論文名	Walking and leisure-time activity and risk of hip fracture in postmenopausal women
著 者	Feskanich D, Willett W, Colditz G.
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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	女性	( )		( )		( )
	年齢	44－77歳			( )		前向き研究
	対象数	10000以上	空白		( )		( )
調査の方法	質問紙	( )					
アウトカム	予 防	な し	な し	な し	転倒・骨折予防	( )	( )
	維持・改善	な し	な し	な し	な し	( )	( )

図 表	
図表掲載箇所	
概 要 (800字まで)	閉経後の女性におけるウォーキング, 余暇時間での身体活動と大腿骨頸部骨折発症の関係を検討することを目的としている。 米国11州において、1986年から12年間追跡調査した「看護師健康調査」に登録した看護師を対象とした前向きの研究である。 ベースラインでがん, 心臓病, 脳卒中,骨粗鬆症の既往のない、6万1200人の閉経後の女性(40-77歳で98%が白人)を対象とした。 軽・中程度の障害による大腿骨頸部骨折がベースラインと追跡期間中に測定した、余暇時間での身体活動量の強度、歩き、座り、立ちにつかった時間との関係が分析された。1986年～1998年の間, 415人の大腿骨頸部骨折が認められた。年齢, BMI、閉経後のホルモン剤の利用, 喫煙, 栄養摂取で調節した大腿骨頸部骨折発症のリスクは身体活動量が、3MET・時/週(普通の速度で1時間/週の歩行)増加すると6%(4%—9%; 95% CI, P<.001)低くなった; 少なくとも24MET・時/週、身体活動する女性は、3MET・時/週未満の活動量が少ない女性と比べて(RR, 0.45; 95% CI, 0.32-0.63)大腿骨頸部骨折のリスクが55%下がった。BMIが高いために、骨折発症のリスクが低い女性でも活動的であることで骨折発症のリスクを小さくしていた。運動をしていない女性でも、少なくても1週間4時間歩いている女性は、1時間も歩いていない女性より大腿骨頸部骨折のリスクが41%減少した(RR, 0.59; 95% CI, 0.37-0.94)。立っている時間もまた独立して大腿骨頸部骨折のリスクを低くしていた。
結 論 (200字まで)	歩きを含む中強度の身体活動は閉経後の女性の大腿骨頸部骨折のリスクを低下させる。
エキスパートによるコメント (200字まで)	女性を対象とした代表的なコホートである the Nurses's Health Study による研究である。

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Original Contribution

Physical Activity and Incident Diabetes in American Indians

The Strong Heart Study

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The authors examined the association between total physical activity (leisure-time plus occupational) and incident diabetes among 1,651 American Indians who participated in the Strong Heart Study, a longitudinal study of cardiovascular disease and its risk factors among 13 American Indian communities in 4 states (North Dakota, South Dakota, Oklahoma, and Arizona). Discrete Cox models were used to examine the association between physical activity level (in tertiles), compared with no physical activity, and incident diabetes, after adjustment for potential confounders. During 10 years of follow-up (f1989–1999), 454 incident cases of diabetes were identified. Compared with participants who reported no physical activity, those who reported any physical activity had a lower risk of diabetes: Odds ratios were 0.67 (95% confidence interval (CI): 0.46, 0.99), 0.67 (95% CI: 0.45, 0.99), and 0.67 (95% CI: 0.45, 0.99) for increasing tertile of physical activity, after adjustment for age, sex, study site, education, smoking, alcohol use, and family history of diabetes. Further adjustment for body mass index and other potential mediators attenuated the risk estimates. These data suggest that physical activity is associated with a lower risk of incident diabetes in American Indians. This study identifies physical activity as an important determinant of diabetes among American Indians and suggests the need for physical activity outreach programs that target inactive American Indians.

diabetes mellitus, type 2; health behavior; Indians, North American; life style; motor activity

Abbreviations: CI, confidence interval; MET, metabolic equivalent; SHS, Strong Heart Study.

Physical activity is a core component of type 2 diabetes prevention programs (1). This recommendation is based on epidemiologic studies and clinical trials that suggest a strong association between physical inactivity and incident type 2 diabetes (2–5). However, this association has not been well studied in American Indians, a population with a strong genetic susceptibility to type 2 diabetes that may have very different physical activity patterns than other segments of the population (6). The few studies that have examined the association between physical activity and diabetes among American Indians have been mostly limited by small sample sizes or cross-sectional analyses (7–9). To date, there have been no published studies of physical activity and incident diabetes in a population-based multitribal cohort of American Indians. In 1 published study, Kriska et al. (10) examined the prospective association between physical activity and incident diabetes in the Gila River Indian community in Arizona. Confirmation of those findings in other American Indian communities is needed.

Our purpose in this study was to examine the association between physical activity and incident diabetes among American Indians in 13 communities who participated in the Strong Heart Study (SHS), a population-based cohort study with repeated examinations over a 10-year follow-up period. The SHS offered us a unique opportunity to assess the association between physical activity and incident diabetes in a high-risk population using a validated

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questionnaire designed specifically for use in studies of American Indians.

MATERIALS AND METHODS

Setting and study population

The SHS is a population-based longitudinal study of cardiovascular disease and its risk factors in 13 American Indian communities in 4 states (Arizona, North Dakota, South Dakota, and Oklahoma). The institutional review board and Indian Health Services office for each participating tribe approved the study, and written informed consent was obtained from all participants at enrollment. For enrollment, lists of eligible persons were obtained from tribal registries, and in each study area approximately 1,500 noninstitutionalized tribal members aged 45–74 years were recruited during 1989–1991. In Arizona and Oklahoma, all eligible persons were invited to participate in the SHS, while in North and South Dakota, a clustering sampling technique was used to recruit study participants. The SHS cohort consisted of 4,549 participants who were seen at the baseline examination, conducted in 1989–1991. Of the original cohort, 3,870 persons also had at least 1 follow-up examination conducted in 1993–1995 or 1998–1999. Details of the study design, survey methods, and laboratory techniques have been reported previously (11).

For the current investigation, SHS participants who did not undergo any follow-up examinations ($n = 679$) or who had diabetes at the baseline examination ($n = 1,838$) were excluded from the analyses. Among participants without diabetes at baseline ($n = 2,032$), those with rheumatic heart disease ($n = 63$), cancer ($n = 93$), emphysema ($n = 33$), kidney failure ($n = 20$), or a history of stroke ($n = 7$), coronary heart disease ($n = 38$), or heart failure ($n = 25$) were excluded, since these conditions may influence both physical activity patterns and diabetes risk. In addition, participants who had no information on baseline physical activity ($n = 84$) or diabetes status ($n = 18$) were excluded from the analyses. The remaining 1,651 persons comprised the study population.

Data collection

The baseline examination included a standardized personal interview, physical examination, and laboratory work-up. Information regarding previous/current medical conditions, education, smoking, alcohol consumption, television viewing habits, and family history of diabetes was collected during the personal interview.

Anthropometric measurements were obtained at the baseline examination with the participant wearing lightweight clothing and no shoes. Body mass index was calculated as body weight (kg) divided by height squared (m^2). Waist circumference was measured at the umbilicus while the participant lay in a supine position. Percentage of body fat was estimated using bioelectrical impedance. Blood pressure was measured 3 times on the right arm using a standard mercury sphygmomanometer while the participant was seated, after 5 minutes' rest; the mean of the second and third measurements was used in this analysis for both systolic and diastolic pressure (11, 12).

Blood samples were collected after a 12-hour overnight fast and were stored at −70°C. Plasma glucose was measured using enzymatic methods, and glycosylated hemoglobin was measured using a high pressure lipid chromatography assay. Insulin was measured using a modified version of the Morgan and Lazarow radioimmunoassay test (11). Low density lipoprotein cholesterol and high density lipoprotein cholesterol were isolated by ultracentrifugation, as described previously (13). Each study participant who was not currently being treated with insulin/oral hypoglycemic agents or did not have a fasting glucose level greater than or equal to 225 mg/dL was given an oral glucose tolerance test (14).

Physical activity assessment

Each SHS participant completed a detailed physical activity questionnaire designed specifically for American Indians at the baseline visit (15). The questionnaire measured leisure-time and occupational physical activities over the past year for estimation of usual level of physical activity. Only leisure-time and occupational activities that required greater energy expenditure than daily living activities, such as bathing, grooming, and eating, were assessed (10). The questionnaire was used previously in the Pima Indian Study of Arizona and has been shown to be valid and reliable. The validity of the questionnaire was assessed in the Pima Indian Study using Caltrac activity monitors (Accusplit Corporation, Livermore, California), and past-week self-reported physical activity was highly correlated with activity monitor counts ($\rho = 0.80$). Likewise, the questionnaire has been shown to be reliable among participants in the Pima Indian Study, with test-retest correlations ranging from 0.63 to 0.92 for past-year occupational and leisure-time activities (15).

