Original Article

When Blue-Collars Feel Blue

Depression and Low Occupational Grade as Synergistic Predictors of Incident Cardiac Events in Middle-Aged Working Individuals

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Background—The association of psychological variables with cardiovascular health might depend on socioeconomic status. We examined the moderating effect of occupational grade on the association between depression and incident cardiac events among middle-aged workers from the GAZEL cohort.

Methods and Results—A total of 10 541 participants (7855 men, mean age: 47.8±3.5 years) free of cardiovascular diseases completed the Center of Epidemiologic Studies Depression scale in 1993. Age, sex, and occupational grade (low, medium, and high) were obtained from company records. Classical cardiovascular risk factors were self-reported. All participants were followed-up for medically certified cardiac events from January 1994 to December 2014. Associations between baseline variables and incident cardiac events were estimated with hazard ratios and 95% confidence intervals computed in Cox regressions. After a median follow-up of 21 years, 592 (5.6%) participants had a cardiac event. There was a significant interaction between depression and occupational grade in both age- and sex-adjusted (P=0.008) and multiadjusted (P=0.009) models. This interaction was mainly explained by an association between depression and incident cardiac events that prevailed among participants of low occupational grade (3.71 versus 1.96 events per 1000 person-years among those depressed versus nondepressed, multiadjusted hazard ratios [95% confidence intervals], 1.99 [1.12–3.48]).

Conclusions—From a research perspective, these results may account for previous conflicting results and constitute an impetus for reanalyzing previous data sets, taking into account the moderating role of socioeconomic status. From a clinical perspective, they urge clinicians and policy makers to consider depressive symptoms and low socioeconomic status as synergistic cardiovascular risk factors. **(*Circ Cardiovasc Qual Outcomes*. 2017;10:e002767. DOI: 10.1161/CIRCOUTCOMES.116.002767.)**

Key Words: cardiovascular diseases ■ coronary disease ■ depression ■ epidemiology ■ risk factors

Major depression and cardiovascular diseases are the leading causes of disability worldwide.[1] In addition, depressed individuals display an increased risk of cardiovascular diseases, especially coronary heart disease (CHD).[2,3] This association has been extensively studied and is not specific to major depression because it is also observed with self-reported depressive symptoms, henceforth referred to as depression.[2] However, it remains debated whether the strength of this association depends on moderating factors, such as socioeconomic status (SES).

Because depression and low SES are associated,[4] SES indicators are typically considered as potentially confounding the association between depression and cardiovascular diseases. Alternatively, depression has been proposed as a potential mediator of social inequalities in cardiovascular health.[5] However, a growing body of evidence suggests that the magnitude of the association between psychological variables and cardiovascular diseases may differ by SES (ie, a moderating factor).[6–11] More specifically, this association may be stronger in individuals of low SES. For instance, in a prospective study by Redmond et al[6] among 24 443 individuals, perceived stress was associated with CHD in participants with low income only. Another prospective study by Lazzarino et al[7] showed that psychological distress and low SES were synergistic predictors

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WHAT IS KNOWN

- Depression and low socioeconomic status are associated with an increased risk of cardiovascular diseases.

WHAT THE STUDY ADDS

- The relationship between depressive symptoms and cardiac events is stronger among individuals of a lower occupational status and mainly explained by coronary heart disease.
- This association is not specifically explained by somatic symptoms of depression.
- There is a need to address social determinants of health to reduce the association between depressive symptoms and coronary heart disease.

of cardiovascular mortality in 66 518 individuals. Studies by our group showed that the association of perceived stress with blood pressure differed according to occupational grade, with a positive association among working participants of low occupational grade and unemployed participants.[9,10] Similarly, job strain may relate to the risk of stroke[11] differently across occupational categories. Occupational grade is a useful proxy for SES because it integrates the educational achievements, the skills required to obtain a job, the long-term associated rewards (including, but not limited to, income), and several job characteristics, such as working conditions and decision-making latitude. Altogether, these findings advocate for stratifying analyses according to SES when examining the links between psychological factors and cardiovascular outcomes. To our knowledge, this critical issue has never been addressed regarding the association of depression with cardiac events.

In this report, we took advantage from the GAZEL cohort to examine the moderating effect of occupational grade on the prospective association between depression and incident cardiac events in a large sample of workers during a median follow-up period of 21 years. Specifically, the main hypothesis of this study was that the association between depressive symptoms and incident cardiac events would be stronger among working participants of low occupational grade.

Methods

Participants

Details of the GAZEL cohort are available elsewhere.[12] The target population consisted of 44 992 employees of the French national gas and electricity company "Electricité de France-Gaz de France": 31 411 men aged 40 to 50 years and 13 511 women aged 35 to 50 years. The study was approved by the French authority for data confidentiality ("Commission Nationale Informatique et Liberté") and by the Ethics Evaluation Committee of the "Institut National de la Santé et de la Recherche Médicale" (Inserm; IRB0000388, FWA00005831). In 1989, 20 625 employees (45.8%; 15 011 men and 5614 women) gave written informed consent to participate. Since 1989, volunteers were followed by annual mailed questionnaires and through administrative databases. Less than 1% of the volunteers were lost to follow-up, and the response rate to annual questionnaires also remained high throughout the follow-up (≈75%).[12]

