Original Contribution

Body Mass Index, Blood Pressure, and Risk of Depression in the Elderly: A Marginal Structural Model

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The authors' objective was to investigate the associations of body mass index (BMI; weight (kg)/height (m)^2) and blood pressure with the risk of developing depression in a large sample of elderly French participants (aged ≥65 years) followed for 10 years (Dijon portion of the Three-City Study, 1999–2010). Depression was defined as either having major depressive symptoms according to the Mini-International Neuropsychiatric Interview or taking antidepressant medication. The authors fitted marginal structural models to examine the relations of BMI and blood pressure with depression. Among subjects who were depression-free at baseline ($n = 3,090$), 478 developed incident depression over 10 years of follow-up. The analyses showed that after baseline values and time-dependent confounders were controlled, subjects with high BMI at follow-up had an increased adjusted risk of developing depression compared with subjects with normal BMI (risk ratio = 1.60, 95% confidence interval: 1.03, 2.51). Compared with subjects with normal blood pressure, those with high blood pressure were not at increased risk of incident depression, whereas those with low blood pressure had a higher risk of developing depression. These findings provide some epidemiologic support for implication of lifestyle risk factors in the development of depression in the elderly. Future studies should focus on evaluating lifestyle and obesity interventions among the elderly.

aging; blood pressure; body mass index; depression; epidemiologic methods; models, statistical

Abbreviations: BMI, body mass index; 3C-Dijon Study, Dijon portion of the Three-City Study; CES-D Scale, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; IPCW, inverse probability of censoring weight; IPTW, inverse probability of treatment weight; MINI, Mini-International Neuropsychiatric Interview; MSM, marginal structural model.

Depression is the most common mental illness in older adults, with concomitant effects on morbidity, mortality, and quality of life. Although sociodemographic and psychological risk factors are now well-established, there is mounting interest in the search for modifiable risk factors that simultaneously affect depression and other chronic comorbidity in the elderly. Hypertension and body mass index (BMI) are among these modifiable risk factors that are increasingly being discussed.

The relation between depression and hypertension (or high blood pressure) in the elderly has been previously investigated, but the results have been heterogeneous, and longitudinal studies of population-based samples are scarce.

Some studies found that high blood pressure is a risk factor for depression (1, 2), whereas others failed to confirm this relation (3, 4). Moreover, other studies have suggested that baseline low blood pressure could be associated with increased risk of developing depression in the elderly (5, 6).

Adjusted associations between BMI and depression have been reported in several cross-sectional analyses, showing an increased risk of developing depression in obese or overweight subjects (7, 8), but longitudinal studies in elderly persons are rare (4, 9). To our knowledge, no studies have investigated the relation between modifiable factors and depression in a longitudinal study among elderly persons with repeated measurements of exposure and outcome.

The underlying mechanisms for a causal effect of these factors on depression onset are not fully understood. One plausible scenario is that the exposures could be risk factors for vascular brain lesions, especially in the frontal and subcortical areas, which play a key role in mood regulation (10). One of the main problems in interpreting an association between vascular factors and depression is that much of the evidence is based on observational data, from which causal inferences are necessarily limited (2).

One way to deal with this limitation is to apply causal models to available observational information. In particular, marginal structural models (MSMs) can provide robust estimators of the causal effect of a time-dependent exposure in the presence of time-dependent covariates that may be confounders and intermediate variables at the same time (11, 12). This approach has not yet been applied to the study of putative modifiable risk factors inducing depression, mainly because of the lack of thorough follow-up data on both exposures and covariates. The association between depression and modifiable risk factors represents a scenario typical of the analyses for which MSMs were created: causal effects that vary longitudinally such that exposures can affect subsequent exposures and covariates, which then become confounders in the later time steps.

In an attempt to understand the magnitude, direction, and nature of the causal association between blood pressure, BMI, and depression, we applied the MSM method to a large population-based cohort of elderly persons followed up for 10 years.

