Exposure to secondhand smoke and depression and anxiety: A report from two studies in the Netherlands

Mariska Bot [a,*], Jacqueline M. Vink [b], Gonneke Willemsen [b], Johannes H. Smit [a], Jacoline Neuteboom [c], Cornelis Kluft [c], Dorret I. Boomsma [b], Brenda W.J.H. Penninx [a]

[a] Department of Psychiatry and the EMGO Institute for Health and Care Research, VU University Medical Centre, and GGZ inGeest, Amsterdam, The Netherlands
[b] Department of Biological Psychology, VU University Amsterdam, Amsterdam, The Netherlands
[c] Good Biomarker Sciences, Leiden, The Netherlands

ABSTRACT

Objective: Previous population-based studies suggest that exposure to secondhand smoke (SHS) is related to increased depressive symptoms and poor mental health among non-smokers. We examined whether these associations could be replicated in two independent Dutch samples.

Methods: Non-smoking adults were selected from two studies: 1) the Netherlands Study of Depression and Anxiety (NESDA), comprising individuals with current and remitted depressive and/or anxiety disorders, and healthy controls and 2) the Netherlands Twin Register (NTR), comprising twin-family studies on health-related behaviors. In both studies, SHS exposure was assessed with plasma cotinine levels (1–14 ng/ml vs. <1 ng/ml). In NESDA, outcomes were current depressive and/or anxiety disorders, and depression and anxiety symptom severity scores. In NTR, the Adult Self Report derived DSM-subscales for depressive and anxiety problems, and anxious depressive scores were analyzed.

Results: In NESDA non-smokers (n = 1757), increased plasma cotinine level (≥1 ng/ml) was not related to current depressive and/or anxiety disorders [odds ratio (OR) 0.96, $P = .77$], nor to depression or anxiety severity indicators. Similarly, in NTR non-smokers (n = 1088) cotinine levels ≥1 ng/ml were not associated with the DSM-subscale for depressive problems [unstandardized regression coefficient (B) 0.04, $P = .88$], nor to other depression and anxiety measures.

Conclusions: In non-smoking adults from patient and population samples, we found no evidence that plasma cotinine levels were related to either depressive and/or anxiety disorders, or to depressive and anxiety symptoms. This suggests that SHS exposure is not related to depression and anxiety in non-smoking adults.

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Introduction

Numerous studies have reported associations between smoking and depressive disorders [1,2]. Compared to non-depressed persons, persons with depression are more likely to be smokers [3,4], are more likely to progress to daily smoking [5], and have more difficulties when they attempt to quit smoking [6]. Furthermore, studies suggest that smoking is related to incident major depression [5,7]. Studies indicate that smoking is not only related to depression, but also to anxiety disorders like panic disorder [8,9] and social phobia [10].

Several recent studies suggest that exposure to secondhand smoke (SHS) is related to depressive symptoms and poor mental health in non-smoking adults [11–14] and in young adolescents [15,16]. Multiple explanations for these positive associations can be given. First, the association may be a consequence of methodological issues or incomplete adjustment for potential confounding factors in the association between exposure to SHS and depression, such as socio-demographical indicators, stressful life events, alcohol use, physical activity and somatic diseases. Furthermore, relatives of smokers may be more at risk for depression due to genetic vulnerability, and not by the exposure of SHS itself. This non-causal explanation is in line with a study in female twins showing that the relationship between smoking and depression can be largely explained by genetic factors predisposing to both smoking and depression [4]. Second, a true causal relationship may exist, which might be mediated by psychosocial factors such as stress or sleep problems [17]. Alternatively, a direct biological link between exposure to smoke and mental health could be present. Although most animal studies ascribe antidepressant and anxiolytic effects to the exposure to nicotine, and an increased likelihood for depression-like states after nicotine withdrawal [18], it has been shown that injections of nicotine in adolescent rats led to a depression-like state during adulthood [19]. Furthermore, nicotine exposure in adolescent rats appeared to induce an anxiogenic profile, which persisted after nicotine withdrawal [20]. Moreover, nicotine has been shown to affect physiological pathways that have

* Corresponding author at: GGZ inGeest, P.O. Box 74077, 1070 BB Amsterdam, The Netherlands. Tel.: +31 20 788 5506; fax: +31 20 788 5664.
E-mail address: m.bot@ggzingeest.nl (M. Bot).

been related to depression and anxiety, such as the dopaminergic system, hypothalamic pituitary adrenal axis, and inflammation [18,21]. Although direct evidence is lacking at the moment, these systems may likely be involved in the potential relationship of exposure to SHS and poor mental health.

