Associations Between Physical Activity and Incident Hypertension Across Strata of Body Mass Index: A Prospective Investigation in a Large Cohort of French Women.

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ORIGINAL RESEARCH

Associations Between Physical Activity and Incident Hypertension Across Strata of Body Mass Index: A Prospective Investigation in a Large Cohort of French Women

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BACKGROUND: High body mass index (BMI) and low physical activity are associated with increased risk of hypertension. Few studies have assessed their joint impact or the relation of physical activity and hypertension among individuals within a healthy BMI range. The objective of this study was to investigate the associations between physical activity and hypertension across strata of BMI.

METHODS AND RESULTS: We used data from the E3N (Etude Epidémiologique de femmes de la Mutuelle Générale de l´Education) cohort, a French prospective study of women aged 40 to 65 years. We included participants who completed a diet history questionnaire and who did not have prevalent hypertension at baseline, resulting in a total of 41 607 women. Questionnaires assessed time spent undertaking various types of physical activity. Hypertension cases were self-reported. Cox models were used to calculate hazard ratios (HRs) for physical activity. Associations were assessed over strata of BMI. Among the 41 607 included women, 10 182 cases of hypertension were identified in an average follow-up time of 14.5 years. Total physical activity was associated with a lower hypertension risk in women within the high-normal BMI range (BMI, 22.5–24.9) ($HR_{Quartile\ 1–Quartile\ 4}$, 0.89; 95% CI, 0.79–0.99). An inverse relationship was observed between sports ($HR_{sports\ >2\ hours}$, 0.87; 95% CI, 0.83–0.93), walking ($HR_{walk\ >6.5\ hours}$, 0.94; 95% CI, 0.90–1.00), and gardening ($HR_{gardening\ >2.5\ hours}$, 0.94; 95% CI, 0.89–0.99). Sports were associated with a reduced risk of hypertension in women with a healthy weight, but evidence was weaker in overweight/obese or underweight women.

CONCLUSIONS: Women with a healthy weight were those who could benefit most from practicing sports, and sports provided the largest risk reduction compared with other types of activity.

Key Words: epidemiology ■ hypertension ■ obesity ■ physical activity

Hypertension presents a worldwide public health challenge because of its high prevalence and its association with the development of cardiovascular diseases and kidney damage, and occurs more in women than men with greater disease burden.[1,2] Estimates of global burden suggest that nearly 1 billion adults worldwide have hypertension.[3,4]

Numerous modifiable risk factors for hypertension are known, such as obesity,[5] physical inactivity,[6] poor diet,[7] smoking,[8] and alcohol consumption.[8] As nonoptimal blood pressure is noted as the largest attributable

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CLINICAL PERSPECTIVE

What Is New?

- Among women with a healthy weight, a reduced risk of hypertension is associated with increased time spent undertaking sports, and weaker associations are associated with walking and gardening.
- In women who are overweight and obese, no level of physical activity was associated with a reduced risk of hypertension.

What Are the Clinical Implications?

- Further work should determine if longer lengths of low intensity physical activity are associated with reduced cardiovascular risk and if these relationships are consistent in women who are obese.

Nonstandard Abbreviations and Acronyms

E3N	Etude Epidémiologique de femmes de la Mutuelle Générale de l´Education
METs	metabolic equivalents
MGEN	Mutuelle Générale de l´Education Nationale

risk factor for various forms of cardiovascular disease,[9] prevention is of the upmost importance. High physical activity is well known to reduce the risk of incident hypertension in overweight or obese individuals,[10–16] but risk reduction is not consistent across different weight ranges,[17,18] races, or sexes.[19] The effect of physical activity in healthy weight individuals is also little studied in prospective studies.

The type of physical activity undertaken has been demonstrated to have a large effect on the risk of hypertension and mortality.[20] Wen et al[21] demonstrated that the greatest reduction in all-cause mortality could be attributed to more vigorous physical activities such as running. Similarly, Forman[22] in the second Nurses' Health Study demonstrated an inverse dose-dependent response from vigorous exercise (defined as jogging, running, cycling, or other sports) with regard to hypertension risk, but made no comparison with lower intensity physical activities. Equivalent energy expenditure by walking and running has been shown to produce similar risk reductions for hypertension previously.[23]

Few studies have assessed the potential effect modification of body mass index (BMI) on the impact of physical activity and the risk of hypertension. Increased weight has an impact on chronic inflammation,[24] which is one mechanism for hypertension onset. Regular physical activity is associated with reduced concentrations of inflammatory markers,[25] but it is unclear if the relationship between physical activity and hypertension is the same for different ranges of BMI. Asides from these biological reasons, in the setting of the obesity pandemic, strategies should be identified that can reduce the onset of chronic diseases associated with obesity, and physical activity would likely be an extremely cost-effective measure.[26] Thus, we aimed to analyze the associations on hypertension from physical activity for different strata of BMI, including an assessment of the different intensities of physical activity, in a large prospective study of women.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

The E3N (Etude Epidémiologique de femmes de la Mutuelle Générale de l´Education)[27] cohort is a French prospective cohort started in 1990 comprising 98 995 women aged 40 to 65 years at baseline and insured by the MGEN (Mutuelle Générale de l´Education Nationale), a health insurance plan for workers in the National Education System and their families. The objective of the E3N was to study the main risk factors of cancer and chronic diseases. The E3N is the French component of the European Prospective Investigation Into Cancer and Nutrition. The cohort received ethical approval from the French National Commission for Computerized Data and Individual Freedom, and all participants in the study signed an informed consent.

Participants returned mailed questionnaires on lifestyle information and disease occurrence. Questionnaires were completed every 2 to 3 years. The average response rate at each questionnaire cycle was 83%, and the total loss to follow-up was 3%.

We excluded women who did not respond to a dietary questionnaire in 1993 (n=24 473) and women with an unrealistic energy consumption or physical activity (the 1st and 99th percentiles of the distribution in the population) (n=2644), prevalent hypertension, cardiovascular disease, or cancer (n=30 271) before or at the 1993 questionnaire. The final study population included 41 607 women. A comparison between included and excluded women is presented in Table S1.

Assessment of Physical Activity and BMI

We assessed total physical activity with questionnaires in 1993 and 1997 that included questions on weekly hours spent walking, cycling, performing light and heavy household chores/cleaning, or recreational activities and sports (eg, swimming and tennis) considering the winter and summer seasons. It included questions on the time spent walking (to work, shopping, and leisure time), cycling (to work, shopping, and leisure time), housework, and sports activities (such as racket sports, swimming, running).

