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Isotemporal Substitution Analysis for Physical Activity, Television Watching, and Risk of Depression

Rania A. Mekary*, Michel Lucas, An Pan, Olivia I. Okereke, Walter C. Willett, Frank B. Hu, and Eric L. Ding

* Correspondence to Dr. Rania A. Mekary, Harvard School of Public Health, Building 2, 665 Huntington Avenue, Boston, MA 02115 (e-mail: rania.mekary@channing.harvard.edu).

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The isotemporal substitution model (ISM) was previously developed as a methodology to study the time-substitution effects of 1 type of activity for another in a data setting with continuous outcomes. To demonstrate the application of ISM with a dichotomous outcome, we prospectively examined the associations of different activities with various activity displacements with depression risk among 32,900 US women from the Nurses' Health Study who were free from depressive symptoms at baseline (in 1996). During a 10-year follow-up, 5,730 incident depression cases were documented. Results from the ISMs indicated that for each physical activity, differences in magnitude of effects of each activity type were observed, dependent on the activity being displaced/substituted. Notably, an isotemporal substitution gradient was found for television watching, in which its association with depression risk varied by its substitution for slow-, average-, or brisk-paced walking in a gradient toward high depression risk when television watching replaced a faster walking pace (relative risk = 1.18, 95% confidence interval: 1.05, 1.31). Conversely, no association with depression was found for replacement of television watching with 60 minutes/day of slow walking, whereas a lower depression risk (relative risk = 0.85, 95% confidence interval: 0.76, 0.95) was found when 60 minutes/day of brisk walking replaced 60 minutes/day of television watching. Thus, the ISM could offer a more meaningful alternative to the standard nonsubstitution models to support public health recommendations.

cohort; depression; isotemporal substitution; Nurses' Health Study; physical activity; television watching; walking; women

Abbreviations: CI, confidence interval; MHI-5, 5-item Mental Health Index; RR, relative risk.

Because time is finite, a certain activity partaken at a certain time will have heterogeneous effects on an outcome depending on the other activities being displaced. A recently developed analytical model, the isotemporal substitution model (ISM) (1), was created to study time substitution effects of 1 activity substituting for another.

The isotemporal substitution analysis simultaneously models the specific activity being performed and the specific activity being displaced in an equal time-exchange manner. Therefore, the model not only controls for the confounding effect of other activities but, more importantly, it captures the effect of time substitution and reduces heterogeneity in the associations. Because of these advantages, the interpretation of this model will be more relevant to public health recommendations. For instance, we have recently demonstrated how this model could work with physical activity and a continuous outcome such as weight change in premenopausal women (1). The application of this model on a binary outcome has never been demonstrated.

In fact, the substitution effects of physical activity types or intensities in association with depression have never been described or analyzed in cohort studies. Previously, we reported data on physical activity and clinical depression risk among participants in the Nurses' Health Study by using a conventional nonsubstitution model (2). In this study, we used the same cohort to examine the relationship between physical activity and television watching with incident depression risk by assessing different time displacements while using ISMs.

MATERIALS AND METHODS

Study population

The Nurses' Health Study is a prospective cohort of 121,700 female registered nurses in the United States who were aged 30–55 years at enrollment (in 1976). Every 2 years, participants provide updated information via mailed questionnaires about lifestyle, medical history, and newly diagnosed illnesses. For the current analysis, the follow-up period began at the return of the 1996 questionnaire and ended in June 2006. Women were first asked to report their use of antidepressants in 1996 and to report the year of their first physician-diagnosed depression in 2000 (as 1996 or before, 1997, 1998, 1999, or 2000). This information on antidepressant use and physician-diagnosed depression was updated biennially through 2006, and the 1996 questionnaire cycle was considered baseline. To prospectively examine the relationship between physical activity and depression, we excluded women who did not report their depressive status in 1996, 1998, or 2000 or who did not return or answer the 5-item Mental Health Index (MHI-5) questionnaire (a mental health subscale of the 36-item Short-Form Health Status Survey) (3, 4) in 1992 or 1996 because their depression history by 1996 could not be ascertained ($n = 36,401$). By 2000, 60,702 women were alive and had completed the 1996–2000 questionnaires. Women who reported using antidepressants in 1996 ($n = 2,036$) or who had a physician-diagnosed episode of depression in 1996 or before ($n = 3,424$) were excluded from the baseline population; women who presented severe depressive symptoms (score $\leq$52 on the 1992 or 1996 MHI-5 questionnaires) were also excluded ($n = 4,637$). A total of 50,605 women were considered depression free in 1996. Because major physical and/or functional limitations are 1 of the main known risk factors for late-life depression (5), we excluded women with physical limitations ($n = 16,278$) to reduce bias in assessing the relationship between activities and depression risk. Women with physical limitations were defined as women who reported "a lot" of limitation in 1992 in vigorous activities (e.g., running), lifting/carrying groceries, climbing several flights of stairs, or bending, kneeling, stooping, or walking more than a mile (1 mile = 1.6 km) and women who reported "a lot or a little" limitation in 1992 in moderate activities (e.g., golfing, bowling), climbing 1 flight of stairs, walking several blocks, walking 1 block, or bathing/dressing. Furthermore, women with missing data on physical limitation ($n = 453$) were excluded. We also excluded women who reported physical activity of more than 4 hours/day on any returned questionnaire ($n = 783$) because these were considered outliers. The final analytical sample comprised 32,900 women. The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and the Harvard School of Public Health (both in Boston, Massachusetts).