While most studies that examined the relationship between exposure to SHS and mental health showed positive associations, one conflicting result has been reported [22]. In addition, some previous studies were limited by using self-reported measures for smoking exposure [13,14] rather than using cotinine as a biological marker for exposure to SHS [11,12,15]. Cotinine is the primary proximate metabolite of nicotine, and marks the exposure of an individual to tobacco over the previous few days [23]. Cotinine is preferred as a marker for exposure to SHS [24], even over nicotine itself, as the half-life of cotinine in the body is much longer than that of nicotine (17 h vs. 2 h) [23]. Furthermore, previous studies that examined the relationship between SHS and mental health lacked information about depression history [11], or relied on self-reported mental health rather than diagnostic criteria for mental health disorders [11–13]. Hence, the association between SHS and depression deserves further study, in particular by using diagnostic criteria for the presence of depression. Furthermore, as exposure to SHS appears to be related to a wider scope of mental health problems in young adolescents [15], and possibly in adults [12], it would be relevant to examine its association with anxiety as well.

Therefore, the aim of the present study was to assess the relationship of exposure to SHS, measured as the presence of detectable cotinine in plasma, with depression and anxiety in non-smoking adults in two large cohorts from the Netherlands.

Method

Data were derived from two studies conducted in the Netherlands: the Netherlands Study of Depression and Anxiety (NESDA) and ongoing twin family studies of the Netherlands Twin Register (NTR).

Sample selection of NESDA

NESDA is an ongoing longitudinal cohort study on the predictors, course and consequences of depressive and anxiety disorders [25]. The NESDA sample consists of 2981 participants aged 18 to 65 years, comprising persons with no depressive or anxiety disorder, persons who have had a disorder in the past, and persons with a current depressive and/or anxiety disorder. To represent the various stages of the depression and anxiety psychopathology, individuals were recruited from different settings, i.e. general population (n = 564), primary care (n = 1610), and specialized mental health care (n = 807). Between September 2004 and February 2007, all participants completed the 4-hour baseline assessment, which included a face-to-face interview, written questionnaires, and biological measurements. The research protocol was approved by the Ethical Committee of the participating centers, and all participants provided written informed consent.

For the purpose of the current study, only non-smokers were selected. From the 2981 NESDA participants, we excluded self-reported smokers (n = 1149). Subsequently, non-smoking participants with missing cotinine levels (n = 35) and cotinine levels ≥15 ng/ml (n = 40) were excluded, as the latter may be indicative for smoking. Although lower cut-offs (e.g. 3, 10 or 12 ng/ml) have been suggested to distinguish smokers from non-smokers [26,27], we applied the frequently used higher cut-off of 15 ng/ml in order to prevent misclassification of self-reported non-smokers who are exposed to high levels of SHS. This resulted in a sample of 1757 non-smokers.

Depression and anxiety in NESDA

During the baseline visit, the presence of depression (major depressive disorder and dysthymia) and anxiety disorders (panic disorder, social phobia, generalized anxiety disorder, and agoraphobia) was ascertained

with the DSM-IV based Composite Interview Diagnostic Instrument (CIDI, version 2.1) by specially trained research staff. The CIDI has a high reliability and validity for the assessment of depressive and anxiety disorders [28]. We distinguished participants with current disorders (depressive and/or anxiety disorder in the past 6 months), remitted disorders (lifetime depressive and/or anxiety disorder, but not in the past 6 months) and healthy controls (no lifetime depressive and anxiety disorder). In addition, the severity of depression in the past week was measured in all participants using the 30-item Inventory of Depressive Symptomatology, Self-Report version (IDS-SR) [29]. Furthermore, the severity of anxiety in the past week was measured in all participants with the 21-item Beck Anxiety Inventory (BAI) [30]. Higher scores indicate increased severity.

