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Mortality associated with depression as compared with other severe mental disorders: A 20-year follow-up study of the GAZEL cohort.

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ABSTRACT

Individuals with severe mental disorders (SMD) have an increased risk of mortality from somatic diseases. This study examined whether this risk is different in persons with depressive disorders compared to those with other SMD (i.e. schizophrenia and bipolar disorder). In 1989, 20,625 employees of the French national gas and electricity company (15,011 men and 5614 women, aged 35–50) agreed to participate in the GAZEL cohort study. Three diagnosis groups were created based on sick leave spells from 1978 onwards: 1) no SMD, 2) depressive disorders and 3) other SMD. Dates and causes of death were available from January 1, 1990 to December 31, 2010. The association of diagnosis groups with mortality was estimated with hazard ratios (HR) and 95% confidence intervals (CI) computed using Cox regression. During a mean follow-up of 19.8 years, 1544 participants died, including 1343 from a natural cause, of which 258 died from cardiovascular diseases. After adjustment for age, gender, occupational status, alcohol consumption, smoking and body-mass index, participants with a history of sickness absence for SMD had a greater risk of natural mortality (HR: 1.24, CI: 1.08–1.43), cardiovascular mortality (HR: 1.49, CI: 1.08–2.05) and non-cardiovascular natural mortality (HR: 1.19, CI: 1.02–1.39). Compared to depressive disorders, other SMD were associated with an increased risk of natural mortality (HR: 1.94, CI: 1.17–3.22) and cardiovascular mortality (HR: 3.58, CI: 1.53–8.39). Job security and systematic medical follow-up may fall short of preventing premature death among workers with sickness absence due to SMD.

1. Introduction

Compared to the general population, individuals with severe mental disorders (SMD) have a two to three-fold higher mortality rate and a lower life expectancy of at least 10 years (Dembling et al., 1999; Hannerz et al., 2001; Colton and Manderscheid, 2006; Chang et al., 2011). Contrary to lay beliefs, suicide accounts for only a small part of this increased premature mortality. Indeed, accumulating evidence suggests that patients with depressive disorders and other SMD (i.e. schizophrenia, schizoaffective disorder and bipolar disorder) have an increased risk of mortality from somatic diseases, henceforth referred to as natural mortality. Regarding schizophrenia, a meta-analysis of 37 studies conducted in 25 countries found a median standardized mortality ratio of 2.41 for natural mortality (Saha et al., 2007) with a trend for an increase between the 1970s and the mid-1990s. Although cardiovascular mortality might account for most of this increased risk among patients with schizophrenia, schizoaffective disorder and bipolar disorder (Osborn et al., 2007; Roshanaei-Moghaddam and Katon, 2009), several studies found an increased risk of death from other causes such as respiratory diseases and cancer (Hansen et al., 2001; Joukamaa et al., 2001; Tran et al., 2009). Regarding depressive disorders, both clinical and subclinical depression have been associated with an increased risk of all-cause mortality (Cuijpers and Smit, 2002). As for other SMD, this increased risk may mostly result from increased cardiovascular mortality (Nicholson et al., 2006). However, depressive disorders may also relate to increased

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cancer mortality (Lemogne et al., 2012; Pinquart and Duberstein, 2010). Nonetheless, it remains unclear whether depressive disorders are associated with increased mortality to the same extent than other SMD.

Although this issue has implication for both clinical practice and health policy, it has been little explored yet. First, many studies considered either depressive disorders or other SMD only, or merged these diagnoses into a single category (Colton and Manderscheid, 2006; Osborn et al., 2007; Ferrie et al., 2009). Second, although many studies that examined these disorders separately found a smaller excess risk for natural mortality associated with depression than other SMD (Joukamaa et al., 2001; Kilbourne et al., 2009; Laursen et al., 2007 but see also Lawrence et al., 2003), only one study had sufficient statistical power to directly compare these two categories (Laursen et al., 2007). Third, most of these studies, including the later, adjusted their analyses for age and gender only (Hannerz et al., 2001; Hansen et al., 2001; Joukamaa et al., 2001; Colton and Manderscheid, 2006; Laursen et al., 2007, 2009). Fourth, many studies were based on convenience samples of individuals selected through psychiatric hospital discharge registries (Hannerz et al., 2001; Hansen et al., 2001) or mental healthcare provider databases (Lawrence et al., 2003; Colton and Manderscheid, 2006; Kilbourne et al., 2009; Chang et al., 2011). The internal and external validity of these studies is thus threatened by selection biases with an increased likelihood of confounding factors such as disease severity, comorbid somatic condition, poor medical adherence or social isolation (Cuijpers and Smit, 2002; Saha et al., 2007; Roshanaei-Moghaddam and Katon, 2009). Fifth, many studies did not examine specific causes of death, thus failing to separate natural mortality from violent deaths (Chang et al., 2011; Chwastiak et al., 2010; Ferrie et al., 2009; Hannerz et al., 2001).