MATERIALS AND METHODS

Sample

The Three-City Study is a multicenter cohort study being conducted in 3 French cities (Bordeaux, Dijon, and Montpellier) that was designed to estimate dementia risk attributable to vascular factors. A sample of noninstitutionalized subjects aged 65 years or more was randomly selected from the electoral rolls. Among them, 9,294 subjects agreed to participate and were enrolled between January 1999 and March 2001. Eligibility criteria included living in the city, being registered in electoral rolls in 1999, being aged 65 years or older, and not being institutionalized. The study protocol has been published in detail elsewhere (13) and was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre. Each participant gave written informed consent. The current analysis was based on the Dijon subsample (3C-Dijon Study), which was followed up for 10 years (Figure 1).

Data collection

During each study wave, data were collected at the participants' homes by a trained psychologist during face-to-face interviews, using a standardized questionnaire. Information about demographic background, marital status, occupation, medical history, and personal habits was collected. All medications used during the preceding month were recorded based on medical prescriptions and drug packages shown

by the participant. Names of medications were coded according to the Anatomic-Therapeutic-Chemical classification of the World Health Organization. Assessment of cognitive performance included administration of the Mini-Mental State Examination (14).

Measure of depression

Depressive symptomatology was evaluated with the Center for Epidemiologic Studies Depression Scale (CES-D Scale) (15), a 20-item rating scale developed to assess the past-week frequency and severity of depressive symptoms in epidemiologic studies. A high level of depressive symptoms was defined as a CES-D score greater than or equal to 17 for men and greater than or equal to 23 for women (16).

The Mini-International Neuropsychiatric Interview (MINI) (17) was used to assess the existence of lifetime major depressive episodes. The MINI is a short, structured diagnostic interview that was developed jointly by psychiatrists and clinicians to identify psychiatric disorders (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, and *International Classification of Diseases*, Tenth Revision) for clinical trials and epidemiologic studies.

During follow-up, a subject was considered to have an incident case of depression if he or she fulfilled criteria for a current episode of major depression (based on the MINI) or reported use of antidepressant medication and had not been depressed in any of the previous study waves. In the 4-year follow-up wave, because the MINI was not administered, persons with incident depression were identified as those having a high level of depressive symptoms (based on CES-D score) and/or taking antidepressants at that time.

Blood pressure measurement

Measures of systolic and diastolic blood pressure were obtained in each study wave from 3 measurements taken on the right arm after 2 minutes' rest in a sitting position, using a mercury sphygmomanometer. The mean of the 3 measurements was used for the analyses. Subjects were considered hypertensive if systolic blood pressure was greater than or equal to 140 mm Hg or diastolic blood pressure was greater than or equal to 90 mm Hg or they were using antihypertensive medication. Subjects were also categorized as having low blood pressure if systolic blood pressure was less than 120 mm Hg or diastolic blood pressure was less than 75 mm Hg (18). Blood pressure was considered normal if systolic blood pressure was 120–< 140 mm Hg or diastolic blood pressure was 75–< 90 mm Hg.

