CI, 0.40-1.31) times as likely to develop any non–small cell lung cancer and 0.95 (95% CI, 0.41-2.21) times as likely to develop adenocarcinoma. Subjects in the highest tertile of WBC count were 3.04 (95% CI, 1.31-7.07) times more likely to develop non–small cell lung cancer and 2.42 (95% CI, 0.89-6.82) times more likely to develop adenocarcinoma than those in the lowest tertile. Too few cases were available to evaluate other specific cell types according to physical activity or WBC count.

To assess whether the inverse association between physical activity and lung cancer risk was mediated by inflammation, the regression models evaluating the physical activity/lung cancer association were additionally adjusted for WBC count at baseline (Table 2, second column of HR). This adjustment led to very minimal changes in the lung cancer HRs associated with the various measures of physical activity. Similarly, the lung cancer HRs associated with WBC count were not substantially changed after additionally adjusting for total physical activity index (HR, 2.76; 95% CI, 1.54-4.95 and HR, 2.76; 95% CI,1.55-4.91, for 6.4-7.9 × $10^3/\mu L$ and ≥8 × $10^3/\mu L$ versus <6.4 × $10^3/\mu L$, respectively). Finally, WBC count did not seem to modify the relation between total physical activity index and lung cancer risk ($P_{interaction}$ = 0.86).

Discussion

In this study, we found an inverse association between physical activity and lung cancer risk. We also found evidence for a positive association between lung cancer risk and WBC count, but not serum albumin. It has been hypothesized that physical activity may lower lung cancer risk by reducing chronic inflammation. We found no evidence, however, that the associations of physical activity and WBC count with lung cancer risk were mediated through the same biological pathway.

Clearly smoking is a strong causal factor of lung cancer in both men and women, with a population attributable risk of approximately 75% to 90% in the United States (39, 40). Smoking prevention and cessation are the primary prevention strategies needed to reduce lung cancer incidence. However, the elucidation of other risk factors would aid in lung cancer prevention, particularly in never and former smokers, in whom ~50% of all new lung cancers are diagnosed (41). This study adds additional evidence to the body of literature that suggests that physical activity is a protective factor against the development of lung cancer.

We observed an inverse association between physical activity and lung cancer at the upper end of the 10% to 40% range of risk reductions observed in the majority of past studies (14). Given the strong relation between smoking and lung cancer risk, residual confounding of the relation between lung cancer risk and both physical activity and WBC count remains a concern. In models adjusted for sex, body mass index, alcohol, and education, but not smoking, the relations between lung cancer and physical activity and WBC count were stronger (HR, 0.43 and HR, 5.05 for third tertile versus first tertile of total physical activity index and WBC count, respectively) than in models fully adjusted for smoking (HR, 0.55 and HR, 2.81, respectively). Thus, it is possible that better measurement of smoking (e.g., more accurate reporting, biomarkers of smoking history) would further attenuate our findings. However, we were able to adjust for a number of prospectively obtained self-reported smoking parameters, including smoking status, amount of smoking (pack-years), and time since smoking cessation. In analyses stratified by smoking status, physical activity seemed to be associated with reduced lung cancer risk among never and former smokers combined, although this did not reach statistical significance. Too few cases were observed among never smokers (n = 16) to examine this stratum separately. The relation between smoking and adenocarcinoma is weaker than for other cell types (42). In our data, adenocarcinoma was associated with WBC count but not total physical activity index score. Although this was based on only 31 events, it suggests additional caution in interpreting the physical activity/lung cancer association.

Exercise is associated with reduced systemic inflammation (particularly C-reactive protein) both between persons in cross-sectional studies and within persons after the initiation of training regimens (21). Inflammation has been proposed to promote carcinogenesis in a wide spectrum of cancers, including lung, through its effects on cell proliferation, survival, and migration (24-26). Inflammatory lung conditions, such as chronic bronchitis and asthma, have previously been linked with increased lung cancer risk (43). Furthermore, the use of aspirin and other nonsteroidal anti-inflammatory drugs has been associated with reduced lung cancer risk (44, 45).

We investigated the relation between two inflammatory markers and lung cancer. WBC count is a widely used nonspecific marker of systemic inflammation (26, 46, 47). We observed reduced WBC counts in participants who reported higher physical activity levels, consistent with previous findings (19, 23, 48). Notably, we found that this relation persisted after adjustment for self-reported smoking history. Three studies have reported positive associations between WBC count and lung cancer incidence or mortality after adjustment for smoking (30, 46, 47). Similar to our study, Shankar et al. (46) reported increased lung cancer mortality among subjects in the upper quartile of WBC count compared with those in the lowest quartile (risk ratio, 2.58; 95% CI, 0.72-9.26 for quartile 4 versus quartile 1). The results from our study (incidence HR, 2.81; 95% CI, 1.58-5.01, and mortality HR, 3.75; 95% CI, 1.89-7.42) and Shankar et al. (46) provide greater risk estimates than those for quartile 4 versus quartile 1 of WBC count in Erlinger et al. (ref. 47; mortality HR, 1.79; 95% CI, 0.88-3.62) and the recently reported results of the Women's Health Initiative (ref. 30; incidence HR, 1.63; 95% CI, 1.35-1.97). The Women's Health Initiative observed little difference between lung cancer incidence and mortality HRs in relation to WBC count.

Serum albumin is a negative acute phase protein: its concentration in the blood is reduced in response to inflammation (49, 50). At least one study has reported an approximate 25% reduction in cancer mortality among middle-aged men with a 1 SD increase in serum albumin (51). We observed little difference in serum albumin among participants according to physical activity level, and no association between serum albumin and lung cancer risk.

To investigate the hypothesis that physical activity lowers lung cancer risk by decreasing systemic inflammation, we further adjusted the regression model of physical activity and lung cancer risk for WBC count. In an adequately adjusted model, one would expect the association between physical activity and lung cancer risk to be attenuated if the relation was mediated at least in part by inflammation (represented by WBC count; ref. 52). However, we found that the associations between lung cancer risk and both physical activity and WBC count were practically unchanged after simultaneous adjustment. Thus, the effect of physical activity on lung cancer risk does not seem to be mediated by inflammation, as represented by WBC count. Importantly, WBC count is only one marker of inflammation; it remains possible that other measures of inflammation may be more relevant to the relation of physical activity and lung cancer.

Physical activity has been proposed to lower lung cancer risk by a variety of other mechanisms. Physical activity might reduce the concentration of carcinogenic agents in the airways, the duration of agent-airway interaction, and particle deposition through increased ventilation and perfusion (53). Physical activity also reduces insulin-like growth factor levels that stimulate cell proliferation (54). Furthermore, physical activity may enhance immune function or endogenous antioxidant defenses (17, 55, 56).

A number of limitations must be considered in the interpretation of this study. We used a simple assessment of physical activity. Although an increased heart rate is an objective measure associated with lack of physical activity (57, 58), heart rate is also modified by general health, stress, and other psychosocial factors. Questions regarding the number of blocks walked per week and flights of stairs climbed per day have previously been used in combination with data on recreational physical activity to measure the relation between physical activity and cancer risk in the Harvard Alumni Health Study (5, 6, 59). We did not collect data on specific participation in recreational physical activities, but rather episodes of sweat-inducing activities. A moderate correlation (r = 0.54-0.62) has been reported between episodes of sweat-inducing activities and the Harvard Alumni Activity Survey scores (60, 61), including one study in a population of older women (62). The association between sweat-inducing activities and physical fitness measured on a cycle ergometer, however, has been reported to be stronger in men (r = 0.46) than in women (r = 0.26; ref. 60). Our summary physical activity measure that combined blocks walked, stairs climbed, and sweat-inducing activities was more strongly related to lung cancer risk among men than in women (Table 3), although the test for effect modification did not reach statistical significance ($P_{\text{interaction}}$ = 0.46).

The limited scope of our physical activity assessment failed to capture variation in the intensity and duration of sweat-inducing activities. To create our total physical activity index, we assumed a typical duration of 30 minutes for sweat-inducing activities, with an intensity level equivalent to jogging (multiple of resting metabolic rate = 7). The results did not seem sensitive to variation in these assumptions: assuming a multiple of resting metabolic rate of 5 for 30 minutes or a multiple of resting metabolic rate of 9 for 1 hour for sweat-inducing activities, both resulted in a HR of 0.55 for the third tertile of total physical activity index compared with the first tertile.

Notably, our physical activity assessment also failed to capture past history of physical activity. Our failure to capture variation in duration, intensity, and past history of activity would be expected to attenuate the reductions in risk observed in our study. Much more sophisticated assessments of physical activity have been developed since the initiation of our study. Further studies are necessary, in particular, to evaluate lung cancer risk in relation to cumulative lifetime physical activity and to discriminate the effects of physical activity during different time periods in life.

Other unmeasured aspects of a healthy lifestyle may confound the relation between physical activity and lung cancer. A diet high in fruits and vegetables has been associated with reduced lung cancer risk (63). Unfortunately, we had limited information on diet and were unable to control for this in our analysis.

The strengths of this study included a population-based cohort of both sexes with excellent follow-up, the prospective assessment of physical activity and inflammatory markers, and the ability to control for a number of prospectively obtained smoking parameters. It is possible that lower levels of physical activity among future cases might be expected at the baseline exam due to symptoms related to undiagnosed lung cancer, such as pain or fatigue. To reduce the potential for this bias, we excluded all lung cancer cases who were diagnosed within 12 months of the baseline examination (n = 13). Other diseases, particularly of the lung, may also influence physical activity, inflammation, and lung cancer risk. However, we observed little change in the relations among lung cancer risk, physical activity, and WBC count after adjusting for self-reported emphysema and diabetes.