Center of Epidemiologic Studies Depression Scale

Depressive mood was assessed in 1993 with the Center of Epidemiologic Studies Depression scale (CES-D). This 20-item questionnaire has been designed for use in community studies and has a high internal consistency (α=0.8 to α=0.9 across samples).[13] The CES-D asks participants how often they have experienced specific symptoms during the previous week (eg, I felt depressed, I felt everything I did was an effort, and My sleep was restless). Responses range from 0 (hardly ever) to 3 (most of the time). On the basis of the validation of the French version, a global score ≥17 among men and ≥23 among women was used as our primary indicator of depression.[14] In sensitivity analyses, the CES-D was successively used both as a binary variable based on the more frequently used, yet not validated in French, cutoff of ≥16 among both men and women and as a continuous variable, taking the interval between the 25th and the 75th percentile as unit to provide clinically meaningful hazard ratios (HR). Finally, exploratory analyses were based on tertiles of the 4 CES-D subscales: depressed affect (7 items), positive affects (4 items), somatic complains (7 items), and disturbed interpersonal relationships (2 items).

Assessment of Incident Cardiac Events

All participants were followed-up for cardiac events from January 1, 1994, to December 31, 2014. Diagnoses during the period of employment came from a registry kept by the medical department at "Electricité de France-Gaz de France" and were medically validated.[15] Diagnoses after retirement came from the systematic validation of each self-reported cardiac event. Each annual questionnaire asked participants to report whether or not they had been hospitalized or diagnosed with several conditions, including cardiac events (ie, angina pectoris or myocardial infarction) in the preceding 12 months. All participants who self-reported at least 1 cardiac event during the follow-up were contacted (if they had given consent and were still alive) and asked to transmit all relevant records, including results of diagnostic tests and procedures, and to give consent for a detailed diagnostic investigation with their physician. All events were independently validated by 2 trained investigators on the basis of these data. Among cardiac events, CHD cases were confirmed by radiological reports or when meeting a combination of clinical, biological, and electrocardiographic criteria, as appropriate. Ambiguous cases were re-examined during a dedicated meeting until a consensus was reached. In primary analyses, we considered as cases only participants with validated cardiac events. In sensitivity analyses, we also considered as cases those who died from a CHD. Causes of death were available from January 1, 1994, to December 31, 2014, and coded by the French national cause-of-death registry (CépiDc, Inserm) according to the *International Classification of Diseases*, 9th and 10th revision, codes 410 to 414 and I20 to I25, respectively. In exploratory analyses, we also restricted our main analysis to CHD cases (codes 410–414 and I20–I25), excluding non-CHD cardiac events. Because of statistical power issue, this was done for our main analysis only.

Covariates

Age, sex, and occupational grade (low: blue-collar workers or clerks; medium: first-line supervisors or sales representatives; high: management) were obtained from company human resource records in 1993. Alcohol consumption, smoking, height, weight, physical activity (at least 1 time per week, occasionally, or none), history of parental cardiovascular diseases (ie, the occurrence of CHD before the age of 60 years in the mother or the father), sleep complaints, hypertension, dyslipidemia, and diabetes mellitus were self-reported in 1993. Alcohol consumption, assessed as drinks per week, was categorized as follows: nondrinkers, light drinkers (1–13 for men, 1–6 for women), moderate drinkers (14–27 for men, 7–20 for women), and heavy drinkers (≥28 for men, ≥21 for women). Smoking in the same period was categorized into 3 classes: never-smokers, ex-smokers, and current smokers. Body mass index was categorized as optimal (body mass index <25 kg/m^2), overweight (25 kg/m^2 ≤ body mass index < 30 kg/m^2), or obese (body mass index ≥30 kg/m^2).

Statistical Analyses

All statistical analyses were computed with the statistical discovery software JMP 12 and the statistical analysis system 9.4 (SAS, Cary, NC). *P* values are 2-sided and were considered significant when <0.05. Associations between depression (exposure), as well as covariates (potential confounders), and incident cardiac events (outcome) were estimated with HR and 95% confidence intervals (CI) using Cox regressions. The follow-up ran from January 1, 1994, to the date of the first validated cardiac event or the date of the last follow-up questionnaire, whichever occurred first. Covariates were a priori selected on the basis of their established association with cardiovascular risk. According to our main hypothesis, analyses stratified according to the occupational grade (moderating factor or effect modifier) were a priori planned, and we examined whether the interaction between depression and occupational grade was significant. This was done by adding the interaction term to the model, together with the 2 main effects. The proportionality of hazards was verified by stratified Kaplan-Meier curves, which showed graphically (curves roughly parallel after log(-log(survival)) versus log(time) transformation) that the assumption holds when testing depression in the low occupational grade where the main results were observed.

Results

Study Population

Among the 20 488 GAZEL volunteers still alive in 1993, 14 893 (72.2%) completed the CES-D in 1993. Compared with those who did not, they were older, more likely to be men, to have a higher occupational grade, to be less physically active, and to report hypertension, dyslipidemia, diabetes mellitus, and sleep complaints (Table I in the Data Supplement).

Among the volunteers who completed the CES-D in 1993, 332 (2.2%) were not included in this study because they had a first cardiac event before January 1, 1994, (N=112) or an undetermined status at the end of follow-up, despite a self-reported cardiac event (N=220) owing to: (a) a lack of written consent to participate in the diagnosis validation survey (N=34), (b) failure to contact the volunteer and his or her physician (N=60), (c) refusal to respond to the survey when contacted (N=10), or (d) ongoing validation at the time of the study (N=116). Finally, 4020 volunteers were excluded because of at least 1 missing covariate. Compared with the volunteers excluded for missing data, the selected 10 541 participants were older, more likely to be men, less depressed, to have a higher occupational grade, to report dyslipidemia and sleep complaints, and less likely to be nondrinkers or heavy drinkers, smokers, and obese (Table II in the Data Supplement).