For assessment of leisure-time activity, each participant was asked to document the frequency and duration of 24 structured leisure-time activities common to the cohort, such as running, swimming, bicycling, fishing, and hiking, performed during the last 12 months. For occupational activity, participants were asked to list all jobs held during the past 12 months. For each job entry, data were collected for the amount of time spent walking or cycling to work per day, as well as the average job schedule (months per year, days per week, and hours per day of working). Activity on the job was determined by the number of hours spent sitting at work and selection of the category that best described the most frequent physical activities performed when not sitting (light; moderate, which included carrying light loads, continuous walking, heavy cleaning, plumbing, and electrical work; or hard, which included carrying heavy loads, heavy construction, farming, digging ditches, sawing, shoveling, and chopping). Persons who were retired or unemployed documented the non-leisure-time activities that they performed in a normal 8-hour day.

The average number of hours per week spent in each activity was multiplied by an estimate of the metabolic cost of the activity to obtain a measure of metabolic equivalent (MET)-hours per week. MET-hours per week represent an

estimate of total energy expenditure in all activities captured by the questionnaire. One MET represents the energy expenditure of a resting individual, while a 10-MET activity requires 10 times the resting energy expenditure (15). MET-hours per week of activity were calculated for leisure-time and moderate-to-high-intensity occupational activities separately and then summed (leisure and moderate-to-high-intensity occupational activities combined) to obtain a measure of total physical activity. Thus, total physical activity is a summary measure of the MET-hours per week of participation in 24 leisure-time activities and moderate-to-high-intensity occupational activities. Changes in physical activity after the baseline examination were not assessed for the purpose of this analysis; the level of total physical activity reported at the baseline examination was assumed to represent the participant's level of total physical activity throughout the follow-up period.

Diabetes assessment

Based on the 1999 World Health Organization definition (16), any participant taking insulin or oral antidiabetic medication or with a follow-up fasting plasma glucose level greater than or equal to 126 mg/dL or a 2-hour oral plasma glucose level greater than or equal to 200 mg/dL was considered diabetic. Since type 1 diabetes is rare in Indian populations and all SHS participants were at least 45 years of age at baseline, we assumed that all new occurrences of diabetes were type 2.

World Health Organization criteria (16) were used to define incident diabetes because it is the measure most frequently used in other SHS publications. However, since it has been shown that the World Health Organization criteria for diabetes diagnosis may give higher diabetes estimates than the American Diabetes Association criteria (17, 18), we also performed a sensitivity analysis using American Diabetes Association criteria. The American Diabetes Association criteria simply exclude the 2-hour glucose measure.

Statistical analyses

All statistical analyses were conducted using STATA, version 9.0 (Stata Corporation, College Station, Texas). Among persons who reported any leisure-time or occupational activity, reported physical activity was divided into tertiles based on the distribution of physical activity in the study cohort in order to assess the potential for a dose-response. The total physical activity tertiles used were <30 MET-hours/week, 30–106 MET-hours/week, and >106 MET-hours/week, with the referent group being persons with no reported leisure-time or moderate-to-high-intensity occupational physical activity. Physical activity was categorized into tertiles for the primary analyses, since finer stratification would have resulted in very few participants in each stratum and limited statistical power to assess the association between physical activity and incident diabetes. The use of other cutpoints, such as quartiles and quintiles, for categorizing physical activity was assessed in sensitivity analyses.

Multivariate discrete Cox models were used to assess the association between baseline physical activity and incident diabetes, considering death from any cause or loss to follow-up as censoring events. We calculated odds ratios and 95% confidence intervals to compare the risk of diabetes for a particular category of physical activity with the risk of diabetes in the referent group: persons with no reported leisure-time or moderate-to-high-intensity occupational physical activity. To better understand whether the association between physical activity and diabetes risk differed by type of physical activity, we performed separate analyses for total physical activity, leisure-time physical activity, and occupational activity. All analyses were adjusted for age, sex, and study site (Oklahoma, Arizona, North Dakota, or South Dakota). Potential confounders included smoking status, alcohol consumption, education, and family history of diabetes.

We examined the potential interaction of total physical activity with sex, body mass index (<25, 25–<30, 30–<35, or ≥35), and age (<55, 55–<65, or ≥65 years) to investigate whether these factors modified the association between physical activity and diabetes. To test the statistical significance of the interaction, we included the product of the factors in a discrete Cox model and tested for the effect of each interaction term, adjusting for age, sex, and site as appropriate.

In additional models, we adjusted for all of the covariates in model 1 (age, sex, and site) as well as possible mediators, such as systolic and diastolic blood pressure, high and low density lipoprotein cholesterol, and plasma fibrinogen. Since risk of diabetes is associated with markers of obesity, such as body mass index, waist circumference, and percentage of body fat (1), we examined the effects of including these variables in the models in sensitivity analyses to better understand whether they mediated the association between physical activity and incident diabetes.

RESULTS

Among the 1,651 SHS participants who comprised the analytic cohort, 944 (57.2%) were female, and the mean age at baseline examination was 55.1 years. Baseline characteristics of the study participants according to category of total physical activity are shown in Table 1. Participants with higher levels of physical activity were younger, more educated, and had a lower body mass index, percentage of body fat, and waist circumference than those who reported less activity. In addition, persons who reported higher levels of physical activity had lower systolic blood pressures, resting heart rates, and plasma fibrinogen, fasting insulin, and fasting glucose levels. However, participants who reported more physical activity were more likely to smoke and had a higher diastolic blood pressure and low density lipoprotein cholesterol level than those who reported less physical activity.

In general, male SHS participants were more active than female participants. The median level of total physical activity was 81.3 MET-hours/week for males and 43.3 MET-hours/week for females. The most common past-year leisure-time activities reported were gardening, walking, and hunting for males and gardening, walking, and dancing for females. There were 130 (7.9%) participants who reported no moderate-to-high-intensity occupational activity

Table 1. Baseline Characteristics of Participants According to Category of Total Physical Activity, Strong Heart Study, 1989–1999[a]

	Total Physical Activity[b], MET-hours/week[c]												P-Trend
	No Activity (*n* = 130)			<30 (Median, 12.1) (*n* = 495)			30–106 (Median, 69.0) (*n* = 474)			>106 (Median, 165.0) (*n* = 552)			
	No.	%	Mean (SE)	No.	%	Mean (SE)	No.	%	Mean (SE)	No.	%	Mean (SE)	
Female sex	86	66.15		334	67.47		264	55.70		260	47.10		<0.01
Age, years			59.51 (0.72)			55.63 (0.36)			55.27 (0.37)			53.48 (0.30)	<0.01
Body mass index[d]			30.88 (0.60)			29.98 (0.29)			29.54 (0.25)			29.64 (0.23)	<0.05
Body fat, %			38.92 (0.85)			36.93 (0.40)			35.04 (0.40)			33.64 (0.38)	<0.01
Waist circumference, cm			105.70 (1.43)			101.90 (0.69)			101.56 (0.60)			101.00 (0.55)	<0.01
Systolic blood pressure, mm Hg			127.29 (1.58)			125.03 (0.82)			124.03 (0.81)			122.77 (0.70)	<0.01
Diastolic blood pressure, mm Hg			74.74 (0.79)			76.23 (0.47)			76.40 (0.46)			77.38 (0.41)	<0.01
High density lipoprotein cholesterol, mg/dL			47.56 (1.17)			48.38 (0.63)			47.91 (0.70)			47.42 (0.60)	NS
Low density lipoprotein cholesterol, mg/dL			111.68 (2.82)			120.43 (1.50)			121.78 (1.53)			123.66 (1.43)	<0.01
Triglycerides, mg/dL			111.93 (5.42)			116.94 (2.87)			135.18 (6.01)			130.95 (3.74)	NS
Fibrinogen, mg/dL			309.89 (6.71)			289.90 (3.07)			281.00 (3.15)			269.66 (2.65)	<0.01
Heart rate, beats/minute			69.50 (0.09)			68.72 (0.46)			66.53 (0.50)			66.57 (0.44)	<0.01
Glycosylated hemoglobin, %			5.17 (0.05)			5.18 (0.04)			5.14 (0.03)			5.08 (0.03)	NS
Fasting glucose, mg/dL			103.80 (0.94)			101.98 (0.51)			101.50 (0.49)			101.47 (0.46)	<0.01
Fasting insulin, μU/mL			17.28 (0.98)			15.76 (0.67)			15.18 (0.51)			13.92 (0.43)	<0.01
Education, years			11.14 (0.26)			12.43 (0.14)			12.92 (0.14)			12.85 (0.12)	<0.01
Cigarette smoking													
Former smoker	35	26.92		139	28.08		150	31.65		180	32.61		NS
Current smoker	43	33.08		179	36.16		203	42.83		229	41.49		<0.05
Family history of diabetes	49	37.69		195	39.39		182	38.40		221	40.04		NS

Abbreviations: MET, metabolic equivalent; NS, not significant; SE, standard error.
[a] Sample sizes vary slightly because of occasional missing values.
[b] Activity categories were determined by the distribution of total physical activity within the cohort.
[c] MET-hours/week were calculated as the average amount of time spent in each activity per week multiplied by the MET value for each activity.
[d] Weight (kg)/height $(m)^2$.

or leisure-time activity, 621 (37.6%) participants who reported leisure-time activity but no moderate-to-high-intensity occupational activity, 73 (4.4%) participants who reported moderate-to-high-intensity occupational activity but no leisure-time activity, and 827 (50.1%) participants who reported both leisure-time and moderate-to-high-intensity occupational activity.