Body mass index

Weight and height were measured in each study wave and used to calculate BMI as the ratio of weight (kg) to the square of height (m^2). Subjects were categorized as normal-weight (BMI <25), overweight (BMI 25–< 30), or obese (BMI ≥30).
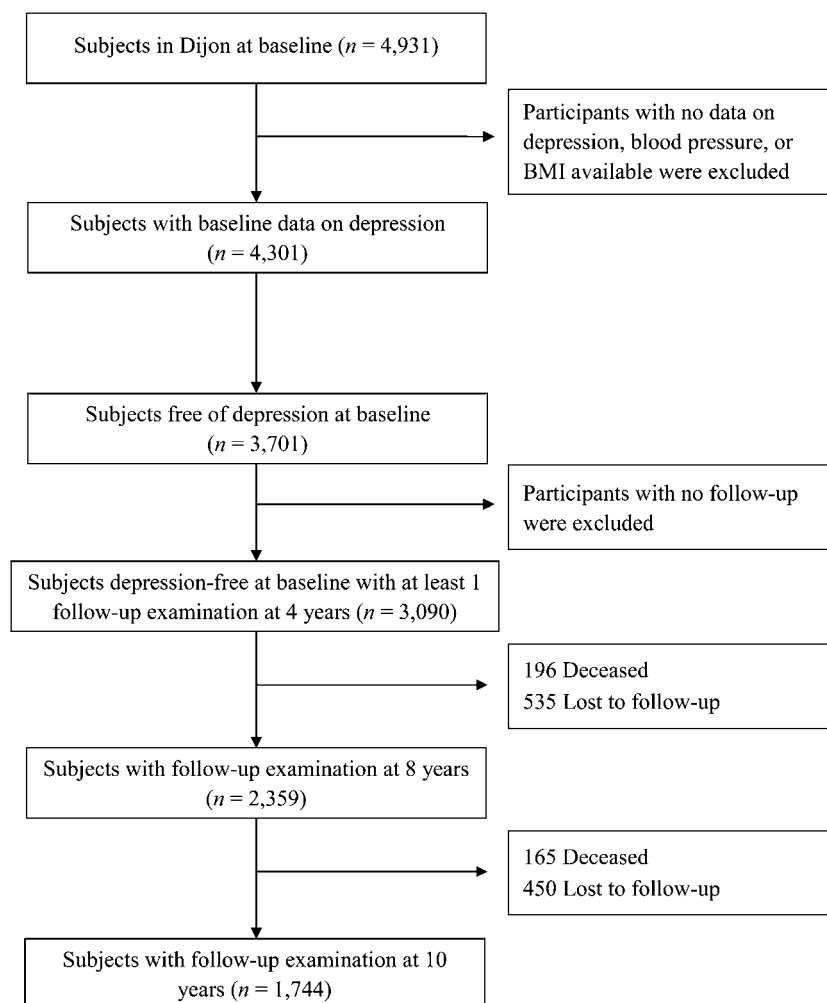
Figure 1.   Selection of the baseline and follow-up samples in the Dijon portion of the Three-City Study, Dijon, France, 1999–2010. (BMI, body mass index).

Confounders

Education was dichotomized as a low level of education versus a high level (baccalaureate degree or higher). Self-reported general health was categorized as good, medium, or poor. Marital status was categorized as single or not single. Smoking status was classified as current smoker, past smoker, or never smoker. Alcohol consumption was the reported number of drinks per week and was categorized into quartiles. Participants were asked whether they were being treated for hypercholesterolemia or diabetes at each follow-up. We recorded medical prescriptions for all medications used during the preceding month. Baseline physical activity was self-reported as a variable assessing the daily duration of walking and other activities (never, sometimes, or regularly).

Statistical methods

Subjects with baseline depression were excluded from the analysis, leaving an analytic sample of 3,090 persons who were free of depression at baseline (Figure 1). Binomial MSMs were fitted to estimate the adjusted effects of blood pressure and BMI on depression.

The MSM (19, 20) is a statistical tool that may be used in the presence of time-varying exposure and time-dependent confounders (11, 12, 19). MSM coefficients are estimated using the inverse probability of treatment weight (IPTW) (21). For each individual, at each follow-up, we estimated the probability of receiving the exposure that the individual actually received, conditional on the observed fixed and time-varying covariates up to that time. Participants were then weighted by the inverse of their predicted probability of exposure in order to create a "pseudopopulation" consisting of fractional copies of each subject.

Subjects who are underrepresented in exposure assignment, given their covariates and previous exposures, receive proportionally higher weights, while persons who are highly represented in exposure assignment, conditional on the past, receive proportionally lower weights. One therefore obtains comparable populations in terms of the propensity to be

exposed at each time point, as a function of past measures. The resulting "pseudopopulation" is balanced with regard to the distribution of potential confounders across exposure levels and can thus be used to estimate the unconfounded relation between exposure and outcome under the assumptions of exchangeability, consistency, positivity, and correct specification of the models (22, 23).