In addition, only one large cohort study examined natural mortality among people with SMD in France. It only included patients with schizophrenia and showed an excess mortality rate from cancer comparatively to the general population (Tran et al., 2009). Most data about natural mortality in people with SMD have been generated by studies conducted in the US, the UK and Scandinavian countries (Cuijpers and Smit, 2002; Saha et al., 2007; Roshanaei-Moghaddam and Katon, 2009; Pinquart and Duberstein, 2010), where the distribution of health characteristics as well as associated risk factors, the organization of the healthcare system or the prescription of psychotropic medications differ from those observed in France. Finally, to the best of our knowledge, this issue was never addressed in a working population.

The present study took advantage of the large French GAZEL cohort to examine associations between depressive disorders, other SMD and natural mortality, adjusting for age, gender, occupational grade, alcohol consumption, smoking and body-mass index. In this working population, patients with SMD were identified through sickness absence spells. Preliminary findings from the GAZEL cohort suggest that sickness absence for any mental disorder is associated with all-cause mortality (Ferrie et al., 2009) and suicide (Melchior et al., 2010) but these studies did not examine depression and other SMD separately. Here we aimed to compare the risk of natural mortality associated with depressive disorders vs. no SMD, other SMD vs. no SMD and other SMD vs. depressive disorders.

2. Materials and methods

2.1. Participants

Details of the GAZEL cohort study are available elsewhere (Goldberg et al., 2007). The target population consisted of 44,992 employees of the French national gas and electricity company "Electricité de France-Gaz de France" (EDF-GDF): 31,411 men aged 40–50 and 13,511 women aged 35–50. The study protocol 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) agreed to participate in the GAZEL cohort study. Since 1989, participants have been followed by means of an annual mailed questionnaire, as well as through administrative databases. After 20 years of follow-up, the number of subjects lost to follow-up was exceptionally low (i.e. 0.5%) (Zins et al., 2009).

2.2. Sickness absence for mental disorder

All episodes of sickness absence available from 1978 onwards were extracted from the database of the EDF-GDF medical department. These data include the medical cause of absence verified by a company physician and coded using the abridged version of the International Classification of Diseases (ICD), 9th and 10th Revisions. For the present study, three groups were created: 1) "no major mental disorder" group included participants without psychiatric-related sickness absence, 2) "depressive disorder" group included participants who had received a diagnosis of dysthymic disorder (ICD-9: 300.4), depressive episode or recurrent depressive disorder (ICD-10: F32–F33) or mixed anxiety and depressive disorder (ICD-10: F41.2) and 3) "other severe mental disorder" group included participants who had received a diagnosis of psychosis (ICD-9: 290–299), schizophrenia or delusional disorder (ICD-10: F20–F29), manic episode or bipolar disorder (ICD-10: F30–F31).

2.3. Covariates

Age, gender, and occupational grade (blue-collar workers or clerks, first-line supervisors or sales representatives, management or training) were obtained from the employer's human resources files at baseline. Alcohol consumption, smoking, height and weight were self-reported. Alcohol consumption, as drinks per week, was categorized as none, occasional (1–13 for men, 1–6 for women), moderate (14–27 for men, 7–20 for women) or heavy drinkers ($\geq$28 for men, $\geq$21 for women). Smoking was categorized in 5 classes: never-smokers, ex-smokers and current smokers of fewer than 20 pack-years, and ex-smokers and current smokers of more than 20 pack-years. Body-mass index (BMI) was calculated and categorized as $<$18.5, 18.5–24.9, 25–29.9 or $\geq$30 kg/m^2.

