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## Parsing the heterogeneity of Major Depression

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# Chapter 3

## **Prevalence of internalizing disorders, symptoms, and traits across age using advanced nonlinear models**

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## Abstract

### Background

Most epidemiological studies show a decrease of internalizing disorders at older ages, but it is unclear how the prevalence exactly changes over the life course, and whether there are different patterns for internalizing traits, and for men and women. This study investigates the impact of age and sex on the point prevalence across different mood and anxiety disorders, internalizing symptoms, and neuroticism.

### Methods

We used cross-sectional data on 146,315 subjects, aged 18–80 years, from the Lifelines Cohort Study, a Dutch general population sample. Between 2012–2016, five current internalizing disorders – major depression, dysthymia, generalized anxiety disorder, social phobia and panic disorder – were assessed according to DSM-IV criteria. Depressive symptoms, anxiety symptoms, neuroticism, and negative affect were also measured. Generalized additive models were used to identify nonlinear patterns of internalizing disorders and traits over lifetime, and to investigate sex differences.

### Results

The point prevalence of internalizing disorders generally increased between the ages of 18–30 years, stabilized between 30–50, and decreased after age 50. The patterns of internalizing symptoms and traits were different. NA and neuroticism gradually decreased after age 18. Women reported more internalizing disorders than men, but the relative difference remained stable across age (relative risk ~ 1.7).

### Conclusions

The point prevalence of internalizing disorders was typically highest between age 30–50, but there were differences between the disorders, which could indicate differences in etiology. The relative gender gap remained similar across age, suggesting that changes in sex hormones around the menopause do not significantly influence women's risk of internalizing disorders.

## Introduction

Depressive and anxiety disorders occur across all age ranges and are associated with significant disability.<sup>1,2</sup> Yet, how exactly internalizing disorders differ across age and sex is a subject of debate and few studies have been able to study their patterns over lifetime in detail. More insight into these patterns can be used to identify target populations for public health interventions.<sup>3</sup> Furthermore, this insight could inform hypotheses on specific risk factors for internalizing disorders over the course of life. For example, it has been suggested that changes in women's reproductive hormones during the menopause increase their risk for internalizing disorders, but results are inconclusive.<sup>4-8</sup> Different developments in prevalence in men and women around the age of menopause could support this hypothesis.

The first question concerns the exact development of different internalizing disorders over lifetime. Most studies in the general population find a decrease of internalizing disorders in older age.<sup>9-14</sup> However, it remains unclear whether this decrease in prevalence is linear or nonlinear<sup>12</sup>, and whether there are significant differences in trajectories across these various highly comorbid internalizing disorders<sup>13</sup>.

Second, there is a clear gender gap in the prevalence of depression and anxiety disorders, with women being affected roughly twice as often as men.<sup>4,15-17</sup> However, is this true over the entire lifespan? Some studies suggest that the gender gap remains the same across the lifespan,<sup>1,12,16,18,19</sup> but other studies found a decreased<sup>12,20,21</sup> as well as an increased gap<sup>22</sup> in older ages.

Lastly, it is unclear whether there are significant differences in trajectories across these various highly comorbid internalizing disorders, and how these trajectories of internalizing disorders compare with the trajectories of internalizing symptoms and traits, such as depressive symptoms, anxiety symptoms, negative affect (NA), and neuroticism.<sup>3,12,23</sup> Insight in the difference between the trajectories of internalizing disorders, symptoms, and traits can inform discussions on classification, such as whether internalizing disorders and traits are sufficiently similar constructs so that traits could serve as measures of internalizing disorders for research and clinical purposes.<sup>24,25</sup>

The study of these questions requires large general population samples with well-measured phenotypes, and statistical methods that are able to identify potentially nonlinear developments. To date, no studies have used advanced nonlinear statistical methods to investigate the point prevalence of different internalizing disorders, symptoms and traits over the lifetime and compared these across sex.

Our aim is to investigate the prevalence of different internalizing disorders across age and sex, and compare the results of internalizing disorders with internalizing symptoms and traits. We investigate the point prevalence of major depression (MD), dysthymia (DYS), generalized anxiety disorder (GAD), panic disorder (PD), and social phobia (SPH) diagnosed at interview by DSM-IV criteria in a sample of 146,315 participants aged 18-80 years from Lifelines, a study in the Dutch general population. We also study the rates of depressive and anxiety symptoms, NA, and neuroticism. Generalized additive models (GAMs) allow us to model nonlinear patterns and test for significant differences in the development of the different internalizing disorders, symptoms and traits, and compare results for men and women.