To deal with censoring, we calculate weights for the probability of remaining uncensored up to time t. Each individual observation is weighted by the IPTW multiplied by the inverse probability of censoring weight (IPCW). The outcome of interest was depression, coded as a binary variable. The primary exposure was blood pressure and the secondary exposure was BMI, both coded as 3-level categorical variables; the third exposure was hypertension. IPTWs were estimated from predicted probabilities obtained by means of logistic and polytomous logistic models. We used logistic models to obtain censoring weights, where the outcome was whether or not the individual was censored at that time (persons who were lost to follow-up were coded as 1; participants were coded as 0 otherwise). Polytomous regression was used to obtain the weights for each category of the exposures. In those models, blood pressure, hypertension, and BMI were the dependent variables.

Simple IPTW can result in excessively large weights, and these weights can fail to be approximately normally distributed. Therefore, we used stabilized weights to reduce variability and improve the precision of the estimates (24). A stabilized version of the IPTW is

$$sw_i = \prod_{k=0}^{t} \frac{\begin{array}{c}\Pr[C(k) = 0|\bar{C}(k-1) = 0, \bar{A}(k-1) \\ = \bar{a}_i(k-1), \mathbf{V} = v_i]\end{array}}{\begin{array}{c}\Pr[C(k) = 0|\bar{C}(k-1) = 0, \bar{A}(k-1) \\ = \bar{a}_i(k-1), \bar{\mathbf{L}}(k-1) = \bar{l}_i(k-1)]\end{array}},$$

where $C(k)$ represents the censored status at time k, $A(k)$ represents the exposure at time k, $\bar{A}(k-1)$ represents the exposure history prior to time k, $\mathbf{V}$ represents the vector of baseline covariates, and $\bar{\mathbf{L}}$ represents the vector of time-varying covariates through time k, which includes baseline variables V.

For the stabilized IPTW, the numerator of the weights contains all covariates measured at baseline (age, sex, educational level, physical activity, and marital status), as well as baseline blood pressure or BMI, while the denominator contains baseline and time-varying confounders (tobacco use, alcohol consumption, BMI, blood pressure, hypercholesterolemia, antihypertensive treatment, general health, global cognition, and diabetes).

A stabilized version of the IPTW is

$$sw_i(t) = \prod_{k=0}^{t} \frac{\begin{array}{c}\Pr[A(k) = a_i(k)|\bar{A}(k-1) \\ = \bar{a}_i(k-1), \mathbf{V} = v_i]\end{array}}{\begin{array}{c}\Pr[A(k) = a_i(k)|\bar{A}(k-1) \\ = \bar{a}_i(k-1), \bar{\mathbf{L}}(k) = \bar{l}_i(k-1)]\end{array}},$$

where $\bar{A}(-1) = 0$ and $\bar{C}(-1) = 0$, $A(k)$ represents the exposure at time k, $\bar{A}(k-1)$ represents the exposure history

prior to time k, $\mathbf{V}$ represents the vector of baseline covariates, and $\bar{\mathbf{L}}$ represents the vector of time-varying covariates through time k, which includes baseline variables V. We use the collapsible risk ratio measure, as opposed to an odds ratio or hazard ratio, to allow for a direct comparison between the standard model and the MSM (25). We used estimates from Poisson regression if the binomial model did not converge. We used PROC GENMOD in SAS (release 9.1; SAS Institute, Inc., Cary, North Carolina) to fit the final weighted pooled models.

To evaluate risk factors for blood pressure and BMI, we used χ^2 tests for categorical variables and analysis of variance for continuous variables. We fitted 3 generalized estimating equations models, with an independent working correlation matrix, to evaluate the relation between depression and each exposure. The first model adjusted for all baseline variables (including BMI and blood pressure); the second adjusted for time-fixed covariates (sex, age, educational level, physical activity, and marital status) and time-varying variables (BMI/blood pressure, tobacco use, alcohol consumption, hypercholesterolemia, antihypertensive treatment, general health, global cognition, and diabetes) without IPTW; and the last model was the weighted MSM. When BMI was the main exposure, we adjusted for blood pressure and vice versa. The final binomial MSM was

$$\begin{aligned}\log(\Pr[D(t) = 1|D(t-1) &= 0, \bar{A}(t), V, L]) \\ &= \beta_0(t) + \beta_1 A(t) + \beta_2 V_1 + \beta_2 V_2 \ldots \\ &\quad \beta_k V_{k+} \ldots \beta_x L_x,\end{aligned}$$

where D is depression, A is either blood pressure or BMI, the V's are baseline covariates, and the L's are time-varying covariates.