Lung cancer is both the most common cancer diagnosis in the world and the most common cause of death from cancer (64). The global burden of smoking-related disease is overwhelming, with over 1.3 million new cases of lung cancer and approximately 1.2 million deaths in 2002 (64). Smoking prevention and cessation are imperative in reducing the mortality associated with this disease. Continued study of physical activity in relation to lung cancer risk, particularly among never smokers, may further our understanding of this disease and reveal additional strategies for reducing its burden.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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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	男女混合	( )		( )		( )
年齢	43-86歳	[redacted]		( )		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	な し	ガン予防	な し	( )	( )
維持・改善	な し	な し	な し	な し	( )	( )

図 表

Table 2. HR and 95% CI of lung cancer according to physical activity levels and inflammatory markers

	No. cases	Person-years*	HR (95% CI)†	P_{trend}†	HR (95% CI)‡	P_{trend}‡
Episodes of sweat-inducing activities/wk						
0	105	36,753	1		1	
1-3	10	10,862	0.44 (0.23-0.85)		0.45 (0.23-0.87)	
≥4	19	9,611	0.75 (0.45-1.24)	0.08	0.76 (0.46-1.26)	0.09
City blocks walked/d						
0	73	25,117	1		1	
1-11	44	19,633	0.93 (0.63-1.37)		0.92 (0.62-1.35)	
≥12	17	12,292	0.53 (0.31-0.90)	0.03	0.52 (0.30-0.89)	0.02
Flights of stairs climbed/d						
0-1	44	17,715	1		1	
2-5	60	20,224	1.53 (1.02-2.29)		1.53 (1.02-2.29)	
>5	30	19,254	0.84 (0.52-1.36)	0.58	0.86 (0.53-1.40)	0.67
Total physical activity index (kcal/wk)§						
0-174	65	18,531	1		1	
175-874	38	19,120	0.72 (0.47-1.09)		0.72 (0.48-1.09)	
≥875	31	19,358	0.55 (0.35-0.86)	0.01	0.56 (0.35-0.87)	0.01
Heart rate (30 s)						
21-33	27	12,065	1		1	
34-42	70	33,925	0.93 (0.59-1.46)		0.95 (0.60-1.49)	
>42	37	11,235	1.30 (0.80-2.16)	0.27	1.25 (0.75-2.09)	0.35
WBC tertile ($\times 10^3/\mu L$)						
<6.4	16	19,605	1		—	
6.4-7.9	50	19,421	2.74 (1.53-4.90)		—	
≥8	68	18,019	2.81 (1.58-5.01)	0.001	—	
Albumin tertile (g/dL)						
<4.6	52	19,307	1		—	
4.6-4.8	51	20,321	1.02 (0.69-1.52)		—	
≥4.9	31	17,427	0.85 (0.54-1.34)	0.52	—	

*Total person-years for cases and noncases in category of activity.
†Models are adjusted for age, sex, pack-years of smoking, time since smoking cessation, body mass index, alcohol intake, and education.
‡Models are adjusted for all variables in †, plus WBC count.
§Kilocalories per week from city blocks walked, flights of stairs climbed, and sweat-inducing activities (see Materials and Methods).

図表掲載箇所	P2716, Table2
概 要 (800字まで)	本研究は、アメリカのウィスコンシン州で行われた国民調査に参加した男女4,831名を対象に平均12.8年間の追跡調査を行い、身体活動量と肺がん発症の関連を検討したものである。身体活動については、1日当たり何ブロック(12ブロック=1マイル)歩いているか、1日当たり何度階段を使用するか、1週間当たり汗をかくような身体活動を何回行うかを尋ね、1ブロック/日を56kcal/週、階段1回は28kcal/週、汗をかくような活動1回を266kcalとし、合計消費カロリー数を総身体活動量とした。週当たり12ブロック以上の歩行を行う集団は、全く行わない集団と比較すると、肺がん発症リスクが0.52(95%信頼区間:0.30-0.89)と有意に低下した。汗をかくような活動を週当たり1-3回行う集団で、全く行わない集団と比較すると、肺がん発症リスクが0.45(0.23-0.87)と低下した。また総身体活動量が174kcal/週未満の集団と比較すると、875kcal/週以上で発症リスクが0.56(0.35-0.87)と有意に低下した(Ptrend=0.01)。また、喫煙者で総身体活動量が多い集団で肺がん発症リスクが量反応的に低下し(Ptrend=0.02)、同様に男性で総身体活動量が多い集団で発症リスクが低下した(Ptrend=0.01)。非喫煙者や喫煙経験者、または女性における関連はみられなかった。また、全身性炎症を示すマーカである白血球数が低い集団と比較すると、高い集団で肺がん発症リスクが2.81(1.58-5.01)と量反応的に上昇した
結 論 (200字まで)	アメリカ人コホートにおいて、身体活動量と白血球数は独立して肺がん発症リスクに関連していることが明らかとなった。特に、男性または喫煙者において、肺がんリスクに対する身体活動の保護効果が明らかとなった。
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。肺がんは日本においてがんによる死因の第1位であり、肺がんを予防することは重要な課題である。非喫煙者や女性においては、身体活動と肺がんのリスクとの間に関連は認められなかったものの、喫煙者において、身体活動量が多いものほど肺がんのリスク低下が認められており、特に喫煙者に対する身体活動の奨励を行う重要性が示唆された。

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Effect of Physical Activity on Breast Cancer Risk: Findings of the Japan Collaborative Cohort Study

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Abstract

Purpose: **This study aimed to examine prospectively the association between physical activity and breast cancer risk in a non-Western population.**
Methods: **We analyzed data from the Japan Collaborative Cohort Study, which included 30,157 women, ages 40 to 69 years at baseline (1988-1990), who reported no previous history of breast cancer, and provided information on their walking and exercise habits. The subjects were followed prospectively from enrollment until 2001 (median follow-up period, 12.4 years). Breast cancer incidence during this period was confirmed using records held at population-based cancer registries. The Cox proportional hazards model was used to estimate the hazard ratio (HR) for the association of breast cancer incidence with physical activity.**
Results: **During the 340,055 person-years of follow-up, we identified 207 incident cases of breast cancer. The most physically active group (who walked for ≥1 hour per day and exercised for ≥1 hour per week) had a lower risk of breast cancer (HR, 0.45; 95% confidence interval, 0.25-0.78) compared with the least active group after adjusting for potential confounding factors. The inverse association of exercise on breast cancer was stronger among those who walked for ≥1 hour per day than those who walked for <1 hour per day (P = 0.042). These results were not significantly modified by menopausal status or body mass index (BMI).**
Conclusions: **Our analysis provided evidence that physical activity decreased the risk of breast cancer. Walking for 1 hour per day and undertaking additional weekly exercise both seemed to be protective against breast cancer, regardless of menopausal status or BMI.** (Cancer Epidemiol Biomarkers Prev 2008;17(12):3396–401)

Introduction

Since the early 1990s, breast cancer has been the most commonly diagnosed cancer, even among Japanese women (1). The continuous increase in breast cancer incidence during recent decades has been an important public health concern in Japan, and there has been growing interest in physical activity as a means of primary prevention. Worldwide, numerous epidemiologic studies have reported associations between physical activity and cancer risk, with most observing a protective effect. Reviews published in 2002 concluded that there was sufficient evidence to support the role of physical activity in preventing breast cancer (2, 3). A systematic review published in 2007 (4) showed a decreased relative risk (<0.8) associated with leisure activities in 8 of 17 cohort studies (5-12), whereas the remaining 9 reported no association (13-21). Three more-recent cohort studies supported the risk reduction (22-24), whereas one found no evidence of a protective effect of physical activity on breast cancer (25). In addition to the 20% to 40% overall risk reduction of breast cancer among the more physically active women (2), the effects of menstrual characteristics, obesity, use of sex hormones, hormone-receptor status, and immune function have also been discussed in previous reports (24, 26, 27). However, these have been based on data from Western populations, and to our knowledge there have been no prospective reports from Asia. Different factors might influence Asian populations, as their characteristics (such as breast cancer incidence, physical activity, and body size) tend to differ from those of Western populations. Here, we analyzed data from a large-cohort study, the Japan Collaborative Cohort (JACC) Study, to examine the relationship between physical activity and breast cancer with a particular emphasis on the interactions with other risk factors, such as menopausal status and obesity.

Materials and Methods

Study Population. The present analysis was based on data from the JACC Study. This prospective cohort study evaluated the cancer risk associated with lifestyle factors

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among the Japanese population. At baseline (1988-1990), 110,792 subjects (46,465 men and 64,327 women), ages 40 to 79 y, were enrolled from 45 areas throughout Japan. All of the participants were subsequently followed up for all-cause mortality. Of the women in the baseline cohort, 34,086 lived in the 22 areas where data on both cancer incidence and physical activity were available. The JACC Study has been described in detail elsewhere (28, 29). Informed consent for participation was obtained from all individuals, with the exception of those in a few study areas where informed consent was provided at the group level, after the aims and data confidentiality had been explained to community leaders. The Ethics Board of Nagoya University School of Medicine, Japan, approved the JACC Study protocol.