## Methods

### Sample

The Lifelines Cohort Study is a multidisciplinary prospective population-based cohort study of 167,729 subjects in the north of the Netherlands. It was established as a resource for research on complex interactions between environmental, phenotypic and genomic factors in the development of chronic diseases and healthy ageing. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical, and psychological factors contributing to health and disease, with a special focus on multimorbidity and complex genetics.<sup>26,27</sup> Between 2006 and 2013, an index population aged 25–49 years was recruited via participating general practitioners. Subsequently, older and younger family members were invited to participate in Lifelines. In addition, adults could self-register via the Lifelines website. In total, 49% of the included participants were invited through their GP, 38% were recruited via participating family members, and 13% self-registered<sup>27</sup>. Most participants (57%) were included in 2012-2013.<sup>28</sup> Baseline data were collected for 167,729 participants.

The Lifelines adult study population is broadly representative for the adult population of the north of the Netherlands. Demographic, socioeconomic, and general health characteristics of the Lifelines cohort are described elsewhere.<sup>28</sup> All participants provided written informed consent. The Lifelines Cohort Study was approved by the Medical Ethics Committee of the University Medical Center Groningen, The Netherlands. In the current study, we included all baseline participants aged 18-80 years ( $n = 146,315$ ) who had available data on one or more of the internalizing disorders or symptoms. We

excluded 299 participants over 80 years because of the low sample size for the statistical analyses.

## Measurements

### *Internalizing disorders*

Current MD, DYS, SPH, and GAD were assessed according to DSM-IV-TR criteria with a standardized diagnostic interview based on the Mini-International Neuropsychiatric Interview (MINI).<sup>29</sup> Trained medical assistants administered sections of the MINI to all participants during their visit to the research facilities and entered the responses into the computer. Conform DSM-IV-TR duration criteria, MD, DYS, GAD, and PD were rated as present if the subject reported the required symptoms in the past 2 weeks, 2 years, 6 months, and 1 month, respectively.<sup>30</sup> SPH was assessed during the past month. For further details, see Supplementary Methods.

### *Internalizing traits*

#### *Depressive and anxiety symptoms*

Using the symptoms of MD and GAD assessed with the MINI, we created two sum scores for depressive (range 0-9) and anxiety symptoms (range 0-7). As above, MD symptoms were assessed in the past 2 weeks, and GAD symptoms in the past 6 months. Due to changes in the design of the interview, only part of the sample ( $n = 73,805$ ) had data on additional symptoms of MD and GAD if the core criteria were absent. This subsample with complete data was used for the analyses of MD and GAD symptoms (Supplementary Methods).

#### *Negative affect*

Negative affect (NA) was assessed with the Positive and Negative Affect Schedule (PANAS) using 10 items including feeling irritable, ashamed, upset, nervous, guilty, scared, hostile, jittery, afraid, and distressed.<sup>31,32</sup> Subjects were asked to rate how often they experienced each item in the past 4 weeks on a 5-point Likert scale resulting in a score ranging from 10-50.

#### *Neuroticism*

Current neuroticism was assessed with the Revised NEO Personality Inventory.<sup>33,34</sup> The NEO PI-R Neuroticism subscale consists of 48 items covering the facets of anxiety, angry/hostility, depression, self-consciousness, impulsiveness, and vulnerability. Items were answered on a 5-point Likert scale resulting in a sum score ranging from 48 to 240.

The initial questionnaire excluded the depression and anxiety facets to limit the total length of the questionnaires, but these were added later. Here we only studied participants for whom complete data on all subscales on the NEO were available ( $n = 42,658$ ).

## **Statistical analysis**

### *Weighted point prevalence*

Because women and certain age groups were overrepresented in Lifelines (Supplementary Figure 1), we used a person weighting factor based on age and sex to estimate the point prevalence of internalizing disorders and traits for the Dutch general population. Data on the sex and age distribution of the Dutch population in 2011 were derived from the CBS Statline data (Supplementary Methods).<sup>35</sup>

