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Cognitive hostility and suicide.

Running title: Cognitive hostility and suicide.

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Abstract

Objective

To determine whether a specific component of hostility (i.e. cognitive or behavioural) may predict suicide in a prospective design, controlling for depressive mood.

Method

14,752 members of the “GAZ et ELectricité” (GAZEL) cohort (10,819 men, mean age = 49.0 years; 3,933 women, mean age = 46.2 years) completed the Center of Epidemiologic Studies Depression Scale and at least one subscale (i.e. cognitive or behavioural hostility) of the Buss and Durkee Hostility Inventory in 1993. Dates and causes of death were obtained annually.

Results

During a mean follow-up of 15.7 years, 28 participants completed suicide (24 men, 4 women). Suicide was predicted by depressive mood [Relative Index of Inequality (RII) (95% CI) = 8.16 (1.97-33.85)] and cognitive hostility [RII (95% CI) = 10.76 (2.50-46.42)], but not behavioural hostility [RII (95% CI) = 1.37 (0.38-4.97)]. These associations remained significant after adjustment for potential confounders. After mutual adjustment, however, suicide remained significantly associated with cognitive hostility [RII (95% CI) = 8.87 (1.52-51.71)] (RII reduction: 34.6%), but no longer with depressive mood [RII (95% CI) = 2.03 (0.41-10.07)] (RII reduction: 79.1%).

Conclusion

Cognitive rather than behavioural hostility is associated with an increased risk of suicide, independently of baseline depressive mood.

Key words (MeSH)

Epidemiology; Hostility; Personality; Risk; Suicide.

Significant Outcomes

- Cognitive rather than behavioural hostility is associated with an increased risk of suicide.
- Cognitive hostility (i.e. a mixture of resentment and suspicion) may partially explain the association between baseline depressive mood and suicide.
- Further studies should examine the value of addressing cognitive hostility when assessing the risk of suicide associated with depressive mood in a clinical setting.

Limitations

- These results should not be generalized to suicide attempts, as we only recorded completed suicides.
- The “GAZ et ELectricité” cohort is not representative of the general population as it included only middle-aged working individuals.
- The lack of association between behavioural hostility and suicide may have resulted from a lack of statistical power due to a relatively small number of events.

Introduction

Over one million people die by suicide worldwide each year (1). This huge yet preventable public health burden urges to better understand its risk factors. Although depression is one of the most important risk factor for suicide attempts (2), most depressed individuals never attempt suicide. Besides environmental factors, other psychological factors may play a role in attempted and completed suicide. State factors, including some specific depressive dimensions such as pessimism or hopelessness, as well as trait factors, including personality traits such as impulsivity or hostility, have been associated with an increased risk of suicide attempts (3).

Many studies addressed the association between hostility and suicidal behaviour. Some of these studies were based on non-clinical samples or targeted the wider phenomenon of deliberate self-harm and thus yielded only indirect evidence (4, 5). Most of the studies that found direct evidence linking hostility with completed suicide were indeed retrospective, comparing suicide attempters with either healthy subjects (see ref. 6 for a review of these early studies) or non-suicidal psychiatric patients (7-9), or suicide completers with accident victims (10). Some prospective studies were carried out on relatively small sample of depressed patients (11, 12), and then focused on suicide attempts, being underpowered to examine completed suicides. To our knowledge, only one large-scale cohort study found hostility to predict suicide (13). However, completed suicides and suicide attempts were not analyzed separately but merged into one single dependent variable. Additionally, this study considered hostility as being a single psychological construct, leaving unanswered the question of a specific association between suicide and one component of hostility. For instance, hostility scales generally discriminate at least between a behavioural (or overt) and a cognitive (or covert) component. More importantly, this study did not control for depressive

mood, which is associated with both hostility and suicide and thus may account for their statistical association (6).

Aims of the study

The aim of this prospective study was to refine our understanding of the association between hostility and completed suicide. We took advantage of the large-scale French “GAZ et ELectricité” (GAZEL) cohort to determine whether the association between hostility and completed suicide, henceforth referred to as ‘suicide’, is explained by a specific component of hostility (i.e. cognitive or behavioural), controlling for depressive mood.