Physical Activity Assessment. A self-administered questionnaire was used to obtain information on physical activity at baseline (30). The items covered included amount of time spent walking, amount of time spent exercising, and physical activity at the work place. Time spent walking daily was classified into three categories (<30 min, 30-59 min, and ≥1 h), as was time spent exercising (never or seldom, 1-2 h/wk, ≥3 h/wk). The validity of the estimates of time spent participating in sports and leisure activities was examined in a sample of the baseline subjects, suggesting that measuring physical activity level with the single-item question may be appropriate for establishing baseline data that reflect long-term physical activity in a large-scale cohort study (30, 31). We did not analyze the metabolic equivalent intensity, because of a lack of information on the strength of the exercise.

Other Variables. Information on additional potential breast cancer risk factors, such as family history, body mass index (BMI), tobacco and alcohol use, age at menarche, marital status, parity, age at birth of first child, menopausal status, and hormone use, was collected via the baseline questionnaire.

Follow-up and Identification of Breast Cancer Cases. The study participants were followed up from the time of enrollment until 2001, excluding five areas in which they were halted earlier. During this period, population registry data from each municipality were used to ascertain the residential and vital status of the participants. In Japan, the registration of death is required by the Family Registration Law, theoretically providing complete mortality data. Breast cancer incidence was confirmed mainly through the records of the population-based cancer registries in each area. During the study period, only 1,189 (3.9%) of the subjects were lost to follow-up due to moving out of the given study areas. The proportion of death-certificate-only cases was 6.3% (13 of 207). The mortality-to-incidence ratio for breast cancer was 0.26 (50 of 194) in the cohort covered by the cancer registries, which was within the range calculated using the available data from population-based cancer registries in Japan (0.20-0.30; ref. 32). We expect 37.4 breast cancer incidence cases who cannot be found from the cancer registries. The present analysis excluded 246 women who reported a previous diagnosis of breast cancer and 3,683 women who did not provide information on physical activity at baseline. Thus, a total of 30,157 women were included in the present analysis.

Statistical Analysis. For all participants, the person-years of follow-up was calculated as the time from enrollment until the diagnosis of breast cancer, death from any cause, moving out of the study area, or the end of follow-up, whichever occurred first. For the breast cancer cases ascertained by death-certificate-only, the person-years of follow-up were calculated from the time of enrollment until the time of death from breast cancer. Those individuals who died from causes other than breast cancer (n = 2,518) or who moved out of the study areas were treated as censored cases. We used Cox proportional hazards models to estimate the hazard ratios (HR) and 95% confidence intervals (95% CI) for the association of breast cancer incidence with physical activity. We evaluated the relationship using two models: an age-adjusted model (using 5-y age groups), and a multivariable model with adjustments for age, BMI (<22.0 kg/m^2, 22.0-23.9 kg/m^2, 24.0-25.9 kg/m^2, ≥26.0 kg/m^2, or unknown), alcohol drinking (never, past, current, or unknown), age at menarche (<15 y, 15-16 y, ≥17 y, or unknown), education level (attended school until the age of <16 y, 16-18 y, ≥19 y, or unknown), parity (nulliparous, 1 birth, 2-3 births, ≥4 births, or unknown), age at birth of first child (<22 y, 22-23 y, 24-25 y, ≥26 y, or unknown), use of exogenous female hormone (yes, no, or unknown), family history of breast cancer in a first-degree relative (yes, no, or unknown), menopausal status (premenopausal or postmenopausal), and menopausal age for postmenopausal women (<45 y, 45-49 y, ≥50 y, or unknown). In this study, those who provided menopausal age or who were at the average age at menopause, i.e., ≥49 y at baseline, were treated as postmenopausal women, and only those who were <49 y without information of menopausal age were treated as premenopausal women. Each "unknown" category included 5% to 9% of all women. All analyses were stratified by six study areas (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku, and Kyushu). Trend tests were done for category-based scores, which were assessed by allocating values ranging from 1 to 3 to each individual according to the selected physical activity variables.

To estimate the interaction of time spent walking and time spent exercising, we recategorized the subjects into four groups using the following cutoff points for physical activity: daily walking for <1 h or ≥1 h, and weekly exercising for <1 h or ≥1 h. Furthermore, the HR for the most active group (those who walked for ≥1 h/d and exercised for ≥1 h/wk) compared with the other groups was estimated according to menopausal status and BMI (<24 or ≥24 kg/m^2), and we examined the interaction between physical activity and these factors (Table 5). We used a BMI of 24 kg/m^2 instead of 25 kg/m^2 as a cutoff point for overweight. That was because there were only 47 cases for BMI ≥24 kg/m^2, which were too few to discuss interaction. For instance, we estimated the two HRs for physical activity among women who were premenopausal and postmenopausal at baseline, and then the P value for the interaction term of menopausal status and physical activity was calculated to test the difference between these HRs. We repeated the analysis after excluding the initial 2 y of follow-up, during which 37 cases of breast cancer were diagnosed. All of the P values were two-sided, with $P < 0.05$ indicating statistical significance. All of the analyses were done with SAS version 9.1 (SAS Institute, Inc.).

Table 1. Baseline characteristics associated with age in the JACC Study

Characteristics	Age group				Total
	40-49 y	50-59 y	60-69 y	70-79 y	
Number, *n* (row %)	7,561 (25.1)	9,361 (31.0)	9,098 (30.2)	4,137 (13.7)	30,157 (100.0)
Time spent walking per day					
Never or seldom, *n* (%)	868 (11.5)	1,013 (10.8)	807 (8.9)	403 (9.7)	3,091 (10.2)
Around 30 min, *n* (%)	1,393 (18.4)	1,650 (17.6)	1,794 (19.7)	876 (21.2)	5,713 (18.9)
30-59 min, *n* (%)	1,584 (20.9)	1,989 (21.2)	1,945 (21.4)	956 (23.1)	6,474 (21.5)
≥1 h, *n* (%)	3,716 (49.1)	4,709 (50.3)	4,552 (50.0)	1,902 (46.0)	14,879 (49.3)
Time spent exercising per wk					
Never or seldom, *n* (%)	5,890 (77.9)	7,365 (78.7)	6,591 (72.4)	2,842 (68.7)	22,688 (75.2)
1-2 h, *n* (%)	1,176 (15.6)	1,298 (13.9)	1,412 (15.5)	617 (14.9)	4,503 (14.9)
3-4 h, *n* (%)	338 (4.5)	399 (4.3)	572 (6.3)	306 (7.4)	1,615 (5.4)
≥5 h, *n* (%)	157 (2.1)	299 (3.2)	523 (5.7)	372 (9.0)	1,351 (4.5)

NOTE: Mean (SD) or %, calculated for participants with complete physical activity data.

Results

The average age at baseline was 57.6 ± 10.1 years, and the median follow-up time was 12.4 years. During the 340,055 person-years of follow-up, we identified 207 incident cases of breast cancer. The annual incidence of breast cancer in the cohort per 1,000 women was 0.61. Table 1 shows the distributions of physical activity according to age. Time spent walking was distributed similarly in the four age groups, with ~50% of the subjects walking for ≥1 hour per day. By contrast, for time spent exercising and physical activity at the work place, the older the subjects, the more physically active they tended to be. Regardless of the age group, more than two thirds of the participants never or seldom exercised.

Table 2 presents the risk of breast cancer in relation to physical activity. After adjusting for potential confounding factors, the HR was marginally decreased among those who walked for ≥1 hour per day (HR, 0.73; 95% CI, 0.53-1.01). However, those who exercised for ≥3 hours per week were not statistically decreased (HR, 0.85; 95% CI, 0.51-1.40). The P value for the linear trend of time spent walking was 0.043, which indicated that the dose-response effect of time spent walking and breast cancer risk was significant. The adjusted HR for those who walked for ≥1 hour compared with the rest of the women was significantly different (HR, 0.70; 95% CI, 0.53-0.93), although that for those who exercised for ≥3 hours per week was not significant (HR, 0.83; 95% CI, 0.59-1.16).

To investigate the joint effect of walking and exercise, we recategorized the data using the following cutoff points for physical activity: daily walking for <1 hour and exercising for <1 hour per week. Table 3 shows the mean values and distributions of risk factors for breast cancer according to the walking and exercise time categories. The subjects who walked and exercised more tended to be older and to drink more alcohol. The BMI values did not significantly differ between categories (range, 22.7-22.8 kg/m^2).

Table 4 shows the HRs of breast cancer associated with the joint effect of time spent walking and time spent exercising. The most physically active group (those who walked for ≥1 hour per day and exercised for ≥1 hour per week) had a lower risk of breast cancer (HR, 0.45; 95% CI, 0.25-0.78) compared with the least active group after adjusting for potential confounding factors. A significant interaction (P = 0.042) was observed between time spent walking and time spent exercising, meaning that the combined effect of exercise and walking on breast cancer was significant.

The HR of the most physically active group compared with the rest of the women was estimated for the subgroups according to menopausal status and BMI in Table 5, to examine the effects modification of these factors on the association between physical activity and breast cancer onset. The marginal inverse association was

Table 2. HR of breast cancer associated with physical activity in the JACC study

Physical activity	Cases	Person-years	Age adjusted	Multivariate*
			HR (95% CI)	HR (95% CI)
Time spent walking per day				
<30 min	69	96,752	1.00 (Reference)	1.00 (Reference)
30–59 min	56	71,411	1.14 (0.71 – 1.84)	1.13 (0.80 – 1.61)
≥1 h	82	171,892	0.70 (0.51 – 0.97)	0.73 (0.53 – 1.01)
P for trend			0.021	0.043
Time spent exercising per week				
Never or seldom	161	255,829	1.00 (Reference)	1.00 (Reference)
1–2 h	29	51,043	0.87 (0.59 – 1.30)	0.83 (0.56 – 1.23)
≥3 h	17	33,183	0.87 (0.53 – 1.45)	0.85 (0.51 – 1.40)
P for trend			0.45	0.33

*Adjusted for age, BMI, alcohol drinking, age at menarche, education level, parity, age at birth of first child, use of exogenous female hormone, family history of breast cancer in a first-degree relative, menopausal status, and menopausal age for postmenopausal women.