We tested interactions by adding interaction terms to the final models, but none were significant ($P < 0.10$).

RESULTS

Baseline characteristics of the sample are displayed in Table 1. The mean age of the participants was 73.5 years (standard deviation, 4.8), and 60% of the sample was female. Forty percent of participants were overweight, and 13.2% were obese. Seventy-nine percent of the sample had high blood pressure, and 4% had low blood pressure.

Table 2 shows baseline factors associated with blood pressure and BMI. Overweight, obesity, and high blood pressure were more prevalent in men. Age was associated with blood pressure but not with BMI. Subjects with diabetes, subjects with hypercholesterolemia, smokers, and alcohol drinkers had higher blood pressure and BMI. Lower cognition, lower physical activity, and a lower educational level were related to higher BMI and higher blood pressure. In addition, BMI and blood pressure were highly correlated; overweight or obese subjects were more likely to be hypertensive than normal-weight subjects. The prevalence of self-reported poorer health was substantially lower in subjects with high blood pressure than in hypotensive or normotensive subjects. Subjects with high blood pressure

Table 1.   Demographic Characteristics of Participants at Baseline and at the 10-Year Follow-up in the Dijon Portion of the Three-City Study, Dijon, France, 1999–2010

	Entire Sample at Baseline ($n = 3,090$)		Participants With Follow-up Visit at 10 Years ($n = 1,744$)	
	%	Mean (SD)	%	Mean (SD)
Female sex	59.9		62.6	
Age, years		73.5 (4.8)		72.5 (4.5)
Low educational level	66.3		64.0	
Single marital status	39.8		41.2	
Subjective health				
Good	63.3		68.1	
Medium	34.0		30.0	
Poor	2.7		1.8	
Physical activity				
Never	55.6		52.4	
Sometimes	33.5		35.4	
Regularly	10.9		12.2	
Diabetes	9.0		8.4	
Hypercholesterolemia	35.8		35.9	
Alcohol consumption, g/day		12.6 (14.1)		12.2 (13.6)
Tobacco use				
Never smoker	61.4		63.4	
Former smoker	33.3		31.6	
Current smoker	5.2		5.0	
Body mass index[a]		25.7 (4.0)		25.5 (3.8)
Systolic blood pressure in mm Hg		149.9 (22.7)		147.9 (21.8)
Diastolic blood pressure in mm Hg		84.4 (11.5)		84.3 (11.5)
Hypertension[b]	79.1		75.8	
MMSE score		27.5 (1.8)		27.8 (1.6)
Use of antihypertensive medication	47.5		42.6	

Abbreviations: MMSE, Mini-Mental State Examination; SD, standard deviation.

[a] Weight (kg)/height (m)^2.

[b] Defined as systolic blood pressure $\geq$140 mm Hg or diastolic blood pressure $\geq$90 mm Hg or use of antihypertensive medication.

and high BMI had a lower educational level than subjects with normal or low blood pressure.

Among subjects who were depression-free at baseline ($n = 3,090$), 478 developed incident depression over the 10 years of follow-up. Adjusted risk ratios and 95% confidence intervals for the estimated relations of BMI, hypertension, and blood pressure with depression are shown in Table 3. For each exposure-outcome relation, the table shows 3 models; the first represents the effect estimates adjusted only for baseline variables, the second is the unweighted model adjusting for baseline and time-varying covariates as a standard regression model, and the third is the MSM adjusted for baseline variables and time-varying covariates through IPTW and IPCW. Having a high BMI is a risk factor for depression in the elderly, but the relation was observed only for obesity. In the first two models, obese subjects had a 1.5 times' higher risk of developing depression (risk ratios were 1.48 (95% confidence interval

(CI): 1.00, 2.27) and 1.54 (95% CI: 1.02, 2.36), respectively) compared with normal-weight subjects. The MSM showed similar findings: In the fully adjusted models, among subjects with the same BMI category at baseline, high BMI at follow-up implied a 60% increased risk of developing depression compared with normal BMI at follow-up. Hypertension was not associated with depression risk. When blood pressure was studied in 3 categories ranging from low to high, in comparison with the normal blood pressure group, we observed an association between low blood pressure and depression onset during follow-up (risk ratio = 1.70, 95% CI: 1.16, 2.48). Adjustment for time-varying covariates in the standard and MSM models produced similar results.