Material and methods

Participants

Details of the GAZEL cohort study are available elsewhere (14). The target population consisted of 44,992 employees of the French national gas and electricity company (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 5,614 women) gave written informed consent to participate in the GAZEL cohort study. In 1993, questionnaires were mailed to the 20,488 remaining members of the GAZEL cohort to assess depressive mood and hostility (15).

Depressive mood

Depressive mood was assessed with the French version of the 20-item Center of Epidemiologic Studies Depression Scale (CESD), which has been designed for use in community studies with a high internal consistency ranging from $\alpha=0.8$ to $\alpha=0.9$ across samples and a moderate 2-week test-retest reliability ($r=0.51$) (16, 17). The CESD asks participants how often they have experienced specific symptoms during the previous week (e.g. “I felt depressed”, “I felt everything I did was an effort”, “My sleep was restless.”). Responses range from 0 (“hardly ever”) to 3 (“most of the time”). Based on the validation of the French version, a global score ≥ 17 among men and ≥ 23 among women may signal clinically significant depression according to the International Classification of Diseases (ICD) or the Diagnosis and Statistical Manual of Mental Disorders (16).

Hostility

Hostility was assessed with the Buss and Durkee Hostility Inventory (BDHI). The BDHI was previously validated in French on 408 randomly selected participants of the GAZEL cohort study (15). The BDHI is composed of 75 items with 'true-false' answers (18). It has eight subscales, seven of which are designed to measure different components of hostility: assault, verbal aggression, indirect hostility, irritability, negativism, resentment, and suspicion. The sum of these seven sub-scales leads to a 'total hostility' score with a high 3-month test-retest reliability ($r=0.87$) (15). Several factor analyses identified two overarching factors, namely 'behavioural' (i.e. hostile behaviours) and 'cognitive' hostility (i.e. hostile thoughts), formed by the first three sub-scales (i.e. assault, verbal aggression, indirect hostility) and the last two sub-scales (i.e. resentment, suspicion), respectively (19). In the present study, the internal consistency was high for total, behavioural and cognitive hostility scores ($\alpha=0.87$, 0.78 and 0.77, respectively).

Mortality

Vital status and date of death were obtained annually for all participants from the French national gas and electricity company itself as it pays out retirement benefits. Dates and causes of death were available from baseline (i.e. 1 January 1993) to 31 December 2008. Causes of death were coded by the French national cause-of-death registry (CépiDc, INSERM) using the ICD, 10th Revision (20). Completed suicides correspond to the codes X60 to X84.

Covariates

Age, sex, education level (primary, lower secondary, higher secondary or tertiary), and occupation grade (unskilled workers, skilled workers, managers) were obtained from

employer's human resources files at baseline. Marital status (living in couple or not), income (<1600€, 1600–2592€, >2592€), alcohol consumption, and smoking were self-reported in 1993. Alcohol consumption, as drinks per week, was categorized as non-drinkers, occasional drinkers (1–13 for men, 1–6 for women), moderate drinkers (14–27 for men, 7–20 for women) or heavy drinkers (≥ 28 for men, ≥ 21 for women). Smoking in the same period was categorized as non-smoker and as smoker of 1–10, 11–20 or ≥ 21 cigarettes per day.

Statistical analyses

All statistical analyses were computed with SPSS 16.0.1 software (SPSS Inc.).

The association between discrete variables and suicide was estimated with the Hazard Ratio computed in Cox regressions. Discrete variables with more than 2 classes were considered as nominal covariates and, if necessary, classes were merged to obtain at least 4 events (i.e. completed suicide) by class. Coefficients of correlation were computed to examine the relation between depressive mood and hostility scores (i.e. total, cognitive, and behavioural hostility). The association between continuous variables and suicide was modelled using the Relative Index of Inequality (RII) computed through Cox regression (21).

The RII is computed by ranking the predictor on a scale from 0 to 1. For a given predictor, each score covers a range on this scale that is proportional to the number of participants who have that score and is given a value on the scale corresponding to the cumulative midpoint of its range. The RII resembles relative risk in that it compares suicide occurrence at the extremes of the predictor but it is estimated using the data on all scores and is weighted to account for the distribution of the personality scores. An RII of 2 indicates a doubling of the risk of suicide for individuals at the extremes of the predictor.