Table 3. Baseline characteristics associated with physical activity in the JACC study

Characteristics	Time spent exercising <1 h/wk		Time spent exercising ≥1 h/wk	
	Time spent walking per day		Time spent walking per day	
	<1 h	≥1 h	<1 h	≥1 h
Number, *n* (row %)	11,864 (39.3)	10,824 (35.9)	3,414 (11.3)	4,055 (13.4)
BMI, mean ± SD (kg/m^2)	22.8 ± 3.2	22.7 ± 3.0	22.8 ± 3.0	22.7 ± 2.9
Age at baseline, mean ± SD, y	57.5 ± 10.3	56.8 ± 9.6	58.5 ± 10.3	59.2 ± 10.4
Age at menarche, mean ± SD, y	14.8 ± 1.8	14.9 ± 1.8	14.8 ± 1.8	14.9 ± 1.8
Age at birth of first child, mean ± SD, y	25.2 ± 3.3	25.0 ± 3.3	25.1 ± 3.2	24.9 ± 3.1
Age at menopause, mean ± SD, y	48.7 ± 4.8	48.6 ± 4.6	48.8 ± 4.7	48.9 ± 4.5
Age of the end of education, mean ± SD, y	16.6 ± 2.1	16.5 ± 2.1	16.9 ± 2.2	16.7 ± 2.1
Postmenopausal, *n* (%)	8,946 (75.4)	8,176 (75.5)	2,657 (77.8)	3,225 (79.5)
Nulliparous, *n* (%)	612 (5.2)	387 (3.6)	142 (4.2)	163 (4.0)
Not married, *n* (%)	223 (2.0)	120 (1.2)	65 (2.1)	42 (1.1)
Exogenous female hormone use, *n* (%)	580 (5.4)	474 (4.8)	191 (6.2)	207 (5.7)
Family history of breast cancer,* *n* (%)	191 (1.6)	159 (1.5)	63 (1.9)	65 (1.6)
Current smoker, *n* (%)	606 (5.6)	556 (5.7)	133 (4.3)	183 (5.0)
Current drinker, *n* (%)	2,594 (23.1)	2,447 (24.0)	906 (27.9)	1,122 (29.4)

NOTE: Mean (SD) or %, calculated for participants with complete physical activity data.
*In a first-degree relative.

observed in each subgroup, and no significant interaction was observed. This suggests that the inverse association was not modified by these factors. Similar results were found after excluding the initial 2 years of follow-up, during which 37 cases of breast cancer were diagnosed.

Discussion

Our prospective analysis of the relationship between physical activity and breast cancer in Japanese women revealed a significant inverse association. In particular, the combined effect of walking and exercise was stronger than that expected based on the individual effects. Moreover, the combined protective effect of walking and exercise was not modified significantly by menopausal status or BMI. This suggests that physical activity has a protective effect regardless of menopausal status or weight. Previous studies of Western populations have provided convincing evidence of an inverse association between physical activity and breast cancer risk (2, 3), as supported by a recent systematic review (4). Adding more recent cohort studies (22-25), 10 of 21 showed a significantly decreased breast cancer risk associated with physical activity. Despite the comparatively lower incidence of breast cancer in Japan (1), an inverse association between physical activity and breast cancer incidence has also been observed, which was consistent with the findings of previous case-control studies in Japan (33-35).

The present study showed an interactive effect of walking and exercise. This could be explained in several ways. For instance, multiple types of exercise might work more effectively than a single type of exercise, the effect of physical activity might be quadratic, or walkers might tend to exercise more intensely. Whatever the reason, our results indicate that walking for ≥1 hour per day should initially be recommended, and additional weekly exercise should be undertaken to improve the protective effect against breast cancer.

In the present study, menopausal status and BMI did not affect the relationship between physical activity and breast cancer. Of the two, the modifying effect of menopausal status is the more controversial. Among the previous cohort studies that have analyzed this association according to menopausal status, only two have observed a significantly decreased breast cancer risk among premenopausal women (11, 22), and the evidence is weaker among premenopausal women (5, 10, 17). This difference might be partly due to the way in which menopause has been treated in the analyses. All of the studies, including the present one, reporting a protective effect of physical activity among premenopausal women have used only baseline menopausal status and have not updated this measure. By contrast, a study that found no association did update the menopausal status (19), and menopause was included as one of its end points.

Compared with menopausal status, the effect modification of BMI on the association between physical

Table 4. HR of breast cancer associated with physical activity in the JACC study

Physical activity		Cases	Person-years	Age adjusted	Multivariate*
Time spent walking (h/d)	Time spent exercising (h/wk)			HR (95% CI)	HR (95% CI)
<1	<1	93	130,279	1.00 (Reference)	1.00 (Reference)
≥1	<1	68	125,550	1.18 (0.79 – 1.77)	1.13 (0.75 – 1.69)
<1	≥1	32	37,885	0.76 (0.56 – 1.04)	0.82 (0.60 – 1.12)
≥1	≥1	14	46,342	0.42 (0.24 – 0.74)	0.45 (0.25 – 0.78)
P for interaction				0.035	0.041

*Adjusted for age, BMI, alcohol drinking, age at menarche, education level, parity, age at birth of first child, use of exogenous female hormone, family history of breast cancer in a first-degree relative, menopausal status, and menopausal age for postmenopausal women.

Table 5. HR of breast cancer among the most physically active group compared with the rest of the women by subgroup of menopausal status and BMI in the JACC study

Subgroup	Age adjusted	Multivariate*
	HR (95% CI)	HR (95% CI)
Menopausal status		
Premenopausal	0.14 (0.02 - 0.97)	0.13 (0.02 - 0.91)
Postmenopausal	0.53 (0.29 - 0.96)	0.53 (0.29 - 0.96)
P for interaction	0.524	0.528
BMI (kg/m^2)		
<24	0.43 (0.20 - 0.91)	0.42 (0.19 - 0.90)
≥24	0.45 (0.18 - 1.10)	0.44 (0.18 - 1.09)
P for interaction	0.940	0.949

*Adjusted for age, BMI, alcohol drinking, age at menarche, education level, parity, age at birth of first child, use of exogenous female hormone, family history of breast cancer in a first-degree relative, menopausal status, and menopausal age for postmenopausal women.

activity and breast cancer risk has been more consistent, as previous studies have failed to show general effects (5, 6, 8-10, 13, 14, 16, 18, 19, 21). These findings suggest that the effect of physical activity is independent of menopausal status (despite the possibility of a less precise effect among premenopausal women) and BMI. Therefore, the recommendation to undertake physical activity to prevent breast cancer does not need to be altered according to differences in these factors.

A major strength of the present study is its prospective design, which might avoid the recall bias that is possible in case-control studies. Moreover, information on other risk factors for breast cancer was included, and potential confounding factors were controlled for in the analyses when examining the association.

Our study had some limitations that should be considered when interpreting the results. First, because we used only a simple questionnaire at baseline, neither metric equivalent nor updated values were available to evaluate physical activity. In general, assessing physical activity in epidemiologic studies is difficult, which might explain the heterogeneous results observed across studies of its association with breast cancer (36). Although it is possible that the reported levels might have overestimated or underestimated the actual physical activity, the information was collected before diagnosis and should not have differed according to the end point status. Thus, the misclassification of physical activity in the present study for both reasons is nondifferential. It means the estimated HRs tend to be close to the null, and true HRs should be smaller due to the misclassification. In addition, because more than two thirds of the women in our cohort never or seldom exercised, we expect less serious misclassification. Second, updated information on menopausal status was lacking, which could modify the relationship between physical activity and breast cancer. Thus, from an etiologic viewpoint, the misclassification of menopausal status at the onset of breast cancer should be important. However, from the viewpoint of cancer prevention, the menopausal status at cancer onset is comparatively less important, and the HR could be naturally interpreted for premenopausal women at baseline. Third, misclassification of menopausal status at baseline should also be considered. However, the point estimate of the HR among premenopausal women was smaller than that among postmenopausal women, which could not be explained from misclassification. In addition, the results were not essentially changed when we removed women who were 47 to 50 years old from the premenopausal group. More studies are needed of premenopausal women in larger subjects.

