIDDM. A dose-response gradient of increased exercise with decreased risk of NIDDM was observed. The age-adjusted RR of NIDDM declined from 1.0 in the referent category (less than once per week) to 0.77 for once weekly, 0.62 for two to four times per week, and 0.58 for five or more times per week (*P*, trend, .0002). After adjustment for both age and BMI (quartiles), a significant inverse trend persisted, and the corresponding RRs were 1.0, 0.78, 0.68, and 0.71, respectively (*P*, trend, .009). Further adjustment for BMI categorized by deciles did not appreciably alter these results (*P*, trend, .016).

Table 2.—Physical Activity and Relative Risk of Non–Insulin-Dependent Diabetes Mellitus During 5 Years of Follow-up

Vigorous Exercise*	Person-Years of Follow-up	No. of Cases	Relative Risk (95% Confidence Interval) Adjusted for Age†	Adjusted for Age† and Body-Mass Index‡
Less than weekly	28 587	107	1.00 (Referent)	1.00 (Referent)
At least weekly	76 554	178	0.64 (0.51 to 0.82)	0.71 (0.56 to 0.91)
Total	**105 141**	**285**	*P*=.0003	*P*=.006
Times/wk				
0	28 587	107	1.00 (Referent)	1.00 (Referent)
1	19 469	53	0.77 (0.55 to 1.07)	0.78 (0.56 to 1.09)
2-4	39 887	88	0.62 (0.46 to 0.82)	0.68 (0.51 to 0.90)
≥5	17 198	37	0.58 (0.40 to 0.84)	0.71 (0.49 to 1.03)
Total	**105 141**	**285**	χ^2, trend=13.7§; *P*=.0002	χ^2, trend=6.8§; *P*=.009

*Physical activity long enough to work up a sweat.
†Adjusted for age in 1-year categories.
‡Adjusted by quartiles of body-mass index, (kg/m²).
§1 *df*.

We next examined the modifying effect of BMI on the association between exercise and incidence of NIDDM (Fig 2). Increased BMI was a strong determinant of risk of NIDDM (138 cases of NIDDM in the highest quartile compared with 32 cases in the lowest quartile of BMI). Comparing incidence rates of NIDDM in men exercising less than once per week with those exercising at least once weekly, reduced rates of NIDDM were observed among exercisers in all but the leanest quartile of BMI (<23 kg/m²). The small number of NIDDM cases in the leanest quartile, however, may have impaired the ability to detect an exercise effect in that subgroup. Risk reductions were particularly pronounced in obese men (BMI >26.4 kg/m²), among whom the incidence rate was 448 cases per 100 000 person-years in exercisers and 733 in their sedentary counterparts (RR, 0.61; *P*=.005).

The relative contributions of vigorous exercise, BMI, and history of hypertension as predictors of NIDDM risk are presented in Table 3. Even mild overweight (BMI, 24.5 to 26.4 kg/m²) was associated with a significant elevation in the risk of NIDDM, and the incidence was tripled among those in the highest quartile of BMI (>26.4 kg/m²). History of hypertension was also a strong predictor of subsequent diagnosis of NIDDM (RR, 2.03; 95% CI, 1.47 to 2.80).

COMMENT

In this prospective study of US male physicians, regular vigorous exercise was associated with a decreased incidence of NIDDM. A dose-response gradient of increased frequency of exercise and reduced risk was observed, and vigorous exercise five or more times per week was associated with a 42% reduction in the age-adjusted risk of NIDDM compared with those who exercised less than once weekly. Apparent benefits of exercise persisted after adjustment for BMI as well as after simultaneous control for all available coronary risk factors and health habits. Risk reductions related to exercise were particularly pronounced among the obese. These data suggest that, in the general US population, in which more than 60% of adults do not exercise regularly,[31] at least 25% of the incidence of NIDDM may be attributable to sedentary life-style. Elevated BMI and history of hypertension were also predictors of NIDDM incidence in the cohort.