Each activity was assigned metabolic equivalents (METs) based on values from the Compendium of Physical Activities.[28] A MET is defined as the ratio of work metabolic rate to a standard resting metabolic rate of 1.0 (4.184 kJ)·kg^{-1} h^{-1}; 1 MET is considered a resting metabolic rate while sitting. These included MET values of 3.0 for household activities and cleaning, 4.0 for gardening, 3.0 for walking, 6.0 for cycling, and 6.0 for sports. Using self-reported data, we estimated weekly METs scores for the various activities. METs measurements have been studied in this cohort previously.[29] Activities expending 3 to 6 METs can be grouped as moderate, and those >6 as vigorous.[30] We considered subgroups of physical activity as sports, walking, cycling, housework/cleaning, and gardening separately.

Self-reported height and weight from the 1992 questionnaire were used to calculate BMI, defined as weight (kg) divided by squared height (m^2). In the cohort, self-reported anthropometry has proven reliable in a validation study.[31] Participants were split into groups depending on BMI resulting in 5 BMI categories for assessment (underweight BMI, <18.5; low-normal BMI, 18.5–20.4; mid-normal BMI, 20.5–22.5; high-normal BMI, 22.5–25.0; overweight/obese, ie, excess weight, BMI, >25.0).

Hypertension Assessment

Participants were asked to report whether they had hypertension at baseline (1993) and in each follow-up questionnaire (1995, 1997, 2000, 2002, 2005, 2008), the date of diagnosis, and the use of antihypertensive treatments. The month and year of diagnosis were provided for most cases (69%). For individuals who were missing the month of diagnosis (14% of cases), it was imputed to June of the year of diagnosis. The median time between the date of diagnosis and the date of response to the first questionnaire after diagnosis was 12 months. Thus, for the cases with no year of diagnosis (n=17%), we assigned it to be 12 months before they reported hypertension in a questionnaire. In 2004, a drug reimbursement database became available for 97.6% of participants. We used the self-reported date of diagnosis or the first date of drug reimbursement for antihypertensive medications (Anatomical Therapeutic Chemical Classification System codes C02, C03, C07, C08, and C09) whatever happened first, as the date of diagnosis for cases identified after 2004.

In addition, using the information of the MGEN health insurance plan drug claim database, we assessed the validity of self-reported hypertension within the E3N cohort. We compared hypertension self-report to antihypertensive drug reimbursement (any of the previously specified codes). A positive predictive value of 82% was observed among women alive in January 2004 and followed up to their response to the last considered questionnaire in 2008.[32]

Assessment of Covariates

We used information from the 1992 questionnaire whenever possible. Family history of cardiovascular disease (ie, stroke or coronary disease), education (no high school diploma, high school diploma), and smoking (former smoker, current smoker, or never smoker) were based on self-reports, and for diabetes mellitus we used cases that had been validated through the use of a drug reimbursement database.[33]

In 1993, dietary data were collected using a 2-part questionnaire that has been shown to be valid and reproducible detailing the consumption of 208 food items.[34] From this questionnaire and using a detailed food composition table, mean daily intakes of energy (excluding energy from alcohol), alcohol, magnesium, phosphate, potassium, and lipids were estimated.

Statistical Analysis

Participants were split into 4 quartiles of total METs per week based on the population distribution. We categorized participants according to both physical activity (with the lowest quartile as reference) and BMI (with the low-normal BMI group as reference). Time at entry was the age at the beginning of follow-up (1993), and exit time was the age when participants were diagnosed with hypertension, died (dates of death were obtained from the participants' medical insurance records), were lost to follow-up, or were censored at the end of the follow-up period (June 25, 2008), whichever occurred first. Hazard ratios (HRs) and 95% CIs were estimated from Cox regression models with age as the timescale. *P* values for trends were calculated using the median category value as a semicontinuous variable in the models.

The relationship between physical activity and BMI is complicated because changes in BMI can be caused by changes in physical activity levels, and in the extremity BMI can affect partaking in physical activity. Selection bias can be introduced when

a variable that is affected by the exposure is used in stratification or for adjustment in the statistical model. For the current analyses we used BMI (in 1992) reported before baseline physical activity (1993) in an effort to address the possibility of introducing bias in our stratified analyses.

We used directed acyclic graphs (Figures S1 and S2)[35] to articulate our research question and guide our analytical strategies (ie, variable selection to adjust for confounding). Multivariable models were first unadjusted with the age as the timescale (M0) and then mutually adjusted as BMI and physical activity (M1). Next, the models were adjusted for known risk factors for hypertension development (prevalent diabetes mellitus, family history of hypertension or cardiovascular disease [yes/no], smoking [never, former, and current at baseline], education [no high school diploma, high school diploma], and menopause) (M2) and then for dietary variables (calories, potassium, magnesium, phosphates, lipids, salt, alcohol, and caffeine) (M3). Next, the models stratified into groups of BMI were assessed using total physical activity as the exposure.

Analysis was then performed for specific activities reported in hours per week. Sports, gardening, and walking were considered as quartiles, and because of lower participation in housework and cycling, these were considered as tertiles and yes/no, respectively. Next, the models stratified into groups of BMI were assessed using sports, gardening, and walking as the exposures.

Spline regression,[36] which fits low-order polynomials between fixed equidistant points known as "knots" to smooth the variable, was used to assess the shape of the association between types of physical activity and the risk of hypertension. The spline term was included as a variable in a Cox regression model. The splines were then plotted, showing the relationship between the HR for hypertension and the METs for the types of physical activity.

We performed sensitivity analyses to test for potential reverse causation by excluding cases that occurred within 5 years of follow-up. We also considered a model with physical activity estimated at 1997 (in the same manner as described for the 1993 questionnaire, including types of activity) to further separate the physical activity and BMI estimates to ensure that BMI at 1992 would not be affecting physical activity and introducing bias. Participants were grouped according to quartiles of the population distribution for physical activity. Baseline for this analysis was 1997, and prevalent hypertension cases were excluded. We considered exposures of total activity and sport and then stratified BMI analysis in the same manner as in the main analysis.

One supplementary analysis was conducted. Total physical activity and BMI were considered as a joint exposure by crossing the categorical physical activity and BMI variables and is presented in Table S2. The joint interaction term was then included in a fully adjusted Cox model along with continuous BMI and physical activity, with the low-normal BMI, highly active group as reference. The *P* value for this variable was used to determine if interaction was likely.