Assessment of physical activity and television watching

In 1992, 1994, 1996, 1998, and 2000, participants reported the average amount of time they spent per week on each of the following recreational activities in the past year: walking, jogging (slower than 10 minutes/mile), running (10 minutes/mile or faster), bicycling, tennis/squash/racquetball, lap swimming, calisthenics/aerobics/aerobic dance/rowing machine, yoga/stretching/toning, and lawn mowing. For each activity, women chose 1 of the 11 duration categories that ranged from 0 minutes/week to 11 more hours/week. Women also reported their usual walking pace in miles per hour as follows: easy (<2), average (2–2.9), brisk (3–3.9), very brisk/striding ($\geq$4), or unable to walk; if a woman reported walking 60 minutes/day and reported her usual walking pace as average, she would be assigned 60 minutes/day of walking at an average pace. Because only 2% of the women reported a very brisk/striding pace, brisk and very brisk paces were combined into 1 category. Moreover, women reported the average number of flights of stairs they climbed daily. Stair climbing in minutes/day was then estimated. Total physical activity (minutes/day) was considered to be the sum of the duration reported for each of the 9 activities plus stair climbing. The reproducibility and validity of the physical activity questionnaire have been described elsewhere by authors (6) who used a random representative sample of participants in the Nurses' Health Study II ($n = 147$). The authors found the correlations between activity reported on questionnaires and that reported on past-week recalls and 7-day diaries to be 0.79 and 0.62, respectively.

In 1992, participants were asked to report their average weekly time spent sitting at home while watching television. Because television watching was positively associated with clinical depression risk in our previous report (2), we included it in our models to assess the benefits of its substitution by different physical activity types. The sum of television watching and total physical activity was grouped under the umbrella of "total discretionary time."

Case ascertainment

Because a significant percentage of depressed women might have never received treatment or might have received treatment other than antidepressants, our analyses were conducted by using a broader definition of depression that required physician diagnosis, regular use of antidepressants, or severe depressive symptoms (MHI-5 score $\leq$52 in 2000 or a Center for Epidemiologic Studies Depression Scale score $\geq$10 in 2004) (7). Analyses that use a stricter definition of clinical depression (both physician's diagnosis and use of antidepressants) have been reported elsewhere (2).

Covariates

Demographic, lifestyle behavior, and comorbidity information was collected by using the standardized questionnaires mailed to the nurses. In the baseline questionnaire (in 1996), we requested information about age, weight, smoking, menopausal status, use of postmenopausal hormone therapy, and previously diagnosed medical conditions including diabetes, cancer, myocardial infarction, angina, high blood pressure, rheumatoid arthritis, asthma, and emphysema. This information has been updated in the biennial follow-up questionnaires. Information on marital status, osteoarthritis, and social or community group involvement (hours each week

spent engaging in any church, volunteer, or other community group) was obtained at baseline and updated in 2000 and 2004. Dietary variables were assessed by using validated semiquantitative food frequency questionnaires (8) in 1994 and every 4 years thereafter. Neighborhood socioeconomic status summary scores (9), which include information from the US Census about wealth and income, education, and occupation, were determined at baseline. Working status (retired, homemaker, or working part- or full-time) was determined at baseline, and educational level (registered nurse, bachelor's degree, master's degree, or doctoral degree) was measured in 1992. Physical function and mental health were assessed by using the 36-item Short-Form Health Status Survey in 1992, 1996, and 2000. The physical functioning score was dichotomized by physical limitations as defined above. Although we excluded women who reported some physical limitations in 1992, we adjusted for remaining physical limitations (continuous variables) to control for any residual confounding and for MHI-5 score (continuous variable), both of which were reported in 1992.

Statistical methods

To reduce random measurement error and optimally represent long-term associations, we used cumulative average physical activity instead of a single measurement. To minimize the possibility of reverse causation (i.e., depression leading to decreased physical activity), we applied a 2-year induction time lag by analyzing all depression risk with a 2-year exposure-outcome lag. For example, the cumulative average of 1992 and 1994 physical activity information was used to predict depression in 1996–1998, and the cumulative average of 1992, 1994, and 1996 physical activity information was used to predict depression in 1998–2000. Moreover, physical activity information in the cumulative average estimate was not updated following a new diagnosis of cardiovascular diseases, diabetes, or cancer because participants may change their physical activities after such diagnoses.