The prospective design of this study minimizes the possibility that the reporting of physical activity is biased by the diagnosis of diabetes. Because physical activity level was recorded before the diagnosis of NIDDM, it is unlikely that exercise habits or recall of activity was altered due to disease status. It is possible, however, that men at high risk of diabetes due to family history of the disorder or to subclinical chemical glucose intolerance may have increased their physical activity to reduce their body weight and decrease their subsequent risk of developing NIDDM. This would have led, however, to an underestimation of the benefits of exercise in relation to NIDDM. The follow-up rate of the study population was extremely high and comparable across categories of physical activity; thus, these results cannot be biased by losses to follow-up. Some limitations of this study, however, deserve comment. Our "nondiabetic" cohort was not screened for glucose intolerance, and nearly half of NIDDM cases

Table 3.—Physical Activity, Body-Mass Index, and History of Hypertension as Independent Predictors of Non–Insulin-Dependent Diabetes Mellitus During 5 Years of Follow-up

Variable	Multivariate* Relative Risk (95% Confidence Interval)	P
Vigorous exercise†		
Less than weekly	1.00 (Referent)	...
At least weekly	0.70 (0.53 to 0.92)	.01
Body-mass index quartile, kg/m²		
<23	1.00 (Referent)	...
23-24.4	1.07 (0.64 to 1.79)	.79
24.5-26.4	1.73 (1.10 to 2.74)	.02
>26.4	3.09 (2.02 to 4.72)	<.001
History of hypertension‡		
No	1.00 (Referent)	...
Yes	2.03 (1.47 to 2.80)	<.001

*The multivariate model included simultaneous control for the variables listed above as well as age (years), cigarette smoking (current, former, never), history of high serum cholesterol level (yes, no), parental infarction before age 60 years (yes, no), alcohol consumption (daily or more often, weekly, monthly, less than monthly), and randomized treatment assignment to aspirin and β-carotene (active agent or placebo).

†Physical activity long enough to work up a sweat.

‡Defined as self-reported systolic blood pressure of 160 mm Hg or greater and/or diastolic blood pressure of 95 mm Hg or greater, or taking antihypertensive medication.

may be undiagnosed, based on national survey rates.[32] However, the prevalence of undiagnosed diabetes is likely to be substantially lower in this cohort of physicians. Moreover, such misclassification should not produce any important alteration in RRs. In our earlier analyses in the Nurses' Health Study, the findings were not appreciably altered when the analyses were restricted to symptomatic NIDDM cases, suggesting that surveillance bias according to activity level is unlikely.[20] Although medical records were not obtained to confirm diagnoses, clinical diabetes would be expected to be reliably reported by the physician participants in this study; a validation study of self-reported diabetes in registered nurses suggested a high rate of corroboration by medical record review.[20] Information about family history of diabetes was not available, but control for this variable in the Nurses' Health Study analyses did not materially alter the results.[20] Although it is plausible that certain antihypertensive medications that reduce glucose tolerance (such as thiazides and β-blockers) may be associated with lower activity levels, our results were not materially altered after excluding men reporting a history of hypertension or those taking antihypertensive medication (data not shown). Further limitations include the imprecise assessment of physical activity and the absence of updated data on exercise throughout the follow-up period. Both of these, however, would tend to underestimate the benefits of exercise. Men who exercise vigorously may also be more likely to have regular mild-to-moderate physical activity. Although less strenuous types of activity were not assessed at baseline, a correlation between vigorous and more moderate activities may at least partially explain the apparent benefit observed among men reporting vigorous exercise only once per week.