During the 10 years of follow-up, diabetes developed in 454 of the 1,651 study participants who were free of diabetes at baseline. Comparisons of baseline characteristics among study participants who developed and did not develop diabetes during the 10 years of follow-up are shown in Table 2. Compared with persons who did not develop diabetes, persons who developed diabetes were more likely to be female and had higher body mass indices, percentages of body fat, waist circumference, high and low density lipoprotein cholesterol, and levels of glycosylated hemoglobin, plasma fibrinogen, fasting glucose, and fasting insulin at baseline. In addition, persons who developed diabetes reported lower levels of physical activity than those who did not develop diabetes.

Using no reported physical activity as the referent group, we used discrete Cox models to analyze the association between categories of total physical activity and incident diabetes (Table 3). Compared with persons who reported no activity, the odds ratio for diabetes among those in the total activity category "<30 MET-hours/week" was 0.65 (95% confidence interval (CI): 0.44, 0.94), after adjustment for age, sex, and site. Similarly, the odds ratios comparing 30–106 MET-hours/week and >106 MET-hours/week of total physical activity with no reported activity were 0.63 (95% CI: 0.43, 0.93) and 0.64 (95% CI: 0.44, 0.94), respectively. Adjustment for other potential confounders (education, smoking, alcohol use, and family history of diabetes) did not alter risk estimates. When body mass index and other mediators (systolic and diastolic blood pressure, high and low density lipoprotein cholesterol, and fibrinogen) were entered into the model, risk estimates were attenuated

Table 2. Baseline Characteristics of Participants According to Diabetes Status, Strong Heart Study, 1989–1999[a]

	Incident Diabetes (n = 454)			No Diabetes (n = 1,197)			P-Trend
	No.	%	Mean (SE) or Median (IQR)	No.	%	Mean (SE) or Median (IQR)	
Female sex	282	62.11		662	55.30		<0.01
Age, years			54.69 (0.36)			55.27 (0.23)	NS
Body mass index[b]			32.31 (0.29)			28.86 (0.16)	<0.01
Body fat, %			38.29 (0.41)			34.37 (0.26)	<0.01
Waist circumference, cm			107.85 (0.66)			99.52 (0.39)	<0.01
Systolic blood pressure, mm Hg			125.40 (0.78)			123.70 (0.51)	NS
Diastolic blood pressure, mm Hg			77.31 (0.45)			76.25 (0.29)	NS
High density lipoprotein cholesterol, mg/dL			45.94 (0.61)			48.59 (0.42)	<0.01
Low density lipoprotein cholesterol, mg/dL			117.20 (1.49)			122.72 (0.98)	<0.01
Triglycerides, mg/dL			141.26 (6.07)			120.82 (2.24)	<0.01
Fibrinogen, mg/dL			288.54 (3.38)			279.75 (1.92)	<0.05
Education, years			12.31 (0.14)			12.72 (0.09)	<0.05
Glycosylated hemoglobin, %			5.37 (0.04)			5.04 (0.02)	<0.01
Fasting glucose, mg/dL			105.90 (0.49)			100.27 (0.31)	<0.01
Fasting insulin, μU/mL			19.74 (0.57)			13.34 (0.34)	<0.01
Cigarette smoking							
Former smoker	139	30.62		365	30.49		NS
Current smoker	156	34.36		498	41.60		<0.01
Physical activity, MET-hours/week[c]							
Total activity			55.50 (9.70–199.00)			66.00 (15.80–139.80)	NS
Leisure-time activity			13.40 (2.50–32.30)			17.80 (5.2–40.10)	<0.01
Occupational activity			18.50 (0–91.40)			18.50 (0–147.70)	NS
Family history of diabetes	195	42.95		452	37.76		NS

Abbreviations: IQR, interquartile range; MET, metabolic equivalent; NS, not significant; SE, standard error.
[a] Sample sizes vary slightly because of occasional missing values.
[b] Weight (kg)/height $(m)^2$.
[c] Data are median values and (in parentheses) interquartile ranges.

and no longer statistically significant. Models that used percentage of body fat or waist circumference as a marker of obesity instead of body mass index produced similarly attenuated risk estimates. Using physical activity quartiles or quintiles to categorize physical activity levels did not materially alter risk estimates.

When leisure-time physical activity was analyzed separately, the results were attenuated (Table 4). Results indicated no difference in diabetes risk when persons in the low leisure-time physical activity group, <8 MET-hours/week, were compared with those with no reported leisure-time activity (odds ratio = 1.04, 95% CI: 0.74, 1.47). The odds ratio for diabetes comparing persons with 8–24 MET-hours/week of leisure-time physical activity with those with no recorded leisure-time physical activity was 0.76 (95% CI: 0.55, 1.07). Persons in the highest tertile of leisure-time physical activity (>24 MET-hours/week) had an odds ratio of 0.68 (95% CI: 0.49, 0.95) in comparison with those with no documented leisure-time physical activity. No association was found between occupational activity and incident diabetes; however, as suggested above, a large portion of the sample reported no occupational activity.

There was no statistically significant interaction between physical activity and age, sex, or body mass index. In sensitivity analyses, we repeated the analyses using American Diabetes Association criteria to define incident diabetes. Use of American Diabetes Association criteria to define diabetes did not alter the reported odds ratios.

DISCUSSION

The results from this analysis indicate that even modest amounts of physical activity are associated with a lower risk of diabetes in American Indians. Since the risks were similar among persons who were physically active, these findings are most consistent with a threshold effect (between no

Table 3. Odds Ratios for Diabetes According to Category of Total Physical Activity, Strong Heart Study, 1989–1999

	Total Physical Activity, MET-hours/week					
	No Activity (OR = 1)	<30		30–106		>106	
		OR	95% CI	OR	95% CI	OR	95% CI
No. of cases	49	136		123		146	
Total no. at risk	130	495		474		552	
Adjustment for age, study site, and sex[a]		0.65	0.44, 0.94	0.63	0.43, 0.93	0.64	0.44, 0.94
Multivariate[b]		0.67	0.46, 0.99	0.67	0.45, 0.99	0.67	0.45, 0.99
Additional adjustment for body mass index[c]		0.74	0.50, 1.09	0.74	0.49, 1.10	0.71	0.48, 1.07
Additional adjustment for waist circumference		0.75	0.50, 1.11	0.73	0.48, 1.09	0.73	0.49, 1.09
Additional adjustment for percentage of body fat		0.79	0.54, 1.17	0.78	0.52, 1.17	0.81	0.54, 1.21
Additional adjustment for mediators[d]		0.70	0.46, 1.03	0.72	0.47, 1.08	0.71	0.47, 1.07

Abbreviations: CI, confidence interval; MET, metabolic equivalent; OR, odds ratio.

[a] All results were adjusted for age (as a continuous variable), study site (Oklahoma, Arizona, North Dakota, South Dakota), and sex.

[b] The model included age, study site, sex, education (less than high school, high school, post-high school), cigarette smoking (never, ever, current), alcohol use (never, ever, current), and family history of diabetes.

[c] There were 11 underweight participants (body mass index $\leq$ 18.5) included in the analyses, of which only 1 developed diabetes during follow-up. Sensitivity analyses indicated that excluding underweight participants did not alter the reported risk estimates.

[d] Results were adjusted for all covariates listed in footnote "b" above, as well as the potential mediators systolic blood pressure, diastolic blood pressure, high density lipoprotein cholesterol, low density lipoprotein cholesterol, plasma fibrinogen, and body mass index as continuous variables.

activity and any activity) on diabetes risk. Alternatively, the lack of dose-response between physical activity level and incident diabetes may reflect the limitations of the physical activity instrument. The questionnaire we used relies on self-reported physical activity and may distinguish between inactive and active participants but not precisely quantify differences in levels of physical activity among participants who report engaging in physical activity.

The findings reported herein support prospective studies in other populations showing an inverse association between physical activity and incident diabetes that is attenuated after adjustment for body mass index (2, 3, 5, 19–21). In a large cohort study that examined the association between vigorous physical activity and incident type 2 diabetes among middle-aged and older (40–84 years) male physicians, Manson et al. (2) demonstrated an inverse association between diabetes development and frequency of vigorous physical activity. In a second study, Hu et al. (3) examined the association of moderate activity (specifically walking) and vigorous activity with incident diabetes among participants in the Nurses' Heath Study and suggested that both moderate- and vigorous-intensity physical activity were associated with a lower risk of incident diabetes. Unfortunately, those studies relied on self-reported diabetes to measure incidence, leaving open the possibility of misclassification of diabetes status.

Our results support the findings of 2 cross-sectional analyses that suggested an inverse association between total physical activity and insulin and glucose concentrations in Pima and Ojibwa-Cree participants (7, 22). In the longitudinal study of Pimas aged 15–59 years residing in the Gila River Indian Community during 1987–2000 (22), baseline physical activity was assessed using a modified version of the same questionnaire that was used in the SHS, and incident diabetes was determined through oral glucose tolerance testing (diabetes diagnosis based on 200 mg/dL 2-hour postload plasma glucose concentration).

