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Risk factors for depression: differential across age?

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ABSTRACT

Introduction: The occurrence of well-established risk factors for depression differs across the lifespan. Risk factors may be more strongly associated with depression at ages when occurrence, and therefore expectance, is relatively low ('on-time off-time' hypothesis). This large-scale study examined absolute and relative risks of established risk factors for depression across the lifespan.

Methods: Participants were 2,215 currently or never depressed adults aged 18-93 years from two cohort studies: NESDA and NESDO. The occurrence of nineteen established risk factors (absolute risk) was examined in different age groups. In addition, the relative risk of these risk factors for depression was compared across age groups by examining risk factor*age interaction.

Results: The occurrence of all risk factors differed significantly across age groups. Although most risk factors had significant associations with depression across the lifespan, for five risk factors the strength of the association was age-dependent. Stronger associations with depression in younger age were found for childhood abuse, pain, higher body mass index (BMI) and number of chronic diseases, whereas low income imposed a stronger risk in older age. Associations with depression were strongest in age groups where occurrence was lowest.

Conclusions: Although the exposure to risk factors changes across the lifespan, the relative risk associating them to depression remains similar for most risk factors. However, some specific risk factors (low income, and health factors pain, BMI, and number of chronic diseases) seem more strongly associated with depression in ages in which occurrence is lowest and least expected.

OBJECTIVE

Major depressive disorder (MDD) is a heterogeneous disorder, with many contributing etiological pathways. A well-known model to explain the development of MDD is the Stress-Vulnerability Model.(1) This model postulates that the likelihood for depression increases due to the interaction between intrinsic vulnerability (e.g. heritability) and risk factors (e.g. life events, unhealthy lifestyle, chronic diseases, and low socioeconomic status). Intrinsic vulnerability to depression is largely innate,(2) and determined by genetic profile and personality, which both were shown to be most strongly associated with early-onset MDD.(3-6) Most risk factors can occur at any point throughout life and the likelihood of their occurrence (constituting the absolute risk) differs across the lifespan. In addition, it could be true that the strength of the associations between these risk factors and depression (relative risk) changes over the lifespan.

When risk factors are more likely to occur at certain ages, it could be that the likelihood for depression related to these risk factors is also increased at these ages. For example, widowhood, a small social network and chronic diseases are more likely to occur among older than among younger persons, and therefore seem important risk factors for MDD especially at an older age. However, it has also been argued that when a risk factor is present in an age group in which its occurrence is usually low, thus when the occurrence of the risk factor is least expected, its association with depression might be larger. This so-called 'on-time, off-time' hypothesis suggests that one's response to stressors might differ depending on the timing of these stressors, with individuals showing better adaptation if stressors occur when most expected (on-time).(7) From this perspective, widowhood and poor health may be considered common phenomena belonging to the aging process, with a high occurrence at older age, while at the same time they carry a stronger relative risk for MDD at younger ages.(8,9)

In a previous review,(10) inconsistencies were found for the association between age and the occurrence of depression, and it was suggested that age-related variability in depression risk factors combined with no adjustment for these risk factors could be one of the mechanisms behind these inconsistencies. Indeed, another study showed that the association between age and depression was reduced after adjusting for impairment and somatic health.(11) However, to our knowledge, very few studies directly studied interaction between risk factors and age in the association with MDD, and the occurrence of risk factors

of MDD and their relative impact on MDD have never been studied across the entire adult lifespan within one study design. Insight into differences in both absolute and relative risks across the lifespan might help improve age-tailored depression prevention strategies. Therefore, the aim of the current study is to examine whether the occurrence of nineteen well-established risk factors for MDD differs across the lifespan, and whether these risk factors exert a stronger association with depression in specific age groups, using a broad age range (18-93 years). We expected reduced social functioning, poor health, and recent negative life events to be more prevalent in older adults. Hence, following the 'on-time, off-time' hypothesis, we expected these risk factors to demonstrate the strongest association with depression in younger ages. For the other risk factors we had no clear rationale to believe that they would differ in occurrence or in the strength of their association with depression across the lifespan.