2.4. Mortality data

Living status and the date of death were annually obtained for all participants directly from EDF-GDF as it pays out retirement benefits. Causes of death were available from baseline (i.e. January 1, 1990) to December 31, 2010 and were coded by the French National Cause-of-Death Registry using the International classification of diseases, 9th and 10th Revisions. We considered six categories of mortality outcome: all-cause mortality, suicide (ICD-9: E95; ICD-10: X60–X84), accidents and other external causes of death (ICD-9: E80–E94 and E96–E99; ICD-10: V00–X58 and X92–Y99), natural mortality (i.e. all-cause mortality excluding suicides and accidents), which was further divided into cardiovascular mortality (ICD-9: 389–460; ICD-10: I00–I99) and non-cardiovascular natural mortality.

2.5. Statistical analyses

All statistical analyses were computed with PASW 18.0.0 software (SPSS Inc.). The association of diagnosis groups and covariates with mortality was estimated with hazard ratios (HR) and 95% confidence intervals (CI) computed in Cox regressions. The follow-up ran from January 1, 1990 or the date of the first sickness absence for mental disorder, whichever occurred last, to the date of death or December 31, 2010, whichever occurred first. Discrete covariates were studied as nominal variables. First, we computed models adjusted for age at the beginning of follow-up and gender. Then, these models were further adjusted for occupational grade, alcohol consumption, smoking and BMI at the beginning of follow-up. Missing data for BMI were used as a 5th BMI category, owing to the number of missing data (i.e. 8.1% vs. less than 2.1% for the other covariates). In post hoc analyses, the "depressive disorder" group was further divided into tertiles according to the cumulative duration of sick leave during the 365 days following the first sick leave. The follow-up ran from January 1, 1990 or the last day of sickness absence for mental disorder of the 365-day period following the first sickness absence, whichever occurred last, to the date of death or December 31, 2010, whichever occurred first.

3. Results

Characteristics of study participants are displayed in Table 1. Among the 4212 participants with depressive disorders, 2783 had received a diagnosis of dysthymic disorder (ICD-9: 300.4), 815 depressive episode (ICD-10: F32), 426 recurrent depressive disorder (ICD-10: F33) and 188 mixed anxiety and depressive disorder (ICD-10: F41.2). Among the 124 participants with other SMD, 66 had psychosis (ICD-9: 290–299), 37 bipolar disorder (ICD-10: F30-F31) and 21 schizophrenia or delusional disorder (ICD-10: F20-F29).

During a mean follow-up of 19.8 years, 1544 (7.5%) participants (1302 men, 242 women) died, including 1343 (6.5%) who died from a natural cause. Among these participants, 258 (19.2%) died from a cardiovascular cause. Table 2 displays causes of mortality by diagnosis group. Since there was only one case of death by accident among the participants of the "other SMD" group, this category was not considered apart in further analyses.

All covariates were significantly associated with each of the mortality categories, except age for suicide and alcohol consumption for suicide and cardiovascular mortality (Table 3).

HR and 95% CI according to each diagnosis group and cause of mortality are displayed in Table 4. After adjustment for age, gender, occupational status, alcohol consumption, smoking and body-mass index, the risk of death was significantly higher among participants with depressive disorders and those with other SMD, compared to those without any major mental disorder. There was no significant interaction between gender and diagnosis groups (all $P > 0.10$). Mortality was significantly higher among patients with other SMD than among those with a depressive disorder, except for non-cardiovascular natural mortality.

Table 5 displays the association between psychiatric diagnoses and mortality when further dividing the "depressive disorder" group into tertiles according to the cumulative duration of sick leave during the 365 days following the first sick leave (i.e. first tertile: 1–14 days; second tertile: 14–31 days; third tertile: 32–365 days). After adjustment for age, gender, occupational status, alcohol consumption, smoking and body-mass index, the risk of death remained significantly higher in the "other SMD" group than in the third tertile of the "depressive disorder" group, except for non-cardiovascular natural mortality.

Table 1
Characteristics of the participants.