Person-years of follow-up were calculated from the date of return of the 1996 questionnaire to the first occurrence of depression, death, end of follow-up (June 1, 2006), or return of the last questionnaire, whichever came first. Cox proportional hazards models stratified on age in months and questionnaire cycle were used to estimate the relative risks of developing depression. Initially, the relative risks in the first model were adjusted for known and putative risk factors of depression, including current postmenopausal hormonal use, body mass index (weight (kg)/height $(m)^2$), marital status, social or community group involvement, smoking, total energy intake, coffee intake, diabetes, cancer, myocardial infarction or angina, high blood pressure, rheumatoid arthritis, osteoarthritis, asthma, and emphysema. A dummy category was used for missing data. In the second model, we further adjusted for physical limitations (binary) and MHI-5 scores 53–75, 76–85, or 86–100 in 1992.

Because walking is by far the most prevalent physical activity among older adults (10), we examined the relationship between minutes walked per day at each walking pace and the risk of depression by using an ISM (1), which, by definition, estimated the effect of substituting 1 activity type for another for the same amount of time (in this case, 60 minutes/day). Moreover, our study sample consisted of older women (mean age = 62 years) who spent very little of their physical activity time (1.1%) jogging or running. Our ISM was originally expressed as a basic proportional hazards model describing the relationship between physical activity and depression as follows:

$$h(t) = h_0(t)\exp(\beta_1 \text{ total physical activity} + \beta_2 \text{ total discretionary time} + \beta_3 \text{ covariates}),$$

where $h(t)$ is the hazard for becoming depressed instantaneously per unit time while adjusting for other covariates, and $\beta_1 - \beta_3$ are the coefficients of respective activities or covariates. Total physical activity can be further broken down into its components as follows:

$$h(t) = h_0(t)\exp(\beta_4 \text{ easy walking pace} + \beta_5 \text{ average walking pace} + \beta_6 \text{ brisk walking pace} + \beta_7 \text{ jogging/running} + \beta_8 \text{ other physical activities} + \beta_9 \text{ total discretionary time} + \beta_{10} \text{ covariates}),$$

where other physical activities = biking + yoga + swimming + lawn mowing + aerobics + tennis + stair climbing, and total discretionary time = total physical activity + television watching time.

By eliminating 1 activity component from the model (herein, television watching), the coefficient (β_4) represents the effect of substituting 60 minutes/day of easy walking pace for 60 minutes/day of television watching while holding total discretionary time constant; the coefficient (β_5) represents the effect of substituting 60 minutes/day of average walking pace for 60 minutes/day of television watching while holding total discretionary time constant, and so on. The coefficient (β_9) for total discretionary time represents the omitted activity component time (television watching). Similar interpretation for the remaining substitution models can be applied when other activity components are omitted from the model.

The partition model, which by definition partitions "total discretionary time" into its components, is expressed as follows:

$$h(t) = h_0(t)\exp(\beta_0 \text{ television watching} + \beta_1 \text{ easy walking pace} + \beta_2 \text{ average walking pace} + \beta_3 \text{ brisk walking pace} + \beta_4 \text{ jogging/running} + \beta_5 \text{ other physical activities} + \beta_6 \text{ covariates}).$$

Because "total discretionary time" is not included in the model, it is not held constant. Each coefficient for a certain physical activity type represents the effect of adding rather than substituting that activity type, which requires the major assumption that time per day is infinite and has no effect on time displacement of other activities. The rationale behind

supporting the isotemporal model over the partition model is centered on this major difference, as previously described (1).

All analyses were performed with SAS, version 9.1, software (SAS Institute, Inc., Cary, North Carolina). All *P* values are 2-sided.

RESULTS

Among the 32,900 women who were free from depressive symptoms at baseline, we documented 5,730 incident depression cases during the 10-year follow-up (1996–2006) accounting for 297,676 person-years. The distributions of selected age-standardized characteristics according to categories of physical activity are outlined in Table 1. Compared with less active women, physically active women consumed more calories and alcohol and had lower body mass index values, better MHI-5 scores, and the lowest prevalence of diagnosed diseases. They were more likely to be involved in social or community groups and less likely to be current smokers, have physical limitations, and spend ≥21 hours/week watching television. The mean time spent in physical activity was 39 minutes/day, and the median was 31 minutes/day. In this cohort, walking was the most frequent physical activity, contributing to 53% of the total minutes of physical activity reported daily. Study participants spent most of their time watching television (66%) and less time walking (18%), jogging or running (0.5%), or engaging in other physical activities such as biking, yoga, swimming, lawn mowing, aerobics, tennis, and stair climbing (16%). In comparison, women who were excluded from the analysis were less physically active, smoked more, and had a higher disease prevalence at baseline (data not shown).