Covariates in NESDA

Data on the following covariates were collected during the baseline assessment: sex, age, education level, north-European ancestry, body mass index (BMI), physical activity, alcohol use, self-reported number of chronic diseases under treatment, and self-reported past smoking status (never vs. former smoker). Educational level was classified as low (elementary education either completed or not completed, lower vocational education), medium (general intermediate education, intermediate vocational education, general secondary education), and high (higher vocational education, college education, university education). Weight and height were measured by trained staff, and BMI was calculated as the weight (kg)/height (m)^2. Physical activity was assessed with the International Physical Activity Questionnaire (IPAQ), and expressed in 1000 metabolic equivalent (MET) minutes per week [31]. Alcohol use was determined with the Alcohol Use Disorders Identification Test (AUDIT), and higher scores indicate more hazardous and harmful alcohol use [32].

Sample selection of NTR

NTR comprises ongoing twin-family studies on health-related behavior and assesses families with adolescent and (young) adult twins since 1991 [33]. Participants are invited every two/three years to complete a survey that contains questions about health, lifestyle, personality and psychopathology. Between 2004 and 2008, blood was sampled in a large number of NTR participants who took part in the NTR Biobank (n = 9530) [34]. Depressive and anxiety symptoms were assessed in the NTR survey that was sent in 2009, resulting in an average time interval of 3 years (SD 1.1 years, ranging from 0.6 to 7 years) between the NTR Biobank assessment and the mental health assessment.

Plasma cotinine levels were determined in 4099 NTR participants. From these, we excluded self-reported smokers at the time of biobank collection (1930 current smokers, 53 occasional smokers, and 1 cannabis smoker). Non-smokers with cotinine levels ≥15 ng/ml (n = 45) were also removed as this may be indicative for active smoking, resulting in a sample size of 2070 non-smokers. The main depression outcome was available for 1241 non-smokers in this group. After removing one monozygotic twin from each pair (n = 65) and one person from each spouse pair if only the spouse pair participated (n = 88), the final NTR sample consisted of 1088 non-smoking persons.

Depression and anxiety in NTR

Depressive and anxiety symptoms were measured with the 126-item Adult Self Report (ASR) [35] in the survey of 2009. The ASR assesses behavioral and emotional problems in adults in the past six months. From the ASR, we derived the DSM-orientated subscale for depressive problems (range 0–25) [35,36], which was our main outcome for the NTR sample. As secondary outcomes, we derived DSM-oriented subscale for anxiety problems and the syndrome scale anxious depression [35,36]. The two DSM-oriented scales are expert-based and reflect depressive

and anxiety problems rather than disorders [36], with higher scores indicating more problems in these areas [36].

Covariates in NTR

Data on the following covariates were collected during blood sampling for the NTR biobank: sex, age, body mass index, and whether participants smoked in the past. For data on physical activity, alcohol use, and self-reported health, we used data collected in the survey of 2009. North European ancestry and educational level were also based on earlier assessments in the NTR study, and the same classification as in NESDA was used for these variables.

Body mass index was calculated as self-reported weight / (self-reported height)^2; former smoking status was classified as never smoker and former smoker. Physical activity was assessed with the questions on sport activities and expressed in 1000 MET minutes per week [31]. Alcohol use was determined with the AUDIT, with higher scores reflecting more hazardous and harmful alcohol use [32].

Cotinine levels in NESDA and NTR

For NESDA, fasting blood samples were collected between 8:00 and 9:30 am during the baseline visit at one of the research centers, and kept frozen at −80 °C. Fasting blood samples from NTR biobank participants were collected during a morning home visit between 7:00 and 10:00 am, and kept frozen at −27 °C. Cotinine concentrations were determined in the Lab of Good Biomarker Sciences (Leiden, The Netherlands) and were assessed in blood plasma by solid phase competitive ELISA (Cotinine Direct ELISA kit, cat. no: CO096D, Calbiotech, CA, USA) according to the manufacturer's instructions. The detection limit was 1 ng/ml. The acceptance criteria for the inter-assay for coefficient of variation (cv) was 20% for cotinine values between 2 and 10 ng/ml and 15% for values >10 ng/ml. The acceptance criteria for the intra-assay cv ranged from 10 to 15%. All but one quality control fulfilled the established acceptance criteria. This control was, however, deemed acceptable for the value. The distribution of cotinine was highly skewed and a large number of values were below the detection limit (74% in NESDA; 67% in NTR). To distinguish individuals that were exposed to SHS from those who were not, cotinine levels were categorized in values below the detection limit (<1 ng/ml) and values above this limit (1–14 ng/ml).

Statistical analyses of NESDA and NTR

Sample characteristics were shown in Table 1 for both studies.