Missing values were imputed using the mean for continuous or median for categorical variables. Differences between continuous normal variables were assessed using Student *t* test, the Wilcoxon test for non-normal variables, and for categorical variables the Mann–Whitney *U* test. All statistical analyses used R version 3.5.1 (www.r-project.org) and the survival package (www.github.com/therneau/survival), with an α of statistical significance equal to 0.05. Results from the Cox models were interpreted as HR (95% CI).

RESULTS

A total of 41 607 women were included in this study. The mean age at inclusion was 50.1±6.2 years, and the mean BMI was 22.2±2.6 kg/m^2. The mean physical activity at inclusion was 53.7±27.7 METs-hours per week. After an average of 14.5 years of follow-up and 604 361 person-years, 10 182 cases of incident hypertension were identified, corresponding to an incidence rate of 16.8 per 1000 person-years. Compared with women who developed hypertension, those who did not were younger at inclusion, had a lower BMI, were less likely to have diabetes mellitus or obesity, and reported slightly lower levels of total physical activity, but more sport. When considering participants grouped according to their physical activity, those reporting higher levels of activity were slightly older at inclusion and consumed more calories (Table 1).

Higher physical activity was associated with a lower risk of hypertension in the adjusted models (Table 2). An interaction was likely when considering the joint variable of BMI and physical activity. When women were stratified into the 5 BMI groups (Table 3), higher physical activity was associated with a lower risk of hypertension only within the high-normal BMI range 22.5 to 25.0 ($HR_{Quartile\ 1–Quartile\ 4}$, 0.89; 95% CI, 0.79–0.99). In a sensitivity analysis, excluding cases diagnosed within 5 years after baseline, the associations remained stable (data not tabulated).

When physical activity was partitioned to specific types (Table 4), high levels of sports were strongly associated with a lower risk of hypertension in a dose-respondent manner in both unadjusted and adjusted models ($HR_{sport\ >2\ hours}$, 0.87; 95% CI, 0.83–0.93). High levels of walking and gardening were also associated

with a lower risk of hypertension ($HR_{walk\ >6.5\ hours}$, 0.94; 95% CI, 0.90–1.00; $HR_{gardening,\ >2.5\ hours}$, 0.94; 95% CI, 0.89–0.99). Housework/cleaning was associated with an increased risk of hypertension ($HR_{housework\ >7.5\ hours}$, 1.05; 95% CI, 1.00–1.10). Cycling was not associated with the risk of hypertension.

Specific types of physical activity did not show a likely interaction with BMI, except sports (*P* interaction <0.01). In models stratified on BMI groups (Table 5), high levels of sports were associated with a lower risk of hypertension in a dose-respondent manner in all categories of healthy-range BMI, but not in women who were underweight (BMI, <18.5) or had excess weight (BMI, >25.0). The hypertension incidence rate in women partaking in the lowest level of sports was 18.6 per 1000 person-years compared with 15.6 in those partaking in the highest level of sports. In low normal-weight women partaking reporting zero sports, the incidence rate was 14.5 compared with 12.1 in those reporting >2 hours of sports.

Using spline regression, an inverse dose-dependent relation between sports, gardening, and walking and the risk of hypertension was observed (Figure). The shape of the curve regarding sports (Figure—Panel A) showed that even low levels of sport were associated with a reduced risk of hypertension. Both

Table 1. Participant Characteristics at Baseline (N=41 607) According to Outcome and Quartiles of Total Physical Activity in 1993

	Noncases (n=31 425)	Cases (n=10 182)	Quartiles of Physical Activity, METs/wk			
			Quartile 1 (N=10 491) (<32.0)	Quartile 2 (N=10 465) (32.0–47.3)	Quartile 3 (N=10 391) (48.8–67.5)	Quartile 4 (N=10 260) (>67.5)
Cases of hypertension	…	…	2516	2524	2486	2656
Age, y, mean (SD)	49.8 (6.1)	51.1 (6.5)*	49.2 (5.8)	49.7 (6.2)	50.3 (6.6)	51.2 (6.6)
Weekly total physical activity at 1993, METs/wk, mean (SD)	53.6 (27.3)	54.6 (28.0)*	23.3 (6.0)	39.8 (4.7)	56.8 (6.3)	88.2 (17.1)
Walking, h/wk, mean (SD)	4.62 (3.88)	4.69 (3.92)	3.1 (5.0)	3.7 (7.9)	5.2 (10.9)	7.5 (14.2)
Gardening, h/wk, mean (SD)	1.78 (2.31)	1.84 (2.34)*	0.6 (0.8)	1.2 (1.4)	1.9 (2.1)	3.5 (3.2)
Housework/cleaning, h/wk, mean (SD)	6.65 (4.67)	7.05 (4.91)*	3.4 (1.7)	5.2 (2.8)	7.1 (3.8)	11.1 (5.7)
Cycling, h/wk, mean (SD)	0.52 (1.07)	0.48 (1.03)*	0.2 (0.4)	0.4 (0.7)	0.6 (1.1)	1.0 (1.5)
Sports, h/wk, mean (SD)	1.33 (1.62)	1.18 (1.56)*	0.6 (0.8)	1.1 (1.2)	1.5 (1.6)	2.1 (2.2)
BMI at 1992, kg/m^2, mean (SD)	22.0 (2.4)	22.8 (2.7)*	22.2 (2.5)	22.1 (2.5)	22.1 (2.4)	22.3 (2.5)
Underweight BMI (<18.5), %	3.9	2.7	3.6	3.9	3.7	3.1
Low-normal BMI (18.5–19.9), %	16.1	11.7*	15.2	15.4	14.7	15.0
Mid-normal BMI (20.0–22.4), %	44.0	37.8*	42.0	42.7	42.5	42.6
High-normal BMI (22.5–25.0), %	25.0	28.2*	25.4	26.4	25.7	26.8
Overweight/obese BMI (>25.0), %	11.1	19.6*	13.8	12.8	12.0	13.7
Family history of cardiovascular disease, %	32.0	39.7*	33.3	34.0	33.9	34.4
Diabetes mellitus, %	0.8	1.2*	0.9	0.8	0.9	1.0
Smoking status, %						
Never	51.8	52.8	50.9	51.6	52.3	54.8
Former	33.8	33.3	34.2	34.6	33.5	32.4
Current	14.4	13.8	14.9	13.8	14.2	14.0
With high school diploma, %	94.0	93.0*	94.7	95.6	93.5	92.9
Dietary factors, median (SD)						
Energy without alcohol, kcal/d	2157 (548)	2160 (556)	2113 (543)	2151 (541)	2175 (553)	2196 (559)
Alcohol, g/d	11 (13)	12 (14)	7 (13)	7 (13)	7 (14)	7 (14)
Caffeine, mg/d	174 (150)	175 (152)	173 (152)	175 (148)	175 (151)	176 (152)
Lipids, mg/d	86 (26)	86 (27)	84 (26)	86 (26)	86 (27)	87 (27)
Magnesium, mg/d	420 (141)	425 (143)*	410 (142)	419 (138)	425 (142)	431 (143)
Phosphates, mg/d	1430 (384)	1482 (384)*	1407 (381)	1430 (379)	1449 (387)	1452 (389)
Potassium, mg/d	3716 (1020)	3889 (1047)*	3620 (1024)	3706 (996)	3757 (1027)	3818 (1045)
Sodium, mg/d	2726 (892)	2762 (908)*	2671 (898)	2709 (886)	2765 (890)	2791 (905)