	No SMD ($N = 16{,}261$)	Depressive disorder ($N = 4212$)	SMD ($N = 124$)
Continuous variables	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age (years)	45.0 (3.4)	43.6 (3.8)	44.0 (3.6)
Categorical variables	***N* (%)**	***N* (%)**	***N* (%)**
Gender			
Male	12,999 (79.9)	1909 (45.3)	79 (63.7)
Female	3262 (20.1)	2303 (54.7)	45 (36.3)
Occupational grade			
Blue-collar workers, clerks	2411 (14.8)	1221 (29.0)	43 (34.7)
First-line supervisors, sales representatives	9335 (57.4)	2606 (61.9)	60 (48.4)
Management	4497 (27.7)	381 (9.0)	20 (16.1)
Missing data	18 (0.1)	4 (0.1)	1 (0.8)
Alcohol consumption			
None	346 (2.1)	376 (8.9)	16 (12.9)
Occasional	11,305 (69.5)	2761 (65.6)	81 (65.3)
Moderate	2683 (16.5)	589 (14.0)	14 (11.3)
Heavy	1600 (9.8)	393 (9.3)	5 (4.0)
Missing data	327 (2.0)	93 (2.2)	8 (6.5)
Smoking status			
Never-smokers	6751 (41.5)	1985 (47.1)	46 (37.1)
Ex-smokers < 20 pack-years	4969 (30.6)	957 (22.7)	33 (26.6)
Ex-smokers ≥ 20 pack-years	1808 (11.1)	419 (10.0)	19 (15.3)
Current smokers < 20 pack-years	1878 (11.5)	557 (13.2)	13 (10.5)
Current smokers ≥ 20 pack-years	731 (4.5)	265 (6.3)	11 (8.9)
Missing data	124 (0.8)	29 (0.7)	2 (1.6)
BMI (kg/m^2)			
<18.5	178 (1.1)	94 (2.2)	2 (1.6)
18.5–24.99	8080 (49.7)	2326 (55.2)	61 (49.2)
25–29.99	5809 (35.7)	1104 (26.2)	32 (25.8)
≥30	815 (5.0)	280 (6.6)	13 (10.5)
Missing data	1379 (8.5)	408 (9.7)	16 (12.9)

BMI: body-mass index; *N*: number of participants; SD: standard deviation; SMD: severe mental disorder.

4. Discussion

The aim of this community-based study was to compare the strength of the association between depression and other SMD with mortality. Adjusting for age, gender, occupational grade, alcohol consumption, smoking and body-mass index, all-cause mortality was significantly higher among participants with a history of sickness absence for any SMD, compared to those without any SMD. However, this risk was significantly stronger in participants with other SMD than in participants with depressive disorders (i.e. 3-fold higher vs. 30% higher), even compared with those having the greatest duration of sickness absence. This was also the case for the risk of death from suicide and cardiovascular disease.

The higher rate of suicide among individuals with other SMD than depressive disorders is consistent with prior evidence (Laursen et al., 2007; Saha et al., 2007). As regards natural mortality, our results are also in line with some previous studies that examined these disorders separately (Joukamaa et al., 2001; Kilbourne et al., 2009; Laursen et al., 2007). To our knowledge, among studies separating natural deaths from unnatural deaths, only one

Table 2
Causes of death by diagnosis groups (from January 1, 1990 to December 31, 2010).

All participants	No SMD ($N = 16,261$)	Depressive disorder ($N = 4212$)	SMD ($N = 124$)
All-cause mortality	1169	351	24
Suicide	39	30	6
Accident	67	22	1
Natural mortality	1033	293	17
Cardiovascular mortality	199	53	6
Non-cardiovascular natural mortality	834	240	11
Participants without missing data[a]	**No SMD ($N = 15,819$)**	**Depressive disorder ($N = 4093$)**	**SMD ($N = 115$)**
All-cause mortality	1121	337	23
Suicide	37	30	6
Accident	64	21	1
Natural mortality	992	280	16
Cardiovascular mortality	188	50	6
Non-cardiovascular natural mortality	804	230	10

[a] Participants with missing BMI were included as missing data for BMI were used as a 5th BMI category.

study found higher natural mortality among individuals once admitted for depression than among those admitted for other SMD, but in women only (Lawrence et al., 2003). Indeed, a large register-based study, which had sufficient statistical power to examine natural mortality across five age categories, found higher risks associated with other SMD than depressive disorders, regardless of age and gender (Laursen et al., 2007). However, these results were not adjusted for occupational status or health behaviors.