Results

Participants and events

Among the GAZEL cohort members who completed the CESD, 14,691 (71.7%) completed the BDHI cognitive subscale, 14,752 (72.0%) completed the BDHI behavioural subscale and 14,595 (71.2%) completed the whole BDHI. In the present study, participants were those who completed the CESD and at least one of the BDHI subscales (i.e. total, cognitive, and behavioural hostility). Compared with non participants, participants (10,819 men, mean age = 49.0 years, standard deviation = 2.9 years, and 3,933 women, mean age = 46.2 years, standard deviation = 4.2 years) were more likely to be male, older, educated, and skilled workers, and less likely to complete suicide (all $P < 0.05$).

During a mean follow-up of 15.7 years, 744 (5.0%) participants had died, including 28 (24 men, 4 women) who completed suicide (0.2%) at a mean age of 54.1 years (standard deviation = 5.7 years). Suicide were completed by firearm discharge (N=11), hanging (N=9), self-poisoning (N=4), using a sharp object (N=1), jumping from high place (N=1) or before a moving object (N=1), and by an unspecified mean (N=1).

Education level, occupational grade and self-reported covariates (i.e. income, marital status, alcohol consumption, and smoking) were available for 12,665 (85.9%) participants. These participants were more likely to be male, less depressed, and less hostile (all $P < 0.05$). Because there was no linear association between age and suicide ($F = 0.00$, $P = 0.993$), age was considered as a discrete 3-class nominal covariate (40-46, 47-50, 51-54 years old).

Suicide predictors

Regarding covariates, suicide was predicted by being a non-drinker, being a smoker, and not living in couple (Table 1), but not by age, sex, education level, occupational grade, or

income (all $P > 0.10$). Both depressive mood and hostility scores were associated with sex, education level, occupational grade, income, marital status, and alcohol consumption (all $P < 0.01$). Additionally, depressive mood, total and cognitive hostility were associated with age and income (all $P < 0.05$), and hostility scores were associated with smoking (all $P < 0.01$). Depressive mood was positively correlated with hostility scores (Table 2).

Regarding psychological variables and univariate analyses, suicide was predicted by depressive mood and cognitive hostility, but not by total or behavioural hostility (Table 3). We subsequently examined the associations of depressive mood and hostility scores with suicide before and after adjustment for each other. In a first set of analyses, all models were adjusted for the covariates that were found to be associated with suicide in univariate analyses with a P value < 0.10 (i.e. marital status, alcohol consumption, and smoking). These covariates were available for 13,433 participants, including 27 who completed suicide (Table 4). Before mutual adjustment, suicide was predicted by depressive mood and cognitive hostility (Table 4).

After adjustment for cognitive hostility, depressive mood was no longer significantly associated with suicide, with a RII reduction of 79.1%. In contrast, cognitive hostility remained significantly associated with suicide, with a RII reduction of only 34.6%. Because each covariate was associated at least with depressive mood or cognitive hostility, all covariates were taken into account in a second set of analyses that included 25 cases of suicide among 11,723 participants and yielded similar results (Table 5). Given the small number of events, we did not perform further subgroup-specific analyses, such as sex-specific analyses.

Discussion

To our knowledge, this is the first prospective study to examine the association between suicide and the behavioural and cognitive components of hostility (i.e. hostile behaviour and hostile thoughts), controlling for depressive mood. First, suicide was predicted by cognitive but not behavioural hostility, even after adjustment for depressive mood and the whole set of covariates. Second, although depressive mood predicted suicide in the GAZEL cohort, this association was dramatically reduced, and indeed disappeared, after adjustment for cognitive hostility. The present lack of association between behavioural hostility and completed suicide does not challenge available evidence for the association between behavioural hostility and suicide attempts (3-13), as we only recorded completed suicides. Although the focus on completed suicides is strength of the study, it does not allow discriminating between factors increasing the lethality of suicide attempts and those increasing the risk of suicide attempts, which may differentially relate to cognitive and behavioural hostility. For instance, cognitive hostility may specifically increase the risk of violent suicide attempts, as suggested by the relatively high rate of suicides by firearm discharge in the present study.