Previous studies of physical activity and risk of diabetes have been predominantly cross-sectional investigations in high-risk populations. Indirect evidence from descriptive comparisons of NIDDM prevalence in rural vs urban populations in Western Samoa[11,12] and the South Pacific[12] have supported the hypothesis that higher levels of physical activity may be protective against NIDDM. However, other aspects of urban living, including differences in diet, could have accounted for the variation in diabetes risk. Cross-sectional studies among Polynesians,[13] Melanesian and Indian Fijians,[14,15] Micronesians,[15] Swedes,[16] and Mauritians[17] have also proposed an association of physical activity with reduced prevalence of NIDDM. The absence of an association between physical activity and glucose intolerance, however, also has been observed.[33,34] In one retrospective study, a reduced risk of diabetes was observed among women who engaged in regular sports in college compared with those who did not, but obesity was not controlled in the analysis.[18] To our knowledge, only two previous prospective studies of physical activity and incidence of NIDDM have been reported, both supporting a protective effect of exercise.[19,20] Our results in male physicians are similar to our earlier findings in female nurses,[20] suggesting that gender does not appreciably modify the relation between physical activity and NIDDM incidence.

Several known biological mechanisms could explain a benefit of physical activity in reducing the risk of NIDDM. Skeletal muscle is a principal site of insulin resistance in NIDDM,[6] which may be ameliorated by exercise training.[7,8] Exercise can improve glycemic control and insulin sensitivity in both patients with preexisting NIDDM and nondiabetic individuals, an effect that can persist up to 72 hours after cessation of exercise.[3-5] Such improvements in insulin sensitivity may require intensive and sustained physical training,[9] however, and may not explain benefits observed with more modest levels of activity. In addition to independent effects of exercise on insulin resistance, studies in nondiabetic individuals suggest that the addition of exercise to caloric restriction will facilitate weight loss, particularly of adipose mass, and will assist in the maintainance of reduced body weight.[35]

In conclusion, these prospective data from the Physicians' Health Study support the hypothesis that regular vigorous exercise reduces the incidence of NIDDM. Benefits of exercise were independent of BMI and were most pronounced among the obese, who have the highest risk of NIDDM. Physical activity appears to be a promising approach to the primary prevention of NIDDM; further research is needed to assess the intensity, duration, and frequency of exercise that will be most effective in reducing the incidence of NIDDM.

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We are grateful to the Steering Committee and staff of the Physicians' Health Study, and, in particular, to the 22 071 dedicated and conscientious physicians who are participating in this ongoing trial.

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対象の内訳		ヒト	動物	地 域	欧米	研究の種類	縦断研究
	対象	一般健常者	空白		( )		コホート研究
	性別	男性	( )		( )		( )
	年齢	40-84歳			( )		前向き研究
	対象数	10000以上			( )		( )
調査の方法	質問紙	( )					
アウトカム	予 防	な し	糖尿病予防	な し	な し	( )	( )
	維持・改善	な し	な し	な し	な し	( )	( )

図 表

Table 2.—Physical Activity and Relative Risk of Non–Insulin-Dependent Diabetes Mellitus During 5 Years of Follow-up

Vigorous Exercise*	Person-Years of Follow-up	No. of Cases	Relative Risk (95% Confidence Interval) Adjusted for Age†	Adjusted for Age† and Body-Mass Index‡
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Times/wk				
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≥5	17 198	37	0.58 (0.40 to 0.84)	0.71 (0.49 to 1.03)
Total	**105 141**	**285**	χ^2, trend=13.7§; *P*=.0002	χ^2, trend=6.8§; *P*=.009

*Physical activity long enough to work up a sweat.
†Adjusted for age in 1-year categories.
‡Adjusted by quartiles of body-mass index, (kg/m²).
§1 *df*.