Web Table 1 and Web Table 2 show the distributions of the stabilized and unstabilized weights across time intervals for associations of depression with BMI and blood pressure, respectively. Stabilized weights have a mean value

Table 2. Factors Associated With Blood Pressure and Body Mass Index at Baseline in the Dijon Portion of the Three-City Study, Dijon, France, 1999–2010

	Blood Pressure[a]						P Value[b]	Body Mass Index[c]						P Value
	Normal (n = 520)		High (n = 2,444)		Low (n = 126)			Normal (n = 1,457)		Overweight (n = 1,226)		Obese (n = 407)		
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)		%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	
Female sex	68.5		57.1		78.6		<0.0001	67.6		50.5		60.4		<0.0001
Age, years		72.3 (4.5)		73.9 (4.8)		71.2 (4.3)	<0.0001		73.6 (4.9)		73.4 (4.4)		73.3 (4.5)	0.31
Low educational level	60.8		67.8		61.9		0.005	62.9		66.8		77.2		<0.0001
Single marital status	41.9		38.9		49.2		0.04	43.7		38.1		44.8		0.002
Physical activity							0.02							<0.0001
Never	53.5		56.6		45.2			50.7		55.9		72.2		
Sometimes	32.6		33.3		41.1			36.2		34.1		22.3		
Regularly	13.9		10.1		13.7			13.1		10.0		5.5		
Subjective health							0.03							0.15
Good	67.2		62.1		71.8			64.3		63.8		58.4		
Medium	29.9		35.3		25.0			32.8		33.6		39.4		
Poor	2.9		2.6		3.2			2.9		2.6		2.2		
Diabetes	3.5		8.4		0.8		<0.0001	4.3		8.2		14.9		<0.0001
Alcohol consumption, g/day		10.9 (11.5)		13.2 (14.7)		8.6 (10.7)	<0.0001		11.2 (12.1)		14.0 (15.2)		13.3 (16.8)	<0.0001
Tobacco use							0.0003							<0.0001
Never smoker	67.7		59.7		69.1			68.0		54.6		58.5		
Former smoker	27.5		35.2		22.2			26.2		40.6		37.1		
Current smoker	4.8		5.1		8.7			5.8		4.7		4.4		
Body mass index		24.6 (3.6)		26.1 (4.0)		23.1 (3.1)	<0.0001							
MMSE score		27.8 (1.7)		27.5 (1.8)		28.0 (1.7)	0.0001		27.7 (1.8)		27.5 (1.8)		27.2 (1.9)	<0.0001
Hypertension								71.9		84.3		89.4		<0.0001
Hypercholesterolemia	31.0		37.1		29.4		0.009	32.3		39.6		36.4		0.0004

Abbreviations: MMSE, Mini-Mental State Examination; SD, standard deviation.

[a] Low blood pressure was defined as systolic blood pressure <120 mm Hg or diastolic blood pressure <75 mm Hg. High blood pressure (hypertension) was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or use of antihypertensive medication. Blood pressure was considered normal otherwise.

[b] Based on the chi-square test for categorical variables and analysis of variance for continuous variables.

[c] Body mass index (weight (kg)/height (m)^2) was classified as normal (<25), overweight (25–<30), or obese (≥30).