The association between suicide and cognitive hostility could be partially confounded by other suicide risk factors, such as genetic factors, psychosocial adversity, or impulsivity (3, 22). However, although some facets of impulsivity may be associated with an increased risk of suicide attempts (23-25), evidence linking impulsivity with lethality of suicide is more conflicting (26, 27), especially outside adolescents and young adults (28, 29). Furthermore, if impulsivity was accounting for the association between hostility and suicide, one should have expected an association with behavioural (i.e. behavioural) rather than cognitive hostility. Note that impulsivity has also been dichotomized in 'cognitive' and 'behavioural' factors, which may both relate to the risk of suicide attempts in the context of major depression (24). However, one should not assume that 'cognitive' impulsivity (i.e. a lack of cognitive control),

is conceptually closer to 'cognitive hostility' (i.e. covert feelings of resentment and suspicion) than behavioural impulsivity. Although both cognitive and behavioural impulsivity may contribute to behavioural hostility, they are less likely to contribute to hostile thoughts per se.

Although the naturalistic design of the present study prevents any causal conclusions to be drawn, causal hypotheses should nonetheless be considered as well. First, cognitive hostility may promote suicidal intent. Several motives may precipitate suicide attempt, and eventually suicide, including not only ending one's own life or escaping from an unbearable state, but also questioning the benevolence of fate, securing the attention of others, or inducing guilt in others. The two last motives suggest that hostile thoughts toward others may play a role in motivating suicide (6). The will to end one's own life is also consistent with early psychodynamic views of suicide as a hostile act directed inwards on the self (30). Second, cognitive hostility may prevent individuals with suicidal intent to seek and find supportive social support and medical help (31), resulting in higher risk to actually commit suicide. Third, cognitive hostility may promote access to firearm, which were used in almost half of the cases here (32).

These results suggest that the association between baseline depressive mood and suicide may be explained by cognitive hostility (33). For instance, cognitive hostility may independently promote depressive mood (e.g. through an increased risk of interpersonal conflicts) and precipitate suicide, thus confounding their association (34). However, assuming no causal association between depressive mood and suicide is difficult to reconcile with available evidence (2). Alternatively, depressive mood may promote hostile thoughts through a pessimistic view of others as being at best unhelpful, if not harmful (35). Such hostile thoughts may in turn increase the risk of suicide (i.e. mediate a causal association between depressive mood and suicide). In the absence of a longitudinal assessment of hostility, these two hypotheses are not distinguishable on a statistical ground (33). Note that both may have

the same implications for clinical practice, leading to consider cognitive hostility when assessing the suicide risk associated with depressive mood. Future studies should examine whether resentment and suspicion are associated with an increased risk of suicide in a clinical depression.

Some limitations should be considered. First, although the GAZEL cohort covers all regions of France, various neighbourhoods 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 includes only middle-aged working individuals with employment security and excluded certain categories of the population (e.g. agricultural workers, self-employed, foreigners) (14). However, the suicide rate observed in participants of the present study (i.e. 12.1 per 100,000 per year) was roughly similar to the suicide rate observed in France in the late 90's (i.e. 14.5 per 100,000 per year) (36). Second, the suicide rate was higher in non-participants. One can reasonably speculate about a somewhat higher level of cognitive hostility in these survey non-responders. Our results may thus have underestimated the strength of the association between cognitive hostility and suicide. Third, the increased risk of suicide among absolute non-drinkers rather than among moderate and heavy drinkers may seem counterintuitive. A possible explanation is that the lack of alcohol dependence assessment may have blurred the relationship between alcohol consumption and suicide, as absolute non-drinkers were more likely to include participants with a past history of alcohol dependence than occasional drinkers (37). Absolute non-drinkers may also include participants presenting with a psychotropic medication or a medical condition preventing alcohol consumption. Fourth, given the relatively small number of events, our study was underpowered to allow subgroup-specific analyses (e.g. sex-specific analyses). The lack of association between behavioural hostility and suicide may have resulted from a lack of statistical power. Using ICD codes to define suicide may have been a bit conservative as

coders may have avoided using such codes when alternative options were available. However, although these limitations could explain negative findings (e.g. regarding behavioural hostility), they are less likely to account for the significant association between cognitive hostility and suicide.