For NESDA data, we used multinomial logistic regression analyses to explore the association between detectable cotinine levels and depressive and anxiety disorders in non-smokers. Individuals without a lifetime history of depression and anxiety (healthy controls) served as reference group and were compared to individuals with current depressive and/or anxiety disorders and to individuals with remitted disorders. In sensitivity analyses, we repeated the analyses using different outcomes for depression and anxiety, i.e. 1) current and remitted depressive disorders (vs. no lifetime depressive disorder), 2) current and remitted anxiety disorders (vs. no lifetime anxiety disorder), 3) current depressive disorder(s) only, current anxiety disorder(s) only, and comorbid depression and anxiety (vs. no lifetime disorder), 4) depressive symptom score (IDS), and 5) anxiety symptom score (BAI). The IDS and BAI scores were transformed with a square root transformation to normalize residuals and analyzed in linear regression models. All statistical analyses were conducted in SPSS version 20 (SPSS Inc., Chicago, IL, USA).

For NTR data, linear regression analyses were used to explore the association between the ASR–DSM depressive problem score and cotinine levels (<1 ng/ml versus 1–14 ng/ml) in non-smokers. Analyses were repeated using secondary outcomes for depression and anxiety, i.e. 1) ASR–DSM anxiety problem score and 2) ASR anxious depression score.

Table 1
Sample characteristics of non-smokers in the NESDA and NTR studies

	NESDA (n = 1757)	NTR (n = 1088)
Female	1204 (68.5%)	740 (68.0%)
Age, yrs (mean, SD)	42.8 (13.4)	42.8 (13.3)
Education level		
Low	315 (18.9%)	252 (22.9%)
Medium	738 (42.0%)	362 (30.5%)
High	704 (40.1%)	552 (46.5%)
North European ancestry	1660 (94.5%)	1067 (98.1%)
BMI kg/m^2 (mean, SD)	25.8 (4.9)	25.0 (4.0)
Physical activity, 1000 MET minutes/week (mean, SD)	3.6 (2.9)	9.3 (17.3)
Alcohol use AUDIT score (mean, SD)	4.0 (3.8)	3.8 (3.6)
Number of diseases treated (mean, SD)	0.6 (0.9)	–
Former smoker	945 (53.8%)	445 (40.9%)
Cotinine >=1 ng/ml	449 (25.6%)	356 (32.7%)
Cotinine >=2 ng/ml	250 (14.2%)	229 (21.0%)
Depression and anxiety measures		
Current depressive and/or anxiety disorder[a]	907 (51.6%)	–
Remitted depressive and/or anxiety disorder[a]	391 (22.3%)	–
Healthy controls[a]	459 (26.1%)	–
Current depressive disorder[a]	605 (34.4%)	–
Remitted depressive disorder[a]	471 (26.8%)	–
No lifetime depressive disorder[a]	681 (38.8%)	–
Current anxiety disorder[a]	680 (38.7%)	–
Remitted anxiety disorder[a]	298 (17.0%)	–
No lifetime anxiety disorder*	779 (44.3%)	–
Current depressive disorder only[a]	227 (12.9%)	–
Current anxiety disorder only[a]	302 (17.2%)	–
Comorbid depressive and/or anxiety disorder[a]	378 (21.5%)	–
IDS30 score (mean, SD)	19.9 (13.6)	–
BAI score (mean, SD)	10.6 (9.6)	–
ASR–DSM depression (mean, SD)[b]	–	3.6 (3.6)
ASR–DSM anxiety (mean, SD)[b]	–	3.2 (2.4)
ASR anxious depression (mean, SD)[b]	–	4.6 (4.9)

[a] Depressive disorders were MDD and/or dysthymia. Anxiety disorders were panic disorder, social phobia, generalized anxiety disorder, and/or agoraphobia. Current disorder: disorder(s) in the past 6 months. Remitted disorder: lifetime history of the disorder(s), but not in the past 6 months. Healthy controls: no lifetime depressive or anxiety disorder.

[b] For NTR, the number of participants differs per definition: ASR–DSM depression (n = 1088), ASR DSM anxiety (n = 1054), ASR anxious depression (n = 1000).

As family members were included in NTR, all regression analyses were corrected for family clustering by employing a correction for clustering due to family membership in STATA (version 9.0).