Table 3. Crude and Adjusted Associations of Blood Pressure, Hypertension, and Body Mass Index With Depression in the Dijon Portion of the Three-City Study, Dijon, France, 1999–2010

	Model With Baseline Adjustment[a]		Model With Baseline and Time-Varying Adjustment[b]		Marginal Structural Model	
	RR	95% CI	RR	95% CI	RR	95% CI
Body mass index[c]						
Normal	1	Reference	1	Reference	1	Reference
Overweight	1.04	0.83, 1.32	1.03	0.81, 1.30	1.01	0.79, 1.30
Obese	1.48	1.00, 2.27	1.54	1.02, 2.36	1.60	1.03, 2.51
Hypertension						
No	1	Reference	1	Reference	1	Reference
Yes	1.02	0.79, 1.30	0.97	0.76, 1.22	0.96	0.76, 1.23
Blood pressure[d]						
Low	1.70	1.16, 2.48	1.63	1.23, 2.36	1.65	1.11, 2.44
Normal	1	Reference	1	Reference	1	Reference
High	1.18	0.90, 1.58	1.12	0.84, 1.46	1.14	0.85, 1.51

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

[a] Included baseline measurement of age, sex, educational level, general health status, physical activity, marital status, tobacco use, alcohol consumption, body mass index, blood pressure, hypercholesterolemia, global cognition, antihypertensive treatment, and diabetes.

[b] Results were adjusted for time-fixed covariates (sex, age, educational level, physical activity, and marital status) and time-varying variables (tobacco use, alcohol consumption, body mass index, blood pressure, hypercholesterolemia, antihypertensive treatment, general health, global cognition, and diabetes).

[c] Body mass index (weight (kg)/height (m)^2) was classified as normal (<25), overweight (25–<30), or obese (≥30).

[d] Low blood pressure was defined as systolic blood pressure <120 mm Hg or diastolic blood pressure <75 mm Hg. High blood pressure (hypertension) was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or use of antihypertensive medication. Blood pressure was considered normal otherwise.

close to 1 and a narrower range, as also shown in Web Figure 1.

Stratified analyses were performed by age, sex, and educational level. For obesity and low blood pressure, estimated effects were stronger in men and in subjects with a low educational level, but all interaction-term *P* values were greater than 0.10.

DISCUSSION

In a large cohort of elderly subjects, BMI was associated prospectively with depression risk. Subjects with higher BMI at follow-up had an increased risk of developing depression over a 10-year follow-up period compared with subjects with normal weight, holding baseline values constant. Compared with subjects in the normal blood pressure range, subjects with low blood pressure had an increased risk of depression during follow-up, whereas those with hypertension did not.

Our results for BMI are consistent with previous reports from population-based settings that also showed that higher BMI is a risk factor for depression (26, 27). In a recent longitudinal meta-analysis based on a large sample of subjects aged 11–72 years, the risk of developing depression over time was increased by 55% in subjects who were obese at baseline. Those investigators also reported that the relation between depression and obesity was stronger than the association between overweight and depression, reflecting a dose-response gradient (27). These results were confirmed in 2 other longitudinal studies involving older adults and showing that obesity markers such as BMI, waist circumference, or visceral fat were strong predictors of depressive syndromes (9, 28).

Overall, we found no associations between high blood pressure status over time and the risk of depression, but we observed a relation between low blood pressure and depression, as was reported in previous studies (6, 29). The magnitude and direction of the association between high blood pressure and depression differ widely between studies, and the link between blood pressure and depression remains unclear in the literature. The inconsistent findings can be at least partly explained by the different study designs used, the different questions/hypotheses being investigated, and the inherent challenges of obtaining epidemiologic measurements of intricate and time-varying constructs such as depression and cardiovascular status. Blood pressure measurements may vary according to psychological, physiologic, or environmental factors, especially in the elderly (30).

Previous population-based studies have mostly used cross-sectional designs, and researchers have reported inconsistent associations between high blood pressure or hypertension and depressive syndromes (5, 31–33). Only a few population-based studies have investigated longitudinally the relation between blood pressure and depression,

and most of these studies had baseline data for blood pressure only, along with self-reported data for height and weight (1, 4, 34). In a sample of 964 elderly persons, hypertension was associated with elevated depressive symptoms at 2-year follow-up (1), whereas 2 other studies found no association between hypertension and depression (4, 34). Similarly, there are inconsistent reports of an association between low blood pressure and depressive symptoms, but recent population studies in elderly persons have found higher levels of depressive symptoms in subjects with low blood pressure (5, 6, 18).