図表掲載箇所	P65, Table2
概 要 (800字まで)	the Physicians' Health sutdyに参加している21271名の男性(40－84歳)を対象に5年間の追跡調査を行い、高強度身体活動がインスリン非依存性糖尿病の発症に及ぼす影響を検討した論文である。身体活動は、How often do you exercise vigorously enough to work up a sweat?"という質問に"毎日" "週5-6回" "週2-4回" "週1回" " 月に1-3回" "全くしない、ほとんどしない"で回答した。高強度身体活動をまったく行っていない人(0回/週)と比較して、1回/週、2－4回/週、5回以上行っている人では、糖尿病の発症が、0.79(0.56-1.09)、0.68(0.51-0.91)、0.71(0.49-1.03)と減少する傾向にあった。またまったく行っていない人と比較して、少なくとも1回以上行っている人で比較すると、有意なリスク低下が認められた。
結 論 (200字まで)	高強度身体活動を少なくとも1回以上行うことで、まったく行わない人と比較して、糖尿病の発症リスクが低減されることが明らかとなった。
エキスパートによるコメント (200字まで)	糖尿病の罹患率の増加は我が国において懸念される課題であり、こういった研究が多く実施され、運動や身体活動の重要性が広く認識されることで、糖尿病の予防につながることを期待したい。

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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 asociations (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.[3–6] 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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	ヒト	動物		欧米		縦断研究
対象	一般健常者	空白		( )		コホート研究
性別	女性	( )		( )		( )
年齢	34-59歳 (平均46.1歳)	[redacted]		( )		前向きコホート
対象数	10000以上			( )		( )
対象の内訳			地 域		研究の種類	
調査の方法	質問紙	( )				
アウトカム 予 防	なし	糖尿病予防	なし	なし		( )
アウトカム 維持・改善	な し	な し	な し	なし	( )	( )

図 表

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)
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Total	655 195	1267	..	..

Differences in numbers of person-years and cases from table 4 are due to exclusion of women with missing information on frequency of exercise.

図表掲載箇所	P776, Table3
概 要 (800字まで)	本研究はThe Nurses' Health Studyに参加している34-59歳の女性87,253を対象に8年間の追跡調査を行い、定期的な高強度身体活動とインスリン非依存性糖尿病の発症との関連について検討を行った。身体活動については、「少なくとも週1回、キビキビしたウォーキング、ジョギング、自転車等の汗をかくような活動を行っていますか？」「はい、であれば週に何回行っていますか？」といった質問を行い、高強度運動を週に行っている回数を調査した。全く行っていない、週1回、週2回、週3回、週4回以上の集団において、インスリン非依存性糖尿病の発症リスクは、それぞれ1.0、0.89(0.72-1.11)、0.71(0.56-0.89)、0.93(0.75-1.16)、0.86(0.71-1.04)であり、高強度身体活動を全く行っていない人と比較して、週2回以上実施することでそのリスクが減少が認められた。しかしながら、高強度身体活動とリスク低下における量反応関係については認められなかった。
結 論 (200字まで)	週2回の高強度身体活動は、女性におけるインスリン非依存性糖尿病のリスクを低下させた。しかしながら、明確な量反応関連は認められなかった。
エキスパートによるコメント (200字まで)	本研究において、週2回の高強度身体活動がインスリン非依存性糖尿病の発症にリスクの低下に関連することが示されているものの、量反応関係は認められておらず、今後は、強度と量との関連について更に詳細に検討することが必要であろう。

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Original Contribution

Physical Activity during Adulthood and Adolescence in Relation to Renal Cell Cancer

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Evidence for a relation between physical activity and renal cell cancer has been inconsistent. The authors examined physical activity in relation to renal cell cancer in a large, prospective US cohort study of 482,386 participants (289,503 men and 192,883 women) aged 50–71 years at baseline (1995–1996). At baseline, participants reported their frequency of exercise of at least 20 minutes' duration, intensity of daily routine activity, and frequency of physical activity during adolescence. During 8.2 years of follow-up (through December 2003), 1,238 cases of renal cell cancer were ascertained. In multivariate Cox regression models adjusted for renal cell cancer risk factors, the authors observed that current exercise, routine physical activity, and activity during adolescence were associated with a reduced risk of renal cell cancer. The multivariate relative risks for the highest activity level as compared with the lowest were 0.77 (95% confidence interval (CI): 0.64, 0.92; $p_{trend} = 0.10$) for current exercise, 0.84 (95% CI: 0.57, 1.22; $p_{trend} = 0.03$) for routine physical activity, and 0.82 (95% CI: 0.68, 1.00; $p_{trend} = 0.05$) for activity during adolescence. The authors conclude that increased physical activity, including activity during adolescence, is associated with reduced risk of renal cell cancer.

adolescent; exercise; kidney; kidney neoplasms; motor activity; neoplasms

Abbreviation: NIH, National Institutes of Health.