For both NESDA and NTR, we conducted sensitivity analyses with a higher cut-off for the cotinine level, namely <2 versus 2–14 ng/ml. Furthermore, analysis in the NTR sample was stratified according to the time interval between the cotinine and mental health assessment (<2 year, 2–3 years, and ≥4 years interval), to study whether increased time interval may reduce the strength of the association.

Previous studies indicate that the relationship may differ between men and women and across former smoking status (never vs. former smokers) [11,12]. Therefore, we tested interactions between cotinine * sex and cotinine * former smoking status for our main psychopathology outcomes. None of the interactions were significant (for NESDA [current disorder y/n]: cotinine * sex P = .61, cotinine * former smoking status P = .54; for NTR [ASR–DSM depressive problem score]: cotinine * sex P = .58, cotinine * former smoking status P = .79). Hence, we performed and showed total group analyses for both studies.

Results

Cotinine levels and current depressive and/or anxiety disorder in NESDA

Table 1 shows the characteristics of the non-smoking sample of NESDA (first column). In this sample, 907 participants (52%) had a current depressive and/or anxiety disorder,

391 participants (22%) were classified as having remitted disorder(s), and 459 participants (26%) never had a disorder in their lifetime (healthy controls). In total, 1204 participants (69%) were females and the mean age was 43 years (SD 13). 812 participants (46%) were never smokers. One-quarter of the non-smokers (n = 449, 26%) had cotinine levels above or equal to the detection limit of 1 ng/ml.

As shown in Table 2, individuals with cotinine levels ≥1 ng/ml were neither more likely to have a current depressive and/or anxiety disorder (fully adjusted model OR 0.96, 95% CI 0.73–1.27, P = .77), nor more likely to have a remitted disorder (fully adjusted model OR 1.10, 95% CI 0.79–1.53, P = .57) when compared to healthy controls (reference).

Sensitivity analyses

After repeating the multinomial logistic regression analyses separately for the depressive disorders and anxiety disorders, we found that cotinine values above the cut-off of ≥1 ng/ml were not related to current depressive disorders (fully adjusted model: OR 0.89; 95% CI 0.68–1.17, P = .40) or to anxiety disorders (fully adjusted model: OR 1.05; 95% CI 0.82–1.35, P = .70; see Table 2). Similarly, in sensitivity analyses we found no significant association between cotinine and depression severity (IDS score; fully adjusted model: unstandardized regression coefficient (B) −0.75; 95% CI −2.20–0.69; P = .31) or anxiety severity (BAI score; fully adjusted model B 0.23; 95% CI −0.80–1.26; P = .66).

When we used a different cut-off for exposure to SHS (cotinine ≥2 ng/ml), having cotinine levels above this cut-off (n = 250, 14%) was not related to current depressive and/or anxiety disorders (fully adjusted model: OR 0.78; 95% CI 0.56–1.10, P = .15), nor to remitted disorders (fully adjusted model: OR 0.90; 95% CI 0.60–1.35, P = .62) when compared to healthy controls.

Cotinine levels and depression in NTR

Of the NTR sample, 68% were females, and the mean age was 43 years (Table 1). 356 participants (33%) had cotinine levels above the cut-off of 1 ng/ml. The mean ASR DSM depressive problem score was 3.6 (SD 3.6). Table 3 shows the association between cotinine levels and the ASR–DSM depressive problem scale. Cotinine values above the cut-off of 1 ng/ml were not related to ASR–DSM depressive problem score (fully adjusted model: B 0.04, 95% CI −0.52–0.44, P = .88).

Sensitivity analyses

In sensitivity analyses, we found that cotinine levels ≥1 ng/ml were not related to ASR–DSM anxiety problem scores (fully adjusted model B 0.01, 95% CI −0.31–0.33, P = .95) or to anxious depressive scores (fully adjusted model B −0.15, 95% CI −0.81–0.52, P = .66).

When we used a different cut-off for exposure to SHS (cotinine ≥2 ng/ml, n = 229, 21%), having cotinine levels above this cut-off was not related to ASR–DSM depression score (fully adjusted model: B −0.17; 95% CI −0.73–0.39, P = .55). Finally, none of the stratified analysis for time interval between cotinine and mental health assessment yielded a statistically significant association between cotinine and ASR–DSM depressive problem scores (fully adjusted model P range: .67–.92).