METHODS

Study sample

Data in this study were derived from two on-going, naturalistic cohort studies that used similar measurements and had comparable infrastructures: the Netherlands Study of Depression and Anxiety (NESDA), with participants aged 18 to 65 years, and the Netherlands Study of Depression in Older Persons (NESDO), of which participants are between 60 and 93 years old. Both cohorts are set up to study the natural course, predictors, and prognosis of MDD, and are described in detail elsewhere.(12,13)

Briefly, NESDA consists of 2,981 persons with a current depressive and/or anxiety disorder (n=1,701), a remitted depressive and/or anxiety disorder (n=628), or no lifetime depressive and anxiety disorder (n=652). Sampling areas were the general population (overall response rate 56.0%), primary health care (response rate 45.0%), and outpatient mental health care facilities (response rate 57.0%). NESDO consists of 510 persons with either a current depressive disorder (n=378) or no lifetime depressive and anxiety disorder (n=132), who were recruited through primary healthcare (response rate 63.5%), and out- and inpatient mental health care facilities (response rate 48.7%). NESDA and NESDO used the following exclusion criteria: 1) insufficient command of the Dutch language or insufficient capability to participate; 2) a primary clinical diagnosis of a psychiatric disorder other than depressive and anxiety disorders; and for NESDO additionally 3) (clinician-suspected) dementia, or having a Mini-Mental State Examination (MMSE) (14) score below 18 (out of 30). In order to establish whether participants had a current, remitted, or lifetime diagnosis of depressive and anxiety disorders or were never-depressed comparisons, the Composite International Diagnostic Interview (CIDI, lifetime, version 2.1) (15), based on DSM-IV criteria, was conducted by trained research staff during baseline assessment.

In the current study we used baseline data from both NESDA and NESDO, thereby including those who either had a current MDD diagnosis (present in the past 6 months) at baseline and were outpatients, and those who had no lifetime diagnosis of MDD nor any anxiety disorder (comparisons), resulting in a sample size of 2,215 participants for the current study (1,431 with MDD and 784 comparisons). Baseline face-to-face assessments were completed at participating centers between 2004 and 2007 for NESDA, and between

2007 and 2010 for NESDO. Ethical approval was obtained by both NESDA and NESDO from all Ethical Review Boards of the participating centers, and all participants provided written informed consent.

Measures

Risk factors for depression

Socio-economic status

Education in years and income in Euros (per 1000 per month) were obtained during the baseline face-to-face assessment using standard questions.

Life stressors

Childhood abuse was assessed in the face-to-face interview with the Childhood Trauma Inventory, following the procedure of the Netherlands Mental Health Survey and Incidence Study (NEMESIS).(16) Participants were asked to report whether four types of childhood abuse had taken place before they reached age 16: emotional neglect, psychological abuse, physical abuse, and sexual abuse. For each type of abuse, answer categories were 'never', 'once', 'sometimes', 'regularly', 'often', or 'very often'. Answers were then recoded into three groups: 'never' (0), 'once or sometimes' (1), and 'regularly, often, or very often' (2). Using the sum of these groups, the childhood abuse index was created (range 0-8) as an indicator of cumulative exposure to childhood abuse.(17)

The List of Threatening Experiences(18) was also part of the face-to-face interview and was used to establish the presence of 12 negative life events in the past five years (i.e. participant was seriously ill/wounded/victim of violence; participant's family member was seriously ill/wounded/victim of violence; parent, child, brother or sister died, friend or family member died, friendship with a close friend/family member ended, having serious problems with close friend/family member, something worthwhile/money was stolen or lost, participant separated from partner; participant became unemployed; participant got fired; participant had serious financial problems; participant had contact with police or justice for misdemeanor). The total number of life events in the past five years was examined by creating a sum score of the

individual events. In all ages the presence of the same set of life events was asked.