The baseline correlations among the different activity components were weak (Table 2); however, the strong correlation ($r = 0.95$) between television watching and "total discretionary time" suggests a potential for confounding, especially because television watching has been shown to be associated with the outcome (2). As for the correlations between the different physical activity variables, the largest was an inverse correlation of 0.28 between average walking pace and brisk/very brisk walking pace.

In Table 3, physical activity is broken down into its different components. Two different statistical models—substitution (models A through F) and partition (model G)—were used to predict the associations between 60-minute increases in specific physical activity forms and depression risk. Walking was broken down into easy, average, and brisk/very brisk walking pace. Jogging and running were combined. Other physical activities included biking, yoga, swimming, lawn mowing, aerobics, tennis, and stair climbing. The substitution model A2 suggests that, whereas replacing 60 minutes/day of television watching with 60 minutes/day of average walking pace was associated with 10% lower risk of depression ($P \geq 0.05$), replacing 60 minutes/day of television watching with 60 minutes/day of brisk/very brisk walking pace was associated with an even lower depression risk of 15%. However, walking at an easy pace for 60 minutes/day instead of watching television for 60 minutes/day appeared not to be associated with a lower risk of depression. As expected, the opposite was also seen when walking at an easy pace was dropped out of the model (model B2). The results showed that watching television for 60 minutes/day instead of walking at an easy pace for 60 minutes/day was not associated with depression risk (multivariate relative risk (RR) = 0.95, 95% confidence interval (CI): 0.54, 1.68). However, watching television for 60 minutes/day instead of walking at a brisk/very brisk pace for 60 minutes/day (model D2) was associated with 18% higher depression risk (multivariate RR = 1.18, 95% CI: 1.05, 1.31). Furthermore, a 60-minute/day increase in walking at a brisk/very brisk pace was protective only if it was substituting for the same amount of television watching (model A2) or for other physical activities (model F2). Substituting 60 minutes/day of other physical activities did not seem to be protective against the outcome regardless of the activity type being displaced (models A2 through E2).

The coefficient for "total discretionary time" in these substitution models represents the activity component dropped out of the model (e.g., television watching in model A, walking at an easy pace in model B). Notably, these coefficients in the substitution models are close to those in the partition model (model G), in which "total discretionary time" was partitioned into television watching and the different physical activities. In this partition model (model G2), the estimated decrease in risk of depression associated with a 60-minute/day increase was significantly stronger for brisk/very brisk walking (multivariate RR = 0.87, 95% CI: 0.78, 0.97) than for average-paced walking (multivariate RR = 0.92, 95% CI: 0.81, 1.05), other physical activities (multivariate RR = 1.02, 95% CI: 0.94, 1.11), easy walking (multivariate RR = 0.96, 95% CI: 0.51, 1.81), or television watching (multivariate RR = 1.02, 95% CI: 1.01, 1.04). Hence, for the same amount of increased activity time, the different activity intensities were associated with different degrees of lowered depression risk. Moreover, calculating the difference in relative risks for the activities being compared in the partition model (e.g., relative risk for easy walking – relative risk for television watching = 0.96 − 1.02 = −0.06) and taking its exponential (exponential of −0.06 = 0.94) would lead to the relative risk found in substitution model A (model 2); this is equivalent to substituting 1 activity (easy walking) for another (television watching).

Physical activity can also be broken down into light, moderate, and vigorous physical activity and can be used in the same ISM used above (Web Table 1 available at http://aje.oxfordjournals.org/).

DISCUSSION

The main hypothetical reason for the positive association we noted between television watching and depression risk is that television watching typically displaces physical activity. In our cohort, women who spent more time watching television tended to exercise less. Moreover, a joint effect of television watching and physical activity on depression risk has been previously shown in the same cohort, in which women who spent the most time watching television (≥21 hours/week) and the least time engaging in physical activity (<10 minutes/day) were at the highest risk of depression (2). Another hypothetical reason is that increasing duration of

Table 1. Age-Standardized Characteristics[a] of the Cohort by Daily Levels of Discretionary Physical Activity, Nurses' Health Study, United States, 1992–2000