Finally, a common caveat of most prospective studies addressing the links between psychosocial variables and mental health relates to the implicit assumption that these variables are stable over time. Although personality is considered to be stable through adulthood (38), life events may promote high levels of cognitive hostility, as illustrated by the clinical concept of 'posttraumatic embitterment disorder' (39). Depressive mood is even more likely to encompass both state and trait components, which may be differentially linked to suicide risk. It is possible that a more proximal measure of depressive mood would have been more directly related to suicide and less prone to be confounded or mediated by baseline cognitive hostility. Furthermore, the CESD is not a diagnosis tool and overlooks the distinction between minor, major and bipolar depression. A more comprehensive and longitudinal assessment of psychological variables associated with suicide, such as depressive mood, impulsivity or hostility is warranted.

In conclusion, this study suggests that cognitive hostility is associated with an increased risk of suicide over time, independently of baseline depressive mood. Further studies should explore the mechanisms linking cognitive hostility and suicide, as potential prevention strategies should address the processes through which cognitive hostility is associated with suicide, rather than cognitive hostility per se.

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Declaration of Interest

None of the authors have conflicts of interest to report. CL has accepted paid speaking engagements in industry-sponsored symposia from Bristol Myers Squibb. PF has accepted paid speaking engagements in industry-sponsored symposia from Euthérapie and Lundbeck, and received a grant from Servier. FL has accepted paid speaking engagements in industry-sponsored symposia from Bristol Myers Squibb, Euthérapie, Janssen, and Lundbeck. SMC has accepted paid speaking engagements in industry-sponsored symposia from Astra Zeneca, Boehringer Ingelheim, Euthérapie, Lundbeck, and Pfizer. HN, GE, and SB have no industry-related interests to report.

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Table 1. Associations between discrete socio-demographic and behavioural variables and suicide in univariate analyses.

	N events / N participants	Suicide N (%)	No suicide N (%)	Hazard Ratio (95% CI)
Age	28 / 14,752			
Low (40-46 years)		12 (42.9)	4,947 (33.6)	1.65 (0.68-4.04)
Middle (47-50 years)		8 (28.6)	5,487 (37.3)	Reference
High (51-54 years)		8 (28.6)	4,290 (29.1)	1.28 (0.48-3.42)
Sex	28 / 14,752			
Male		24 (85.7)	10,795 (73.3)	2.20 (0.76-6.35)
Female		4 (14.3)	3,929 (26.7)	Reference
Education level	27 / 14,131			
Primary & Lower secondary		19 (70.4)	10,347 (73.4)	Reference
Higher secondary & tertiary		8 (29.6)	3,757 (26.6)	1.15 (0.51-2.64)
Occupational grade	28 / 14,698			
Unskilled & skilled workers		23 (82.1)	10,128 (69.0)	2.07 (0.79-5.44)
Managers		5 (17.9)	4,542 (31.0)	Reference
Income	28 / 14,281			
<1600€		14 (50.0)	5,795 (40.7)	1.84 (0.71-4.78)
1600–2592€		8 (28.6)	3,923 (27.5)	1.54 (0.54-4.45)
>2592€		6 (21.4)	4,535 (31.8)	Reference
Marital status	27 / 13,705			
Single, separated, divorced, widowed		8 (29.6)	1,628 (11.9)	3.15 (1.38-7.18)**
Living in couple		19 (70.4)	12,050 (88.1)	Reference
Alcohol consumption	27 / 13,704			
Non-drinkers		7 (26.0)	1,653 (12.1)	3.04 (1.16-8.00)*
Occasional drinkers		10 (37.0)	7,138 (52.2)	Reference
Moderate & heavy drinkers		10 (37.0)	4,886 (35.7)	1.47 (0.61-3.53)
Smoking	27 / 13,530			
Non-smokers		16 (59.3)	10,815 (80.1)	Reference

Smokers	11 (40.7)	2,688 (19.9)	2.80 (1.30-6.04)**
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* $P \leq 0.05$; ** $P \leq 0.01$; CI: Confidence Interval.

Table 2. Correlations between depressive mood and hostility scores.

	Total hostility	Cognitive hostility	Behavioural hostility
Depressive mood	0.41	0.52	0.15
Total hostility		0.71	0.86
Cognitive hostility			0.33

Note. $P \leq 0.01$ for all coefficients.

Table 3. Associations between psychological variables and suicide in univariate analyses.