Tables 1 and 2 display the characteristics of the 10 541 participants included in the study according to depressive symptoms status and occupational grade, respectively. Depression was associated with female sex, lower occupational status, alcohol abstinence or heavy drinking, smoking, less physical activity, hypertension, dyslipidemia, and sleep complaints (Table 1). Lower occupational grade was associated with depression, female sex, lower age, more frequent history of parental cardiovascular diseases, alcohol abstinence or heavy drinking, being a nonsmoking rather than an ex-smoker, less physical activity, and more frequent obesity, hypertension, diabetes mellitus, and sleep complaints (Table 2).

Table 1. Characteristics of the Participants According to Depression Status

	Without Depression (N=8173)		With Depression* (N=2368)		*P*
Continuous variables					
Age	47.8	3.5	47.8	3.5	0.88
CES-D	8.8	4.9	25.5	7.2	<0.0001
Discrete variables					
Sex					
Women	2039	25.0	647	27.3	0.02
Men	6134	75.0	1721	72.7	
Occupational grade					
Low	876	10.7	363	15.3	<0.0001
Medium	4484	54.9	1370	57.9	
High	2813	34.4	635	26.8	
History of parental CVD					
No	7207	88.2	2067	87.3	0.24
Yes	966	11.8	301	12.7	
Alcohol consumption					
Nondrinkers	928	11.3	322	13.6	0.0009
Light drinkers†	4304	52.7	1242	52.5	
Moderate drinkers‡	1932	23.6	488	20.6	
Heavy drinkers§	1009	12.4	316	13.3	
Smoking status					
Never smokers	3635	44.5	996	42.1	0.03
Ex-smokers	3050	37.3	890	37.6	
Smokers	1488	18.2	482	20.3	
Physical activity					
No	2416	29.6	876	37.0	<0.0001
Yes	5757	70.4	1492	63.0	
Body mass index, kg/m^2					
<25	4391	53.7	1275	53.8	0.22
25–30	3312	40.5	935	39.5	
>30	470	5.8	158	6.7	
Hypertension					
No	7451	91.2	2100	88.7	0.0003
Yes	722	8.8	268	11.3	
Dyslipidemia					
No	6928	84.8	1949	82.3	0.004
Yes	1245	15.2	419	17.7	
Diabetes mellitus					
No	8056	98.6	2326	98.2	0.24
Yes	117	1.4	42	1.8	

(*Continued*)

Table 1. Continued

	Without Depression (N=8173)		With Depression* (N=2368)		*P*
Sleep complaints					
No	6507	79.6	1289	54.4	<0.0001
Yes	1666	20.4	1079	45.6	

ANOVA and χ^2 tests (or Fisher exact test when necessary) were used for continuous and discrete variables, respectively. Continuous variables are expressed as mean and SD and discrete variables as N and percentage. CES-D indicates Center of Epidemiologic Studies Depression scale; and CVD, cardiovascular disease.

*CES-D score ≥17 for men or ≥23 for women.

†Men (women) reporting 1 to 13 (1–6) drinks per week.

‡Men (women) reporting 14 to 27 (7–20) drinks per week.

§Men (women) reporting at least 28 (14) drinks per week.

Incident Cardiac Events

During the follow-up period (mean±SD, 19.2±4.1 years; median, 21 years), 592 (5.6%) participants had a cardiac event, corresponding to 2.92 events per 1000 person-years. Among these participants, the mean duration of follow-up before the first cardiac events was 11.3±6.3 years (median, 12 years). Most of these cardiac events were CHD cases (N=475), corresponding to 2.36 events per 1000 person-years.

Associations between each variable in 1993 and cardiac events incidence are displayed in Table 3. These associations were significant for each traditional cardiovascular risk factor in age- and sex-adjusted analyses. In contrast, neither depression nor occupational grade was associated with incident cardiac events in the whole population. However, as hypothesized, there was a significant interaction between depression and occupational grade in both age- and sex-adjusted (*P*=0.008) and multiadjusted (*P*=0.009) models. Owing to the small number of cases among women (N=24), interactions with sex were not tested.

Subsequent analyses were stratified according to occupational grade as a priori planned. Associations between depression and incident cardiac events in each category of occupational grade are displayed in Table 4. Despite the increasing number of estimated parameters, the Akaike's information criteria was roughly similar for both age- and sex-adjusted and multiadjusted models, whatever the occupational category. As hypothesized, the association was strong and significant among participants of low occupational grade in both age- and sex-adjusted (HR [95% CI], 1.95 [1.15–3.28]) and multiadjusted (HR [95% CI], 1.99 [1.12–3.48]) models (25 events/363 depressed participants versus 33 events/876 nondepressed participants, corresponding to 3.71 versus 1.96 events per 1000 person-years among those depressed versus nondepressed). In contrast, there was no association in the medium category (70 events/1370 depressed participants versus 220 events/4484 nondepressed participants), and there was even some indication of an unexpected, negative association among participants of high occupational grade (35 events/635 depressed participants versus 209 events/2813 nondepressed participants) in the multiadjusted model (HR [95% CI], 0.68 [0.46–0.98]).