Characteristic	Physical Activity Category									
	Lowest[b]		Low[c]		Moderate[d]		High[e]		Highest[f]	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Age, years	61.2 (6.7)		61.5 (6.8)		62.1 (7.0)		62.6 (7.0)		63.1 (6.8)	
Body mass index[g]	26.5 (4.9)		25.9 (4.5)		25.4 (4.2)		24.9 (4.0)		24.5 (4.0)	
Total energy intake (in 1994), kcal/day	1,643 (499)		1,701 (486)		1,741 (493)		1,781 (515)		1,837 (528)	
Alcohol intake (in 1994), g/day	5.3 (10.1)		5.3 (9.0)		5.6 (8.9)		5.9 (9.1)		6.4 (9.7)	
Easy walking, minutes/day	0.2 (0.9)		0.2 (1.8)		0.2 (2.4)		0.3 (4.0)		0.3 (5.1)	
Average walking, minutes/day	2.2 (2.6)		6.0 (7.0)		9.5 (13.6)		14.4 (22.6)		17.6 (30.8)	
Brisk/very brisk walking, minutes/day	0.8 (2.0)		4.6 (7.1)		13.1 (15.2)		22.8 (24.2)		36.6 (35.5)	
Jogging/running, minutes/day	0.0 (0.3)		0.2 (1.1)		0.2 (1.1)		1.3 (5.6)		2.7 (10.0)	
Other physical activities[h], minutes/day	2.2 (2.1)		8.6 (6.2)		19.6 (12.4)		34.2 (20.1)		61.2 (33.3)	
Television watching (in 1992), minutes/day	100.8 (91.3)		101.0 (90.3)		100.7 (96.2)		98.2 (94.4)		91.7 (86.7)	
Coffee intake (in 1994)										
<1 time/month		25.7		26.9		27.8		28.1		28.2
<2 times/day		28.3		28.8		28.6		28.2		28.2
≥2 times/day		46.0		44.3		43.6		43.7		43.5
MHI-5 score (1992)[i]										
≥86		33.4		35.0		37.2		39.5		40.1
76–85		38.4		40.9		40.9		39.2		41.0
53–75		28.2		24.1		21.9		21.3		18.9
Caucasian		97.6		98.1		98.3		98.1		98.3
Involved in social or community group (≥1 hour/week)		54.9		62.4		65.2		65.3		67.3
Marital status										
Married/partnership		80.8		81.2		80.9		80.9		79.9
Widowed		12.2		11.9		11.6		11.2		11.2
Separated/divorced/single		6.9		6.9		7.5		7.9		8.8
Current menopausal hormone use		37.5		42.1		42.7		43.4		41.5

Table continues

daily television watching is associated with higher depression risk independent of total discretionary time spent in physical activity, as observed in our partition model. Although this explanation is valid, it is not practical because it does not take into account the displaced time that television watching is substituting, nor does it control for total discretionary time, although time is finite; hence, it is still confounded by it. Although the substitution and partition models are mathematically equivalent, their interpretations are quite different. Although only 1 effect is estimated from each activity type in the partition model, heterogeneous effects can be obtained from each activity type from the substitution models.

Several studies have attempted to assess the relationships between physical activity, television watching, and clinical depression risk (2, 11–15); however, none of these studies accounted for the different physical activity types and the time being displaced by a certain activity. Although ISMs have been previously used to assess the relationships between different activity types and weight loss maintenance (a continuous outcome) (1), this is the first study to our knowledge to apply the substitution model to assess depression risk (a dichotomous outcome) among older women.

Detailed considerations of the isotemporal substitution model

Ideally, our statistical model would include data on all of subjects' daily activities, including time spent exercising, watching television, eating, working, playing video games, and sleeping. Because all such data are not available, we used the available data, making the time spent in "total discretionary time" the sum of the time engaged in the different

Table 1. Continued

Characteristic	Physical Activity Category									
	Lowest[b]		Low[c]		Moderate[d]		High[e]		Highest[f]	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Reported diagnosis of										
Arthritis		2.2		2.5		2.5		2.7		3.0
Asthma		3.3		3.7		4.0		3.5		3.8
Cancer		6.6		5.4		5.2		5.4		6.2
Diabetes		4.2		3.0		2.2		2.4		2.5
Emphysema		1.8		1.4		1.3		1.2		1.1
High blood pressure		26.9		25.3		24.8		23.1		21.2
Myocardial infarction or angina		2.5		2.0		1.9		2.0		2.5
Osteoarthritis		13.6		13.5		14.6		13.2		15.2
Current smoking		14.5		10.7		8.7		9.3		9.9
Body mass index[g]										
<25		43.9		48.4		53.8		57.8		62.3
25–29.9		34.4		35.4		33.2		31.8		29.0
≥30		21.6		16.2		13.0		10.4		8.7

Abbreviations: MHI-5, 5-item Mental Health Index; SD, standard deviation.

[a] All characteristics are for 1996 excepted as otherwise indicated. All characteristics are age standardized with the exception of age. Physical activity was computed as the cumulative average of physical activity from 1992 through 2000. A 2-year latency period was used to compute physical activity exposure. For example, 1992 and 1994 physical activity information was used to predict clinical depression in 1996–1998, and the cumulative average of 1992, 1994, and 1996 physical activity information was used to predict clinical depression in 1998–2000. We stopped updating physical activity information in the cumulative average estimate after new diagnoses of nonfatal myocardial infarction, angina, nonfatal stroke, diabetes, or cancer.