Our results are also in line with previous evidence suggesting that cardiovascular mortality might account for most of the increased mortality of patients with other SMD (Osborn et al., 2007; Roshanaei-Moghaddam and Katon, 2009). Several mechanisms may account for the increased risk of cardiovascular mortality among patients with mental disorders. First, mental disorders are associated with an increased prevalence of many cardiovascular risk factors, such as smoking (De Leon and Diaz, 2005; Aubin et al., 2012), poor diet (Le Port et al., 2012), low physical activity (Daumit et al., 2005; Ströhle et al., 2007), obesity (Limosin et al., 2008; Simon et al., 2006) and Type 2 diabetes (Golden et al., 2008; Holt et al., 2005; McIntyre et al., 2005). Antipsychotic drugs may worsen many of these risk factors (Newcomer, 2005). Second, patients with mental disorders may experience lower access to healthcare or benefit from less adequate healthcare, especially regarding cardiovascular risk factors (Nasrallah et al., 2006) and diseases (Druss et al., 2001; Lawrence et al., 2003). Third, mental disorders, especially mood disorders, may share some biological pathways with cardiovascular diseases, such as inflammatory processes (Howren et al., 2009), elevated activation of the hypothalamic-pituitary axis (Stetler and Miller, 2011) or sympathetic nervous system (Kibler and Ma, 2004; Lemogne et al., 2011).

The higher risk of natural mortality observed among participants in the "other SMD" group compared to "depressive disorder"

Table 3
Associations between covariates and mortality (from January 1, 1990 to December 31, 2010).

	All-cause mortality ($N = 1481$)	Suicide ($N = 73$)	Natural mortality ($N = 1288$)	Cardiovascular mortality ($N = 244$)	Non-cardiovascular natural mortality ($N = 1044$)
	HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI]
Age (years)[a]	1.10*** [1.09–1.12]	1.05 [0.98–1.12]	1.11*** [1.09–1.13]	1.11*** [1.06–1.15]	1.11*** [1.09–1.13]
Gender					
Male	1.53*** [1.30–1.78]	2.73** [1.29–5.80]	1.41*** [1.20–1.67]	3.96*** [2.32–6.76]	1.19* [1.00–1.43]
Female	1.00	1.00	1.00	1.00	1.00
Occupational grade					
Blue-collar workers, clerks	1.82*** [1.54–2.14]	2.47* [1.11–5.5]	1.86*** [1.57–2.22]	1.70** [1.14–2.53]	1.90*** [1.57–2.31]
First-line supervisors, sales representatives	1.36*** [1.19–1.55]	2.09* [1.05–4.18]	1.37*** [1.19–1.58]	1.39* [1.00–1.91]	1.37*** [1.16–1.61]
Management	1.00	1.00	1.00	1.00	1.00
Alcohol consumption					
None	1.31* [1.01–1.70]	1.49 [0.53–4.20]	1.33* [1.01–1.76]	1.53 [0.82–2.85]	1.3† [0.96–1.77]
Occasional	1.00	1.00	1.00	1.00	1.00
Moderate	1.04 [0.90–1.19]	0.68 [0.33–1.40]	1.10 [0.95–1.28]	1.07 [0.76–1.49]	1.11 [0.94–1.31]
Heavy	1.39*** [1.21–1.60]	1.21 [0.65–2.27]	1.43*** [1.23–1.66]	1.31 [0.93–1.86]	1.46*** [1.23–1.72]
Smoking status					
Never-smokers	1.00	1.00	1.00	1.00	1.00
Ex-smokers < 20 pack-years	1.34*** [1.16–1.55]	1.07 [0.55–2.08]	1.43*** [1.22–1.67]	1.32 [0.93–1.86]	1.45*** [1.22–1.72]
Ex-smokers ≥ 20 pack-years	1.21† [0.99–1.48]	0.98 [0.39–2.47]	1.26* [1.02–1.56]	1.13 [0.69–1.85]	1.29* [1.02–1.64]
Current smokers < 20 pack-years	2.62*** [2.25–3.06]	2.32* [1.19–4.53]	2.74*** [2.32–3.24]	2.12*** [1.44–3.12]	2.9*** [2.42–3.49]
Current smokers ≥ 20 pack-years	4.14*** [3.47–4.93]	3.35** [1.55–7.26]	4.36*** [3.61–5.26]	3.44*** [2.23–5.33]	4.59*** [3.73–5.66]
BMI (kg/m^2)					
<18.5	2.94*** [2.05–4.23]	10.06*** [3.34–30.30]	2.82*** [1.90–4.17]	1.91 [0.46–7.85]	2.90*** [1.93–4.37]
18.5–24.99	1.00	1.00	1.00	1.00	1.00
25–29.99	0.98 [0.86–1.11]	1.02 [0.56–1.88]	1.01 [0.88–1.15]	1.02 [0.75–1.40]	1.01 [0.87–1.17]
≥30	1.48*** [1.21–1.81]	0.97 [0.29–3.24]	1.56*** [1.26–1.93]	2.79*** [1.85–4.21]	1.31* [1.02–1.68]
Missing BMI	2.21*** [1.91–2.56]	4.87*** [2.71–8.77]	2.03*** [1.73–2.39]	2.91*** [2.04–4.16]	1.86*** [1.55–2.23]

BMI: body-mass index; CI: confidence interval; HR: hazard ratios; *N*: number of events.
†$P < 0.10$; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
HR and 95% CI were computed through Cox regressions.
[a] HR is calculated per unit.