Table 2. Characteristics of the Participants According to Occupational Grade

	Low (N=1239)		Medium (N=5854)		High (N=3448)		*P*
Continuous variables							
Age	47.0	3.8	47.7	3.5	48.4	3.2	<0.0001
CES-D	15.0	10.2	13.0	9.0	10.9	7.8	<0.0001
Discrete variables							
Sex							
Women	499	40.3	1855	31.7	332	9.6	<0.0001
Men	740	59.7	3999	68.3	3116	90.4	
History of parental CVD							
No	1064	85.9	5140	87.8	3070	89.0	0.01
Yes	175	14.1	714	12.2	378	11.0	
Alcohol consumption							
Nondrinkers	214	17.3	773	13.2	263	7.6	<0.0001
Light drinkers*	608	49.0	3038	51.9	1900	55.1	
Moderate drinkers†	255	20.6	1308	22.3	857	24.9	
Heavy drinkers‡	162	13.1	735	12.6	428	12.4	
Smoking status							
Never smokers	605	48.8	2637	45.1	1389	40.3	<0.0001
Ex-smokers	393	31.7	2120	36.2	1427	41.4	
Smokers	241	19.5	1097	18.7	632	18.3	
Physical activity							
No	477	38.5	1951	33.3	864	25.1	<0.0001
Yes	762	61.5	3903	66.7	2584	74.9	
Body mass index, kg/m^2							
<25	690	55.7	3194	54.5	1782	51.7	0.0002
25–30	452	36.5	2323	39.7	1472	42.7	
>30	97	7.8	337	5.8	194	5.6	
Hypertension							
No	1105	89.2	5290	90.4	3156	91.5	0.03
Yes	134	10.8	564	9.6	292	8.5	
Dyslipidemia							
No	1057	85.3	4943	84.4	2877	83.4	0.23
Yes	182	14.7	911	15.6	571	16.6	
Diabetes mellitus							
No	1207	97.4	5774	98.6	3401	98.6	0.01
Yes	32	2.6	80	1.4	47	1.4	

(*Continued*)

Table 2. Continued

	Low (N=1239)		Medium (N=5854)		High (N=3448)		*P*
Sleep complaints							
No	890	71.8	4251	72.6	2655	77.0	<0.0001
Yes	349	28.2	1603	27.4	793	23.0	

ANOVA and χ^2 tests (or Fisher exact test when necessary) were used for continuous and discrete variables, respectively. Continuous variables are expressed as mean and SD and discrete variables as N and percentage. CES-D indicates Center of Epidemiologic Studies Depression scale; and CVD, cardiovascular disease.

*Men (women) reporting 1 to 13 (1–6) drinks per week.

†Men (women) reporting 14 to 27 (7–20) drinks per week.

‡Men (women) reporting at least 28 (14) drinks per week.

Sensitivity Analyses

Sensitivity analyses based on the more frequently used, yet not validated in French, cutoff of ≥16 or the CES-D score as a continuous variable also yielded a significantly positive association between depression and cardiac events among participants of low occupational grade only, whereas the negative association among those of high occupational grade was no longer significant (Table 4).

When excluding the 1130 participants (10.7%) whose occupational grade has changed during the follow-up, the interaction between depression and occupational grade remained significant in the multiadjusted model (*P*=0.005), with a positive, yet only marginally significant because of reduced statistical power, association among participants of low occupational grade (multiadjusted HR [95% CI], 1.83 [0.99–3.31]), no association in the medium category (multiadjusted HR [95% CI], 1.02 [0.76–1.35]), and a negative association among participants of high occupational grade (multiadjusted HR [95% CI], 0.67 [0.45–0.96]).

Overall, the all-cause mortality rate over the follow-up period was 2.62, 2.97, and 3.20 events per 1000 person-years among participants of high, medium, and low occupation grade, respectively. When adding to nonfatal cardiac events those who died from a CHD (ie, a total of 3.31 events per 1000 person-years), the interaction between depression and occupational grade remained significant (*P*=0.02 in multiadjusted model) with a significantly positive association between depression and both fatal and nonfatal cardiac events among participants of low occupation grade (multiadjusted HR [95% CI], 1.98 [1.16–3.35]; *P*=0.01), whereas the negative association among those of high occupational grade was no longer significant (multiadjusted HR [95% CI], 0.81 [0.57–1.13]; *P*=0.22).

Exploratory Analyses

In addition to the analyses based on the CES-D score as a continuous variable, analyses based on CES-D tertiles provided some evidence for a dose-response relationship between depression and incident cardiac events among participants of low occupation grade (HR [95% CI] for the second and third tertiles versus the first tertile: 1.39 [0.67–3.06] and 2.22 [1.09–4.82]; *P* for trend=0.08).

Exploratory analyses based on CES-D subscore tertiles explored whether the association between depression and incident cardiac events was explained by specific depressive symptoms. Among participants of low occupational status, incident cardiac events seem to be associated with depressed affect and somatic complaints to a similar extent (Table III in the Data Supplement) but not with positive affect or interpersonal relationships. The interaction with occupational grade was significant in both age- and sex-adjusted and multiadjusted models for depressed affect (*P*=0.02 and *P*=0.03, respectively) but not for other depressive symptoms.