Physical activity may decrease the risk of developing diabetes through effects on body weight and insulin sensitivity. Since visceral fat is strongly associated with insulin resistance, lean persons may be less likely to develop diabetes. In addition, physical activity has been shown to increase insulin-/non-insulin-mediated glucose disposal independent of body composition (3). Observed risk estimates for total physical activity were attenuated and no longer statistically significant after adjustment for body mass index, waist circumference, or percentage of body fat. Such attenuation may be due to the independent effects of obesity on both physical activity levels and diabetes risk (3). However, since obesity may be causally related to physical activity—that is, physical inactivity causes weight gain and obesity—the models that adjusted for body mass index, waist circumference, or percentage of body fat may have underestimated the effect of physical activity on diabetes risk.

Unlike most other studies, which rely on self-reported diabetes, the SHS had oral glucose tolerance and fasting

Table 4. Odds Ratios for Diabetes According to Category of Leisure-Time Physical Activity, Strong Heart Study, 1989–1999

	Leisure-Time Physical Activity, MET-hours/week					
	No Activity (OR = 1)	<8		8–24		>24	
		OR	95% CI	OR	95% CI	OR	95% CI
No. of cases	65	116		125		148	
Total no. at risk	203	346		468		634	
Adjustment for age, study site, and sex[a]		1.04	0.74, 1.47	0.76	0.55, 1.07	0.68	0.49, 0.95
Multivariate[b]		1.06	0.75, 1.49	0.79	0.56, 1.11	0.71	0.51, 0.99
Additional adjustment for body mass index[c]		1.11	0.78, 1.59	0.84	0.59, 1.20	0.74	0.52, 1.05
Additional adjustment for waist circumference		1.09	0.77, 1.56	0.84	0.59, 1.19	0.74	0.52, 1.05
Additional adjustment for percentage of body fat		1.14	0.80, 1.62	0.85	0.60, 1.21	0.78	0.55, 1.10
Additional adjustment for mediators[d]		1.09	0.76, 1.56	0.80	0.56, 1.15	0.75	0.53, 1.06

Abbreviations: CI, confidence interval; MET, metabolic equivalent; OR, odds ratio.

[a] All results were adjusted for age (as a continuous variable), study site (Oklahoma, Arizona, North Dakota, South Dakota), and sex.

[b] The model included age, study site, sex, education (less than high school, high school, post-high school), cigarette smoking (never, ever, current), alcohol use (never, ever, current), and family history of diabetes.

[c] There were 11 underweight participants (body mass index $\leq$ 18.5) included in the analyses, of which only 1 developed diabetes during follow-up. Sensitivity analyses indicated that excluding underweight participants did not alter the reported risk estimates.

[d] Results were adjusted for all covariates listed in footnote "b" above, as well as the potential mediators systolic blood pressure, diastolic blood pressure, high density lipoprotein cholesterol, low density lipoprotein cholesterol, plasma fibrinogen, and body mass index as continuous variables.

plasma glucose measurements for all study participants at baseline and 2 follow-up examinations. Other strengths of this study include its use of a culturally specific and sensitive instrument to measure physical activity. In addition, few published studies have analyzed the association between total physical activity and risk of diabetes in American Indians, a population with an exceedingly high burden of diabetes (6).

This study had several limitations. Although we measured physical activity with an instrument that was shown to be reliable and valid in the American Indian population, physical activity estimation was based on self-report and may have been subject to potential misclassification. Since the questionnaire was developed to assess popular leisure-time and moderate-to-high-intensity occupational activities, the role of light-intensity activities was not considered. We considered death from any cause or loss to follow-up a censoring event. As such, persons who developed and died of diabetes between study examinations were not captured in our case definition. In addition, although we considered potential confounding by socioeconomic status, health behaviors, and prior morbidity, the influence of unmeasured confounding variables such as diet was not assessed. Because it is well established that healthy lifestyle factors cluster (23), it is plausible that persons who report greater amounts of physical activity may also have other healthy lifestyle behaviors, such as healthier diets, than persons who report less physical activity. Since data on dietary intake were not available at the SHS baseline examination, we could not determine whether a dietary difference was a confounder in the observed association between physical activity and incident diabetes. Finally, although subjects with cancer, renal disease, cardiovascular disease, emphysema, and arthritis were excluded from analyses, inclusion of participants with other, nonmeasured comorbid conditions that influence diabetes risk and physical activity may have altered risk estimates.

Nevertheless, these results suggest that physical inactivity is associated with a higher risk of diabetes in American Indians. This study adds to the growing body of evidence identifying physical activity as an important determinant of incident diabetes and suggests the need for physical activity education and outreach programs that target inactive American Indians.

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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	男女混合	( )		( )		( )
年齢	平均55.1歳			( )		前向き研究
対象数	1000～5000			( )		( )
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 3. Odds Ratios for Diabetes According to Category of Total Physical Activity, Strong Heart Study, 1989–1999

		Total Physical Activity, MET-hours/week					
	No Activity (OR = 1)	<30		30–106		>106	
		OR	95% CI	OR	95% CI	OR	95% CI
No. of cases	49	135		123		146	
Total no. at risk	130	495		474		552	
Adjustment for age, study site, and sex[a]		0.65	0.44, 0.94	0.63	0.43, 0.93	0.64	0.44, 0.94
Multivariate[b]		0.67	0.46, 0.99	0.67	0.45, 0.99	0.67	0.45, 0.99
Additional adjustment for body mass index[c]		0.74	0.50, 1.09	0.74	0.49, 1.10	0.71	0.48, 1.07
Additional adjustment for waist circumference		0.75	0.50, 1.11	0.73	0.48, 1.09	0.73	0.49, 1.09
Additional adjustment for percentage of body fat		0.79	0.54, 1.17	0.78	0.52, 1.17	0.81	0.54, 1.21
Additional adjustment for mediators[d]		0.70	0.46, 1.03	0.72	0.47, 1.08	0.71	0.47, 1.07

Abbreviations: CI, confidence interval; MET, metabolic equivalent; OR, odds ratio.

[a] All results were adjusted for age (as a continuous variable), study site (Oklahoma, Arizona, North Dakota, South Dakota), and sex.

[b] The model included age, study site, sex, education (less than high school, high school, post-high school), cigarette smoking (never, ever, current), alcohol use (never, ever, current), and family history of diabetes.

[c] There were 11 underweight participants (body mass index ≤ 18.5) included in the analyses, of which only 1 developed diabetes during follow-up. Sensitivity analyses indicated that excluding underweight participants did not alter the reported risk estimates.

[d] Results were adjusted for all covariates listed in footnote "b" above, as well as the potential mediators systolic blood pressure, diastolic blood pressure, high density lipoprotein cholesterol, low density lipoprotein cholesterol, plasma fibrinogen, and body mass index as continuous variables.

図表掲載箇所	P637, 表3
概 要 (800字まで)	本研究は，総身体活動と糖尿病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．the Strong Heart Studyの参加者1651名のアメリカン・インディアンの男女が10年間にわたり追跡された．過去1年間の余暇時間と仕事における身体活動が評価された．余暇時間の身体活動は，ランニング，水泳，自転車，釣り，ハイキングなどを実施する頻度と時間が調査された．仕事での身体活動は，通勤における歩行や自転車の時間，労働の頻度や時間，座位の時間，仕事の活動強度について調査された．身体活動に関するこれらの調査から週あたりの各活動における時間がメッツ・時に換算された．余暇時間と仕事にける身体活動を合わせた総身体活動と糖尿病発症リスクについて検討した結果，全く活動を実施していない人と比較して(0メッツ・時/週)，30メッツ・時/週未満の者の調整オッズ比は0.70(95%CI:0.46-1.03)，30-106メッツ・時/週の者では0.72(0.47-1.08)，106メッツ・時/週以上では0.71(0.47-1.07)となり，関連性は認められなかった．また，余暇時間における身体活動のみで同様に解析した結果，全く活動を実施していない人と比較して(0メッツ・時/週)，8メッツ・時/週未満の者の調整オッズ比は1.09(0.76-1.56)，8-24メッツ・時/週の者では0.80(0.56-1.15)，24メッツ・時/週以上の者では0.75(0.53-1.06)となり，糖尿病発症リスクとの関連は認められなかった．
結 論 (200字まで)	アメリカン・インディアンを対象とした本研究において，身体活動は糖尿病発症と関連することが示された．しかしながら，BMIや腹囲，体脂肪率等で調整するとこれらの関連性は認められなくなった．
エキスパートによるコメント (200字まで)	総身体活動と糖尿病発症リスクとの関連について検討したコホート研究である．調整因子にBMIや腹囲，体脂肪率を含めると，有意な関連性が認められなくなる．本研究の身体活動量は質問紙による評価であり，信頼性が乏しい．今後，更なる検討が要される．

担当者 川上諒子

ELSEVIER

Time-Dependent Confounding in the Study of the Effects of Regular Physical Activity in Chronic Obstructive Pulmonary Disease: An Application of the Marginal Structural Model