In summary, our analysis provided evidence that physical activity decreased the risk of breast cancer among Japanese women. Another encouraging finding of this study is that the effect of physical activity on breast cancer risk is not modified by menopausal status and BMI. We recommend walking for 1 hour per day along with additional weekly exercise to protect against breast cancer, regardless of menopausal status and BMI.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Appendix 1. The Japan Collaborative Cohort Study Group

The present members of the JACC Study and their affiliations are as follows: Dr. Akiko Tamakoshi (present chairman of the study group), Aichi Medical University School of Medicine; Dr. Mitsuru Mori, Sapporo Medical University School of Medicine; Dr. Yutaka Motohashi, Akita University School of Medicine; Dr. Ichiro Tsuji, Tohoku University Graduate School of Medicine; Dr. Yosikazu Nakamura, Jichi Medical School; Dr. Hiroyasu Iso, Institute of Community Medicine, University of Tsukuba; Dr. Haruo Mikami, Chiba Cancer Center; Dr. Yutaka Inaba, Juntendo University School of Medicine; Dr. Yoshiharu Hoshiyama, University of Human Arts and Sciences Graduate School; Dr. Hiroshi Suzuki, Niigata University Graduate School of Medical and Dental Sciences; Dr. Hiroyuki Shimizu, Gifu University School of Medicine; Dr. Hideaki Toyoshima, Nagoya University Graduate School of Medicine; Dr. Shinkan Tokudome, Nagoya City University Graduate School of Medical Sciences; Dr. Yoshinori Ito, Fujita Health University School of Health Sciences; Dr. Shuji Hashimoto, Fujita Health University School of Medicine; Dr. Shogo Kikuchi, Aichi Medical University School of Medicine; Dr. Kenji Wakai, Nayoga University Graduate School of Medicine; Dr. Akio Koizumi, Graduate School of Medicine and Faculty of Medicine, Kyoto University; Dr. Takashi Kawamura, Kyoto University Center for Student Health; Dr. Yoshiyuki Watanabe and Dr. Tsuneharu Miki, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Chigusa Date, Faculty of Human Environmental Sciences, Mukogawa Women's University; Dr. Kiyomi Sakata, Wakayama Medical University; Dr. Takayuki Nose, Tottori University Faculty of Medicine; Dr. Norihiko Hayakawa, Research Institute for Radiation Biology and Medicine, Hiroshima University; Dr. Takesumi Yoshimura, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Japan; Dr. Akira Shibata, Kurume

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The past investigators of the study group were listed in ref. 28 except for the following eight members (affiliations are those at the time they participated in the study): Dr. Takashi Shimamoto, Institute of Community Medicine, University of Tsukuba; Dr. Heizo Tanaka, Medical Research Institute, Tokyo Medical and Dental University; Dr. Shigeru Hisamichi, Tohoku University Graduate School of Medicine; Dr. Masahiro Nakao, Kyoto Prefectural University of Medicine; Dr. Takaichiro Suzuki, Research Institute, Osaka Medical Center for Cancer and Cardiovascular Diseases; Dr. Tsutomu Hashimoto, Wakayama Medical University; Dr. Teruo Ishibashi, Asama General Hospital; and Dr. Katsuhiro Fukuda, Kurume University School of Medicine.

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対象の内訳

	ヒト	動物	地域	国内	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	57.6±10.1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	なし	ガン予防	なし	( )	( )
維持・改善	なし	なし	なし	なし	( )	( )

図表

Table 2. HR of breast cancer associated with physical activity in the JACC study

Physical activity	Cases	Person-years	Age adjusted HR (95% CI)	Multivariate* HR (95% CI)
Time spent walking per day				
<30 min	69	96,752	1.00 (Reference)	1.00 (Reference)
30–59 min	56	71,411	1.14 (0.71 – 1.84)	1.13 (0.80 – 1.61)
≥1 h	82	171,692	0.70 (0.51 – 0.97)	0.73 (0.53 – 1.01)
P for trend			0.021	0.043
Time spent exercising per week				
Never or seldom	161	255,829	1.00 (Reference)	1.00 (Reference)
1–2 h	29	51,043	0.87 (0.59 – 1.30)	0.83 (0.56 – 1.23)
≥3 h	17	33,183	0.87 (0.53 – 1.45)	0.85 (0.51 – 1.40)
P for trend			0.45	0.33

*Adjusted for age, BMI, alcohol drinking, age at menarche, education level, parity, age at birth of first child, use of exogenous female hormone, family history of breast cancer in a first-degree relative, menopausal status, and menopausal age for postmenopausal women.

Table 4. HR of breast cancer associated with physical activity in the JACC study

Physical activity: Time spent walking (h/d)	Physical activity: Time spent exercising (h/wk)	Cases	Person-years	Age adjusted HR (95% CI)	Multivariate* HR (95% CI)
<1	<1	93	130,279	1.00 (Reference)	1.00 (Reference)
≥1	<1	68	125,550	1.18 (0.79 – 1.77)	1.13 (0.75 – 1.69)
<1	≥1	32	37,885	0.76 (0.56 – 1.04)	0.82 (0.60 – 1.12)
≥1	≥1	14	46,342	0.42 (0.24 – 0.74)	0.45 (0.25 – 0.78)
P for interaction				0.035	0.041

*Adjusted for age, BMI, alcohol drinking, age at menarche, education level, parity, age at birth of first child, use of exogenous female hormone, family history of breast cancer in a first-degree relative, menopausal status, and menopausal age for postmenopausal women.

図表掲載箇所	P3398, Table2, P3399, Table4
概要（800字まで）	本研究は、日本のThe Japan Collaborative Cohort (JACC) Studyに参加した女性30,157名を対象に平均12.4年間の追跡調査を行い、身体活動と乳がん発症リスクの関連を検討したものである。質問紙によって、1日当たり歩行に費やす時間、週当たりの運動実施時間を尋ねた。歩行時間を、30分/日未満、30-59分/日、60分/日以上の3群に、運動実施時間を、ほとんどなし、1-2時間/週、3時間/週以上の3群に分類した。乳がん発症リスクにおける歩行時間の延長にはリスク減少傾向がみられたものの、有意な差はみられなかった。同様に運動実施時間についても有意な差はみられなかった。次に、歩行時間と運動時間の複合効果を検討するために、歩行時間1時間/日未満かつ運動時間1時間/週未満の集団(最も不活動な集団)と比較すると、歩行時間1時間/日以上かつ運動時間1時間/週以上の集団(最も活動的な集団)では乳がん発症リスクが0.45(95%信頼区間:0.25-0.78)と有意に減少することが明らかとなった(Pinteraction=0.041)。
結論（200字まで）	日本人の中年女性コホートにおいて、活動的でいることは閉経状態や肥満度に関わらず乳がん発症リスクを減少させ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）	身体活動基準の策定に用いられた研究の1つである。日本人を対象に、かつ大規模に乳がんの発症と身体活動との関連を検討しており、非常に重要な研究である。歩行時間と運動実施時間を各々単独に乳がん発症との関連を検討した場合には、関連は認められていないが、複合的に検討することで歩行時間が長く運動を実施していることで乳がんのリスクが下がることが示された。今後は総身体活動量との関係や、他の身体活動のドメインとの関連についても詳細に検討されることが期待される。

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Associations Between Lifestyle and Depressed Mood: Longitudinal Results From the Maastricht Aging Study

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Objectives. We examined whether healthy lifestyles are associated with absence of depressed mood.

Methods. A sample of 1169 adult participants in the Maastricht Aging Study provided baseline and 6-year follow-up data on smoking, alcohol use, physical exercise, body mass index, and mood. We examined associations between lifestyles and depressed mood using longitudinal analyses controlling for baseline depressive symptoms and covariates.

Results. Reports of excessive alcohol use at baseline predicted depressed mood at follow-up (relative risk [RR]=2.48; 95% confidence interval [CI]=1.08, 5.69), and reports of more than 30 minutes of physical exercise per day at baseline were associated with an absence of depressed mood at follow-up (RR=0.52; 95% CI=0.29, 0.92). Reports of being engaged in physical exercise throughout the 6-year follow-up period were also associated with absence of depressed mood (RR=0.56; 95% CI=0.34, 0.93).

Conclusions. In this relatively healthy population sample, certain lifestyles either predicted or protected against depressed mood. Adopting or maintaining healthy lifestyles might be a starting point in preventing or treating depressed mood over time. (*Am J Public Health.* 2006;96:887–894. doi:10.2105/AJPH.2004.053199)

Depressed mood is presumed to be caused by a variety of physical, psychological, and socioenvironmental factors.[1] For example, unhealthy lifestyles such as smoking, excessive alcohol use, low levels of physical exercise, or being overweight or obese may provoke chronic diseases[2,3] or worsen one's health status over time.[4] Chronic diseases frequently coincide with increased symptoms of depression,[5] and feelings of depression may in turn result in unhealthy lifestyles.[6] Potentially intensifying this "downward spiral," unhealthy lifestyles might elicit or exacerbate feelings of depression,[7,8] and depression may subsequently provoke or worsen the consequences associated with chronic diseases.[9,10] However, it is not unequivocally clear how unhealthy lifestyles and the emergence of depressed mood (i.e., a clinically relevant level of depressive symptoms[11]) are associated over time.

Although research has consistently established that there is a cross-sectional association between smoking and depressed mood,[12–14] little evidence is available regarding whether there is a longitudinal association, that is, whether smoking precedes or follows depressed mood. It has been shown that, in general, heavy alcohol use is associated with depressed mood.[15,16] Moreover, depressed mood is more often secondary to alcoholism than primary (i.e., clinicians more often treat individuals with alcoholism who have also developed depressed mood as a secondary reason for treatment than vice versa).[15] Physical activity seems to help counteract prevalent depressive symptoms and protect against subsequent depression, but longitudinal studies are necessary to further unravel this association.[17,18] The relation between being overweight or obese and being depressed is controversial; different studies have revealed negative, positive, and no associations between these conditions.[19–22]

If healthy lifestyles are associated with the absence of depressed mood or protect against the emergence of depressed mood, this common and debilitating condition might be prevented or treated in the future through promoting healthy lifestyles. We sought to determine whether healthy lifestyles are associated, over time, with absence of depressed mood in the general population.