### *Generalized additive models*

Generalized additive models (GAM) were used to assess the prevalence of internalizing disorders and traits over the lifetime. GAM are regression models that can identify and characterize nonlinear regression effects, by automatically determining the optimal combination of nonlinear basis functions (e.g. linear terms, polynomial terms, cubic terms, etc.).<sup>36–38</sup> Overfitting is prevented by minimizing a combination of the error and a non-linearity penalty.<sup>37</sup> All analyses were performed in R using the packages *mgcv\_1.9.29* and *itsadug\_2.3*.<sup>38–40</sup> We modeled the prevalence of each internalizing disorder, and the means of the symptom scores and neuroticism score as a (potentially) nonlinear function of age, and tested if there was a significant interaction effect between sex and age, i.e. if the patterns across age varied depending on sex. Subsequently, we modelled the patterns of the five internalizing disorders to investigate if the intercept and the pattern across age varied depending on the disorder type. For these models, the prevalence of any disorder served as the dependent variable, and the type of disorder was used as the independent variable. The reference classes were varied to make sure the results were robust.

### *Sensitivity analysis*

Internalizing disorders are highly comorbid.<sup>41,42</sup> Therefore, we performed a sensitivity analysis by including a random intercept for each subject in the GAM. This random intercept accounted for individual variation in vulnerability for internalizing disorders, irrespective of age, so that the fixed effect of age on internalizing disorders on a group level could be estimated. As the current software was not able to run a generalized additive model with random effects for the full sample, we divided the sample in 10 random subsamples of 14,624 individuals each. These subsamples were matched to the full sample

based on age and sex distributions. Then, we performed the GAM *without* and *with* random intercepts for these 10 subsamples, and compared the results.

Because family history is an important risk for developing internalizing disorders, we also performed a sensitivity analysis by including a random intercept in the GAMs for individual disorders in the full sample. This random intercept accounted for family variation in vulnerability for internalizing disorders.

## Results

### Point prevalence

The included 146,315 participants had a mean age of 44.2 years (SD 12.7) and 58.6% were women (Table 1). The age and sex weighted point prevalence rates showed that current GAD was reported most frequently (3.7%), followed by MD (2.0%), DYS (1.0%), and SPH (0.8%). PD in the past month was rare (0.21%). The point prevalence rates differed significantly between all disorders as indicated by the significant intercepts (Supplementary Table 2). The unweighted prevalence rates were somewhat higher for all disorders because of the sex and age composition of Lifelines participants, including a higher percentage of women than the general Dutch population (Supplementary Table 1).

### Lifetime patterns of internalizing disorders

All internalizing disorders showed significant nonlinear patterns over the lifetime (Figure 1, Supplementary Table 2). The general trend was that their prevalence increased from the age of 18 until the age of 30, stabilized until the age of 50, and then decreased. However, there were also differences between the disorders, as indicated by their significantly different curves. The prevalence of SPH and PD decreased relatively early in life, whereas the prevalence of MD peaked at two ages, around 30 years and 50 years, a pattern not seen with other disorders. Additionally, the prevalence of GAD and DYS dropped more steeply after the age of 50 than did the other disorders. The curves for GAD-DYS and for PD-SPH were not significantly different when changing the reference class, indicating no robust difference in their curves.