Table 3
Linear regression analyses in NTR: association of cotinine ≥1 ng/ml with depression and anxiety

Dependent variables	Model 1[a]		Model 2[b]	
	B (95% CI)	P	B (95% CI)	P
ASR DSM depression scale	−0.076 (−0.53–0.38)	.74	0.038 (−0.52–0.44)	.88
ASR DSM anxiety scale	0.008 (−0.30–0.31)	.96	0.010 (−0.31–0.33)	.95
ASR anxious depression	−0.163 (−0.79–0.46)	.61	−0.147 (−0.81–0.52)	.66

[a] Model 1 adjusted for age and sex.
[b] Model 2 adjusted for age, sex, education level, North-European ancestry, body mass index, physical activity, alcohol use, self-reported health, and former smoker. The model 2 adjusted R-square was 0.08 for each outcome.

Discussion

The aim of the study was to explore the association between exposure to secondhand smoke (SHS) and depression and anxiety. We observed no significant association of biologically assessed exposure to SHS with depression and/or anxiety in two independent Dutch non-smoking samples, comprising individuals from the general population as well as individuals with depressive and/or anxiety disorders. This is in contrast to previous studies that reported significant associations of exposure to SHS with depressive symptoms or poor mental health [11–14], but in line with another study [22].

Epidemiological studies show that smoking and depression often go together. Although this may be the result of common genetic and environmental factors, it has also been argued that depression and smoking are related in a causal matter in both directions [37]. People with depressive symptoms may start smoking or increase their tobacco consumption to relieve their depressed mood. On the other hand, smoking also increases the risk for depression [37]. Several studies suggest that exposure to SHS is related to increased depressive symptoms or poor mental health [11–13], also in longitudinal designs [12]. We did not find such an association in our sample. Several potential explanations for the discrepant results can be given. Compared to

Table 2
Multinomial logistic regression and linear regression analyses in NESDA: association of cotinine ≥1 ng/ml with depression and anxiety outcomes

Dependent variables	Model 1[a]		Model 2[b]	
	OR (95% CI)	P	OR (95% CI)	P
Current depressive and/or anxiety disorder	1.02 (0.78–1.34)	.89	0.96 (0.73–1.27)	.77
Remitted depressive and/or anxiety disorder	1.11 (0.80–1.53)	.53	1.10 (0.79–1.53)	.57
Healthy controls (reference)	1	–	1	–
Current depressive disorder	0.95 (0.73–1.24)	.72	0.89 (0.68–1.17)	.40
Remitted depressive disorder	1.10 (0.83–1.45)	.51	1.08 (0.82–1.43)	.58
No lifetime depressive disorder (reference)	1	–	1	–
Current anxiety disorder	1.11 (0.87–1.42)	.40	1.05 (0.82–1.35)	.70
Remitted anxiety disorder	1.24 (0.90–1.70)	.19	1.22 (0.89–1.69)	.21
No lifetime anxiety disorder (reference)	1	–	1	–
Current depressive disorder	0.89 (0.60–1.32)	.56	0.84 (0.56–1.25)	.39
Current anxiety disorder	1.10 (0.78–1.55)	.59	1.08 (0.76–1.53)	.69
Comorbid depression and anxiety disorder	1.02 (0.74–1.42)	.89	0.90 (0.64–1.27)	.56
Healthy controls (reference)	1	–	1	–
	B (95% CI)	P	B (95% CI)	P
Depression severity (IDS score)	−0.01 (−1.52–1.50)	.99	−0.75 (−2.20–0.69)	.31
Anxiety severity (BAI score)	0.71 (−0.36–1.78)	.19	0.23 (−0.80–1.26)	.66

Owing to missing covariates, sample sizes for fully adjusted models for clinical diagnosis of depressive and anxiety disorders and anxiety severity are n = 1647. Sample sizes for analyses with depression severity are n = 1646.
[a] Model 1 adjusted for age and sex.
[b] Model 2 adjusted for age, sex, education level, North-European ancestry, body mass index, physical activity, alcohol use, number of chronic diseases under treatment, and former smoker. In the multinomial regression analyses, model 2 pseudo R-square Nagelkerke value ranged between 0.05 and 0.08. In the linear regression analyses, model 2 adjusted R-square was 0.10 for both depression and anxiety severity.