Personality

The 'Big Five' personality traits (neuroticism, agreeableness, openness, conscientiousness and extraversion) were assessed using the NEO-Five Factor Inventory (NEO-FFI) questionnaire.(19) Each personality trait is measured using 12 items (e.g. 'I laugh easily') on a 1 (strongly disagree) to 5 (strongly agree) scale. Consequently, scores for each domain range from 12 to 60, a higher score indicating larger presence of the personality trait. In addition, the 5-item version of the Pearlin Mastery Scale(20) (ranging from 0 to 25) was included to assess mastery.

Social functioning

Loneliness was assessed using the 11-item Loneliness and Affiliation Scale(21) questionnaire with a total score range from 'no loneliness at all (0)' to 'very severe loneliness (11)'. Social network size was measured with a questionnaire as well and depicted the number of adults with whom participants had regular and important contacts. It was dichotomized into having a small social network (0-5 persons) or a large social network (6 or more persons). Partner status was measured face-to-face by asking standard questions and was dichotomized into 'being married or having a partner' versus 'not being married and not having a partner'. Social support was measured using the Close Person Inventory questionnaire,(22) in which questions about confiding and emotional support, practical support, and negative aspects of relationships were assessed for a partner, a first confidant and a second confidant. In case participants had no partner, the partner items were coded as missing. In case participants had no first or second confidant, their items were coded as zero. Social support was expressed in the mean of all items across all three relationships, with items belonging to negative aspects of relationships recoded.

Lifestyle

Alcohol use was measured using a questionnaire and operationalized as the number of alcoholic drinks per week. Physical activity was assessed using a questionnaire as well, by

conducting the International Physical Activity Questionnaire (IPAQ) (23) and expressed in 1000 Metabolic Equivalent Total (MET)-minutes per week ((MET-level*minutes of activity*events per week)/1000). A higher number of MET-minutes indicates higher physical activity.(24) Smoking was dichotomized, into current smoker (1) or no smoker (0).

Health

Pain was assessed in the face-to-face interview using the Chronic Pain Grade,(25) and participants were categorized into five grades based on a combination of pain intensity and pain disability experienced: grade 0 (no pain symptoms); grade 1 (low pain intensity-low disability); grade 2 (high intensity-low disability); grade 3 (high disability-moderately limiting); grade 4 (high disability-severely limiting). These grades were used as a continuous variable. Body Mass Index (BMI) was calculated using measured weight and height (kg/m^2) as measured by the research assistants. Furthermore, the number of chronic diseases under treatment was established during the face-to-face interview. Included diseases were lung disease, heart disease, diabetes mellitus, stroke, osteoarthritis, cancer, ulcers, intestinal disease, liver disease, epilepsy, and thyroid disease.(26)

Outcomes

Depression diagnosis and severity

Two outcome measures were used. First, a dichotomous indicator of current (6-month recency) MDD presence established using the CIDI. Second, a continuous indicator for severity of depressive symptoms was based on the self-report Inventory of Depressive Symptomatology (IDS-SR),(27) ranging from 0 to 84.

Age

Participants provided their age (range 18 to 93 years) during the baseline interview. Age was used as a continuous variable to include in interaction terms, as well as a categorical variable consisting of three categories (18-39 years (n=787), 40-59 years

(n=852), and 60+ years (n=576)) for stratification and illustration purposes.

Statistical analysis

In order to see whether the occurrence (in percentages or means) of risk factors differed between the three age groups, chi-square analyses were performed for categorical risk factors, and analysis of variance for continuous risk factors. We also performed simple linear regression analyses using age (per 10 years) as a continuous dependent variable and the risk factor as independent variable.

Next, to test the associations between risk factors and depression, logistic regression analyses were performed for each risk factor separately. In each analysis, the risk factor was the independent variable, and MDD presence (current MDD versus no lifetime diagnosis of MDD) was the dependent variable. Two models were tested: model 1 only included the risk factor for depression, adjusted for sex and age (continuous); in model 2 an interaction term between the risk factor for depression and age (continuous) was added. All continuous variables used in interaction terms were centered. The same two models were then assessed using linear regression with severity of depressive symptoms as outcome measure.