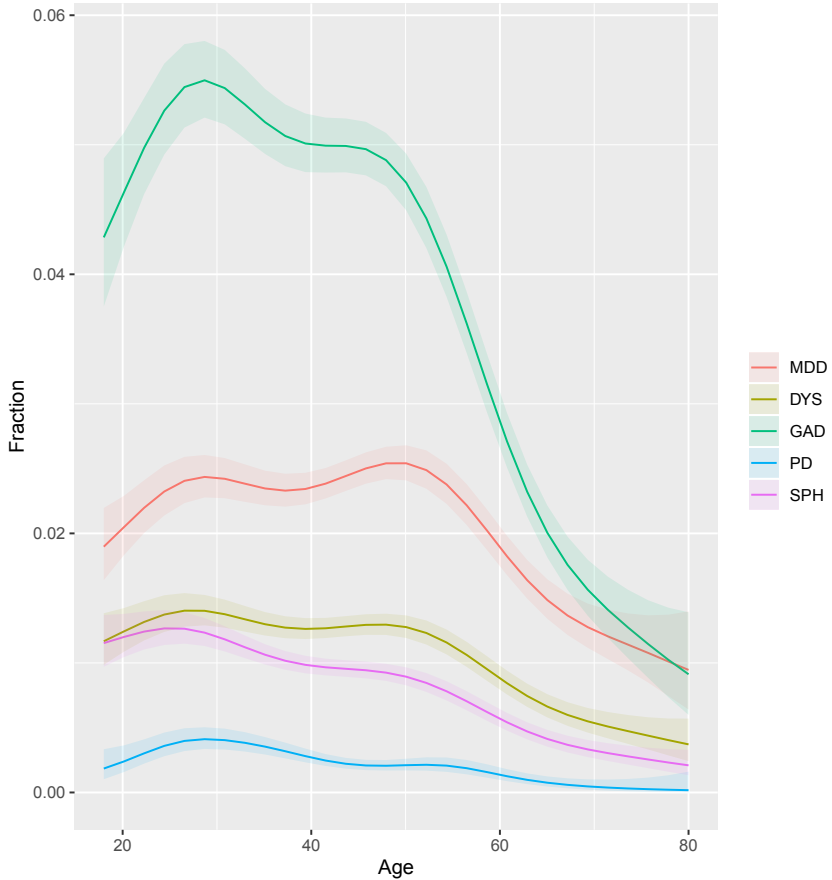
**Table 1.** Baseline characteristics

	<b>n</b>	<b>Total</b>	<b>Men</b>	<b>Women</b>
<b>Demographics</b>				
<b>Sex</b>	146315		41.42%	58.58%
<b>Age, mean (SD)</b>	146315	44.21 (12.74)	44.84 (12.78)	43.77 (12.69)
<b>Education level, % (SE)*</b>				
<b>Low</b>	142735	29.61 (0.12)	29.68 (0.19)	29.56 (0.16)
<b>Intermediate</b>	142735	40.12 (0.13)	38.67 (0.20)	41.15 (0.17)
<b>High</b>	142735	30.27 (0.12)	31.65 (0.19)	29.29 (0.16)
<b>Internalizing disorders, % (SE)*</b>				
<b>MD (2 weeks)</b>	146314	1.98 (0.04)	1.42 (0.05)	2.53 (0.06)
<b>Dysthymia (2 years)</b>	142549	1.04 (0.03)	0.77 (0.04)	1.30 (0.04)
<b>GAD (6 months)</b>	146315	3.71 (0.05)	2.79 (0.07)	4.62 (0.08)
<b>PD (1 month)</b>	146315	0.21 (0.01)	0.15 (0.02)	0.27 (0.02)
<b>SPH (1 month)</b>	146313	0.84 (0.03)	0.75 (0.04)	0.93 (0.04)
<b>Any mood disorder</b>	145793	3.00 (0.05)	2.19 (0.07)	3.81 (0.08)
<b>Any anxiety disorder</b>	146313	4.32 (0.06)	3.33 (0.08)	5.30 (0.08)
<b>Any internalizing disorder</b>	145956	5.82 (0.07)	4.41 (0.09)	7.22 (0.10)
<b>Internalizing traits, mean (SD)*</b>				
<b>MD symptoms (range: 0-9)</b>	73805	0.53 (1.16)	0.40 (1.02)	0.65 (1.28)
<b>GAD symptoms (range: 0-7)</b>	73805	1.04 (1.76)	0.80 (1.55)	1.27 (1.92)
<b>Neuroticism (range: 48-240)</b>	42658	119.65 (21.14)	115.35 (20.26)	124.15 (21.11)
<b>Negative affect (range: 10-50)</b>	138859	20.54 (5.24)	19.61 (5.02)	21.47 (5.28)

\*Highest completed education: "Low" is completed junior general secondary education (mavo/vmbo-t) or lower, or no education; "Intermediate" is completed secondary vocational education (mbo), senior general secondary education (havo, vwo, hbs, mms); "High" is completed higher vocational education (hbo) or university.

\*Age and sex weighted estimates to the average Dutch population in 2011. For unweighted estimates, see Supplementary Table 1.

DYS, dysthymia; GAD, generalized anxiety disorder; MD, major depression; PD, panic disorder; SD, standard deviation; SE, standard error; SPH, social phobia.



**Figure 1.** Estimated point prevalence for each internalizing disorder by age

Point prevalence for each internalizing disorder by age, as estimated by a generalized additive model. All patterns were nonlinear as indicated by the smoothing curves with effective degrees of freedom larger than 1 with P-values < 0.05 (Supplementary Table 2). The smoothing curves were all significantly different from each other except for SPH-PD and for DYS-GAD.

DYS, dysthymia; GAD, generalized anxiety disorder; MD, major depression; PD, panic disorder; SPH, social phobia.