Taking into account a second measure of CES-D in 1996 to compare the participants depressed in both 1993 and 1996 (N=1189) versus those not depressed in both 1993 and 1996 (N=6117) also yielded similar results. In multiadjusted model, depression remained positively associated with cardiac events among participants of low occupational grade (HR [95% CI], 2.34 [1.08–4.89]), whereas there was no association among those of medium occupational grade (HR [95% CI], 0.97 [0.66–1.39]) and even a nonsignificant trend for a negative association among those of high occupational grade (HR [95% CI], 0.60 [0.34–1.00]; *P* for depression×occupational grade interaction=0.01).

Finally, when excluding non-CHD cardiac events, depression remained positively associated with CHD cases among participants of low occupational grade (3.27 versus 1.50 events per 1000 person-years among those depressed versus nondepressed; HR [95% CI], 2.18 [1.16–4.06]), whereas there was no association among those of medium occupational grade (HR [95% CI], 1.01 [0.74–1.36]), and even a nonsignificant trend for a negative association among those of high occupational grade (HR [95% CI], 0.70 [0.45–1.04]; *P* for depression×occupational grade interaction=0.01).

Discussion

Summary of Main Findings

The present study aimed to explore the moderating effect of occupational grade on the association between depressive symptoms and incident cardiac events. According to our main hypothesis, this association was positive, significant, and robust among individuals of low occupational grade only (ie, clerks and blue-collar workers). The magnitude of this association among these individuals was comparable or even higher than that observed for traditional cardiovascular risk factors in the whole population, including smoking status, hypertension, or diabetes mellitus. Further adjustment for all covariates did not alter our results, suggesting that these traditional cardiovascular risk factors at baseline had no substantial mediating or confounding role in the association between depressive symptoms and cardiac events among individuals of low occupational grade. This association was not specifically explained by somatic symptoms of depression and was mainly explained by CHD cases.

Strengths and Limitations

To our knowledge, this is the first study to show that the association between depression and incident CHD might depend on occupational grade and is substantial only in individuals of low occupational grade. Strengths of the study include the prospective design, the long duration of follow-up, the large sample size allowing subsample analyses, the use of validated

Table 3. Association Between Each Variable and Cardiac Events

	No. Cases	Age- and Sex-Adjusted Associations			Multiadjusted Associations		
		HR	95% CI	*P*	HR	95% CI	*P*
Age, y							
39–45	195	1.00	…	…	1.00	…	…
46–49	197	1.63	1.29–2.07	<0.0001	1.57	1.24–2.00	0.0001
50–54	200	1.82	1.45–2.30	<0.0001	1.68	1.33–2.14	<0.0001
Sex							
Women	24	1.00	…	…	1.00	…	…
Men	568	7.15	4.85–11.1	<0.0001	5.93	3.95–9.31	<0.0001
Depression*							
No	462	1.00	…	…	1.00	…	…
Yes	130	1.01	0.83–1.22	0.94	1.06	0.84–1.34	0.62
Occupational grade							
Low	58	1.00	…	…	1.00	…	…
Medium	290	0.90	0.68–1.20	0.45	0.89	0.67–1.20	0.44
High	244	0.97	0.74–1.31	0.86	0.89	0.65–1.23	0.47
History of parental CVD							
No	467	1.00	…	…	1.00	…	…
Yes	125	2.12	1.73–2.57	<0.0001	2.00	1.64–2.44	<0.0001
Alcohol consumption							
Nondrinkers	65	1.00	…	…	1.00	…	…
Light drinkers†	323	0.80	0.62–1.06	0.12	0.82	0.63–1.07	0.15
Moderate drinkers‡	121	0.65	0.48–0.88	0.006	0.64	0.47–0.87	0.004
Heavy drinkers§	83	0.74	0.53–1.03	0.07	0.64	0.46–0.89	0.008
Smoking status							
Never smokers	169	1.00	…	…	1.00	…	…
Ex-smokers	277	1.47	1.21–1.79	<0.0001	1.38	1.13–1.68	0.0013
Smokers	146	1.78	1.43–2.23	<0.0001	1.83	1.46–2.29	<0.0001
Physical activity							
No	199	1.00	…	…	1.00	…	…
Yes	393	0.81	0.68–0.96	0.02	0.91	0.77–1.09	0.30
Body mass index, kg/m^2							
<25	224	1.00	…	…	1.00	…	…
25–30	306	1.35	1.13–1.61	0.0007	1.22	1.03–1.46	0.03
>30	62	2.08	1.55–2.73	<0.0001	1.56	1.16–2.09	0.003
Hypertension							
No	495	1.00	…	…	1.00	…	…
Yes	97	1.89	1.51–2.34	<0.0001	1.59	1.27–2.00	<0.0001
Dyslipidemia							
No	423	1.00	…	…	1.00	…	…
Yes	169	1.85	1.54–2.20	<0.0001	1.66	1.38–1.99	<0.0001
Diabetes mellitus							
No	570	1.00	…	…	1.00	…	…
Yes	22	2.29	1.45–3.42	0.0007	1.72	1.08–2.65	0.015

(*Continued*)

Table 3. Continued

	No. Cases	Age- and Sex-Adjusted Associations			Multiadjusted Associations		
		HR	95% CI	*P*	HR	95% CI	*P*
Sleep complaints							
No	459	1.00	…	…	1.00	…	…
Yes	133	0.95	0.78–1.15	0.64	0.92	0.76–1.13	0.44

Hazard ratios (HRs) and 95% confidence intervals (CIs) were computed with Cox regression models adjusted for age and sex for each variable separately and then multiadjusted for all the covariates shown in the table, including the interaction between depression and occupational grade (*P*=0.009). CES-D indicates Center of Epidemiologic Studies Depression scale; and CVD, cardiovascular disease.