Renal cell carcinoma is the seventh-leading incident cancer among US men and the 12th-leading cancer among US women (1). The incidence rates of renal cell cancer increase with age and are higher among men than among women (1). Established risk factors for renal cell cancer include smoking, high body weight, and high blood pressure (2).

Physical activity has been hypothesized to decrease the risk of renal cell cancer through reductions in body fat, blood pressure (3, 4), and concentrations of circulating growth factors (5). However, evidence that physical activity, or lack thereof, is related to renal cell cancer is inconclusive (6–17). Reasons for the inconsistent findings may include the relatively small sample sizes in existing prospective cohort studies and potential selection and recall bias in case-control studies. In addition, the inverse relation may be strongest for physical activity performed at younger ages (11), which few investigators have been able to examine. In order to address these issues, we examined renal cell cancer risk in a large, prospective cohort study of 482,386 AARP (formerly the American Association of Retired Persons) members with available data on physical activity at cohort entry and during adolescence.

MATERIALS AND METHODS

Men and women in this study were enrolled in the National Institutes of Health (NIH)-AARP Diet and Health

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Study, the design of which has been previously described (18). Briefly, the cohort study was initiated in 1995–1996 when a baseline questionnaire eliciting information on usual dietary intake, physical activity, and other health-related behaviors was sent to 3.5 million AARP members aged 50–71 years who resided in one of six US states (California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana) or two US metropolitan areas (Atlanta, Georgia, and Detroit, Michigan). A total of 617,119 persons responded, among whom 567,169 persons completed the questionnaire to a satisfactory degree. In late 1996, a supplementary questionnaire was mailed to participants who satisfactorily completed the baseline questionnaire, who still lived in the study area, and who did not have prevalent cancer of the colon, breast, or prostate. The supplementary questionnaire inquired about history of hypertension and weight at age 18 years, among other health-related questions. In total, 334,908 participants responded to the supplementary questionnaire.

Of the 567,169 respondents to the baseline questionnaire, we excluded participants who returned duplicate questionnaires ($n = 179$), who had died or moved out of the study area prior to baseline ($n = 582$), who withdrew from the study ($n = 6$), who had questionnaires completed by proxy respondents ($n = 15{,}760$), who had a previous diagnosis of cancer ($n = 51{,}205$) or end-stage renal disease ($n = 985$), or who were missing information on physical activity ($n = 16{,}066$). After these exclusions, data for 482,386 participants (289,503 men and 192,883 women) were available for analysis, including 298,246 persons who completed the supplemental questionnaire.

The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the National Cancer Institute. All participants provided written informed consent.

Assessment of physical activity

Our exercise/sports assessment was based upon the 1990 recommendation by the American College of Sports Medicine that all persons engage in the equivalent of at least 20 minutes of vigorous exercise three times per week (19). On the baseline questionnaire, participants were asked to report the number of bouts of exercise and/or sports they had engaged in per month during the past year (i.e., current activity) that had lasted at least 20 minutes and had caused sweating or increased breathing or heart rate. Study members were also asked about the frequency of sports and/or exercise they had engaged in when they were 15–18 years of age. Participants selected their level of activity from six preestablished response options (never, rarely, 1–3 times per month, 1–2 times per week, 3–4 times per week, and five or more times per week). Participants in our cohort were also asked to select their level of activity during their current daily routine (including work routine) from five options (sitting; sitting and walking; standing or walking but not lifting or carrying things; carrying light loads or climbing stairs; or doing heavy work).