METHODS

Design and Study Population

We used data from the longitudinal Maastricht Aging Study, an ongoing investigation examining determinants of normal cognitive aging. Questionnaires were sent to 3449 individuals, aged 24 to 81 years, who were free of medical conditions that interfered with their normal cognitive functioning at their entry into the study. This population was drawn from the Registration Network Family Practices,[23,24] a primary care research sampling frame consisting of 9919 individuals whose native language is Dutch. Our randomly recruited sample was stratified according to general ability level (defined as level of occupational achievement, including degree of complexity associated with professional occupations and knowledge and experience required[25]); women and older individuals were oversampled to ensure adequate representation of these groups in follow-up measurements.

Between 1993 and 1995 (baseline), 1823 respondents returned the questionnaire and underwent cognitive and physical examinations.[26] Six years after completing their baseline assessments, these 1823 participants were invited to take part in follow-up examinations. A total of 294 respondents refused further participation, 116 had died, and 37 had been lost to follow-up; thus, 1376 participants underwent reassessments. Ultimately, 1169 (33.9%) of the 3449 respondents were included in our study sample (207 respondents were lost to subsequent analyses owing to incomplete data on relevant variables at baseline or follow-up).

Measures

Baseline depressive symptoms were assessed with the self-report Symptom Checklist 90 Depression Scale.[27,28] The 16 items on this instrument are rated in 5 categories ranging from no complaint (1) to maximal complaints (5). Scores can range from 16 to 80, with higher scores indicating a higher number of depressive symptoms. At follow-up, we used the self-report Center for Epidemiologic Studies Depression Scale (CES-D),[29] an instrument that has demonstrated good psychometric qualities in epidemiological studies involving older populations.[30] The CES-D's 20 items are rated in 4 categories ranging from no complaint (0) to maximal complaints (3). Scores can range from 0 to 60, again with higher scores indicating a higher number of depressive symptoms. We used a CES-D threshold score of 16 or above in screening for depressed mood.[29] Strong correlations between these 2 depression instruments have been found,[31] and the predictive validity of both scales has been reported elsewhere.[32]

On the basis of respondents' reports of their current and former smoking behavior, they were grouped into the following categories at baseline and follow-up: current smoker (the reference category), former smoker, and never smoker. Transitions in smoking behavior over time were categorized as (1) respondent still does not smoke, (2) respondent quit smoking, (3) respondent initiated smoking, and (4) respondent still smokes (reference category).

Mean alcohol consumption at baseline and follow-up was calculated according to participants' reports of the number of glasses of alcohol (representing approximately 10 g of alcohol in conformance with the unit of alcohol system) they drank per day on average (more than 10 glasses, between 7 and 10 glasses, between 3 and 6 glasses, 1 or 2 glasses, none) and the average number of days per week they consumed alcohol (every day, 5 or 6 days, 3 or 4 days, 1 or 2 days, less than 1 day). These measures were used to group participants into the following categories: nondrinkers (the reference category), those consuming up to 2 drinks per day on average, and those consuming 3 or more drinks per day on average (excessive alcohol use). Transitions in alcohol use over time were categorized as (1) respondent still drinks alcohol, (2) respondent initiated alcohol use, (3) respondent quit drinking alcohol, and (4) respondent still does not drink alcohol (reference category).

Mean numbers of minutes spent daily on physical exercise at baseline and follow-up were computed on the basis of the number of hours participants reported spending each week, on average, engaging in light activities such as ball sports, aerobic exercise, walking, and biking. These measures were used to group participants into the following categories: those not engaging in physical exercise (the reference category), those engaging in physical exercise for up to 30 minutes per day on average, and those engaging in physical exercise for more than 30 minutes per day on average. Transitions in physical exercise over time were categorized as (1) respondent still engages in physical exercise, (2) respondent initiated physical exercise, (3) respondent discontinued physical exercise, and (4) respondent still does not engage in physical exercise (reference category).

Members of the study staff assessed respondents' body weight and height at baseline and follow-up. We used body mass index (weight in kilograms divided by height in meters squared) cutoff scores of 27.8 or above for men and 27.3 or above for women to distinguish between respondents who were (at least) overweight (the reference category) and those who were not.[33] These values corresponded with weights that were roughly 20% or more above the desired weights listed in the 1983 Metropolitan Life Insurance Company tables. Transitions in overweight status over time were categorized as (1) respondent is still not overweight, (2) respondent is no longer overweight, (3) respondent became overweight, and (4) respondent is still overweight (reference category).

Previous research has shown that age, gender, marital status, educational level, ability to engage in instrumental activities of daily living (IADLs), and chronic disease are associated with both lifestyle[34–36] and depression.[10,37–39] We included these variables in our analyses as covariates. Data on marital status, age, gender, and educational level were obtained from the questionnaire completed by the respondents. Marital status was categorized as widowed, not married or no longer married, and married or living with a partner. Educational level was categorized as low (primary education at most), intermediate (junior vocational training), or high (senior vocational or academic training).

The questionnaire asked respondents to indicate whether they needed assistance in the following IADLs as a result of their physical condition: grocery shopping, housekeeping, preparing meals, maintaining personal hygiene, and getting dressed. If respondents answered no on these questions, their IADL status was not considered to be impaired. If they responded yes to 1 or more of these items, their IADL status was considered impaired. Finally, in an interview conducted by a trained research assistant, respondents were given the opportunity to indicate whether a medical doctor had ever diagnosed them with 1 or more of 37 chronic diseases.

Statistical Analyses

After comparing individuals who did not take part in the study or were lost to follow-up with study participants (using *t* tests and χ^2 analyses), analyzing the characteristics of the sample at baseline, and comparing study variables at baseline and follow-up, we examined associations between sociodemographic variables and baseline lifestyle domains and follow-up depressive symptoms. In addition, we examined associations between transitions in lifestyle domains and depressed mood at follow-up. We used cross-sectional and longitudinal techniques in our analyses, specifically paired-samples *t* tests, χ^2 analyses, and McNemar tests; analyses of variance; and multivariate logistic regression models in which transitions in the various lifestyle domains were independent variables and follow-up depressed mood was the outcome variable. SPSS software (SPSS Inc, Chicago, Ill) was used in analyzing the data. The unhealthy lifestyle components served as reference categories, and longitudinal analyses were adjusted for baseline depressive symptoms and covariates.

RESULTS

As can be seen in Table 1, attrition analyses at baseline demonstrated that the 2280 individuals who either were lost to follow-up (n=654) or did not take part in the study (n=1626) were significantly older (mean= 55.1 years, SD=17.6) than the 1169 study

TABLE 1—Baseline Characteristics of Sample Participants and Comparisons on Key Variables at Baseline and Follow-Up: Maastricht Aging Study

	Nonrespondent or Lost to Follow-Up (n = 2280[a])	Sample (n = 1169)	
		Baseline[b]	Follow-Up[c]
Age group, y, %			
24–44	32.2	41.9***	...
45–64	32.3	40.7	...
65–81	35.5	17.4	...
Mean age (continuous), y (SD)	55.1 (17.6)	48.9 (14.7)***	...
Gender, %			
Male	44.2	52.4***	...
Female	55.8	47.6	...
Marital status, %			
Married/living together	74.2	81.3***	...
Not married/no longer married	13.5	13.7	...
Widowed	12.3	5.0	...
Education level, %[d]			
High	21.6	28.8***	...
Intermediate	26.8	34.0	...
Low	51.6	37.2	...
IADL status, %			
Not impaired	79.9	92.6***	...
Impaired	20.9	7.4	...
No. of chronic diseases, %			
None	23.6	33.4***	...
1	27.3	33.8	...
2 or more	49.1	32.8	...
Mean no. of chronic diseases (continuous) (SD)	1.9 (1.8)	1.3 (1.3)***	...
Smoking status, %			
Never smoker	34.4	35.0	37.6***
Former smoker	36.6	38.3	40.4
Current smoker	29.0	26.7	22.0
Average daily alcohol intake, %			
None	24.0	13.8***	15.5*
Up to 2 drinks	68.9	79.4	76.2
3 or more drinks	7.1	6.8	8.3
Mean no. of drinks per week (continuous) (SD)	6.1 (8.9)	6.1 (9.5)	6.2 (8.9)
Average amount of time spent daily on physical exercise, %			
More than 30 min	15.6	22.2***	12.1***
Up to 30 min	23.3	28.4	25.1
None	61.1	49.4	62.8
Mean no. of minutes of physical exercise per day (continuous) (SD)	13.6 (27.3)	18.2 (28.3)***	10.6 (20.5)***
Overweight, %			
No	60.2	67.1**	60.4***
Yes	39.8	32.9	39.6
Mean body mass index (continuous) (SD)	27.1 (4.4)	26.5 (4.1)**	27.0 (4.2)***

Continued

respondents (mean=48.9 years, SD=14.7). In addition, they were more likely to be female (55.8% vs 47.6%) or widowed (12.3% vs 5.0%), to be at low levels of education (51.6% vs 37.2%), to report impairments in IADLs (20.9% vs 7.4%), and to be overweight (39.8% vs 32.9%). Finally, they reported more chronic diseases (mean=1.9, SD=1.8, and mean=1.3, SD=1.3, respectively), fewer minutes of physical activity per day (mean=13.6, SD=27.3, and mean=18.2, SD=28.3, respectively), and more symptoms of depression (mean=22.0, SD=7.9, and mean=20.5, SD=6.1, respectively).