*CES-D score ≥17 for men or ≥23 for women.

†Men (women) reporting 1 to 13 (1–6) drinks per week.

‡Men (women) reporting 14 to 27 (7–20) drinks per week.

§Men (women) reporting at least 28 (14) drinks per week.

cardiac events as outcome rather that self-reported cardiac events or cardiovascular mortality, and our ability to adjust for a broad range of potential confounders.

Some limitations should nevertheless be acknowledged. First, owing to the observational design of this study, no conclusion about causality between depression and cardiac events can be drawn. In addition, some potential confounding or mediating factors were not measured, such as diet, ethnicity, or antidepressant drugs use. Second, cardiovascular risk factors were self-reported. However, most of their associations with cardiac events in the present study were remarkably consistent with the literature. Third, although cardiac events were thoroughly ascertained and validated, thus making false positives unlikely, there may have been false negatives. Because individuals of low occupational status display higher rate of nonresponse,[16] the differences across occupational categories might actually be even stronger. Likewise, because all-cause mortality was higher among individuals of low occupational status, competing risks might also have reduced the strength of the interaction. However, data were censored at the date of the last follow-up questionnaire so that nonresponse, whatever the underlying causes, is unlikely to influence much of our results. Furthermore, sensitivity analyses considering both fatal and nonfatal cardiac events yielded similar results. Fourth, listwise deletion decreased statistical power as well. Because participants were less depressed and had a higher occupational grade than nonparticipants, we might have underestimated the strength of the association of depression with cardiac events among participants of low occupational grade. Fifth, multiadjusted models might have been biased to some extent by the relatively small number of cases among participants of low occupation grade. However, age- and sex-adjusted and multiadjusted models yielded similar results (Table 4), suggesting that our results were not much biased. Indeed, simulation studies suggest that such biases can be within acceptable levels even when there is <10 events per predictor variable, especially for sensitivity analyses.[17] Sixth, adjustment for risk factors measured in 1993 makes confounding effects unlikely

Table 4. Associations Between Depression and Cardiac Events According to Occupational Grade

	Low (N=58 Cardiac Events)			Medium (N=290 Cardiac Events)			High (N=244 Cardiac Events)		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Sex-specific thresholds*									
Adjusted for age and sex	1.95	1.15–3.28	0.01	1.06	0.80–1.38	0.69	0.72	0.50–1.02	0.07
Adjusted for all the variables	1.99	1.12–3.48	0.02	0.99	0.74–1.30	0.95	0.68	0.46–0.98	0.04
≥16 threshold									
Adjusted for age and sex	1.76	1.04–2.97	0.03	1.14	0.88–1.46	0.31	0.86	0.62–1.17	0.34
Adjusted for all the variables	1.82	1.04–3.16	0.04	1.07	0.83–1.39	0.59	0.83	0.59–1.15	0.27
CES-D continuous score†									
Adjusted for age and sex	1.39	1.04–1.81	0.02	1.14	0.98–1.32	0.08	0.90	0.74–1.08	0.28
Adjusted for all the variables	1.39	1.03–1.87	0.03	1.09	0.93–1.27	0.30	0.88	0.72–1.07	0.19

Hazard ratios (HRs) and 95% confidence intervals (CIs) were computed with Cox regression models adjusted for age and sex and multiadjusted for age, sex, parental cardiovascular disease, alcohol consumption, smoking status, physical activity, body mass index, hypertension, dyslipidemia, diabetes and sleep complaints.

CES-D indicates Center of Epidemiologic Studies Depression scale; N, number of events/number of participants.

*≥17 for men; ≥23 for women.

†Values normalized to the interval between the 25th and the 75th percentile.

but cannot rule out potential mediating effects of subsequent changes. However, such mediating effects would not undermine the clinical relevance of the association between depression and CHD and would rather emphasize potential mechanisms. Finally, although the GAZEL cohort relies on a large sample and covers all regions of France, various areas ranging from small villages to large cities and a wide range of SES and occupations, it is not representative of the general population because it includes only middle-aged working individuals.[12] Previous studies found that GAZEL participants were generally in better health than nonparticipants so that it is likely that the strength of associations reported in this cohort is underestimated. Future studies would benefit from reproducing our study in the general population to help clarify whether the present results are specific to low occupational grade or may more broadly apply to individual facing social adversity.

Explanatory Hypotheses

Several mechanisms may account for the association of depression with CHD.[18] Depression has been associated with hazardous health behaviors, such as smoking,[19] physical inactivity, or poor diet.[20] More direct, biological pathways, including imbalanced sympathetic-parasympathetic activity or chronic low-grade inflammation, are also hypothesized although evidence for their actual mediating role is weak.[21,22] Finally, subclinical vascular brain damages leading to poor emotion regulation might partially confound the association.[23] Likewise, several mechanisms may explain social inequalities in cardiovascular health.[5,24] The present study, however, clearly shows that the association between depression and CHD depends on occupational grade. Therefore, specific explanatory hypotheses are warranted to explain this interaction.