BMI indicates body mass index; and METs, metabolic equivalents.
*Statistical difference at the 0.05 level between cases and noncases.

walking (Figure—Panel B) and gardening (Figure—Panel C) showed a shallower dose response than for sports and that higher levels were required to achieve the same reduction in risk.

When considering the joint BMI–physical activity exposure, the joint term was significantly associated to the risk of hypertension (Table S2; *P* interaction <0.01). Compared with low-normal BMI women, with high activity, a higher risk of hypertension was observed in the high-normal and overweight BMI groups, regardless of physical activity levels. Higher physical activity reduced the risk slightly within BMI groups, with a nonsignificant inverse trend (overlapping CIs) in the overweight group ($HR_{\text{overweight Quartile 1}}$, 1.85; 95% CI, 1.61–2.13; $HR_{\text{overweight Quartile 4}}$, 1.69; 95% CI, 1.47–1.94; compared with highly active low-normal BMI; Table S2).

Sensitivity Analysis

In sensitivity analysis, we considered physical activity measurements from a later time point (1997) with BMI and other covariates measured at 1992 (n=39 109, cases=7880) with 1997 as the baseline. Considering total physical activity, the results were similar to the main analysis but were borderline significant ($HR_{\text{Quartile 1–Quartile 4}}$, 0.96; 95% CI, 0.90–1.02; *P* trend=0.07; Table S3). When models were stratified on BMI, no single group showed a significant trend, possibly attributed to the smaller number of cases in this analysis (not tabulated). Results were similar to the main analysis when considering sports separately from other types of physical activity ($HR_{\text{sport >2 hours}}$, 0.85; 95% CI, 0.80–0.91; *P* trend <0.001; not tabulated). When considering sports stratified on BMI, only among women with excess weight was there no clear association between sports and hypertension, although the second quartile showed a reduced risk ($HR_{\text{sport 0–0.5 hours}}$, 0.65; 95% CI, 0.49–0.88; *P* trend=0.31; Table S4), but the sample size was low in this quartile.

DISCUSSION

In the present study, we aimed to understand the relation between physical activity, BMI, and the risk of hypertension. We observed the highest risk of hypertension in participants reporting the lowest levels of physical activity. Sports were most strongly associated with a reduced risk of hypertension in these women, regardless of other risk factors. Walking and gardening were both associated with slight reductions in risk, but cycling was not associated with the risk of hypertension. Results were stable after excluding cases diagnosed within the first 5 years after baseline, providing confidence that this was not attributed to reverse causality. These results provide

Table 2. Cox-ph Models for BMI and Physical Activity

Physical Activity, METs/wk	Cases	Person-Years	M0		M1		M2		M3	
			HR (95% CI)	*P* Trend	HR (95% CI)	*P* Trend	HR (95% CI)	*P* Trend	HR (95% CI)	*P* Trend
Quartile 1 (<32.0)	2516	152 189	Reference	0.03	Reference	0.05	Reference	0.01	Reference	0.02
Quartile 2 (32.0–47.3)	2524	152 369	0.98 (0.92–1.03)		0.98 (0.93–1.04)		0.98 (0.92–1.03)		0.97 (0.92–1.03)	
Quartile 3 (47.3–67.5)	2486	149 375	0.94 (0.89–0.99)		0.96 (0.90–1.01)		0.94 (0.88–0.99)		0.93 (0.88–0.99)	
Quartile 4 (>67.5)	2656	150 429	0.94 (0.89–1.00)		0.96 (0.90–1.01)		0.94 (0.89–0.99)		0.93 (0.88–0.98)	

M0 unadjusted with age as the timescale. M1 adjusted for BMI; M2 adjusted for diabetes mellitus at baseline, family history of hypertension or cardiovascular disease (yes/no), smoking (never, former, and current), and education; and M3 adjusted for dietary variables (calories, potassium, magnesium, phosphates, lipids, salt, alcohol, and caffeine). BMI indicates body mass index; HR, hazard ratio; and METs, metabolic equivalents.

further evidence toward the beneficial effects of practicing sports regularly with regard to cardiovascular disease prevention.

We observed that the relation between physical activity and hypertension differed according to BMI, with inverse associations between physical activity and hypertension only present in women with normal BMI. In overweight women, physical activity was not observed to significantly alter the risk of hypertension development, although when considering the interaction model presented in supplementary analysis, a nonsignificant inverse trend between physical activity and hypertension was observed in women who were overweight and obese. The incident rates of hypertension were much lower in lower weight women (≈13.6 per 1000 person-years) compared with women who were overweight (≈24.3 per 1000 person-years). Sports activity >2 hours per week was associated with a risk reduction of 2 cases per 1000 person-years in the leanest women, but no risk reduction in the heaviest women, a result that was consistent in sensitivity analysis considering later physical activity. These results do not imply that women who are overweight cannot benefit from increasing their physical activity. It is possible that the effect of physical activity in women who are overweight is mediated through changes in weight, which we are unable to account for properly in this analysis and would require dedicated studies with appropriate data collection.