Our assessment of current exercise was similar to that of a previous questionnaire with demonstrated validity (percentage of agreement = 0.71; kappa = 0.40) based upon comparison with an objective measure (i.e., a computer science and applications activity monitor) (20). Our routine exercise measure resembled questions from the Baecke questionnaire that had previously been validated (21).

Identification of cases and follow-up

Incident cases of first primary renal cell cancer were identified by linkage of the NIH-AARP cohort database with the state cancer registries. In order to ascertain cases among AARP members who changed residence during the follow-up period, we also included linkage to three additional state cancer registries (Arizona, Texas, and Nevada) with large numbers of AARP members. Renal cell cancers were indicated by an *International Classification of Diseases for Oncology* code of C649 with a histology code consistent with renal cell cancer (8010, 8032, 8140, 8211, 8246, 8260, 8310, 8312, or 8320). Participants were followed from the date of scanning of the baseline questionnaire to the date of diagnosis of first cancer, death, moving out of the cancer registry ascertainment area, or the end of follow-up (December 31, 2003). In a previous validation study, the estimated sensitivity of cancer identification was approximately 90 percent and the specificity was 99.5 percent (22).

Statistical analysis

Relative risks and 95 percent confidence intervals were estimated using Cox proportional hazards regression models. We collapsed the bottom two categories of exercise and/or sports and activity during adolescence to ensure sufficient numbers of cases in the reference category. For tests of trend, each category was assigned a single value indicating the approximate frequency of physical activity per week (never/rarely = 0.125, 1–3 times per month = 0.5, 1–2 times per week = 1.5, 3–4 times per week = 3.5, and $\geq$5 times per week = 5.5). For routine activity, the five ordered categories were assigned values of 1, 2, 3, 4, and 5. We constructed linear trend variables based upon the assigned values for each variable and tested their statistical significance in regression models.

Covariates were included in multivariate models if previous studies consistently indicated an association with renal cell cancer or if the covariate was a statistically significant predictor of renal cell cancer in the NIH-AARP Diet and Health cohort. All multivariate models were adjusted for age, sex, body mass index (weight (kg)/height $(m)^2$), height, race/ethnicity, smoking, history of diabetes, protein intake, and history of hypertension. For covariates for which data were missing, we used missing indicator variables. For participants who did not complete the supplementary questionnaire, history of hypertension was modeled as a missing indicator variable. In analyses of the subset of participants who completed the supplementary questionnaire, neither hypertension nor body mass index at age 18 years was a confounder of the relation between physical activity and renal cell cancer. Further adjustment for education, number of children, intakes of red meat, fat, and alcohol, and use of multivitamins did not alter the relation of

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TABLE 1. Selected demographic and lifestyle characteristics of study subjects according to frequency of engaging in exercise/sports, routine activity, and activity during adolescence, NIH-AARP Diet and Health Study, 1995–1996*

Characteristic	Current exercise/ sports		Daily routine activity		Physical activity during adolescence	
	Never/ rarely	≥5 times/ week	Mostly sitting	Heavy work	Never/ rarely	≥5 times/ week
No. of participants	87,732	93,412	39,075	14,307	50,635	208,176
Male sex (%)	50.0	66.4	58.1	75.8	37.1	69.9
Age (years)	62.8	62.5	60.5	60.5	62.3	62.1
Race/ethnicity (%)						
White	91.1	93.8	92.5	93.0	92.3	92.6
Black	4.9	3.0	3.3	3.2	3.4	4.0
Other	4.0	3.2	4.2	3.7	4.3	3.4
Smoking status (%)						
Never smoker	33.6	37.3	32.0	33.7	40.9	35.2
Former smoker	47.2	54.6	54.5	50.5	47.4	52.6
Current smoker	19.1	8.1	13.6	15.9	11.8	12.2
Baseline body mass index†	28.5	26.0	29.3	26.8	27.0	27.3
Baseline height (m)	1.70	1.73	1.72	1.75	1.68	1.74
History of diabetes mellitus (%)	13.2	7.3	14.9	6.6	8.7	9.3
Energy-adjusted protein intake (g/day)	68.1	70.5	70.9	67.8	68.2	70.6
History of hypertension (%)‡	49.3	40.0	49.9	39.1	42.7	43.9