Negative associations between psychological risk factors and cardiovascular diseases or risk factors among individuals of high SES have recently been published[8,9,25] and are thus worthy of investigation in the future. Individuals of higher SES might deal with their depressive symptoms in a way that promote cardiovascular health (eg, monitoring their lifestyle more regularly)[8] and be more prompt to consult a mental health professional. They may also display higher levels of emotional awareness,[26] a feature that has been associated with lower cardiovascular mortality.[27] The CES-D score results from both depressive symptoms and the ability to be aware of them. A high CES-D score may thus partially capture high levels of emotional awareness to a greater extent in individuals of high occupational grade than in those of low occupational grade.

However, because the negative association between depression and cardiac events in individuals of high occupational grade was neither expected nor robust in sensitivity analyses, we will mainly focus on the robust, positive association among those of low occupational grade. One may explain this result by a longer exposure to depressive symptoms among individuals of low occupational grade.[28] However, differences between occupational categories remain similar when considering repeated measures of depressive symptoms at 2 points over a 3-year interval, making this hypothesis unlikely.

Regarding behavioral mechanisms, one may argue that participants of low occupational grade might have been less likely to deal with depressive symptoms with adaptive health behaviors (eg, physical activity) and more with detrimental ones (eg, poor diet). However, the magnitude of the association between depressive symptoms and cardiac events remains similar in age and sex model and multiadjusted model. Even if some unmeasured (or crudely measured) behaviors, such as diet or physical activity, might partially mediate the association, at least a part of this mediating effect would have been captured when adjusted with components of the metabolic syndrome, such as diabetes mellitus, obesity, or hypertension. Overall, the behavioral and biomedical risk factors that were measured in the present study did not explain the association, and other hypotheses should be considered.

Regarding more direct, biological mechanisms, some unmeasured biological pathways may be of particular relevance among individuals of low SES. For instance, individuals holding more dominant social positions exhibit lower cortisol levels, a relationship explained by their greater sense of control.[29] Sense of control is typically lower in depressed individuals and has been shown to partially explain social inequalities in CHD incidence.[30] Should the association between depression and CHD be at least partially mediated by increased cortisol levels, high occupational grade might buffer this association. Furthermore, perceived social rank, presumably lower among individuals of low occupational grade, is associated with anatomic and functional changes in brain regions linking depressive symptoms with the sympathetic nervous system and the hypothalamic-pituitary adrenal axis.[24] Such changes might moderate the association of depressive symptoms with detrimental biological outputs.

Conclusions and Future Directions

The current study adds to accumulating evidence that depression screening and management should become a part of standard of care in both cardiovascular medicine and primary care. Furthermore, it suggests that the association between depressive symptoms and CHD depends on occupational grade. In other words, depressive symptoms and low SES should be considered as synergistic rather than merely additive cardiovascular risk factors. From a research perspective, this paradigm shift may account for previous conflicting results and constitute an impetus for reanalyzing previous data sets, taking into account the moderating role of SES. It might also be particularly helpful when searching for potential mediating factors that could ultimately be targeted in prevention strategies.[21,22] From a clinical perspective, the present results urge clinicians to consider depressive symptoms as a cardiovascular risk factor on their own when experienced by individuals of low occupational grade. Therefore, in addition to the management of more traditional risk factors, depressive symptoms could represent a specific target for cardiovascular preventive intervention among these individuals in a personalized medicine approach. Depending on the levels of depressive symptoms, both pharmacological and nonpharmacological approaches could be used. First, some nonpharmacological interventions

that may improve cardiovascular health, such as promoting healthy diet or regular physical exercise, may improve mental health as well.[31,32] Second, cognitive and behavioral interventions have been found to prevent depression at work[33] and could be especially proposed to individuals of low occupational grade. These interventions might pay particular attention to the sense of control, with expected positive impact on sympathetic nervous system and hypothalamic-pituitary axis functions. Finally, these individuals might benefit from more thorough cardiovascular investigations when depressed, looking for subclinical markers of cardiovascular diseases.[34] Although treating depression has not been convincingly associated with better outcome in patients with already known CHD,[35] future studies would benefit from examining whether such interventions are more helpful for individuals of lower SES.

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When Blue-Collars Feel Blue: Depression and Low Occupational Grade as Synergistic Predictors of Incident Cardiac Events in Middle-Aged Working Individuals

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Characteristics of the volunteers who completed the CES-D in 1993 (N=14,893) compared to those who did not (N=5595).

	With CES-D completed		Without CES-D completed		
Continuous variables	**Mean**	**SD**	**Mean**	**SD**	***P***
Age	47.8	3.5	47.6	3.5	0.0003
Discrete variables	**N**	**%**	**N**	**%**	***P***
Gender					
Women	3969	26.6	1623	29.0	0.0007
Men	10,924	73.4	3972	71.0	
Occupational grade					
Low	2036	13.7	1272	22.9	<0.0001
Medium	8267	55.8	3198	57.6	
High	4520	30.5	1083	19.5	
History of parental CVD					
No	11,382	87.7	2137	87.9	0.73
Yes	1597	12.3	293	12.1	
Alcohol consumption					
Non-drinkers	1691	12.2	294	13.6	0.27
Light drinkers †	7222	52.1	1099	50.9	
Moderate drinkers ‡	3191	23.0	486	22.5	
Heavy drinkers §	1760	12.7	282	13.0	
Smoking status					
Never-smokers	5888	43.0	898	42.3	0.22
Ex-smokers	5070	37.0	768	36.1	