To the best of our knowledge, only 2 studies prospectively analyzed the combined associations of BMI and physical activity on risk of hypertension. Hu et al[17] assessed a joint model of BMI and physical activity and observed a reduction in hypertension risk from physical activity in women who were obese. However, the range of BMI in that population was quite different from that of our population, and their study included both men and women, thus making comparisons difficult. Similarly, Jackson et al[10] identified a significant interaction between BMI and physical activity and reported an association between overall physical activity and risk of hypertension in women who were obese, but included a larger proportion of women who were overweight and obese than in our work. In both of these studies, the largest reduction in risk attributed to physical activity was observed in people who were obese (BMI, ≥30), which represented a small proportion of our population, and it is possible that our results in these women could be limited by a small sample size. However, neither investigated associations across various strata of normal range BMI, which is one of the major findings of the present study, despite being unable to confirm the previous associations in women who were obese. The magnitude of associations between

Table 3. Fully Adjusted Models Stratified Into Groups Based on BMI, Showing Associations Between Physical Activity and Hypertension in Each Strata of BMI

Physical Activity, METs/wk	Underweight (BMI, ≤18.4)		Low Normal (BMI, 18.5–19.9)		Mid Normal (BMI, 20.0–22.4)		High Normal (BMI, 22.5–24.9)		Obese/Overweight (BMI, ≥25.0)	
	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)
Quartile 1 (<32.0)	62	Reference	301	Reference	903	Reference	727	Reference	523	Reference
Quartile 2 (32.0–47.3)	68	0.91 (0.56–1.25)	302	0.98 (0.82–1.14)	986	1.04 (0.95–1.13)	676	0.90 (0.79–1.00)	492	0.98 (0.85–1.10)
Quartile 3 (47.3–67.5)	74	1.08 (0.74–1.42)	269	0.89 (0.73–1.06)	985	1.00 (0.90–1.09)	707	0.89 (0.78–0.99)	451	0.95 (0.82–1.07)
Quartile 4 (>67.5)	72	1.19 (0.84–1.53)	318	0.97 (0.81–1.13)	975	0.95 (0.85–1.04)	762	0.89 (0.79–0.99)	529	0.95 (0.83–1.08)
P trend		0.18		0.66		0.10		0.05		0.42

Adjusted for diabetes mellitus at baseline, family history of hypertension or cardiovascular disease (yes/no), smoking (never, former, and current), education, and dietary variables (calories, potassium, magnesium, phosphates, lipids, salt, alcohol, and caffeine) and age as the timescale. BMI indicates body mass index; HR, hazard ratio; and METs, metabolic equivalents.

Table 4. Different Types of Physical Activity and the Risk of Hypertension

	Person-Years	Cases	M0	M1	M2	M3
			HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Sports, h/wk						
0	232 203	4386	Reference	Reference	Reference	Reference
0–1.0	140 892	2252	0.91 (0.86–0.95)	0.94 (0.89–0.99)	0.94 (0.89–0.99)	0.94 (0.89–0.99)
1.0–2.0	133 596	1775	0.88 (0.83–0.93)	0.91 (0.86–0.97)	0.91 (0.86–0.96)	0.91 (0.86–0.96)
>2.0	117 671	1769	0.84 (0.79–0.88)	0.88 (0.83–0.93)	0.88 (0.83–0.93)	0.87 (0.83–0.93)
P trend			<0.0005	<0.0005	<0.0005	<0.0005
Walking, h/wk						
<2.0	194 613	3235	Reference	Reference	Reference	Reference
2.0–3.5	122 308	2046	0.98 (0.93–1.04)	0.99 (0.93–1.05)	0.99 (0.94–1.05)	0.99 (0.94–1.05)
3.5–6.5	140 665	2366	0.95 (0.90–1.00)	0.97 (0.90–1.02)	0.97 (0.92–1.02)	0.96 (0.92–1.02)
>6.5	146 775	2535	0.93 (0.88–0.98)	0.94 (0.88–0.99)	0.94 (0.90–1.00)	0.94 (0.90–1.00)
P trend			0.003	0.02	0.02	0.02
Gardening, h/wk						
0.0	197 211	3349	Reference	Reference	Reference	Reference
0.0–1.0	138 868	2258	1.01 (0.96–1.07)	1.02 (0.96–1.07)	1.01 (0.96–1.07)	1.01 (0.95–1.07)
1.0–2.5	125 975	2087	0.98 (0.93–1.04)	0.98 (0.93–1.04)	0.98 (0.93–1.04)	0.98 (0.92–1.03)
>2.5	142 307	2488	0.95 (0.90–1.01)	0.94 (0.90–1.00)	0.94 (0.89–1.00)	0.94 (0.89–0.99)
P trend			0.04	0.02	0.02	0.02
Housework and cleaning, h/wk						
<4.1	247 228	3836	Reference	Reference	Reference	Reference
4.1–7.5	153 779	2628	1.04 (0.98–1.10)	1.04 (0.98–1.10)	1.04 (0.98–1.10)	1.03 (0.98–1.09)
>7.5	203 353	3718	1.07 (1.02–1.12)	1.05 (1.01–1.10)	1.05 (1.00–1.10)	1.05 (1.00–1.10)
P trend			0.003	0.03	0.05	0.04
Cycling, h/wk						
0	7198	411 248	Reference	Reference	Reference	Reference
>0	2984	193 114	0.97 (0.93–1.02)	0.99 (0.95–1.03)	0.99 (0.94–1.03)	0.98 (0.93–1.02)
P trend			0.18	0.63	0.53	0.48

M0 unadjusted with age as the timescale. M1 adjusted for body mass index; M2 further adjusted for diabetes mellitus at baseline, family history of hypertension or cardiovascular disease (yes/no), smoking (never, former, and current), education; and M3 further adjusted dietary variables (calories, potassium, magnesium, phosphates, lipids, salt, alcohol, and caffeine). HR indicates hazard ratio.

hypertension and BMI were higher than those between physical activity and hypertension. It is therefore possible that the augmented risk from obesity cannot be totally eliminated by increasing physical activity. Similar results have been observed in multiple studies on hypertension[10,17,37] and cardiovascular diseases.[38–41]