Table 1 also presents data on lifestyle at follow-up. Between baseline and follow-up, the percentage of respondents who reported smoking decreased significantly (from 26.7% to 22.0%). The percentage of respondents who reported not drinking alcohol at all increased significantly during this period (from 13.8% to 15.5%; Table 1), as did the percentage reporting that they consumed 3 or more drinks per day on average (from 6.8% to 8.3%).

The percentage of respondents who reported not engaging in physical exercise increased significantly from 49.4% at baseline to 62.8% at follow-up. In addition, average number of minutes spent daily on physical exercise decreased significantly from 18.2 (SD=28.3) at baseline to 10.6 (SD=20.5) at follow-up. Not only did the average body mass index in the sample exhibit a significant increase from 26.5 kg/m^2 (SD=4.1) to 27.0 kg/m^2 (SD=4.2) between baseline and follow-up, the percentage of overweight respondents also increased significantly (from 32.9% at baseline to 39.6% at follow-up). Finally, 14.0% of the respondents had a score of 16 or above (the threshold score for depressed mood) on the CES-D Scale at follow-up (Table 1).

Results of univariate longitudinal analyses focusing on follow-up depressive symptoms, stratified according to baseline sociodemographic variables and lifestyle domains, are shown in Table 2. Respondents aged 65 through 81 years had higher follow-up mean depression scores than respondents in the other age categories. Also, women had significantly higher mean depression scores at follow-up than men, and respondents at low

TABLE 1—Continued

Depressive symptomatology			
Mean Symptom Checklist 90 score (continuous) (SD)	22.0 (7.9)	20.5 (6.1)***	...
Mean CES-D score (continuous) (SD)	...	...	7.9 (6.6)
CES-D score < 16, %	...	...	86.0
CES-D score ≥ 16, %	...	...	14.0

Note. IADL = instrumental activity of daily living; CES-D = Center for Epidemiologic Studies Depression Scale. Continuous variables were compared via paired samples *t* tests and univariate analyses of variance; subcategories were compared via χ^2 analyses; and changes in lifestyle categories between baseline and follow-up were tested with McNemar tests for paired observations.
[a]Nonresponse and loss to follow-up numbers varied from 2280 for sociodemographic characteristics, smoking behavior, alcohol intake, physical exercise, and Symptom Checklist 90 Depression Scale score to 654 for body mass index and number of chronic diseases.
[b]Significance values refer to comparisons with nonrespondents or individuals lost to follow-up.
[c]Significance values refer to differences from baseline.
[d]Educational level was categorized as low (primary education at most), intermediate (junior vocational training), or high (senior vocational or academic training).
*$P<.05$; **$P<.01$; ***$P<.001$.

education levels had higher follow-up depression scores than respondents at intermediate or high education levels.

In addition, respondents with impairments in IADLs at baseline had higher follow-up mean depression scores than respondents with no IADL impairments. Respondents reporting 2 or more chronic diseases at baseline had higher follow-up depression scores than respondents reporting no chronic diseases or no more than 1 chronic disease, and those who reported not engaging in physical exercise at baseline had higher follow-up scores than those in the other physical activity groups. Finally, respondents who were overweight at baseline had higher follow-up mean depression scores than respondents who were not overweight at baseline (Table 2).

Post hoc interaction analyses revealed that neither gender nor age had a modifying effect on the associations between the baseline lifestyle domains assessed and follow-up depressive symptoms (data not shown). Hence, analyses were not carried out separately for women and men or for different age groups.

Table 3 shows relative risks (RRs) and 95% confidence intervals (CIs) derived from longitudinal multivariate logistic regression models with baseline lifestyle domains as determinants of follow-up depressed mood. In comparison with respondents who reported no alcohol use at baseline, those who reported excessive alcohol use at baseline were roughly 2.5 times as likely to be depressed at follow-up (RR=2.48; 95% CI=1.08, 5.69). Also, each glass of alcohol consumed on average per day at baseline was associated with a 17% increased risk of depressed mood at follow-up (RR=1.17; 95% CI=1.03, 1.32). Both of these analyses were adjusted for covariates (Table 3).

Respondents who reported engaging in physical exercise for more than 30 minutes per day on average at baseline had a 48% lower risk of being depressed at follow-up than respondents who reported not engaging in physical exercise at baseline (RR=0.52; 95% CI=0.29, 0.92). Also, each minute of physical exercise per day reported at baseline was associated with a 1% decreased risk of depressed mood at follow-up (RR=0.99; 95% CI=0.98, 1.00). Both analyses were adjusted for covariates (Table 3).

Table 4 shows relative risks and 95% confidence intervals derived from longitudinal multivariate logistic regression models with transitions in lifestyle domains as determinants of follow-up depressed mood. Analyses adjusted for covariates demonstrated that respondents who initiated alcohol use between baseline and follow-up were at lower risk of being depressed at follow-up than respondents who reported no alcohol use at baseline or follow-up (RR=0.18; 95% CI=0.04, 0.76; Table 4). Post hoc analyses revealed that none of the 47 respondents who initiated alcohol use between baseline and follow-up exceeded 11 alcoholic drinks per week on average (data not shown). Finally, analyses adjusted for covariates demonstrated that respondents who reported engaging in physical exercise at baseline as well as at follow-up decreased their risk of being depressed at follow-up by 44% compared with respondents who did not engage in physical exercise throughout the 6-year period (RR=0.56; 95% CI=0.34, 0.93; Table 4).

DISCUSSION

In assessing longitudinal associations between lifestyle domains and depressed mood, we found that excessive alcohol use at baseline (compared with abstinence) predicted depressed mood at follow-up and that engaging in more than 30 minutes of physical exercise on average per day at baseline (compared with not exercising) was associated with an absence of depressed mood at follow-up. In addition, we found that those who initiated alcohol use were at reduced odds of depressed mood at follow-up relative to steady nondrinkers and that those who persistently engaged in physical exercise were less likely to be depressed at follow-up than those who persistently did not engage in physical exercise.

Our results did not show any longitudinal associations between smoking behavior and depressed mood. The increase between baseline and follow-up in the percentage of respondents who reported never having smoked (Table 1) indicates some inconsistency in questionnaire responses over the 6-year period, and this may have diminished the reliability of our data on smoking behavior and weakened the observed associations between smoking behavior and depressive symptoms.

Our finding of a significant longitudinal predictive effect of excessive alcohol use at baseline on the presence of depressed mood at follow-up is in accord, to some extent, with the results of Aneshensel and Huba.[8] In their study involving 742 adults in the Los Angeles metropolitan area, they found contradictory cross-sectional and longitudinal effects of alcohol use on depression. They inferred that high levels of alcohol use were associated with low scores for depressive symptoms (cross sectional) but that high initial levels of alcohol use were associated with subsequent increased depressive symptoms (longitudinal).

TABLE 2—CES-D Depression Scores at Follow-Up (n = 1169) and Comparisons Stratified by Baseline Sociodemographic and Lifestyle Variables: Maastricht Aging Study

	No.	Mean Depression Score[a] (SD)	Depressed[b] (n = 164), Mean (SD) or %	Nondepressed (n = 1005), Mean (SD) or %[c]
Age, y			50.8 (14.5)	48.6 (14.7)*
24-44	490	6.9 (6.5)***	12.4	87.6
45-64	476	8.4 (6.9)	14.7	85.3
65-81	203	8.9 (6.0)	16.3	83.7
Gender				
Male	612	7.0 (5.7)***	9.2	90.8***
Female	557	8.9 (7.3)	19.4	80.6
Marital status				
Married/living together	951	7.9 (6.7)	13.9	85.7
Not married/no longer married	160	7.6 (6.1)	14.4	85.6
Widowed	58	8.6 (6.0)	15.5	84.5
Education level				
High[d]	337	6.8 (6.1)***	11.3	88.7**
Intermediate	398	7.5 (6.4)	10.8	89.2
Low	434	9.1 (7.0)	19.1	80.9
IADL status				
Not impaired	1082	7.6 (6.4)***	12.8	87.2***
Impaired	87	11.3 (7.8)	28.7	71.3
No. of chronic diseases			1.5 (1.5)	1.2 (1.3)*
None	390	6.8 (6.6)***	11.5	88.5*
1	396	7.8 (6.3)	12.9	87.1
2 or more	383	9.0 (6.7)	17.8	82.2
Smoking behavior				
Never smoked	409	7.4 (6.1)	12.0	88.0
Formerly smoked	448	8.1 (6.6)	14.3	85.7
Currently smokes	312	8.2 (7.2)	16.3	83.7
Average daily alcohol intake				
None	161	8.8 (7.7)	18.0	82.0
Up to 2 alcoholic drinks	928	7.7 (6.4)	13.1	86.9
3 or more alcoholic drinks	80	7.7 (6.4)	16.2	83.8
Mean no. of alcoholic drinks per week (SD)			6.1 (10.6)	6.0 (9.3)
Average amount of time spent daily on physical exercise				
More than 30 min	259	6.5 (5.4)***	7.7	92.3**
Up to 30 min	332	7.9 (6.3)	14.5	85.5
None	578	8.5 (7.2)	16.6	83.4
Mean no. of minutes of physical exercise per day (SD)			12.3 (24.3)	19.2 (29.0)**
Overweight				
No	784	7.5 (6.4)**	13.1	86.9
Yes	385	8.6 (7.0)	15.8	84.2
Mean body mass index, kg/m^2 (SD)			26.4 (4.1)	26.5 (4.1)

Note. CES-D = Center for Epidemiologic Studies Depression Scale; IADL = instrumental activity of daily living. Continuous variables were assessed via *t* tests and univariate analyses of variance; categorical variables were assessed via χ^2 analyses.
[a]Significance values refer to subcategory comparisons.
[b]CES-D score of 16 or above.
[c]Significance values refer to differences between depressed and nondepressed participants.
[d]Educational level was categorized as low (primary education at most), intermediate (junior vocational training), or high (senior vocational or academic training).
*P<.05; **P<.01; ***P<.001.