Smokers	2729	19.9	458	21.6	
Physical activity					
No	4510	32.4	1167	37.1	<0.0001
Yes	9389	67.6	1976	62.9	
Body Mass Index					
< 25 kg/m²	6857	53.4	956	53.3	
25-30 kg/m²	5172	40.3	735	40.9	0.61
> 30 kg/m²	817	6.4	104	5.8	
Hypertension					
No	13,516	90.7	5370	96.0	<0.0001
Yes	1377	9.3	225	4.0	
Dyslipidemia					
No	12,692	85.2	5292	94.6	<0.0001
Yes	2201	14.8	303	5.4	
Diabetes					
No	14,670	98.5	5549	99.2	0.0002
Yes	223	1.5	46	0.8	
Sleep complaints					
No	11212	75.3	5030	89.9	<0.0001
Yes	3681	24.7	565	10.1	

† men (women) reporting 1 to 13 (1 to 6) drinks per week; ‡ men (women) reporting 14 to 27 (7 to 20) drinks per week; § men (women) reporting at least 28 (14) drinks per week.

ANOVA and chi-square tests (or Fisher's exact test when necessary) were used for continuous and discrete variables, respectively.

Supplemental Table 2. Characteristics of the included participants (N=10,541) compared to excluded individuals because of missing covariates (N=4020)

	Without missing covariates		With missing covariates		
Continuous variables	**Mean**	**SD**	**Mean**	**SD**	***P***
Age	47.8	3.5	47.6	3.6	0.002
CES-D	12.6	8.9	14.6	9.9	<0.0001
Discrete variables	**N**	**%**	**N**	**%**	***P***
Gender					
Women	2686	25.5	1252	31.1	<0.0001
Men	7855	74.5	2768	68.9	
Depression *					
No	8173	77.5	2859	71.1	<0.0001
Yes	2368	22.5	1161	28.9	
Occupational grade					
Low	1239	11.8	745	18.9	
Medium	5854	55.5	2225	56.3	<0.0001
High	3448	32.7	981	24.8	
History of parental CVD					
No	9274	88.0	1858	87.3	0.36
Yes	1267	12.0	271	12.7	
Alcohol consumption					
Non-drinkers	1250	11.8	399	13.3	
Light drinkers †	5546	52.6	1507	50.1	0.05
Moderate drinkers ‡	2420	23.0	708	23.6	
Heavy drinkers §	1325	12.6	396	13.2	
Smoking status					

Never-smokers	4631	43.9	1192	42.0	
Ex-smokers	3940	37.4	950	33.4	<0.0001
Smokers	1970	18.7	699	24.6	
Physical activity					
No	3292	31.2	1094	36.0	<0.0001
Yes	7249	68.8	1948	64.0	
Body Mass Index					
< 25 kg/m²	5666	53.7	1073	53.4	
25-30 kg/m²	4247	40.3	783	38.9	0.01
> 30 kg/m²	628	6.0	155	7.7	
Hypertension					
No	9551	90.6	3682	91.6	0.06
Yes	990	9.4	338	8.4	
Dyslipidemia					
No	8877	84.2	3565	88.7	<0.0001
Yes	1664	15.8	455	11.3	
Diabetes					
No	10,382	98.5	3965	98.6	0.53
Yes	159	1.5	55	1.4	
Sleep complaints					
No	7796	74.0	3173	78.9	<0.0001
Yes	2745	26.0	847	21.1	

* CES-D score ≥17 for men or ≥23 for women; † men (women) reporting 1 to 13 (1 to 6) drinks per week; ‡ men (women) reporting 14 to 27 (7 to 20) drinks per week; § men (women) reporting at least 28 (14) drinks per week.

ANOVA and chi-square tests (or Fisher's exact test when necessary) were used for continuous and discrete variables, respectively.

Supplemental Table 3. Associations between specific depressive symptoms and cardiac events according to occupational grade

	Low			Medium			High		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Depressed affect									
Adjusted for age and gender	1.78	1.05-2.99	0.03	0.98	0.75-1.27	0.89	0.74	0.52-1.02	0.06
Adjusted for all the variables	1.74	1.00-3.02	0.05	0.93	0.71-1.21	0.61	0.71	0.50-0.99	0.04
Positive affect									
Adjusted for age and gender	1.40	0.79-2.40	0.24	0.95	0.71-1.26	0.75	0.87	0.61-1.23	0.46
Adjusted for all the variables	1.46	0.80-2.57	0.21	0.91	0.68-1.21	0.53	0.87	0.60-1.23	0.45
Somatic complaints									
Adjusted for age and gender	1.81	1.06-3.05	0.03	1.13	0.86-1.47	0.37	0.95	0.67-1.30	0.74
Adjusted for all the variables	1.71	0.95-3.02	0.07	1.05	0.79-1.38	0.73	0.95	0.67-1.33	0.79
Interpersonal relationships									
Adjusted for age and gender	1.04	0.56-1.83	0.90	1.20	0.90-1.59	0.21	1.22	0.86-1.70	0.26
Adjusted for all the variables	1.05	0.55-1.87	0.88	1.15	0.86-1.52	0.34	1.13	0.78-1.58	0.51

The HR is given for the highest tertile versus the others.

Hazard ratios (HR) and 95% confidence intervals (CI) were computed with Cox regression models adjusted for age and gender and multi-adjusted for age, gender, parental cardiovascular disease, alcohol consumption, smoking status, physical activity, body mass index, hypertension, dyslipidemia, diabetes and sleep complaints.