[b] Women ($n = 4,952$) who reported spending less than10 (median, 5.4) minutes/day on physical activity.

[c] Women ($n = 11,103$) who reported spending 10–29 (median, 18.9) minutes/day on physical activity.

[d] Women ($n = 10,104$) who reported spending 30–59 (median, 42.4) minutes/day on physical activity.

[e] Women ($n = 4,162$) who reported spending 60–89 (median, 71.9) minutes/day on physical activity.

[f] Women ($n = 2,579$) who reported spending 90 or more (median, 110.4) minutes/day on physical activity.

[g] Body mass index is calculated as weight (kg)/height (m^2).

[h] The sum of running, jogging, biking, yoga, swimming, lawn mowing, aerobics, tennis, and stair climbing.

[i] The 5-item Mental Health Index score was measured in 1992; a higher score denotes better mental health.

Table 2. Pearson Correlation Coefficients[a] for Total Activity Components in Minutes/Day, Nurses' Health Study, United States, 1992

Activity Components	Total Discretionary Time	Television Watching	Easy Walking Pace (<2 miles[b]/hour)	Average Walking Pace (2–2.9 miles/hour)	Brisk/Very Brisk Walking Pace (≥3 miles/hour)	Jogging/ Running	Other Physical Activities
Total discretionary time[c]	Referent	0.95	0.02	0.14	0.14	0.02	0.22
Television watching		Referent	0.02	0.05	−0.04	−0.04	−0.02
Easy walking			Referent	−0.02	−0.08	−0.01	−0.03
Average walking				Referent	−0.28	−0.05	0.03
Brisk/very brisk walking					Referent	0.07	0.19
Jogging/running						Referent	0.08
Other physical activities[d]							Referent

[a] All $P < 0.001$.

[b] One mile = 1.6 km.

[c] The sum of total physical activity and television watching.

[d] The sum of running, jogging, biking, yoga, swimming, lawn mowing, aerobics, tennis, and stair climbing.

Table 3. Relative Risk of Depression[a] According to Isotemporal Substitution of 60 Minutes/Day of Activities, Nurses' Health Study, United States, 1992–2006

Substitution Model[b]	Television Watching		Easy Walking Pace (<2 miles[c]/hour)		Average Walking Pace (2–2.9 miles/hour)		Brisk/Very Brisk Walking Pace (≥3 miles/hour)		Jogging/ Running		Other Physical Activities[d]		Total Discretionary Time[e]	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Substitution model A (television watching was dropped)														
Multivariate model 1[f]	Dropped		1.32	0.73, 2.38	0.88	0.77, 1.00	0.76	0.68, 0.85	0.76	0.45, 1.29	0.93	0.85, 1.01	1.03	1.02, 1.05
Multivariate model 2[g]	Dropped		0.94	0.50, 1.77	0.90	0.79, 1.03	0.85	0.76, 0.95	0.87	0.51, 1.47	1.00	0.91, 1.09	1.02	1.01, 1.04
Substitution model B (easy walking pace was dropped)														
Multivariate model 1[f]	0.73	0.42, 1.26	Dropped		0.65	0.37, 1.12	0.56	0.32, 0.96	0.56	0.26, 1.19	0.68	0.39, 1.18	1.42	0.82, 2.45
Multivariate model 2[g]	0.95	0.54, 1.68	Dropped		0.86	0.48, 1.52	0.81	0.46, 1.42	0.83	0.38, 1.78	0.95	0.53, 1.69	1.07	0.61, 1.89
Substitution model C (average walking pace was dropped)														
Multivariate model 1[f]	1.13	0.99, 1.29	1.49	0.82, 2.71	Dropped		0.86	0.74, 0.99	0.86	0.50, 1.48	1.05	0.89, 1.24	0.91	0.80, 1.04
Multivariate model 2[h]	1.11	0.97, 1.26	1.04	0.54, 1.97	Dropped		0.94	0.81, 1.08	0.96	0.56, 1.64	1.10	0.93, 1.30	0.93	0.81, 1.06
Substitution model D (brisk/very brisk walking pace was dropped)														
Multivariate model 1[f]	1.32	1.18, 1.47	1.73	0.96, 3.13	1.16	1.00, 1.34	Dropped		1.00	0.58, 1.72	1.22	1.05, 1.42	0.79	0.70, 0.88
Multivariate model 2[g]	1.18	1.05, 1.31	1.10	0.58, 2.08	1.06	0.91, 1.23	Dropped		1.02	0.59, 1.75	1.17	1.01, 1.36	0.87	0.78, 0.97
Substitution model E (jogging/running was dropped)														
Multivariate model 1[f]	1.19	0.74, 1.91	1.56	0.74, 3.32	1.05	0.64, 1.70	0.90	0.55, 1.46	Dropped		1.10	0.68, 1.80	0.87	0.54, 1.40
Multivariate model 2[g]	1.05	0.65, 1.70	0.98	0.45, 2.17	0.95	0.58, 1.54	0.89	0.55, 1.45	Dropped		1.05	0.64, 1.71	0.97	0.60, 1.57
Substitution model F (other physical activities were dropped)														
Multivariate model 1[f]	1.08	0.99, 1.17	1.42	0.78, 2.56	0.95	0.80, 1.11	0.81	0.70, 0.95	0.82	0.48, 1.40	Dropped		0.96	0.88, 1.05
Multivariate model 2[g]	1.00	0.92, 1.09	0.94	0.49, 1.78	0.90	0.76, 1.06	0.85	0.73, 0.99	0.87	0.51, 1.48	Dropped		1.02	0.94, 1.11
Partition model G														
Multivariate model 1[f]	1.03	1.02, 1.05	1.36	0.75, 2.46	0.91	0.80, 1.04	0.78	0.70, 0.87	0.79	0.47, 1.33	0.96	0.88, 1.05		