We were able to assess the associations between hypertension and different types of physical activity. We observed that the largest association was from sports-based activity, followed by gardening and walking, which both showed weaker associations. Even small amounts of sports, <1 hour, were associated with a reduced risk of hypertension. Housework and cleaning was associated with an increased risk of hypertension, possibly attributed to residual confounding from this variable and perhaps explained by considering that this is not "leisure time" physical activity but, rather, occupational and non-leisure-based physical activity, which is associated with chronic disease in other studies.[42,43] Spline regression demonstrated that longer times were required for walking and gardening to achieve the same risk reduction as sports. This suggests that strenuous physical activity is better for reducing hypertension risk. Some previous studies have assessed aerobic fitness as opposed to time spent doing physical activities and have found that a high aerobic capacity is associated with a reduced risk of hypertension.[37] The observed larger effect from sports as opposed to lower intensity physical activity is in agreement with various international guidelines (eg, those of the UK National Health Service or the US Office of Disease Prevention) that recommend 75 minutes of intense physical exercise per week (such as a full game of tennis) or longer durations of lower intensity physical activity such as walking. Emphasis should also be placed on maintaining regular physical activity to

Table 5. Sports Based Physical Activity and Risk of Hypertension Stratified Over BMI

	Underweight (BMI, <18.5)		Low Normal (BMI, 18.5–19.9)		Mid Normal (BMI, 20.0–22.49)		High Normal (BMI, 22.5–25.0)		Obese/Overweight (BMI, >25)	
	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)
Sports-based physical activity, h/wk										
0	115	Reference	477	Reference	1469	Reference	1309	Reference	1016	Reference
0–1.0	64	1.01 (0.74–1.37)	246	0.79 (0.68–0.92)	915	0.97 (0.90–1.06)	606	0.90 (0.82–0.99)	421	1.04 (0.93–1.17)
1.0–2.0	44	0.96 (0.68–1.37)	236	0.87 (0.74–1.02)	718	0.91 (0.83–0.99)	488	0.88 (0.79–0.98)	289	0.98 (0.85–1.11)
>2.0	53	0.88 (0.63–1.23)	231	0.79 (0.67–0.92)	747	0.87 (0.80–0.95)	469	0.84 (0.76–0.94)	269	0.96 (0.84–1.10)
P trend		0.46		0.007		0.001		0.001		0.51

Adjusted for diabetes mellitus at baseline, family history of hypertension or cardiovascular disease (yes/no), smoking (never, former, and current), education, and dietary variables (calories, potassium, magnesium, phosphates, lipids, salt, alcohol, and caffeine) and age as the timescale. BMI indicates body mass index; and HR, hazard ratio.

maintain a healthy BMI as well as for the independent protective effects on metabolic diseases.[44–47] From a public health perspective, these results support efforts to promote weight control and make exercise as accessible as possible.[48]

Strengths and Limitations

Strengths of this study are its prospective design, large sample size, long follow-up (15 years) with minimal loss to follow-up, and a large number of cases. A unique strength of this study is the large number of women in the healthy BMI range, allowing us to analyze 3 groups within the World Health Organization healthy weight range, that is, low normal (18.5–20.4), mid normal (20.5–22.4), and high normal (22.5–25.0). However, we were underpowered to provide a proper assessment of the risk of being underweight or morbidly obese on incident hypertension because these women consisted of fewer than 5% of the total study population, thus these results may not be generalizable to populations with higher rates of obesity or to specific groups with a high BMI. As the study consisted of women, the sizes of the effects may not be generalizable to men. However, we believe there is no biological reason why the general trends observed regarding activity or BMI should not be generalizable to men and to younger people. It is reasonable that BMI could also be considered as a mediator in the relationship between physical activity and hypertension, but few studies assessing this have been conducted. One cross-sectional study in school-aged children identified BMI as a mediator in the relationship between cardiorespiratory fitness and cardiovascular risk for girls,[49] but these results are difficult to extrapolate to elderly and middle-aged women. Future work could assess if the relationship with hypertension is mediated by BMI.

In this study, cases of hypertension were identified through follow-up questionnaires. We assessed the validity of cases of hypertension,[32] and we observed an 82% positive predictive value when we validated self-reported information with the use of a drug reimbursement database. Some degree of misclassification is possible, but because this study is prospective, it should be random and unrelated to the exposure, thus only reducing the study power.

As the interactions between physical activity and BMI are particularly complex (ie, BMI affects the likelihood, ability, and potentially the reasons for undertaking exercise, and physical activity can affect BMI through increased energy expenditure[50]), we considered BMI measured before physical activity to reduce the likelihood of obtaining biased estimates.[51] However, it is still possible that physical activity would be related to BMI at this point and should be considered a limitation of the data used. To address