In case risk factors showed a significant interaction effect with age that was consistent for both MDD presence and severity of depressive symptoms, associations between these risk factors and both outcomes were stratified for the three age groups (18-39 years, 40-59 years, 60+ years), adjusted for sex. An alpha of 5% was used to determine statistical significance. Analyses were performed using SPSS 20 for Windows (IBM SPSS Statistics, IBM Corporation, Armonk, New York).

RESULTS

The occurrence of risk factors for depression, expressed in percentages or means per age group are shown in Table 1. All risk factors were significantly associated with age. Risk factors associated with younger ages were low income, recent negative life events, high neuroticism, low agreeableness, and smoking. Older age was associated with less education, low openness, low conscientiousness, low mastery, loneliness, a higher BMI, low physical activity, and chronic diseases. For some risk factors, their association with age seemed to be non-linear. More specifically, middle-aged persons more often reported childhood abuse, more often had low extraversion or a small social network, had higher alcohol consumption, and had higher levels of pain compared to the youngest and oldest persons. The youngest and oldest participants were more likely not to have a partner, compared to middle-aged persons.

All nineteen risk factors assessed were indeed associated with the presence of MDD and/or the severity or depressive symptoms (Table 2). In addition, this Table illustrates the findings for interaction terms between risk factors and age, testing whether the associations between risk factors and depression differed across age. Fourteen out of the nineteen risk factors (74%) were associated with both MDD presence as well as severity of depressive symptoms, but showed no consistent interaction effect with age for both outcomes (Table 2). Risk factors that showed similar associations with depression across the entire lifespan were: low education, recent negative life events, high neuroticism, low conscientiousness, low extraversion, low agreeableness, low openness, low mastery, loneliness, not having a partner, smaller social network, alcohol consumption, low physical activity, and smoking.

Five risk factors (26%), however, demonstrated interaction effects with age consistently for both MDD and depressive symptom severity (Table 2) and were therefore considered to be age-dependent relative risk factors. Although associations between these risk factors and depression were overall significant in almost all age groups, for five risk factors the risk for depression was stronger at one end of the age spectrum (Table 3). Risk factors that had a significantly larger relative risk in younger persons were childhood abuse, high BMI, high pain, and higher number of chronic diseases. On the contrary, low income was more strongly associated with depression in older age.

Table 4 summarizes in which age-range risk factors that showed an interaction effect with age were most likely to occur, at which age these risk factors showed the strongest association with depression, and whether these findings are in line with the 'on-time, off-time' hypothesis. As can be seen, for all age-dependent variables a high absolute risk was not accompanied by a high relative risk.

CONCLUSIONS

The current study confirmed the importance of a wide range of well-established risk factors for depression, showing that they remain important across the entire lifespan (18 to 93 years). As would be expected, exposure to risk factors changed with age: some risk factors (e.g. loneliness and the number of chronic diseases) are more prevalent in old age, whereas others are more common in young age (e.g. the number of negative life events and smoking). In contrast with this, we found that the relative risk associated with most risk factors remained constant across the lifespan. We found interaction effects between 5 out of 19 risk factors (i.e. low income, childhood abuse, and multiple aspects of poor health) and age on depression, suggesting that the relative risk these factors impose on depression is age-dependent. In line with our hypothesis, these risk factors carried the strongest relative risk in the age group in which the exposure was lowest. Thus, we found some evidence for the 'on-time, off-time' hypothesis,(7) indicating risk factors for depression may have the strongest impact when their timing is least expected.