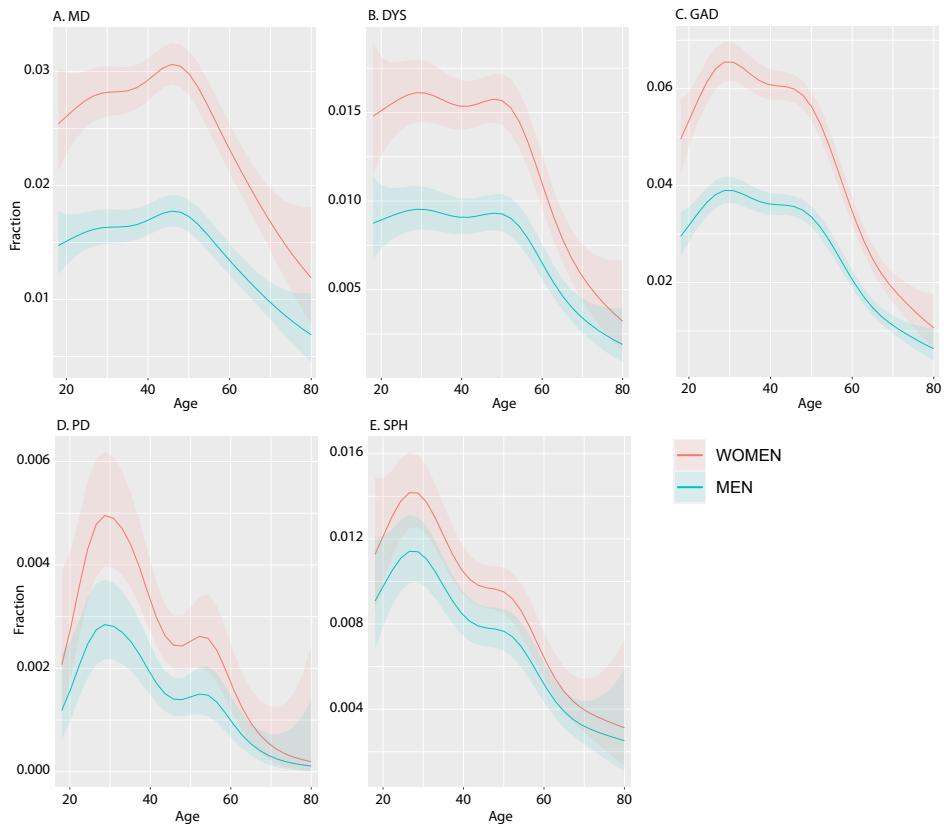
### Sex differences and similarities

As expected, women reported more internalizing disorders than men across the entire age range. The intercepts for each disorder were all significantly different for each disorder (Figure 2, Supplementary Table 3). However, the curves showing the increase and decrease of prevalence over age were not significantly different between the sexes, and this was true for each internalizing disorder. This implied that the odds ratio and the relative risk (i.e., prevalence women/prevalence men) were stable across the different age groups: about 1.7 for MD, DYS, GAD and PD, and 1.2 for SPH (Supplementary Table 4).

### Comparison with internalizing symptoms and neuroticism

Internalizing symptoms and traits showed different patterns across age than did internalizing disorders (Figure 3, Supplementary Table 3). Depressive symptoms decreased slightly from age 18 until the age of 35, increased until the age of 50, and then decreased again until the age of 65, after which symptoms increased again. Anxiety symptoms increased until the age of 40, and then decreased, with a stabilization after age 70. Neuroticism and NA decreased largely linearly from the age of 18 years. NA diminished linearly except from an increase from the age of 45 until the age of 55, but this increase was minor ( $< 0.5$  point on a scale from 10-50), and neuroticism stabilized from the age of 50.