Our study had several strengths, including the large sample size and the population-based sampling. In addition, the longitudinal, prospective design of the 3C-Dijon Study and the repeated measurement of BMI, blood pressure, and depression allowed us to explore the risk factors for depression over a period of 10 years. Finally, we used MSMs to improve causal interpretation of the estimates in the presence of time-varying confounding. To date, no other longitudinal studies have used this method to assess the relation between time-varying modifiable risk factors and the incidence of depression. The results we obtained with MSMs were quite similar to those obtained with traditional models—a comparison that is possible because of our use of a collapsible effect measure so that the marginal and conditional causal effects would have identical interpretations (25). This suggests that there was not a substantial amount of time-varying confounding in our study, but this could not have been known without the use of this model.

Despite the large sample size, the prospective study design, and the robust statistical methods, our study—like all studies on depression and cardiovascular factors—was hampered by the fundamental challenges of measuring time-varying and complex symptoms. Depression is a complex construct that changes with time and that is particularly difficult to measure in epidemiologic studies, wherein the typical instruments used are psychological scales that have some limitations in accuracy as compared with a diagnosis established by a clinician. Nonetheless, our evaluation of depressive symptoms was based on the MINI and the CES-D Scale, two widely documented scales that are commonly used to assess clinically significant depressive symptoms in the elderly (16, 17). We defined depression on the basis of the MINI questionnaire or antidepressant medication use. One could argue that, in some elderly people, antidepressants are prescribed for dementia or cognitive deficits rather than depression, and this could have biased our findings. We performed sensitivity analyses by excluding subjects who were taking antidepressants, and the results pointed in the same direction (data not shown). Another limitation was that 3C-Dijon participants had higher educational and socioeconomic levels and overall were healthier than the general population of the same age. However, the frequency of depression was close to that reported in elderly populations (35). Nonetheless, we cannot exclude the possibility that selection bias might have affected the strength of the association between vascular factors and depression risk. We performed a series of sensitivity analyses (data not shown) such as including subjects with depression at baseline, including those with recurrent depression, excluding incident dementia cases, or adjusting for other potential risk factors (cancer, history of cardiovascular disease risk factors, heart failure, or stroke), and the findings remained unchanged. Finally, causal inference regarding BMI is hampered by ambiguity concerning the mode of intervention, since there are myriad ways of modifying BMI, the impacts of which may be diverse. This ambiguity threatens the validity of the consistency assumption on which causal inference rests (36).

Several biologic mechanisms through which depression could result from elevated BMI have been suggested: Weight gain activates multiple inflammatory pathways, which can play a role in the pathology of depression (37). Another relevant mechanism may be dysregulation of the hypothalamic-pituitary-adrenal axis precipitated by obesity that can lead to the development of depression (38, 39). Finally, obesity is a risk factor for the development of cardiovascular and cerebrovascular disease, which could induce alteration in the brain; depression could then be a direct consequence of brain lesions, particularly through the impact of small-vessel lesions (40). In addition to biologic pathways, psychological factors should be mentioned: Because of the sociocultural environment, a poor self-image in an obese or overweight person could increase psychological distress that can contribute to depression.

Several physiopathologic mechanisms could explain the relation between low blood pressure and depression. Chronic low blood pressure could lead to cerebral hypoperfusion and then to cerebrovascular pathologic changes that could induce psychological disturbances or depression (41). It could also produce chronic somatic symptoms like dizziness and fatigue, leading to depression (42).

Our findings provide some epidemiologic support to better understand risk factors for depression in the elderly. The study of vascular and mood syndromes is becoming a public health priority because both are among the most frequent disorders in Western societies, and their incidence and prevalence are increasing with the worldwide aging of the population. Hence, understanding their associations and etiologic mechanisms is crucially important from a public health perspective. In addition, the availability of longitudinal cohort studies, repeated measurements, and more advanced statistical methods fuels the motivation to understand the depression-cardiovascular association more deeply. Moreover, further study is needed to investigate the benefits of treatment for vascular disease in preventing depression in the elderly.

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