JUDITH GARCIA-AYMERICH, PETER LANGE, IGNASI SERRA, PETER SCHNOHR, AND JOSEP M. ANTÓ

PURPOSE: Results from longitudinal studies about the association between physical activity and chronic obstructive pulmonary disease (COPD) may have been biased because they did not properly adjust for time-dependent confounders. Marginal structural models (MSMs) have been proposed to address this type of confounding. We sought to assess the presence of time-dependent confounding in the association between physical activity and COPD development and course by comparing risk estimates between standard statistical methods and MSMs.
METHODS: By using the population-based cohort Copenhagen City Heart Study, 6,568 subjects selected from the general population in 1976 were followed up until 2004 with three repeated examinations.
RESULTS: Moderate to high compared with low physical activity was associated with a reduced risk of developing COPD both in the standard analysis (odds ratio [OR] 0.76, $p = 0.007$) and in the MSM analysis (OR 0.79, $p = 0.025$). In the subgroup with COPD ($n = 2{,}226$), high physical activity was associated with a reduced risk of COPD admissions during follow-up (standard, incidence rate ratio, 0.74; $p = 0.096$; MSM, 0.68, $p = 0.044$), and with a reduced risk of mortality (standard, hazard ratio 0.80, $p = 0.001$; MSM, 0.81, $p = 0.008$).
CONCLUSION: These results support the previously reported associations between physical activity and reduced risk of COPD development, hospitalizations, and mortality, thereby suggesting they were not due to time-dependent confounding.
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KEY WORDS: Confounding Factors (Epidemiology), Epidemiology, Epidemiologic Methods, Exercise, Models, Statistical, Motor Activity, Pulmonary Disease, Chronic Obstructive.

INTRODUCTION

The regular practice of physical activity has been related to a reduced risk of premature mortality and several chronic diseases and conditions, including cardiovascular diseases, diabetes, or colon cancer (1). Despite the large amount of research on the benefits of physical activity, its effects on respiratory health have hardly been studied (1). Chronic obstructive pulmonary disease (COPD) is one of the main causes of morbidity and mortality worldwide (2); it has been recently reported that the regular practice of physical activity may reduce the risk of developing this disease (3) and improve its prognosis (4, 5).

A limitation of the studies alluded to above is that they could not have sufficiently accounted for confounding. Standard methods of analysis model the probability of the outcome as a function of exposure and covariates. In the study of the effects of physical activity in COPD, as in many other settings, both exposure (physical activity) and many of the covariates (nutritional status, respiratory symptoms, or quality of life) are time varying. When both exposure and covariates change over time, and covariates are confounders that are also affected by prior exposure, standard methods of analysis may be biased (6). This situation has been labeled as time-dependent confounding (7). To appreciate how time-dependent confounding may lead to biased results, consider the role of obesity in a longitudinal study of the association between physical activity and mortality, with repeated measures over time of physical activity and obesity. Physical activity (at time t) is a behavior that reduces the risk of mortality (1). Previous obesity (at t-1) is a covariate that

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Selected Abbreviations and Acronyms

BMI = body mass index
CCHS = Copenhagen City Heart Study
CI = confidence interval
COPD = chronic obstructive pulmonary disease
FEV_1 = forced expiratory volume in 1 second
FVC = forced vital capacity
HR = hazard ratio
ICD = International Classification of Diseases
IQR = interquartile range
IRR = incidence rate ratio
m = mean
MSM = marginal structural model
n = number of cases
OR = odds ratio
SD = standard deviation

relates to a reduced level of physical activity (at t) and it is also associated with higher risk of mortality (8). Therefore, obesity at $t-1$ is a confounder. Additionally, subjects practicing higher levels of physical activity (at t) have a reduced risk of obesity (at $t+1$) (8), so obesity (at each t_n) is also affected by prior exposure (physical activity at t_{n-1}). In this example, the crude association between physical activity (at t) and mortality (at $t+1$) will be biased because subjects with lower level of physical activity (at t) will tend to be those with higher obesity (at $t-1$) and higher risk of mortality (at $t+1$). The estimate obtained after adjusting for obesity at time $t-1$ will be biased because it ignores the fact that, after the start of the study (at t), the level of physical activity may change according to changes in obesity (at t or $t+1$). The control for repeated measures of obesity will also give biased estimates in part because obesity is on the pathway between exposure and outcome (9–11).

Since standard methods for longitudinal analysis do not properly account for the problems derived from time-dependent confounding, marginal structural models (MSMs) have been developed (6). Although these models are relatively easy to implement in common statistical software, their use in applied epidemiology is still scarce. It is interesting to note that several of the studies using MSMs have reported differences between the estimates obtained with MSMs and estimates obtained with standard methods, which in some cases meant even a change in the direction of the association under study (12–15). As a result, all these studies recommend the use of MSMs when time-dependent confounding is likely. In the study of the health effects of physical activity, to our knowledge only two papers have used MSMs (16, 17). These studies pointed to the need to consider repeated measurements of physical activity and body composition to appropriately assess their role as determinants of functional limitations in the elderly, since the changing nature of physical activity and body composition over time could produce the mentioned time-dependent confounding.

In the present study, we used the population-based cohort Copenhagen City Heart Study to assess the presence of time-dependent confounding in the association between physical activity and (i) COPD development, and (ii) COPD course, by comparing standard statistical methods with MSMs.

MATERIAL AND METHODS

Subjects

The Copenhagen City Heart Study (CCHS) involves the study of an ongoing prospective cohort of adults recruited from the general population, with repeated examinations every 5 to 10 years. A random age-stratified sample of the general population aged 20 years or more was drawn from the Copenhagen Population Register as of January 1, 1976, and an initial examination (n = 14,223, 74% of the eligible) took place in 1976–1978. At the second examination 5 years later (1981–1983), the cohort was supplemented with a new sample of subjects aged 20 to 24 years (total n =12,698, 70% of the eligible). In the third examination (1991–1994), the sample was supplemented with 20- to 49-year-old subjects (total n = 10,135, 61% of the eligible) (18, 19). The institutional review board and Danish regional ethics committees approved the research protocol. Participants gave written informed consent.

For the present study, we selected two sets of participants, according to the objective of each analysis. For the study of the association between physical activity and COPD development, all subjects who participated in the first, second, and third CCHS surveys with available data regarding both physical activity and lung function (n = 6,568). The date of participation in the first CCHS examination was considered the start of follow-up. All subjects were followed up to the third CCHS examination, with a mean follow-up of 16 years (range, 14–18 years).

For the study of the association between physical activity and COPD course, subjects with criteria of COPD either in the first or second examination, and with the condition of having participated in at least two surveys, were selected (n = 2,226). COPD was defined on the basis of lung function including forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) as the presence of airway obstruction ($FEV_1/FVC \leq 70\%$) (20). The date of participation in the survey when COPD was first diagnosed was considered the start of the follow-up period. Given that the period with available data for admissions was shorter than for mortality, the study considered two different end points. For the admissions outcome, subjects were followed up either to the time of death or to December 28, 2000 with a mean of 19 years (range, 5–25 years). For the mortality outcome, subjects were followed up either to the time of

death or to March 11, 2004, with a mean of 21 years (range, 5–28 years).

Measures

Identical methods were applied in the first, second, and third CCHS examinations and have been previously described in detail (18, 19). For the present analysis, both baseline and repeated measurements of all variables were considered. A self-administered questionnaire on regular physical activity over the previous 12 months, current smoking and alcohol consumption, socioeconomic factors (gender, age, education, marital status, cohabitation, income), current symptoms (dyspnea [21], sputum, chest pain, leg pain, and intermittent claudication), a diagnosis of comorbidity at any time (asthma, ischemic heart disease, myocardial infarction, stroke, diabetes), and health service use over the previous 12 months was completed and checked by the CCHS staff. Blood pressure, plasma cholesterol, glucose concentrations, and body mass index (BMI) were also measured. Clinical records were reviewed to obtain information about comorbidity.

Physical activity was measured at each survey using a questionnaire originally developed by Saltin and Grimby (22), which discriminates between sedentary persons and their more active counterparts with respect to maximal oxygen uptake (23), and has been widely used to describe the effects of physical activity on health outcomes in similar types of populations (24, 25). Physical activity variables included physical activity at work, during leisure time, jogging, cycling in winter, and cycling in summer. The levels of physical activity were classified as previously suggested (26): low, moderate, and high.

Lung function parameters (FEV_1 and FVC) were measured at the first and second CCHS examination with an electronic spirometer (model N 403; Monaghan, Littleton, CO), which was calibrated daily with a 1-l syringe and weekly against a water-sealed Godard spirometer. At the third examination a dry wedge spirometer (Vitalograph, Maidenhead, UK), calibrated daily with a 1-l syringe, was used. At each examination three repeated valid maneuvers were obtained with at least two measurements differing by less than 5%. The highest measurements of FEV_1 and FVC were used in the analyses as absolute values and as percentage of predicted values, using internally derived reference values based on a subsample of healthy individuals who never smoked (27). A yearly rate of decline in FEV_1 and FVC was defined according to "(final – baseline levels)/follow-up in years" for each subject and period.

Information about hospital admissions (dates and diagnoses on discharge) during follow-up was obtained from the National Patient Register which covers all Danish hospitals and is administered by the National Board of Health. COPD admission was defined as any admission classified as *International Classification of Diseases* (ICD), *8th Revision* codes 490-492 or ICD-10 codes J40–J44 for the main diagnosis. Data on deaths and the causes thereof were obtained from the Danish National Board of Health.