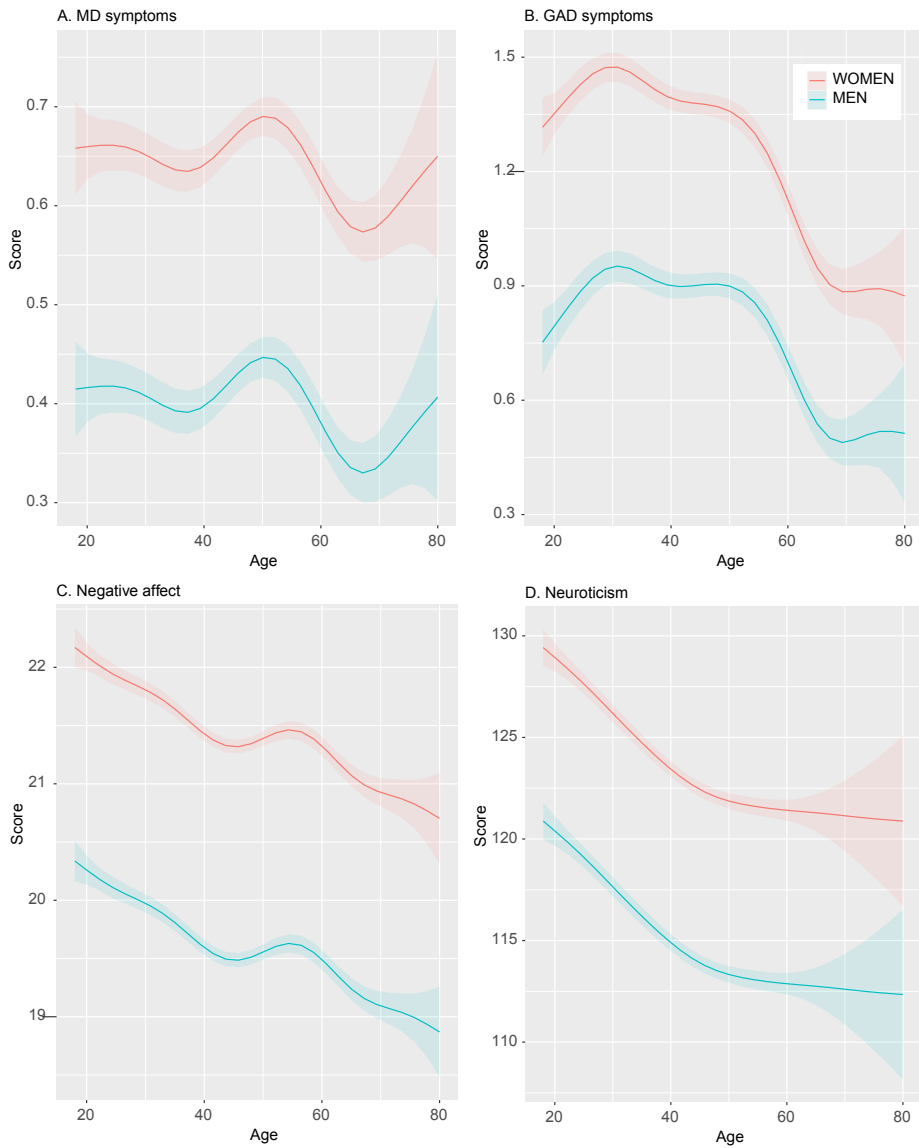
Comparable to the internalizing disorders, women scored higher on all internalizing traits than men, especially in depressive and anxiety symptoms (ratio W/M  $\sim 1.6$ ) and less for NA and neuroticism (ratio W/M  $\sim 1.1$ ) (Supplementary Table 4). The curves for depressive symptoms were similar in men and women, meaning that the absolute difference in the number of depressive symptoms remained constant over lifetime. The curves for generalized anxiety symptoms, neuroticism, and NA were significantly different across sex, although Figure 3 shows that these differences were modest.



**Figure 2.** Estimated point prevalence for internalizing disorders in men and women

Point prevalence for both genders for each internalizing disorder by age, as estimated by generalized additive models for each disorder separately. For all five disorders there were differences in intercepts between men and women but smoothing curves were not significantly different (see Supplementary Table 3). Therefore, this figure is based on the models without interaction term.

DYS, dysthymia; GAD, generalized anxiety disorder; MD, major depression; PD, panic disorder; SPH, social phobia.



**Figure 3.** Estimated curves for internalizing traits in men and women

Average internalizing trait scores for both genders by age, as estimated by generalized additive models for each trait separately. As can be seen in Supplementary Table 3, there were differences in intercepts between men and women for each trait, and smoothing curves were also significantly different except for MD symptoms. Therefore, 3A is based on a model without interaction terms.

GAD, generalized anxiety disorder; MD, major depression.

### Sensitivity analysis

To investigate the potential impact of comorbidity on the different trajectories of the internalizing disorders over lifetime, we performed a sensitivity analysis comparing models excluding and including random intercepts for each subject in 10 random subsamples each including about 10% of the sample. The estimated trajectories of the prevalence of internalizing disorders over lifetime were similar in all models including and excluding random intercepts (online Supplementary Table S5). To investigate the potential impact of the family structure of the Lifelines sample on our results, we performed another sensitivity analysis comparing models excluding and including random intercept for family structure. The estimated trajectories were again similar in all models including and excluding random intercepts (online Supplementary Table S6).