* Distributions of characteristics (except for number of participants and age) were age-standardized using direct adjustment.

† Weight (kg)/height $(m)^2$.

‡ Data were available only for those participants who answered the supplemental questionnaire (~60% of the cohort).

physical activity to renal cell cancer. All multivariate models met the proportional hazards assumption.

We formally tested for potential interactions with the association between physical activity and renal cell cancer using the likelihood ratio test—that is, comparing the likelihood of models with and without multiplicative interaction terms. Interaction terms were calculated using the cross-product of the physical activity categories and the factor of interest (e.g., sex).

Statistical analyses were performed using the Statistical Analysis System, release 9.1.3 (SAS Institute, Inc., Cary, North Carolina). All p values were based upon two-sided tests.

RESULTS

During up to 8.2 years of follow-up, we ascertained 1,238 cases of renal cell cancer (929 in men and 309 in women). As compared with participants who never/rarely engaged in physical activity, participants who engaged in high levels of physical activity were more likely to be male, to be of White race/ethnicity, to have a lower body mass index, and to be free from diabetes (table 1). These findings were generally similar regardless of whether we were examining exercise/sports, routine activity, or activity during adolescence. However, the pattern of participant characteristics differed in certain respects between exercise/sports and routine activity. Frequent exercisers were more likely to be White and to be never or former smokers than persons who never/rarely engaged in exercise or sports. In contrast, participants whose routine activity involved heavy work were more likely to be current smokers but not more likely to be White than persons whose routine involved mostly sitting. The pairwise correlation coefficients of the three activity measures were 0.24 (exercise/sports and routine activity), 0.19 (exercise/sports and activity during adolescence), and 0.06 (routine activity and activity during adolescence).

Study members who engaged in a greater amount of physical activity had a reduced risk of developing renal cell cancer. Persons who engaged in exercise/sports five or more times per week had a 23 percent reduced risk (multivariate relative risk (RR) = 0.77, 95 percent confidence interval (CI): 0.64, 0.92; p for trend = 0.10) as compared with participants who never or rarely engaged in exercise/sports (table 2). Participants who engaged in heavy work during their daily routine had an approximately 16 percent reduced risk (multivariate RR = 0.84, 95 percent CI: 0.57, 1.22; p for trend = 0.03) as compared with those who sat most of the day. Cohort members who had engaged in physical activity five or more times per week during adolescence had an 18 percent reduced risk (multivariate RR = 0.82, 95 percent

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TABLE 2. Relative risk of renal cell cancer in relation to level of physical activity, NIH-AARP Diet and Health Study, 1995–2003