Statistical Methods

We first examined the association between physical activity and COPD development. For this analysis, all subjects contributed with two complete periods of information: from first CCHS survey to the second, and from the second to the third. Repeated measures analysis was used to treat repeated measurements of the same subject. Physical activity (defined as previously (3) as a combined measure between each period and the following) was considered the exposure variable. Three different outcome measures of COPD were used: FEV_1 decline, FVC decline, and COPD development. Multiple linear regression was used for FEV_1 and FVC decline. After exclusion of subjects with COPD during the first or second survey, those with COPD at the third survey were defined as new cases, and modeled using multivariate logistic regression.

Second, we analyzed the association between physical activity and COPD course. For this analysis, subjects contributed with two (45% of the subjects) or three (55%) complete periods of information: from first survey to second, from second to third, and from third to the end of the follow-up. Repeated measures analysis was used to treat repeated measurements of the same subject. Physical activity at each period was considered the exposure variable. Two outcome measures of COPD course were used: number of admissions due to COPD and all-cause mortality. For the COPD admissions outcome, zero-inflated negative binomial regression with the number of COPD admissions, considering time of follow-up, as the outcome was used. For all-cause mortality, Cox regression was not appropriate because the assumption of proportionality of hazards was not satisfied. Instead, parametric regression was used to estimate mortality hazard ratio (HR) among groups of physical activity level. Since there were no losses to follow-up, no censoring was present.

To assess the presence of time-dependent confounding, we compared qualitatively the estimates provided by both standard and marginal structural methods in all analyses: linear regression for FEV_1 and FVC decline, logistic regression for COPD development, negative binomial regression for hospital admissions and parametric regression for mortality.

Briefly, MSMs are based on the concept of counterfactuals, which represent the set of outcomes that a subject would have experienced in case of having had other exposures than those that actually occurred (6). Weighting

subjects by the inverse probability of the observed exposures creates a pseudopopulation in which confounders are no longer associated with the exposure because the distribution of confounder values is the same among subjects in the different exposure levels. Thus, the analysis in the pseudopopulation allows for unbiased estimates of the associations under study (see Robins et al. [6] for an example on how weighting removes time-dependent confounding). As follows, we describe how the MSMs were implemented in our study.

Following the notation by Robins et al. (6), let A_k represent observed levels of physical activity (low, moderate, high) at time k (k = 1, 2, 3), let $\boldsymbol{L_k}$ denote a vector of covariates, and let Y represent the outcome. Covariates in $\boldsymbol{L_k}$ act as confounders since they relate both to exposure A_k and outcome Y, and include gender, age, income, years of school, BMI, sputum, smoking, alcohol, asthma, glucose, systolic blood pressure, FEV_1 and FVC. (Other potential confounders [such as health services use or other socioeconomic factors, symptoms, or comorbidities] were also tested, but they did not fulfill the conditions for being considered confounders in our analysis). Additionally, all confounders in $\boldsymbol{L_k}$ but gender and age are also affected by A_{k-1}.

The contribution of each subject was weighted by the inverse of its probability density function of being in its own level of A_k, conditioned on $\boldsymbol{L_k}$. Given that a strong association between $\boldsymbol{L_k}$ and A_k may produce a large variability in weights (12), we replaced them by the proposed (12) stabilized weights, which include in the numerator the unconditional (unadjusted) probability density function, that is, the probability of each subject of being in its own level of A_k. Thus, stabilized weights were computed, separately for each k study visit, according to the following formula:

$$SW_k = f_{A_k}(a_k) / f_{A_k|L_k}(a_k|l_k) \qquad \text{(equation 1)}$$

Since A_k is a discrete three-category variable (low, moderate, high), a politomic logistic regression was used to calculate the probability of being at each A_k level. The numerator in Equation 1 (unconditional probability of each subject of being in its own level of A_k) was computed as follows:

$$f_{A_k}(a_k) = \Pr(A_k = a_k) = \\ = \exp(\beta_{k_{ak}}) / 1 + \sum_{j=1}^{3} \exp(\beta_{k_j}), a_k = 1,2,3$$

$$\Pr(A_k = 0) = 1/1 + \sum_{j=1}^{3} \exp(\beta_{k_j})$$

(equation 2)

The denominator in Equation 1 (conditional probability density function of each subject being in its own level of A_k) was computed as:

$$f_{A_k|L_k(a_k|l_k)} = \Pr(A_k = a_k | L_k = l_k) = \\ = \exp(\alpha_{k_{ak}} + \alpha_1 l_k) / 1 + \sum_{j=1}^{3} \exp(\alpha_{k_j} + \alpha_1 l_k),$$

$$a_k = 1,2,3$$

$$\Pr(A_k = 0 | L_k = l_k) = 1/1 + \sum_{j=1}^{3} \exp(\alpha_{0_j} + \alpha_1 l_k)$$

(equation 3)

The parameters β_{k1}, β_{k2}, β_{k3}, α_{k1}, α_{k2}, α_{k3} and $\boldsymbol{\alpha_1}$ can be fitted in Stata by using the command for multinomial logit models *mlogit*. Formally, weighting by stabilized weights allows for the estimation of parameters of a marginal structural model (6).

Since we assessed the effects of physical activity on several outcome variables (FEV_1 decline, FVC decline, COPD development, hospital admissions, and mortality), and each of these analyses included a different set of subjects and covariates, weights were computed separately for each outcome analysis. Distribution of weights, with mean values around 1.00, is included in the Appendix. Confounders were defined as published previously (3, 5) and were included in the standard analyses as covariates of the multivariate models, while in the MSMs they were included as covariates ($\boldsymbol{L_k}$) in Equation 3. Some studies have used covariates in $k-1$ to predict exposure in k (12). In our study, the interval between examinations was longer (5–10 years) than in such previous studies and concomitant covariates had stronger associations with levels of exposure than covariates of the previous examinations. Thus, covariates in k provided a better control of confounding. Although the periodicity of 5 to 10 years responded to availability of data, it was appropriate for the outcomes under study because the biology underlying lung function decline and the population-based nature of the sample needed from a longer follow-up and a lower measurements frequency than other outcomes would have required. Therefore, and assuming that $\boldsymbol{L_k}$ preceded A_k, we included concomitant exposure and covariates in Equation 3. Interaction terms for plausible effect modifiers were tested, as previously defined (3, 5), and finally not included because of the lack of statistically significant interactions.

Regarding the general assumptions underlying MSM implementation, we assumed the following: (1) no unmeasured confounding (since we included all the confounders that have been previously reported as related to the risk of COPD development or course[28]); (2) time ordering (since in all analyses exposure preceded the outcome); (3) consistency assumption (observed outcomes is a member of the set

of all possible counterfactual outcomes); (4) experimental treatment (exposure) assignment (all possible exposures are observed for given covariates); and (5) no model misspecification.

Tables 1–4 show results with standard methods and MSMs. Present results with standard methods may be slightly different than previously published results (3, 5) because previous analyses did not include repeated measurements of exposure and confounders. The analysis was performed using Stata, release 8.2 (StataCorp, 2005, College Station, TX). All p values are two sided.

RESULTS

Physical Activity and COPD Development

A total of 6,568 subjects from the general population were included (41% men; mean age at baseline, 49 years) (Table 1). In the standard (adjusted) analysis, higher physical activity levels showed an improved FEV_1 decline by gaining +6.5 and +10.2 mL/yr in the moderate and high physical activity groups, respectively, as compared with the low physical activity group. Corresponding figures in the marginal structural (weighted) approach were very similar: +7.4 and +10.3 (Table 2, *a*). Similarly, subjects in the moderate and high physical activity group showed a reduced FVC decline, in a dose-response manner, and very small differences were found in the estimates between the standard and the marginal structural models (Table 2, *b*). There were a total of 661 new cases of COPD during the follow-up period. Subjects in the moderate to high physical activity group had a statistically significant reduction of COPD development with respect to the low physical activity group: OR 0.76 (95% CI, 0.62–0.93) in the standard and 0.79 (0.64–0.97) in the marginal structural approach (Table 2, *c*).