## Discussion

In this study of 146,315 subjects from the Dutch general population aged 18-80 years, we investigated the patterns of the point prevalences of MD, DYS, GAD, SPH, and PD across different ages and sex. In general, our modeling indicated an increase in the prevalence of internalizing disorders from the age of 18 years, a plateau phase between 30-50 years of age, and a decrease after age 50. There were differences in the nonlinear patterns over lifetime between most disorders. Internalizing symptoms and neuroticism showed a distinctly different pattern over the lifetime compared with internalizing disorders. Although women reported more internalizing disorders and symptoms and higher neuroticism than men, the relative risk over the life course was remarkably similar.

To our knowledge, no previous studies used GAM to investigate the development of different internalizing disorders and traits over lifetime and across sex. Thus, we cannot directly compare the nonlinear patterns and statistical differences between the internalizing disorders, traits, and the sexes with results of previous studies. However, we can compare some key findings with previous findings.

First, our estimated point prevalences of the internalizing disorders are close to estimates of point prevalence in previous studies.<sup>16,43-45</sup> The relative differences in point prevalence for men and women are also as expected.<sup>4,15-17,46</sup>

Second, similar to this study, two reviews found that the point prevalence of internalizing disorders followed a nonlinear development over lifetime following an inversed U-shape.<sup>16,45</sup> Anxiety disorders manifested an initial rise in prevalence until age 30, followed by a decrease which was more pronounced after age 50, similar to our

findings.<sup>16</sup> The pattern for MD was slightly different—a rise in the prevalence of MD until age 50, followed by a decrease, and a second rise after age 75. This review also suggested similar curves for men and women across the lifespan.<sup>16</sup> Another review described an increase in the prevalence of DYS at early ages with a peak around 50 years.<sup>45</sup> Unlike our study, these reviews included studies with substantial heterogeneity, used relatively few data points (e.g., 141<sup>45</sup>), and did not formally test for nonlinearity or sex differences in their results.

Since this is the first study that used advanced nonlinear models to investigate the prevalence of internalizing disorders and traits across age and sex, we should be careful in drawing definitive conclusions. But if the results prove to be robust, they may have several implications.

First, the fact that the relative gender gap remains stable over the lifetime has implications for hypotheses about risk factors for internalizing disorders. Women clearly report more internalizing disorders than men. Previous studies showed that the gender gap in MD prevalence arises in puberty, due to higher incidence rates in women.<sup>4,47,48</sup> One of the hypotheses for this gender gap are changes in female sex hormones during lifetime, for instance around the menopause. There are suggestions that estrogens are neuroprotective, and a decrease in estrogens in menopause would increase women's risk of MD.<sup>49</sup> Several cross-sectional and longitudinal studies have studied the prevalence of MD and anxiety disorders around the menopause in women, but results are inconsistent.<sup>4-8</sup> Our study shows that around the age of the menopause, women indeed report more MD and depressive symptoms. However, there is a similar rise in MD and depressive symptoms in men in this age group. This implies that perimenopausal changes in female sex hormones probably do not significantly influence women's risk of depression, unless male hormonal changes or other male-specific risk factors exist that explain the similar increase in depression prevalence in middle-aged men. It is more likely that shared risk factors -e.g., psychosocial distress- explain the similar rise in depression prevalence in both sexes during midlife.<sup>5</sup> A similar argument can be made for anxiety disorders, in which the relative gender gap is also stable across age.

Second, the prevalence of most internalizing disorders showed different patterns over lifetime, which suggests that these disorders are not entirely identical constructs, but may have meaningful differences in etiology. At the same time, the similarity of the general pattern among the internalizing disorders suggests that there are likely shared risk factors.<sup>50-52</sup>

Third, the lifetime patterns of internalizing disorders differed from those of the internalizing traits, suggesting that the relationship between internalizing disorders and

traits is complex, or at least not stable across the lifespan. For instance, the prevalence of depressive symptoms, but not MD, was rising after the age of 65. This may be due to the fact that older subjects report somatic symptoms of depression more often without having episodes of MD.<sup>53,54</sup> In any case, the difference implies that we should be cautious in reducing internalizing disorders to high scores on symptom dimensions.<sup>25,52</sup>