Frequency or level of physical activity	No. of cases	Person-years of follow-up	Age- and sex-adjusted estimate		Multivariate estimate*		Mutually adjusted estimate†	
			RR‡	95% CI‡	RR	95% CI	RR	95% CI
Current exercise/sports								
Never/rarely	265	587,749	1.00	Referent	1.00	Referent	1.00	Referent
1–3 times/month	153	455,651	0.73	0.60, 0.89	0.77	0.63, 0.95	0.79	0.65, 0.97
1–2 times/week	266	723,952	0.77	0.65, 0.91	0.85	0.72, 1.01	0.89	0.74, 1.06
3–4 times/week	343	898,825	0.76	0.65, 0.89	0.89	0.75, 1.05	0.94	0.79, 1.11
≥5 times/week	211	644,770	0.63	0.53, 0.76	0.77	0.64, 0.92	0.81	0.67, 0.98
p for trend				<0.01		0.10		0.31
Daily routine activity								
Mostly sitting	113	261,331	1.00	Referent	1.00	Referent	1.00	Referent
Sitting and walking	428	1,087,126	0.85	0.69, 1.05	0.95	0.77, 1.17	0.97	0.79, 1.20
Walking and standing	471	1,278,083	0.75	0.61, 0.92	0.88	0.71, 1.09	0.91	0.74, 1.13
Climbing stairs or hills or light lifting	191	584,431	0.66	0.52, 0.83	0.80	0.63, 1.02	0.84	0.66, 1.07
Heavy work	35	99,978	0.72	0.49, 1.05	0.84	0.57, 1.22	0.89	0.60, 1.31
p for trend				<0.01		0.03		0.09
Physical activity during adolescence								
Never/rarely	129	351,281	1.00	Referent	1.00	Referent	1.00	Referent
1–3 times/month	82	225,991	0.93	0.71, 1.23	0.93	0.71, 1.23	0.95	0.72, 1.26
1–2 times/week	184	497,491	0.90	0.71, 1.12	0.90	0.72, 1.13	0.92	0.74, 1.16
3–4 times/week	277	814,691	0.78	0.63, 0.96	0.77	0.62, 0.95	0.79	0.64, 0.98
≥5 times/week	566	1,421,493	0.86	0.70, 1.04	0.82	0.68, 1.00	0.86	0.70, 1.04
p for trend				0.16		0.05		0.11

* Multivariate models included adjustment for age, sex, body mass index (weight (kg)/height $(m)^2$) at baseline (<25, 25–29.9, 30.0–34.9, 35.0–39.9, or ≥40), current height (m), race/ethnicity (White, Black, or other), smoking status (never smoker, current smoker of 1–10, 11–20, 21–30, 31–40, 41–60, or >60 cigarettes/day, or former smoker of 1–10, 11–20, 21–30, 31–40, 41–60, or >60 cigarettes/day), history of diabetes (yes/no), energy-adjusted protein intake (quintiles), and history of hypertension (yes/no).

† Mutually adjusted for current exercise/sports, routine physical activity, and physical activity during adolescence, in addition to the covariates included in the multivariate models.

‡ RR, relative risk; CI, confidence interval.

CI: 0.68, 1.00; *p* for trend = 0.05) of renal cell cancer in comparison with study members who were inactive as adolescents. In multivariate models, adjusting for body mass index modestly attenuated the relative risks, but no other adjustments substantially affected the estimated relation between physical activity and renal cell cancer (i.e., no other adjustments resulted in a change in beta coefficients of 10 percent or more). Mutual adjustment for baseline exercise/sports, daily routine activity, and activity during adolescence modestly attenuated the observed associations for each measure of activity (e.g., for current exercise/sports, the 23 percent risk reduction became a 19 percent risk reduction and the *p* value for trend increased from 0.10 to 0.31), indicating some interdependence between activity measures.

In a secondary analysis, we examined the relation between physical activity and renal cell cancer among only those participants who completed the supplementary questionnaire and reported their history of hypertension (approximately 60 percent of the overall cohort). In this subcohort, we observed similar associations between physical activity and renal cell cancer risk, although reductions in risk were of slightly greater magnitude than the reduction observed in the entire cohort. In this subcohort, the multivariate relative risks for frequent exercise/sports (five or more times per week), a high level of routine activity (heavy work), and frequent activity during adolescence (five or more times per week) were 0.74, 0.73, and 0.80, respectively, as compared with 0.77, 0.84, and 0.82 in the entire cohort.

We also conducted analyses stratified according to whether or not participants were overweight (body mass index ≥ 25.0) but did not find that the relation between physical activity and renal cell cancer varied by baseline body mass index (all *p*'s for interaction > 0.05; table 3).

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