previous studies, our assay had a relatively high detection limit for cotinine [<1 ng/ml for plasma cotinine in our study versus <0.011 ng/ml for serum cotinine [11] and <0.05 ng/ml for saliva cotinine [12]; with cotinine values about 25% higher in saliva than plasma [38]]. This may limit the potential to find significant associations in the low range of SHS exposure. However, as Hamer et al. found a robust dose–response relationship between cotinine and mental health [12], we would expect to find associations with mental health in the higher range of cotinine values. Moreover, Hamer et al. found that the non-smoking group with the highest saliva cotinine values (0.7–14 ng/ml) differed significantly from the non-smoking reference group (<0.05 ng/ml) [12], while the intermediate groups did not differ significantly from the reference group. Furthermore, one study that did use a sensitive assay for cotinine observed no association between exposure to SHS and poor mental health in adults [22], which supports our findings.

The discrepant result of our study compared to previous studies may also be due to time or cultural differences. We measured exposure to SHS between 2004 and 2008, while the other studies, with the exception of the study of Bandiera et al. [11], measured the exposure at earlier points in time (between 1984 and 2003) [12,13,22]. Over the past years, awareness of the potential hazardous relationship of exposure to SHS and physical diseases increased, resulting in the introduction of comprehensive smoking bans in indoor workplaces in several countries and states, starting in Ireland in 2004 [39]. In the Netherlands, the government implemented a smoke-free workplace legislation, except for the hospitality industry, which followed in 2008. These regulations took place when we assessed exposure to SHS in our studies, which may have reduced the average cumulative exposure to SHS. Still, at the time of cotinine collection, smoking in hospitality settings was still allowed and literature suggests that the smoking bans did not affect exposure to SHS at home [40]. More importantly, we observed considerable variation in plasma cotinine in our studies, allowing us to study potential associations between exposure to SHS and poor mental health.

Furthermore, some discrepancy in study outcomes may be explained by the selection of non-smokers. In some studies [13,14], smoking status was based on self-report measures only, while we and others used a combination of self-reported measures and cotinine levels to select our non-smoking samples. In studies that relied on self-report measures only, occasional smokers may have been more likely to be erroneously classified as being non-smokers. Given the higher prevalence of mental health problems in smokers, the association in non-smokers may be overestimated in these studies.

Finally, the study result discrepancy may also be due to differences in study sample characteristics, in the instruments to assess mental health problems, and the assessment and selection of potential confounding factors.

Strengths of the present paper are the inclusion of two large independent studies, including patients as well as individuals from the general population, and the use of diagnostic criteria for depressive and anxiety disorders for the NESDA sample, whereas previous studies merely relied on severity measures that were derived from questionnaires. Furthermore, we used an objective biomarker to assess exposure to SHS, which was not the case in all studies [13,14]. However, our studies were also subject to some limitations. First, both NESDA and NTR are large scale cohort studies which were not specifically designed to assess the association between exposure to SHS and mental health. Second, there was an average time interval of three years between blood sampling and the assessment of mental health in the NTR study. Although longitudinal associations between high SHS exposure and increased psychiatric hospital admissions were observed [12], the large time interval might have reduced the strength of the association. In the NTR sample, however, we did not observe different associations between cotinine and mental health for strata of different time intervals. Hence, we believe that the results of NTR support the cross-sectional null-findings of NESDA, where blood sampling and assessment of mental health took place at the same time. Furthermore, cotinine is

thought to be relatively stable over time, and a single measure of cotinine is considered to be representative for daily exposure [23]. Finally, as cotinine was assessed at a single point of time, causal inferences could not be drawn.

As the current evidence for the association of exposure to SHS and mental health is unequivocal, future research should examine this association, preferably over the lifetime. This will nevertheless not solve the issue whether exposure to SHS and poor mental health is truly causally related. Several animal and human studies suggest that exposure to nicotine has antidepressant and anxiolytic effects [18], which is in contrast to the view that exposure to SHS increases the risk of depression and anxiety. As other constituents of cigarette smoke than nicotine might be involved, and biological effects of long-term SHS are not yet studied [21], more research on the biologically plausible pathways that link SHS exposure to mental health is needed.

In summary, we found no association of objectively measured exposure to SHS with depression and anxiety among non-smoking adults. This is in contrast to previous studies that showed significant associations between exposure to SHS and depression and mental health. Future research is needed, in particular in addressing the potential mechanisms by which exposure to SHS might affect mental health.

Conflicts of interest

The authors have no competing interests to report.

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