In any case, the fact that internalizing disorders show different patterns across age and sex than internalizing symptoms and neuroticism is relevant for the debate on the nature and classification of internalizing disorders. In this debate, psychopathology is assumed to exist on a continuum instead of there being clear boundaries between health and disease.<sup>25,55</sup> Although we only investigated differences in prevalence rates, our data show that there may be important differences between internalizing disorders and symptoms and traits. This difference implies that we should be cautious in reducing internalizing disorders to high scores on symptom dimensions.<sup>25,52</sup> This concern is supported by genetic studies showing that depressive symptoms are not always good proxies for MD.<sup>24,56</sup>

### Strengths and limitations

This is the first study that used advanced nonlinear models to investigate the development of internalizing disorders over lifetime in a large sample from the general population. The disorders were assessed with structured interviews by trained research assistants, and focused on current psychopathology to minimize recall bias.<sup>57,58</sup>

We also note a number of limitations. Our study uses cross-sectional data, and therefore cannot exclude period or cohort effects as an explanation for the change in point prevalence estimates across different ages. It is unlikely, however, that our findings are exclusively based on period and cohort effects. A recent study in 611,880 subjects from the US population controlling for period and cohort effects showed that prevalence of depressive episodes followed an inverse U-shaped curve with increasing prevalence from the age of 18 and decreased after age 32, and that psychological distress declined with age.<sup>3</sup> Also population studies that were performed two decades apart indicate that the reduction of internalizing disorders is associated with older age.<sup>11,16,44</sup> Future assessment waves of Lifelines would allow an investigation of age, period, and cohort effects.

Similar to these population studies, we observed a reduction in the prevalence of internalizing disorders at older age. There are two types of explanations for the decline of internalizing disorders; (1) age is protective against internalizing disorders, (2) age is not protective, but internalizing disorders are less frequently measured in older participants due to biases. Selection bias occurs when older individuals with MD are relatively less often participating in population studies than younger individuals with MD due to increased



risk of death, difficulty in establishing contact or increased refusals.<sup>59–61</sup> Reporting bias might be a result of older people being less likely to report symptoms of depression.<sup>62,63</sup> It is also possible that the prevalence of depression at older age is lower because individuals suffering from depression are more likely to have died earlier due to related causes such as heart problems (i.e. survivor bias).<sup>64,65</sup> However, in Lifelines, we found no interaction effect between age and the presence of an internalizing disorder at baseline when predicting participation at follow up (2014–2017) (data not shown). This means that the impact of having a disorder on attrition for any reason was not different for older as compared to younger subjects, which makes selection bias a less likely explanation for the reduction in prevalence after age 50. Follow-up studies are needed to investigate explanations for the decline of internalizing disorders, symptoms, and traits in older participants.

Third, we assessed current internalizing disorders based on structured interviews with trained research assistants, which can be considered a strength. However, there were two limitations in the assessments. Disability was not assessed for MD and GAD, and DYS was not assessed in subjects who satisfied criteria for MD, which could have biased prevalence rates upwards and downwards, respectively. It is most likely that these biases have been minor given that our estimates of MD, GAD, and DYS are comparable to previous estimates.<sup>11,16,44,45</sup>

Fourth, the presence of internalizing symptoms may influence subjects' reports on internalizing traits like neuroticism, which could complicate disentangling between states and traits. Previous studies showed that subjects with depressive symptoms may temporarily score higher on neuroticism.<sup>66,67</sup> If internalizing symptoms indeed have a strong effect on neuroticism, then we would have expected to see a similarity between the patterns of internalizing symptoms and neuroticism across age. However, in our study, neuroticism scores were not showing the same patterns as depressive symptoms, generalized anxiety symptoms, or NA. For example, neuroticism scores were lower in subjects aged 30–50 years than in younger subjects, whereas depressive symptoms were higher in this age group. Although these findings do not fully exclude that internalizing symptoms may have influenced neuroticism scores, it shows that the influence in our study is probably modest.

## **Conclusion**

This study identified different patterns in point prevalence for most internalizing disorders, symptoms and traits over lifetime. The overall prevalence of internalizing disorders and traits in women was higher than in men, but the patterns across age were remarkably similar in both sexes. These results indicate that certain hypotheses for the gender gap, e.g., the changes in female sex hormones during menopause, are unlikely explanations. Future studies are needed to investigate the causes for the initial rise in internalizing disorders and their decline at older age, taking into account the sex similarities.

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