	N events / N participants	Suicide Mean (SD)	No suicide Mean (SD)	RII (95% CI)
Depressive mood	28 / 14,752	19.20 (12.60)	13.14 (9.21)	8.16 (1.97-33.85)**
Total hostility	26 / 14,595†	32.70 (9.50)	29.20 (9.84)	3.68 (0.92-14.73)
Cognitive hostility	28 / 14,691	8.32 (3.15)	6.59 (3.54)	10.76 (2.50-46.42)**
Behavioural hostility	28 / 14,752	15.68 (6.63)	14.48 (5.39)	1.37 (0.38-4.97)

** $P \leq 0.01$; † the number of participants who have completed all the BDHI subscales (i.e. a conjunction rather than a total); CI: Confidence Interval; SD: Standard Deviation; RII: Relative Index of Inequality.

Table 4. RII of depressive mood and cognitive hostility in predicting suicide before (models 1 & 2) and after (model 3) mutual adjustment, all models being adjusted for marital status, alcohol consumption, and smoking.

Predictive variables	Model 1	Model 2	Model 3
Depressive mood	5.92 (1.41-24.92)*		2.03 (0.41-10.07)
Cognitive hostility		13.03 (2.75-61.78)**	8.87 (1.52-51.71)*
Marital status			
Single, separated, divorced, widowed	2.29 (0.98-5.34)	2.37 (1.03-5.48)*	2.23 (0.95-5.21)
Living in couple	Reference	Reference	Reference
Alcohol consumption			
Non-drinkers	2.69 (1.02-7.10)*	2.61 (0.99-6.87)	2.56 (0.97-6.75)
Occasional drinkers	Reference	Reference	Reference
Moderate & heavy drinkers	1.34 (0.55-3.24)	1.31 (0.54-3.17)	1.32 (0.55-3.20)
Smoking			
Non-smokers	Reference	Reference	Reference
Smokers	2.68 (1.23-5.84)*	2.59 (1.19-5.63)*	2.59 (1.19-5.64)*

* $P \leq 0.05$; ** $P \leq 0.01$.

Table 5. RII of depressive mood and cognitive hostility in predicting suicide before (models 1 & 2) and after (model 3) mutual adjustment, all models being adjusted for age, sex, education level, occupational grade, income, marital status, alcohol consumption and smoking.

Predictive variables	Model 1	Model 2	Model 3
Depressive mood	7.94 (1.72-36.63)**		2.73 (0.49-15.18)
Cognitive hostility		15.22 (2.84-81.49)**	8.68 (1.30-57.72)*
Age			
Low (40-46 years)	1.64 (0.63-4.24)	1.67 (0.64-4.34)	1.68 (0.65-4.35)
Middle (47-50 years)	Reference	Reference	Reference
High (51-54 years)	1.17 (0.42-3.24)	1.20 (0.43-3.31)	1.19 (0.43-3.29)
Sex			
Male	6.44 (1.76-23.65)**	5.32 (1.46-19.36)*	5.85 (1.59-21.51)**
Female	Reference	Reference	Reference
Education level			
Primary & Lower secondary	Reference	Reference	Reference
Higher secondary & tertiary	2.19 (0.85-5.63)	2.26 (0.88-5.80)	2.25 (0.88-5.78)
Occupational grade			
Unskilled & skilled workers	3.57 (0.99-12.75)	2.94 (0.83-10.43)	3.03 (0.85-10.83)
Managers	Reference	Reference	Reference
Income			
<1600€	0.84 (0.25-2.83)	0.80 (0.24-2.67)	0.79 (0.24-2.65)
1600–2592€	1.26 (0.38-4.16)	1.25 (0.38-4.11)	1.24 (0.38-4.09)
>2592€	Reference	Reference	Reference
Marital status			
Single, separated, divorced, widowed	2.72 (1.07-6.96)*	2.88 (1.14-7.30)*	2.66 (1.04-6.78)*
Living in couple	Reference	Reference	Reference
Alcohol consumption			
Non-drinkers	2.85 (1.00-8.12)*	2.77 (0.97-7.89)	2.73 (0.96-7.78)
Occasional drinkers	Reference	Reference	Reference
Moderate & heavy drinkers	1.30 (0.52-3.24)	1.31 (0.52-3.25)	1.30 (0.52-3.24)
Smoking			
Non-smokers	Reference	Reference	Reference
Smokers	2.62 (1.17-5.85)*	2.60 (1.17-5.79)*	2.59 (1.16-5.76)*

* $P \leq 0.05$; ** $P \leq 0.01$.