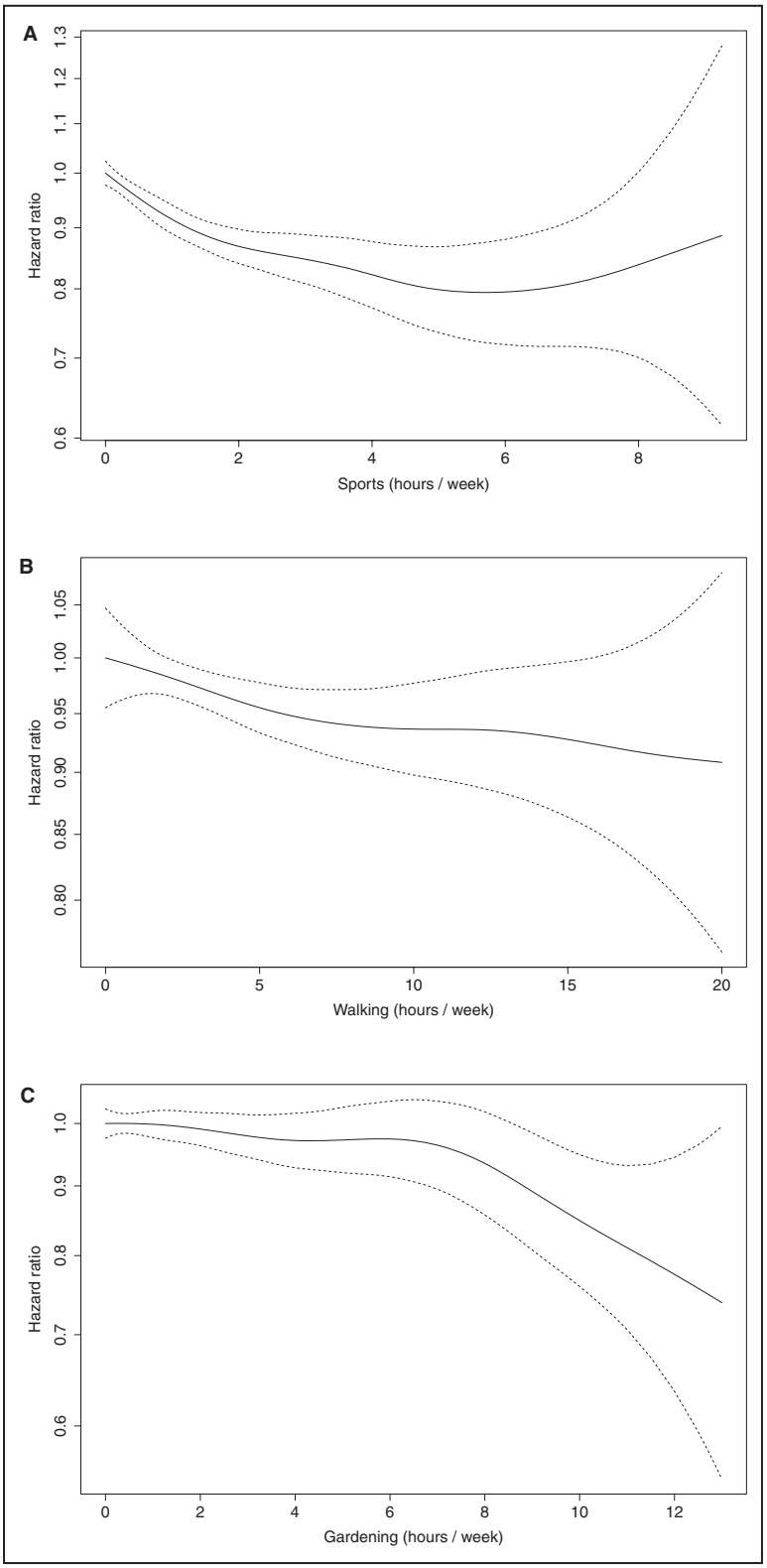

Figure. Spline regression curves demonstrating dose–response relationship for hours of sports-based physical activity (A) and walking (B) and gardening (C) physical activities with regard to hypertension risk. Dashed lines indicate 95% CI.

A strong inverse relationship was observed with sports, and weaker inverse relationships were observed with walking and gardening.

this, we considered a sensitivity analysis using physical activity estimates from 1997, which we assume would be less related to BMI at 1992. We observed similar results when considering sports in this setting, although results with total physical activity were borderline. The smaller number of cases and shorter follow-up can be considered a limitation of this sensitivity analysis.

The inclusion of dietary variables could introduce collider bias as they are associated with both physical activity and BMI. Diet could have a possible independent effect of calorie intake on hypertension such as improving insulin sensitivity[52] but could also represent a critical confounder in the association with physical activity. As the estimates did not drastically change when adjusting on energy intake and dietary variables, it is unlikely that biases could be driving the observed results.

We were able to account for a large amount of potential confounders, including smoking, alcohol and caffeine intakes, dietary factors, and family history. It is nevertheless possible that more active participants live a healthier life and that some confounding was not accounted for. In addition, we could not ascertain whether women were exercising to lose weight or how they gained weight. Similarly, although BMI is useful tool to assess general obesity, it is limited compared with other indexes as a result of differences in risk depending on the location of adiposity. The BMI measurement could be augmented by considering additional measurements such as waist–hip ratio, waist circumference, or weight–height ratio, for example.

CONCLUSIONS

Our results suggest the benefits of sports in women with healthy weight with regard to the prevention of hypertension. In a public health perspective, people should be encouraged to regularly practice sports to reduce their risk of hypertension and the risk of hypertension-associated diseases. Further research could assess the associations between sports and hypertension in women who are overweight.

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Disclosures

None.

Supplementary Materials

Tables S1–S4
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Comparison between included and excluded populations.

	Included (n = 41,607)	Excluded (n = 57,388)
Risk factors		
Prevalent hypertension	0	25,650
Prevalent cardiovascular disease	0	500
Prevalent cancer	0	6,765
Missing dietary data	0	24,473
Weekly total physical activity (METS / week)	53.9 ± 27.5	43.0 ± 28.3
Walking (hours / week)	4.6 ± 3.9	2.4 ± 2.5
Sports (hours / week)	1.3 ± 1.6	1.0 ± 1.2
Gardening (hours / week)	1.8 ± 2.3	1.5 ± 1.8
Housework (hours / week)	7.3 ± 5.4	7.3 ± 6.8
Cycling (hours / week)	0.5 ± 1.1	0.4 ± 0.6
Age (years)	50.1 ± 6.2	51.2 ± 6.6

Body mass index (kg / m^2)	22.2 ± 2.5	23.1 ± 3.5
Underweight BMI (< 18.5) (%)	3.1	4.0
Low-normal BMI (18.5 – 19.9) (%)	13.3	11.9
Mid-normal BMI (20.0 – 22.5) (%)	42.4	36.2
High-normal BMI (22.5 – 24.9) (%)	26.6	24.4
Overweight/obese BMI (> 25.0) (%)	13.1	22.6
Family history of cardiovascular disease (%)	33.9	20.0
Diabetes (%)	0.5	1.1
Smoking status (%)		
Never	52.1	55.8
Former	33.7	27.4
Current	14.2	16.7
With high school diploma (%)	93.7	87.6

BMI: body mass index, Mets: Metabolic equivalents

Table S2. Joint exposures of total physical activity and BMI.

BMI (kg/m^2)	Underweight (BMI <= 18.4)	Low-normal (BMI 18.5 – 19.9)	Mid-normal (BMI 20.0 – 22.49)	High-normal (BMI 22.5 – 24.9)	Obese/overweight (BMI >= 25)
Total physical activity (METS-hours / week), p - joint exposure < 0.01					
Q1 (< 32.0)	0.88 [0.76: 1.15]	1.00 [0.85: 1.17]	1.06 [0.93: 1.20]	1.36 [1.10: 1.56]	1.85 [1.61: 2.13]
Q2 (32.0 – 47.3)	0.81 [0.62: 1.05]	0.98 [0.84: 1.15]	1.10 [0.97: 1.25]	1.22 [1.07: 1.39]	1.79 [1.56: 2.07]
Q3 (47.3 – 67.5)	0.95 [0.74: 1.22]	0.91 [0.77: 1.07]	1.06 [0.94: 1.21]	1.20 [1.05: 1.37]	1.72 [1.49: 1.98]
Q4 (> 67.5)	1.05 [0.81: 1.36]	**Reference**	1.02 [0.90: 1.16]	1.20 [1.05: 1.37]	1.69 [1.47: 1.94]

BMI: body mass index, Mets: Metabolic equivalents

Table S3. Cox-ph models for physical activity in 1997.