Table continues

Table 3. Continued

Substitution Model[b]	Television Watching		Easy Walking Pace (<2 miles[c]/hour)		Average Walking Pace (2–2.9 miles/hour)		Brisk/Very Brisk Walking Pace (≥3 miles/hour)		Jogging/Running		Other Physical Activities[d]		Total Discretionary Time[e]	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Multivariate model 2[g]	1.02	1.01, 1.04	0.96	0.51, 1.81	0.92	0.81, 1.05	0.87	0.78, 0.97	0.89	0.52, 1.50	1.02	0.94, 1.11		

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Depression was defined as antidepressant medication use or physician-diagnosed depression (1996–2006) or severe depressive symptoms (5-item Mental Health Index score ≤52 in 2000 or Center for Epidemiologic Studies Depression Scale 10 score ≥10 in 2004). Physical activity was computed as the cumulative average of physical activity from 1992 through 2000. A 2-year latency period was used to compute physical activity exposure. For example, 1992 and 1994 physical activity information was used to predict clinical depression in 1996–1998, and the cumulative average of 1992, 1994, and 1996 physical activity information was used to predict clinical depression in 1998–2000. We stopped updating physical activity information in the cumulative average estimate after new diagnoses of nonfatal myocardial infarction, angina, nonfatal stroke, diabetes, or cancer.

[b] Substitution of 60 minutes/day of an activity to replace 60 minutes/day of another activity.

[c] One mile = 1.6 km.

[d] The sum of running, jogging, biking, yoga, swimming, lawn mowing, aerobics, tennis, and stair climbing.

[e] The sum of total physical activity and television watching time. The coefficient for total discretionary time represents the omitted activity component (e.g., television watching for substitution model A, easy walking pace for substitution model B).

[f] Adjusted for age (continuous); time interval; current postmenopausal hormone use (binary); body mass index (weight (kg)/height (m^2)) category (<25, 25–29.9, or ≥30); marital status (married/partnership, widowed, separated/divorced/single); involvement in social or community group (binary); smoking status (never smoked, past smoker, currently smoke 1–14 cigarettes/day, 15–24 cigarettes/day, or ≥25 cigarettes/day); total energy intake (continuous); coffee intake (never, <1 time/month, <2 times/day, or ≥2 times/day); and reported diagnosis (binary) of diabetes, cancer, myocardial infarction or angina, high blood pressure, rheumatoid arthritis, osteoarthritis, asthma, or emphysema.

[g] Additional adjustment for physical limitations reported in 1992 (continuous) and for 5-item Mental Health Index score in 1992 (continuous).

activities for which we have data. The interpretation of the regression coefficients is still valid, but it does not allow us to account for other activities such as sleeping or sitting at a desk.

With the the ISM, the outcome of interest can be either continuous, as previously shown (1), or dichotomous, as in the current analysis. The exposure of interest, on the other hand, must be continuous for easier interpretation of the model. The regression coefficient preceding each activity type could then be divided by 30 or 60 minutes/day to reflect an increment of 30 or 60 minutes/day of that specific activity, and its association with the outcome could be interpreted. This would be feasible only if the exposure was continuous rather than categorical.