Table 4
Association between psychiatric diagnoses and mortality (from January 1, 1990 to December 31, 2010).

	HR [95% CI]		
	Depressive disorder vs. no SMD	Other SMD vs. no SMD	Other SMD vs. depressive disorder
Adjustment for age and gender			
All-cause mortality	1.67*** [1.47–1.89]	3.51*** [2.34–5.26]	2.11*** [1.39–3.19]
Suicide	4.92*** [2.97–8.15]	27.02*** [11.38–64.13]	5.49*** [2.28–13.23]
Natural mortality	1.55*** [1.35–1.78]	2.81*** [1.74–4.54]	1.81* [1.11–2.95]
Cardiovascular mortality	1.71*** [1.25–2.36]	5.41*** [2.40–12.21]	3.16** [1.36–7.35]
Non-cardiovascular natural mortality	1.52*** [1.3–1.77]	2.22** [1.22–4.02]	1.46 [0.80–2.68]
Adjustment for all covariates[a]			
All-cause mortality	1.31*** [1.15–1.5]	3.01*** [1.99–4.56]	2.29*** [1.5–3.51]
Suicide	3.88*** [2.3–6.54]	23.64*** [9.77–57.2]	6.09*** [2.50–14.86]
Natural mortality	1.21** [1.05–1.39]	2.34*** [1.43–3.85]	1.94* [1.17–3.22]
Cardiovascular mortality	1.37 [0.98–1.92]	4.91*** [2.16–11.17]	3.58** [1.53–8.39]
Non-cardiovascular natural mortality	1.17* [1–1.38]	1.79 [0.95–3.34]	1.52 [0.81–2.87]

CI: confidence interval; HR: hazard ratios; SMD: severe mental disorder.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
HR and 95% CI were computed through Cox regressions.
[a] Covariates were age, gender, occupational grade, alcohol consumption, smoking and body-mass index. Missing data for BMI were used as a 5th BMI category.

group may be explained by a higher prevalence of the above-mentioned mechanisms. For instance, individuals with other SMD are more likely to smoke tobacco (Aubin et al., 2012) and to take antipsychotic drugs. In the present study, they were more likely than those with depressive disorders to have smoked more than 20 pack-years or to be obese. However, adjusting for alcohol consumption, smoking and body-mass index did not attenuate the differences between the two groups. Besides health risk factors, evidence for a reduced access to healthcare is stronger among patients with schizophrenia or bipolar disorder than depressive disorders (Chwastiak et al., 2008). One might have hypothesized that disparities in healthcare would have been lower in the GAZEL cohort for several reasons: at the time when the GAZEL cohort study began, all employees of EDF-GDF had a civil servant-like status and benefited from job security; an extensive human resources system allowed for a complete follow-up of all workers, even after retirement; EDF-GDF had its own Occupational Health and Social Security system with approximately 300 physicians working for the company and responsible for workers' health surveillance. These peculiarities fit with several suggestions that have been put forward to reduce the increased mortality of patients with mental disorders in the general population (Saha et al., 2007; Roshanaei-Moghaddam and Katon, 2009). Our results and the setting in which they have been obtained suggest that this might not be enough.

Strengths of this study are the following. First, it is based on a large sample, uses a prospective design, benefits from a long follow-up, has very low attrition and was adjusted for several covariates. Second, to our knowledge, this is the first study to directly compare depressive disorders and other SMD with regard to natural mortality while adjusting for basic health risk factors. Third, this is also the first study to address this issue in a working population, adjusting for occupational grade. Occupational status is a useful proxy of socioeconomic status as it integrates educational achievements, the skills required to obtain a job, income and several job characteristics such as working conditions or decision-making latitude. Fourth, this study is the first to address this issue in France.