TABLE 1. Characteristics of 6,568* subjects recruited in the Copenhagen City Heart Study from the general population of Copenhagen in the period 1976–1978 and followed up with physical activity and lung function information until 1991–1994

	CCHS First examination 1976–1978	CCHS Second examination 1981–1983	CCHS Third examination 1991–1994
	n = 6,568	n = 6,568	n = 6,568
Gender (men), No. (%)	2720 (41.4)	2720 (41.4)	2720 (41.4)
Age (yr), mean (SD)	49.43 (10.62)	54.14 (10.62)	65.03 (10.64)
Smoking, self-reported, No. (%)			
Never	1528 (23.3)	1526 (23.3)	1595 (24.4)
Former	1175 (17.9)	1462 (22.3)	1903 (29.1)
Active	3859 (58.8)	3575 (54.5)	3042 (46.5)
FEV_1 (1), mean (SD)	2.76 (0.82)	2.61 (0.85)	2.42 (0.85)
FVC (1), mean (SD)	3.42 (0.96)	3.25 (1.00)	3.17 (1.02)
COPD (FEV_1/FVC ≤ 70%), No. (%)	742 (11.4)	799 (12.2)	1268 (20.3)
Physical activity at each survey, No. (%)			
Low	937 (14.3)	843 (12.8)	884 (13.6)
Moderate	3473 (52.9)	3243 (49.4)	3528 (54.4)
High	2153 (32.8)	2480 (37.8)	2076 (32.0)
Outcomes			
Mean FEV_1 decline (mL/yr), mean (SD)	−27.86 (97.36)		−19.35 (40.89)
Mean FVC decline (mL/yr), mean (SD)	−32.89 (111.57)		−8.82 (15.31)
COPD development (n = 5041), No. (%)			661 (13.1)

CCHS = Copenhagen City Heart Study; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; COPD = chronic obstructive pulmonary disease; SD = standard deviation..
*The numbers do not always add up to reported totals because some values are missing for certain variables: 6 in the first, 5 in the second, and 28 in the third examination for smoking; 68, 39, and 20 for FEV_1 and 5, 2, and 80 for physical activity.

Physical Activity and COPD Course

A total of 2,226 subjects with COPD from the general population were included and followed up (52% men; mean age at baseline, 54 years) (Table 3). Fewer than 23% of them had admissions due to COPD during follow-up. Subjects in the high physical activity group had a lower risk of admissions than those in the low or moderate physical activity group. The association was slightly stronger in the MSM (IRR, 0.68 [95% CI, 0.47–0.99]) than in the standard model (0.74 [0.52–1.06]) (Table 4, *a*). More than half of the subjects died during the follow-up. Being in the moderate or high physical activity group was associated with a statistically significant reduced risk of mortality, in a dose-response manner. The magnitude of the association was slightly lower in the MSM (HR 0.88 [0.76–1.01] and 0.81 [0.69–0.95] for the moderate and high activity groups, respectively, compared to the low physical activity group) than in the adjusted model (HR 0.83 [0.74–0.94], and 0.80 [0.69–0.91], respectively) (Table 4, *b*).

DISCUSSION

We have used MSMs to estimate the effects of physical activity on COPD development and COPD course because standard methods are not appropriate when there are confounders that are affected by previous levels of physical activity. This is the first study assessing time-dependent confounding in the study of the effects of physical activity on respiratory outcomes. The inclusion of several outcomes allowed to test whether the magnitude of this confounding could vary from one outcome to another. It is necessary to point out that standard and MSM approaches cannot be compared quantitatively, and only qualitative differences with respect to inference can be drawn. In our study, the lack of differences between the associations estimated with the standard methods and the ones obtained with the

TABLE 2. Adjusted (standard) and weighted (marginal structural model) association between physical activity and FEV_1 decline (2a),* FVC decline (2b),† and COPD development (2c)‡ in 6,568 subjects from the general population in Copenhagen

	n = 6,568 (13,136 observations)					
	Adjusted§			Weighted§		
2a*	Coefficient	95% CI	p Value	Coefficient	95% CI	p Value
Physical activity						
Low (reference)‖	−27.9			−32.0		
Moderate¶	6.5	3.0–9.9	<0.001	7.4	3.4–11.5	<0.001
High¶	10.2	6.8–13.6	<0.001	10.3	6.6–14.0	<0.001
p for linear trend			<0.001			<0.001
2b†	n = 6,568 (13,136 observations)					
	Adjusted#			Weighted#		
	Coefficient	95% CI	p Value	Coefficient	95% CI	p Value
Physical activity						
Low (reference)	−26.0			−29.3		
Moderate¶	7.1	3.0–11.2	0.001	6.9	1.9–11.8	0.001
High¶	11.9	7.9–16.0	<0.001	10.0	5.5–14.5	<0.001
p for linear trend			<0.001			<0.001
2c‡	n = 5,041 (10,082 observations)					
	Adjusted**			Weighted**		
	OR	95% CI	p Value	OR	95% CI	p Value
Physical activity						
Low	1.00			1.00		
Moderate	0.78	0.62–0.98	0.034	0.81	0.65–1.03	0.082
High	0.73	0.59–0.91	0.006	0.76	0.61–0.95	0.018
Physical activity						
Low	1.00			1.00		
Moderate and high	0.76	0.62–0.93	0.007	0.79	0.64–0.97	0.025

CI = confidence interval; OR = odds ratio.
*Average annual change in FEV_1 (mL/yr) in the low physical activity group and additional relative change (95% CI) in the moderate and high physical activity groups (linear regression model).
†Average annual change in FVC (mL/yr) in the low physical activity group and additional relative change (95% CI) in the moderate and high physical activity groups (linear regression model).
‡Adjusted risk of COPD in each physical activity group (logistic regression model).
§Linear regression models adjusted or weighted for gender, age, years of school, body mass index, sputum, smoking, alcohol, and FEV_1 at baseline.
‖Adjusted mean values based on the linear regression equations. Negative values represent decline.
¶Coefficient (and 95% CI) from the linear regression model. Positive values mean yearly gain in milliliters as compared with the low physical activity group.
#Linear regression models adjusted or weighted for gender, age, years of school, body mass index, sputum, smoking, alcohol, and FVC at baseline.
**Logistic regression models adjusted or weighted for gender, age, years of school, body mass index, sputum, asthma, and smoking.

MSM suggest that our previous reports (3, 5) were not biased by time-dependent confounders.

Regular physical activity had been previously found associated with reduced lung function decline(3, 29–31) and a reduced risk of COPD development (3) in the general population, as well as with a reduced risk of COPD admissions and all-cause mortality in subjects with COPD (4, 5).BMI, baseline lung function, smoking habits, alcohol consumption, chronic respiratory symptoms, and presence of ischemic heart disease are covariates previously included as potential confounders of some of the described associations. All these covariates are most likely affected by prior levels of physical activity, so they satisfy the conditions for time-dependent confounding. Because previous studies did not take into account time-dependent confounding, the provided estimates of effect could have been biased. In the present study, we used MSMs to control for time-dependent confounding, and the comparison of the estimates and their confidence intervals between the standard and MSM approach reveals very small differences, which can be interpreted as random variability. The presence of still strong associations between physical activity and both COPD development and course using the MSM supports our previous reports and reinforces the need of public health measures to increase physical activity practice at both the population and the patient level. These findings also suggest that public health benefits of physical activity may have been underestimated.

Previous studies using MSMs have consistently found a relevant change in the associations under study when these were obtained by using MSM instead of the standard epidemiological analyses. Among them, the effectiveness of zidovudine on the survival of HIV-positive men (12) or the effectiveness of iron supplementation during pregnancy on anemia (13) changed from a positive association (risk factor) in the standard analyses to a negative association

TABLE 3. Baseline characteristics and outcomes of 2,226 subjects with COPD recruited in Copenhagen between 1976 and 1983 and followed up until 2000 for admissions and 2004 for mortality

	All subjects*
Source (CCHS survey)	
First and second admissions	855 (38.4)
First and third admissions	64 (2.9)
First, second, and third admissions	1231 (55.3)
Second and third admissions	76 (3.4)
Gender (men)	1161 (52.2)
Age (yr)†	54.4 (10.3)
Smoking	
Never	298 (13.4)
Former	336 (15.1)
Current	1591 (71.5)
Physical activity	
Low	423 (19.0)
Moderate	1100 (49.5)
High	700 (31.5)
COPD severity	
I – Mild (FEV_1 ≥80%)	966 (43.7)
II – Moderate (FEV_1 <80% and ≥50%)	1027 (46.5)
III – Severe (FEV_1 <50% and ≥30%)	190 (8.6)
IV – Very severe (FEV_1 <30%)	27 (1.2)
Outcomes	
Admissions	
Follow-up period (yr)‡	22.0 (16.0–23.8)
No. of COPD admissions during follow-up	
0	1730 (77.7)
1	170 (7.6)
2	102 (4.6)
≥3	224 (10.1)
Mortality	
Follow-up period (yr)‡	22.1 (16.0–26.6)
Death during follow-up	1427 (64.1)
Time to death (yr)† (n = 1,427)	17.3 (5.7)

COPD = chronic obstructive pulmonary disease; CCHS = Copenhagen City Heart Study; FEV_1 = forced expiratory volume in 1 second.
*Data expressed are numbers of subjects with percentage in parentheses. The numbers do not always add up to reported totals as some values are missing for certain variables: 1 in smoking, 3 in physical activity, and 16 in lung function.
†Data expressed as mean with standard deviation given in parentheses.
‡Data expressed as median value with interquartile range given in parentheses.

(protective factor) in the MSMs. In both cases, the authors interpreted that the amount of confounding due to time-dependent confounders was very high. These results are in contrast to our findings. It could be argued that our study did not include the relevant time-dependent confounders. We believe that this is unlikely since we included all the confounders that have been previously reported as related to the risk of COPD development or course (28). Additionally, authors consider unlikely that the large observed associations are explained by the existence of unknown confounders at once strongly associated with physical activity and COPD outcomes, and with a high frequency in our population (32). Publication bias could be another explanation if other studies showing no differences between standard and MSM analyses have not been published or submitted for publication.