However, we are uncertain about the validity of the observed association between alcohol use initiation and absence of depressed mood at follow-up. Because of the relatively small size of the group initiating alcohol use (n=47) compared with the other groups, the fact that nonrespondents reported more depressive symptoms at baseline than respondents, and the fact that none of the respondents initiating alcohol use between baseline and follow-up exceeded an average of 2 glasses of alcohol per day, we cannot rule out that this finding was a statistical artifact attributable to selection bias.

Our finding of a significant longitudinal protective effect of baseline physical exercise (at recommended levels) on subsequent depressed mood is in line with the results of Strawbridge and colleagues.[17] In a 5-year follow-up investigation, they found that high levels of physical activity were associated with absence of depression and were protective against subsequent depression among 1947 community-dwelling adults aged 50 through 94 years. They used a measure of physical activity focusing on usual frequency (never, sometimes, often) of exercise, taking part in active sports, taking long walks, and swimming.

Furthermore, the protective effect of physical exercise on subsequent depression reported by Strawbridge et al.[17] was confirmed in our analyses examining the effects of physical exercise behavior over time: Respondents who reported engaging in physical activity at both baseline and follow-up were at 44% lower risk of subsequent depression than those who reported not engaging in physical exercise at either baseline or follow-up. Thus, it can be cautiously suggested not only that physical exercise may be an effective element in the treatment of depression[40] but that maintenance of regular physical exercise over a relatively long period of time may protect against the emergence of clinically relevant levels of depressive symptoms. The inhibitory effect of exercise on levels of inflammatory and cardiovascular risk factors may be part of the explanatory pathway through which exercise protects against depression,[41] in that the presence of high levels of these risk factors has also been associated with the presence of high levels of depressive symptoms.[42,43]

TABLE 3—Multivariate Logistic Regression Models for Baseline Lifestyle Domains as Determinants of Depressed Mood at Follow-Up (n = 1169)

		Depression at Follow-Up	
Baseline Lifestyle Domain	No.	Adjusted RR 1[a] (95% CI)	Adjusted RR 2[b] (95% CI)
Smoking behavior			
Currently smokes	312	Reference	Reference
Formerly smoked	448	0.89 (0.57, 1.40)	0.88 (0.56, 1.40)
Never smoked	409	0.73 (0.46, 1.17)	0.67 (0.41, 1.09)
Average daily alcohol intake			
None	161	Reference	Reference
Up to 2 alcoholic drinks	928	0.92 (0.55, 1.54)	1.15 (0.68, 1.96)
3 or more alcoholic drinks[c]	80	1.49 (0.68, 3.24)	2.48 (1.08, 5.69)*
Mean no. of alcoholic drinks per day (continuous)[d]	1169	1.07 (0.95, 1.21)	1.17 (1.03, 1.32)*
Average amount of time spent daily on physical exercise			
None	578	Reference	Reference
Up to 30 min	332	0.86 (0.57, 1.30)	0.87 (0.56, 1.33)
More than 30 min[c]	259	0.43 (0.24, 0.76)**	0.52 (0.29, 0.92)*
Mean no. of minutes of physical exercise per day (continuous)[d]	1169	0.99 (0.98, 1.00)**	0.99 (0.98, 1.00)*
Overweight			
Yes	385	Reference	Reference
No	784	0.90 (0.62, 1.33)	1.03 (0.69, 1.54)
Body mass index (continuous)[d]	1169	0.99 (0.95, 1.04)	0.98 (0.93, 1.02)

Note. RR = relative risk; CI = confidence interval.
[a]Adjusted for baseline depressive symptomatology.
[b]Adjusted for baseline depressive symptomatology, age, gender, marital status, educational level, instrumental activities of daily living status, and number of chronic diseases.
[c]Significance levels refer to differences from reference category.
[d]Values refer to the odds of subsequent depressed mood associated with each 1-unit increase in the continuous lifestyle variable.
*$P<.05$; **$P<.01$.

This study was limited by the considerable attrition because of nonresponse and loss to follow-up. The 6-year follow-up period may have been a key source of selection bias, potentially resulting in the sample included here being less representative of the overall study population than desired. However, this is a frequently encountered problem in longitudinal aging studies and is difficult to avoid.[10,44] In addition, according to Kempen and Van Sonderen, attrition has more adverse effects in the case of descriptive measurements than in the case of measures focusing on longitudinal associations, such as those used in our study.[45]

Bias may also have been introduced through the use of mainly self-report measures. In general, research involving the use of self-reported measures is inexpensive, easy to conduct, and not affected by interrater variability. A downside of such research, however, is the risk of inaccurate recollection of past events and response bias. These factors, if present, may have led to a certain degree of distortion of our findings.

Finally, a pair of suboptimal conditions of our study need to be mentioned. First, CES-D scores were not available at baseline. Therefore, we used Symptom Checklist 90 Depression Scale baseline scores to control our statistical analyses for initial level of depressive symptoms. Because these 2 instruments have been shown to be valid and highly correlated,[31] we believe that our analyses were adequately controlled; however, this may be open to debate. Second, we did not adjust for broad socioeconomic factors, such as unemployment, major life events, and work stressors, that might be associated with both unhealthy lifestyles and depression. Thus, control for educational level alone may not have been sufficient and could have resulted in residual confounding by these broader socioeconomic conditions. These limitations should be considered in interpreting our results and formulating public health recommendations.

We believe that our study involved a number of strengths as well. We comprehensively examined the effects of 4 lifestyle domains on depressive symptoms using longitudinal analysis techniques. The pivotal findings of this study were that (1) excessive alcohol use at baseline predicted depressed mood at follow-up; (2) physical exercise at recommended levels predicted absence of depressed mood at follow-up; and (3) physical exercise over a relatively long period of time was associated with absence of depressed mood.

Our results indicate that the potential downward spiral mentioned in the introduction might be halted through adoption or maintenance of healthy lifestyles, which could prevent the deterioration or even occurrence of depressed mood over time and, in turn, the worsening of chronic disease symptoms. In addition to the role of behavior change, adoption or maintenance of healthy lifestyles might be facilitated by the creation of health-promotive environments[46] in both homes and workplaces (e.g., through offering only low-fat, high-fiber meals in company and school cafeterias or lowering sales taxes on memberships in health and physical fitness clubs), reducing barriers to engaging in healthy behaviors and motivating people to engage in these behaviors. Future research could assess the effects of implementing such health-promotive environments on lifestyle alterations and subsequent changes in both overall health and mental health. ◻

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TABLE 4—Multivariate Logistic Regression Models for Transitions in Lifestyle Domains Between Baseline and Follow-Up as Determinants of Depressed Mood at Follow-Up (n = 1169)

		Depression at Follow-Up	
Lifestyle Transition	No.	Adjusted RR 1[a] (95% CI)	Adjusted RR 2[b] (95% CI)
Smoking behavior			
Still does not smoke	826	0.78 (0.50, 1.22)	0.74 (0.46, 1.17)
Quit smoking	86	0.89 (0.40, 1.95)	0.90 (0.40, 2.00)
Initiated smoking	31	1.09 (0.37, 3.20)	1.23 (0.42, 3.60)
Still smokes	226	Reference	Reference
Alcohol intake			
Still drinks alcohol	941	0.63 (0.37, 1.09)	0.80 (0.45, 1.41)
Initiated alcohol use	47	0.17 (0.04, 0.73)*	0.18 (0.04, 0.76)*
Quit drinking alcohol	67	1.35 (0.60, 3.01)	1.29 (0.57, 2.91)
Still does not drink alcohol	114	Reference	Reference
Physical exercise			
Still engages in physical exercise	328	0.50 (0.31, 0.82)**	0.56 (0.34, 0.93)**
Initiated physical exercise	107	0.64 (0.32, 1.27)	0.66 (0.32, 1.33)
Discontinued physical exercise	263	0.78 (0.49, 1.24)	0.80 (0.50, 1.30)
Still does not engage in physical exercise	471	Reference	Reference
Body mass index			
Still not overweight	661	0.92 (0.61, 1.40)	1.05 (0.68, 1.62)
No longer overweight	45	1.40 (0.57, 3.41)	1.46 (0.58, 3.67)
Became overweight	123	1.07 (0.56, 2.05)	1.20 (0.62, 2.32)
Still overweight	340	Reference	Reference

Note. RR = relative risk; CI = confidence interval. Significance values refer to differences from reference category.
[a]Adjusted for baseline depressive symptomatology.
[b]Adjusted for baseline depressive symptomatology, age, gender, marital status, educational level, instrumental activities of daily-living status, and number of chronic diseases.
*$P<.05$; **$P<.01$.

Contributors

C.H. van Gool and G.I.J.M. Kempen formulated the hypothesis. C.H. van Gool analyzed the data, interpreted the findings, and drafted the article. G.I.J.M. Kempen, H. Bosma, M.P.J. van Boxtel, J. Jolles, and J.T.M. van Eijk assisted with interpretation of findings and critical revision of the article.

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Human Participant Protection

This study was approved by the medical ethics committee of the University Hospital Maastricht. Participants provided written informed consent.

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