Physical activity (METs / week)	**Cases**	**Person-years**	**M0** **HR [95% CI]**	**p trend**	**M1** **HR [95% CI]**	**p trend**	**M2** **HR [95% CI]**	**p trend**	**M3** **HR [95% CI]**	**p trend**
Q1 (< 38.5)	1801	99,674	**Reference**	0.09	**Reference**	0.17	**Reference**	0.08	**Reference**	0.07
Q2 (38.5 – 61.5)	1783	100,404	1.01 [0.95: 1.08]		1.03 [0.96: 1.10]		1.02 [0.96: 1.09]		1.02 [0.96: 1.09]	
Q3 (61.5 – 89.0)	1722	97,729	0.95 [0.89: 1.01]		0.97 [0.90: 1.03]		0.96 [0.90: 1.02]		0.96 [0.90: 1.02]	
Q4 (> 89.0)	1908	98,958	0.96 [0.90: 1.02]		0.97 [0.91: 1.04]		0.95 [0.90: 1.02]		0.96 [0.90: 1.02]	

M0 unadjusted with age as the timescale. M1 adjusted for BMI at 1992, M2 adjusted for diabetes at baseline, family history of hypertension or cardiovascular disease (yes/no), smoking (never, former, and current), education, and M3 adjusted for dietary variables (calories, potassium, magnesium, phosphates, lipids, salt, alcohol, and caffeine).

BMI: body mass index, Mets: Metabolic equivalents

Table S4. Sports based physical activity estimated in 1997, and risk of hypertension stratified over BMI in 1992.

	Underweight (BMI < 18.5)		**Low-normal (BMI 18.5 – 19.9)**		**Mid-normal (BMI 20.0 – 22.49)**		**High-normal (BMI 22.5 – 25.0)**		**Obese/overweight (BMI > 25)**	
	Cases	**HR [95% CI]**	**Cases**	**HR [95% CI]**	**Cases**	**HR [95% CI]**	**Cases**	**HR [95% CI]**	**Cases**	**HR [95% CI]**
Sports-based physical activity (hours / week)										
0	111	**reference**	448	**reference**	1407	**reference**	1168	**reference**	853	**reference**
0 – 0.5	10	0.86 [0.45, 1.65]	55	1.05 [0.80, 1.40]	153	1.00 [0.84, 1.18]	114	0.99 [0.82, 1.20]	47	0.65 [0.49, 0 88]
0.5 – 2.0	59	0.94 [0.68, 1.30]	251	0.82 [0.70, 0.96]	893	0.91 [0.84, 0.99]	567	0.86 [0.78, 0.95]	337	0.98 [0.86, 1.11]
> 2.0	41	0.76 [0.53: 1.09]	199	0.82 [0.69: 0.97]	592	0.83 [0.75: 0.91]	372	0.86 [0.76: 0.97]	205	0.91 [0.78: 1.06]
p-trend		0.12		0.01		< 0.001		0.003		0.31

Adjusted for diabetes at baseline, family history of hypertension or cardiovascular disease (yes/no), smoking (never, former, and current), education, and dietary variables (calories, potassium, magnesium, phosphates, lipids, salt, alcohol, and caffeine), and age as the timescale. BMI: body mass index

Figure S1. Directed acyclic graph used to guide choice of covariates considering BMI in 1992 and activity in 1995.

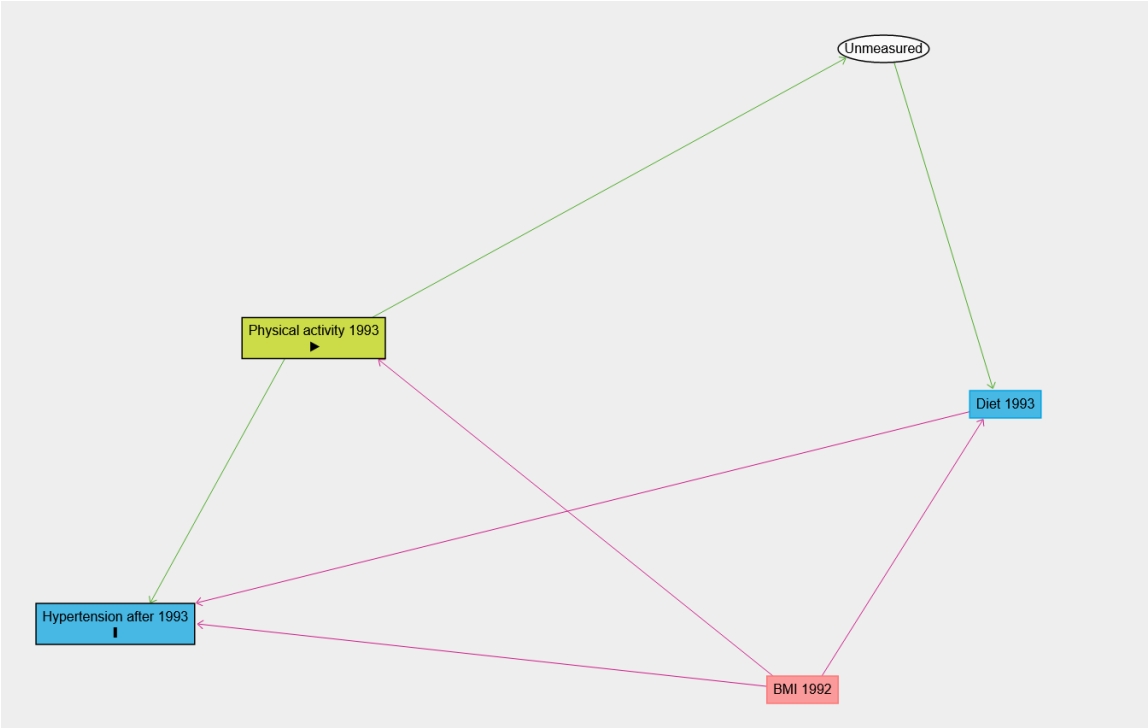

Figure S2. Directed acyclic graph used to guide choice of covariates considering BMI in 1992 and physical activity in 1997.