These results should nonetheless be interpreted in the light of some limitations. First, diagnoses were not based on a structured interview but on medically certified sick leave spells. The use of an abridged version of the ICD, 9th revision did not allow us to discriminate between schizophrenia and bipolar disorder prior to 2000. Second, some potential mediating factors, such as hypertension, dyslipidemia or psychotropic drugs intake were not taken into account. Psychotropic drugs intake was not taken into account as it was not reported in a comprehensive and consistent way over the follow-up. Self-reported admissions for depression were not taken into account as they were only available from 2001 onwards. Third, although the GAZEL cohort covers all regions of France, various neighborhoods from small villages to large cities and a wide range of socioeconomic status and occupations, it is not representative of the general population as it included only middle-aged working individuals with job security and excluded certain categories of the population (e.g. agricultural workers, self-employed, foreigners) (Goldberg et al., 2007). SMD observed among GAZEL participants were therefore likely to be mild or late-onset. Furthermore, GAZEL

Table 5
Association between psychiatric diagnoses and mortality taking into account the duration of sickness absence for depression (from January 1, 1990 to December 31, 2010).

Adjustment for all covariates[a]	HR [95% CI]				
	Depressive disorder vs. no SMD			Other SMD vs. no SMD	Other SMD vs. >31 days
	1–14 Days	15–31 Days	>31 Days		
All-cause mortality	1.21 [0.99–1.49]	1.31** [1.07–1.60]	1.43*** [1.17–1.74]	3.03*** [2.00–4.59]	2.12*** [1.36–3.32]
Suicide	3.94*** [1.91–8.11]	2.41 [0.99–5.85]	5.21*** [2.69–10.06]	23.96*** [9.90–57.99]	4.60** [1.74–12.16]
Natural mortality	1.11 [0.89–1.39]	1.31* [1.06–1.62]	1.21 [0.97–1.51]	2.35*** [1.43–3.86]	1.94* [1.14–3.30]
Cardiovascular mortality	1.28 [0.76–2.15]	1.53 [0.93–2.52]	1.31 [0.77–2.23]	4.92*** [2.16–11.20]	3.74** [1.46–9.61]
Non-cardiovascular natural mortality	1.08 [0.84–1.38]	1.26 [1.00–1.60]	1.19 [0.93–1.52]	1.79 [0.96–3.35]	1.51 [0.78–2.92]

CI: confidence interval; HR: hazard ratios; SMD: severe mental disorder.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
HR and 95% CI were computed through Cox regressions.
[a] Covariates were age, gender, occupational grade, alcohol consumption, smoking and body-mass index. Missing data for BMI were used as a 5th BMI category.

cohort participants were in better health than EDF-GDF employees in general (Goldberg et al., 2001). Overall, the associations between mental disorders and mortality that we observed may thus be weaker than in the general population. Fourth, although the association between mental disorders and mortality may vary in relation to age (Laursen et al., 2007) or gender (Lemogne et al., 2012), the limited age range of the population and the relatively small number of events among participants in the "other SMD" group did not allow for subgroup analyses.

Despite these limitations, the present study suggests that the risk of natural death is higher in individuals presenting with other SMD than depressive disorders, even when adjusting for health risk factors or occupational grade. Importantly, these findings imply that job security and systematic medical follow-up may fall short of preventing premature death among workers with sickness absence for mental disorders. Future studies are warranted to elucidate modifiable mechanisms linking other SMD with increased cardiovascular mortality to a greater extent than depressive disorders. These studies should not only focus on positive factors (i.e. those that are more prevalent in individuals with other SMD), such as the role of antipsychotic drugs, but also on negative factors, such as a reduced access to healthcare or quality of healthcare.

Conflict of interest

CL has accepted paid speaking engagements in industry-sponsored symposia from Astra Zeneca, Lundbeck, Pierre Fabre, Pfizer and Servier. FL has accepted paid speaking engagements in industry-sponsored symposia from Bristol Myers Squibb, Janssen, Lilly, Lundbeck and Servier. SMC has accepted paid speaking engagements in industry-sponsored symposia from Astra Zeneca, Lilly, Lundbeck, Merck Sharp Dohme, Pfizer and Servier.

None of the authors have conflict of interests to report.

Contributors

CL, HN and MM designed the study. CL and HN managed the literature searches. MG and MZ collected the data. CL undertook the statistical analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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None of the study sponsors had any role in the study design or in the collection, analysis, and interpretation of data.

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