It needs to be mentioned that MSMs have also been developed to estimate causal effects in observational studies, either in the presence or not of time-dependent confounding (6). The association measures in observational studies cannot usually be interpreted as causal effect measures because the exposed and the unexposed subjects are rarely exchangeable (i.e., exposed and unexposed rarely share the same set of confounder values). The MSMs use the inverse probability weighting, previously detailed, to create a pseudopopulation in which exposed and non-exposed are exchangeable (within levels of the available confounders), and thus associations can be interpreted as causal effects (6). Obviously, one condition is to have available information about all potential confounders since, in the presence of residual confounding, the associations should not be interpreted as causal effects. Several but not many studies have used MSMs with this aim, like the study of the causal effects of physical activity and body composition on functional limitation in the elderly (16) or the causal effect of methotrexate in mortality of patients with rheumatoid arthritis (33).

Some limitations related to the assumptions of the MSMs, and their use in observational studies, need to be considered. First, the use of weights induces the creation of a pseudopopulation with counterfactual (contrary to the observed) exposures, which may be nonsense for some of the covariates (e.g., gender) and makes the interpretation conceptually difficult. Second, the fact that our data set had only three repeated measurements available could have limited the effectiveness of the MSMs to remove time-varying confounding. However, previous studies with only two repeated measures (13, 16) have successfully applied MSMs. Experimental treatment (exposure) assumption was tested by plotting observed and predicted (given covariates) exposures (data not shown). The wide distribution of observed exposure values for every level of predicted exposure indicated there was no violation of this assumption. Authors assume that all other assumptions required to implement the MSM were met, and actually they are not more restrictive than those of standard methods. Finally, other potential study limitations beyond the use of MSMs (e.g., selection bias, misclassification of the physical activity level, or censoring by death in the analysis of COPD admissions) have been previously discussed in detail (3, 5). In our study, the implementation of the MSM was feasible in linear, logistic, negative binomial, and parametric regression models. In all of our analyses, which included different combinations of subjects and covariates, stabilized weights satisfied the condition of small variability (12).

In conclusion, the results of our study support the previously reported associations between physical activity and a reduced risk of COPD development, hospitalizations,

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TABLE 4. Adjusted (standard) and weighted (MSM) association between physical activity and number of COPD admissions (4a)* and all-cause mortality (4b)† in 2,226 subjects with COPD from the general population in Copenhagen

	n = 2,226 (6,678 observations)					
	Adjusted			Weighted		
4a*	IRR	95% CI	p Value	IRR	95% CI	p Value
Physical activity						
Low	1.00			1.00		
Moderate	1.06	0.78–1.44	0.710	1.10	0.82–1.49	0.522
High	0.74	0.52–1.06	0.096	0.68	0.47–0.99	0.044
4b†	n = 2,226 1,427 deaths (6,678 observations)					
	Adjusted			Weighted		
	HR	95% CI	p Value	HR	95% CI	p Value
Physical activity						
Low	1.00			1.00		
Moderate	0.83	0.74–0.94	0.004	0.88	0.76–1.01	0.085
High	0.80	0.69–0.91	0.001	0.81	0.69–0.95	0.008
p for linear trend			0.002			0.009

IRR = incidence rate ratio; HR = hazard ratio.
*Zero-inflated negative binomial regression model adjusted and weighted for sputum and FEV_1 in the count component; for age, ischemic heart disease, smoking, sputum, visits to doctor, and FEV_1 in the zero-inflated component.
†Parametric regression model adjusted and weighted for gender, age, income, body mass index, smoking, glucose level, systolic blood pressure, and FEV_1.

and mortality, suggesting that they were not due to time-dependent confounding. Despite the lack of relevant differences between the standard and the MSM approaches in our study, the use of MSMs should be considered when time-dependent confounding is likely, given their theoretical appropriateness and the availability of feasible tools.

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APPENDIX.
DISTRIBUTION OF STANDARDIZED WEIGHTS IN EACH OUTCOME ANALYSIS

Analysis	Sample	Examination	Mean	Standard deviation	Min	5th percentile	25th percentile	Median	75th percentile	95th percentile	Max
Physical activity and FEV_1 decline	General population	I	1.000604	0.24	0.37	0.71	0.83	0.93	1.16	1.41	2.95
		II	1.002214	0.31	0.34	0.65	0.84	0.94	1.14	1.42	5.81
Physical activity and FVC decline	General population	I	1.000227	0.25	0.37	0.70	0.83	0.93	1.16	1.42	3.56
		II	1.001875	0.33	0.22	0.64	0.84	0.93	1.14	1.47	6.80
Physical activity and COPD development (physical activity in 3 categories)	General population excluding COPD at baseline	I	1.000281	0.21	0.43	0.74	0.84	0.94	1.15	1.38	2.94
		II	1.000340	0.24	0.20	0.71	0.85	0.95	1.13	1.38	3.89
Physical activity and COPD development (physical activity in 2 categories)	General population excluding COPD at baseline	I	1.000359	0.13	0.43	0.84	0.95	0.99	1.03	1.15	3.01
		II	1.000194	0.18	0.19	0.78	0.94	0.98	1.04	1.21	3.01
Physical activity and COPD admissions	Subjects with COPD from the general population	I	1.000537	0.14	0.56	0.79	0.97	0.98	1.03	1.25	2.40
		II	1.000427	0.20	0.47	0.71	0.94	0.98	1.04	1.36	2.54
		III	1.001560	0.27	0.46	0.78	0.92	0.97	1.03	1.52	3.89
Physical activity and mortality	Subjects with COPD from the general population	I	0.999796	0.30	0.47	0.62	0.81	0.91	1.16	1.50	2.82
		II	1.001648	0.33	0.35	0.62	0.81	0.94	1.12	1.58	5.18
		III	1.000206	0.39	0.41	0.57	0.82	0.93	1.09	1.59	6.10

Min = minimum; Max = maximum; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; COPD = chronic obstructive pulmonary disease.

論文名	Time-dependent confounding in the study of the effects of regular physical activity in chronic obstructive pulmonary disease: an application of the marginal structural model
著 者	Garcia-Aymerich J, Lange P, Serra I, Schnohr P, Anto JM
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PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/18708291

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	男女混合	( )	( )		( )
	年齢	49.43±10.62歳		( )		前向き研究
	対象数	5000～10000		( )		( )
調査の方法	質問紙	( )				

アウトカム	予 防	な し	な し	な し	な し	慢性閉塞性肺疾患	死亡
	維持・改善	な し	な し	な し	な し	( )	( )

図 表

TABLE 4. Adjusted (standard) and weighted (MSM) association between physical activity and number of COPD admissions (4a)* and all-cause mortality (4b)† in 2,226 subjects with COPD from the general population in Copenhagen

	n = 2,226 (6,678 observations)					
	Adjusted			Weighted		
4a*	IRR	95% CI	p Value	IRR	95% CI	p Value
Physical activity						
Low	1.00			1.00		
Moderate	1.06	0.78–1.44	0.710	1.10	0.82–1.49	0.522
High	0.74	0.52–1.06	0.096	0.68	0.47–0.99	0.044

4b†	n = 2,226 1,427 deaths (6,678 observations)					
	Adjusted			Weighted		
	HR	95% CI	p Value	HR	95% CI	p Value
Physical activity						
Low	1.00			1.00		
Moderate	0.83	0.74–0.94	0.004	0.88	0.76–1.01	0.085
High	0.80	0.69–0.91	0.001	0.81	0.69–0.95	0.008
p for linear trend			0.002			0.009

IRR = incidence rate ratio; HR = hazard ratio.
*Zero-inflated negative binomial regression model adjusted and weighted for sputum and FEV_1 in the count component; for age, ischemic heart disease, smoking, sputum, visits to doctor, and FEV_1 in the zero-inflated component.
†Parametric regression model adjusted and weighted for gender, age, income, body mass index, smoking, glucose level, systolic blood pressure, and FEV_1.

図表掲載箇所	P782, Table4
概 要 (800字まで)	本研究は、デンマークのThe Copenhagen City Heart Study(CCHS)に参加した男女6,568名を対象に平均16年間の追跡調査を行い、身体活動と慢性閉塞性肺疾患(COPD)との関連を異なる二つの統計解析方法を用いて検討したものである。身体活動量は、職業活動、余暇時間活動、ジョギング、夏季・冬季の自転車を実施時間を尋ね、合計身体活動量を低い順に、低、中、高の3群に分類した。標準的な統計方法を用いた解析では、3群に分類した身体活動とCOPD発症リスクに有意な関連はみられなかったが低vs中・高で見た場合、有意なリスク減少が認められた。時間依存性交絡要因による影響を考慮することができるMSM法による解析では、COPD発症リスクは身体活動が低の集団と比較すると、高の集団で0.76(0.61-0.95)と減少した。
結 論 (200字まで)	どちらの統計方法を用いても身体活動とCOPD発症リスク、全死因死亡リスクに負の相関がみられたため、それらリスクは時間依存性交絡要因によるものではない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)	身体活動基準の策定に用いられた研究の1つである。COPDは近年、日本においても問題となっている疾患である。身体活動を増大させることでCOPDを予防できる可能性を示した重要な論文である。

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