Intensity seems to matter in terms of protecting against depression, because 60 minutes/day of walking at a brisk/very brisk pace was more protective than the same amount of walking at an average pace when substituted for 60 minutes/day of television watching. Our results also indicate that walking at an easy pace is not protective against depression even when displacing the same amount of television watching. If an increased level of circulating β-endorphins is 1 of the mechanisms explaining the benefits of physical activity on depressive mood (16), our results suggest that physical activity must reach a certain intensity to have such an effect. Because our sample of women spent very little time jogging or running, the observed inverse association with depression risk was nonsignificant when 60 minutes/day of jogging/running replaced 60 minutes/day of television watching, even though the relative risk was almost identical to that for brisk walking.

Similarly, "other physical activities," which included biking, yoga, swimming, lawn mowing, aerobics, tennis, and stair climbing, were not protective against depression risk after accounting for all potential confounders. This could be explained by a misclassification bias. Some of the activities reported in this category, such as biking and swimming, could be carried out at different intensity levels and could be misclassified as vigorous activities as opposed to walking at a certain pace, which is unambiguous.

One advantage of the ISM is that it allows the exploration of heterogeneous effects of a certain activity in displacement of another activity; thus, the public health message derived from the substitution model has a stronger impact and relevance for preventing depression. Moreover, unlike the partition model, the substitution model controls for the confounding effect of "total discretionary time," so that the observed associations between the different physical activity types and depression risk are independent not only of one another but also of how much discretionary time is available.

One disadvantage is the potential confusion when interpreting the results. The coefficient for "total discretionary time" represents the activity component that was dropped out of the model, and the coefficient for the remaining activities represents the effect of substituting an equal amount of time of that activity for the same amount of time of the activity that was dropped out. Another disadvantage is the inability to apply this model when the exposure is categorical. Additionally, our study did not have enough power to assess the effect of other activity types such as yoga or swimming, and these activities were collapsed with others into the "other

activities" category. Ultimately, information on physical activity frequency, sleep duration, and resistance training was also lacking in our data. Had this information been available, this model would have elucidated the optimal physical activity properties to lower depression risk, as well as the association of certain activity types at the expense of sleep with depression risk.

Other nonisotemporal substitution models

With regard to the partition model, detailed methodological considerations of the partition model have been previously explained in a nutrition epidemiology context (17). Although the partition model can be mathematically derived from the substitution model, the regression coefficients in the partition model are equivalent to the regression coefficients of the activities dropped out in the different substitution models, and the interpretation of the coefficients is quite different in these 2 models. First, the partition model reflects the addition rather than the substitution of a certain activity type and its influence on the outcome. Second, it does not account for the activity being displaced. Third, the regression coefficients in this model exhibit only 1 effect. Fourth, the partition model is still confounded by total discretionary time. Overall, the partition model cannot answer the question about whether the different activity types are interchangeable regarding their associations with depression risk.

Other theoretical models, such as residual and density models, are beyond the scope of consideration for most analyses (Web Appendix).

In terms of public health recommendations for older adults, the American College of Sports Medicine (Indianapolis, Indiana) and the American Heart Association (Dallas, Texas) have indicated that all adults aged 65 years or more need moderately intense aerobic physical activity for a minimum of 30 minutes/day on 5 days/week or vigorous aerobic activity for a minimum of 20 minutes/day on 3 days/week (18); however, these results do not address the activity being displaced. Public health campaigns would have a stronger impact if they promoted replacement of television watching with convenient physical activities such as walking at an average or higher pace.

Our physical activity data were inevitably measured imperfectly, especially because our exposure variables were converted from a categorical to a continuous format, which tends to underestimate the association of physical activity with depression risk; however, validity of our physical activity questions has been documented (6), and physical activity has been previously linked to a variety of other outcomes in our cohorts. Furthermore, the interpretation of the results did not change in our previously published study (2) when we used our exposure in the categorical format in relationship to depression risk. Moreover, television watching was measured only in 1992; hence, we were not able to update it as we did for physical activity. Our study has major strengths, however, such as the large sample size, prospective design, long duration of follow-up, and repeated measurements of physical activity and other potential covariates.

In summary, the ISM can be applied to assess the associations of time spent in different activities in displacement of equivalent time spent on other activities with depression risk or other categorical outcomes of interest. This model could offer a more meaningful alternative to public health recommendations than do the standard nonsubstitution models.

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Author affiliations: Department of Pharmaceutical Sciences, Massachusetts College of Pharmacy and Health Sciences, Boston, Massachusetts (Rania A. Mekary); Department of Nutrition, Harvard School of Public Health, Cambridge, Massachusetts (Rania A. Mekary, Michel Lucas, An Pan, Walter C. Willett, Frank B. Hu); Department of Epidemiology, Harvard School of Public Health, Cambridge, Massachusetts (Olivia I. Okereke, Walter C. Willett, Frank B. Hu); Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Olivia I. Okereke, Walter C. Willett, Frank B. Hu, Eric L. Ding); and Saw Swee Hock School of Public Health and Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore, Republic of Singapore (An Pan).

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