Keeping the 'on-time, off-time' hypothesis in mind, we hypothesized that recent negative life events, reduced social functioning and aspects of poor health could be more strongly associated with depression in younger ages, since in this age group these risk factors are less common and occur 'off time'. For poor health, our findings indeed confirmed the 'on-time, off-time' hypothesis, as all negative aspects of health were more common in older age groups, but their association with depression was strongest in young persons. Within the health category, BMI was only associated with depression in young age. Previous studies have found obesity to be a protective factor against dementia and cognitive decline in middle aged and older persons.(28,29) Our findings suggest that the negative consequences of a high BMI may be reduced in old age for depression as well, although this needs to be studied more extensively. Another explanation for this finding could be that being overweight affects body image and perception about one's self, and weight perception has been shown to be a risk factor for depression in young adult men and women (30). As opposed to BMI, pain and the number of chronic diseases were still significantly and substantially associated with depression at an older age as well. Previous research found pain to be associated with depression in older persons(31), but our study found the odds ratio for the youngest age group (OR=2.42) to be highest (compared to OR=2.31 for persons aged 40-59 years and OR=2.09 for 60+ years). Kiviruusu et al.(32) did find chronic illness to be associated

with depression in young adults, but only in males. The current study, however, found these associations in all ages and in a mixed gender sample. Moreover, odds ratios demonstrated that the association between chronic diseases and depression is substantially stronger for the youngest age group (OR=2.26), compared to persons aged between 40-59 years (OR=1.19) and those who are aged 60+ years old (OR=1.43). In addition, Kiviruusu et al.(32) further showed that the association between chronic illness and depression attenuated when taking coping mechanisms and locus of control into account. Poor health is generally mostly associated with the onset of late-life depression,(33,34) for instance in the context of cerebrovascular disease, neurodegeneration, and inflammation, which are all factors that may increase susceptibility to depression.(35) Because it would be expected that these processes are less apparent in young age, perhaps in young age the association between poor health and depression is more driven by a lack of coping when chronic diseases occur 'off time'. So, when chronic diseases occur 'off-time', at young age, appropriate coping mechanisms may help limit the effect of chronic diseases on depression. It is also possible that the mechanisms linking poor health to depression may differ across the life span. For example, one study showed that physical illness was associated with depression in older persons, but in middle-aged persons this association was mediated by medication use (36). Altogether, our findings indicate that, although often linked to late-life depression,(33,34) pain and chronic diseases play an essential role in depression at younger ages as well and should not be overlooked, although the nature of their effects may differ across ages. Depression prevention and treatment strategies in these areas should not be limited to older adults.

Contrary to our expectations we did not find an 'on-time, off-time' effect for reduced social functioning and recent negative life events. Both of these risk factors showed similar associations with depression across the lifespan, and their occurrence was not uniformly highest in old age. For example, the number of recent negative life events was highest in young age, and non-linear patterns were found for the occurrence of not having a partner and having a small social network. In a previous study performed among participants with physical disabilities, the association between social support and depression was also shown to be independent of age (37). The fact that we found the number of negative recent life events to be highest in younger ages and to be equally detrimental with respect to their impact on depression across the lifespan

might have to do with the specific life events included. Possibly, differential associations between recent negative life events and depression across the lifespan can only be observed when looking at these events separately. However, the prevalence for the specific life events of interest, for instance widowhood, was too low in the youngest group to perform reliable analyses. Still, future studies ideally should divide recent negative life events into age-appropriate life events versus life events unexpected for certain ages when occurrence rates allow to do so. In the current study, this measure should best be interpreted as a measure of recent negative life events that occur 'on-time'

Even though we could not confirm the 'on-time, off-time' hypothesis for reduced social functioning and recent negative life events, all age-dependent variables were most strongly associated with depression in the age group in which occurrence of the risk factor was lowest. Although we did not have clear expectations about the association between income and depression across the lifespan, we found low income to be more likely in younger age, whereas the association between low income and depression was highest in older age. Younger persons may expect their income to increase with time. Also, especially when a drop in income has taken place, access to certain aspects of care, such as hiring caregivers to provide home care, may be inaccessible. Given the fact that the need for such care increases with age, this may explain the association between low income and depression in late-life. The association cannot be explained by the lack of access to general practitioners or specialists, which has been suggested previously,(38) since these are part of obligatory health insurance in The Netherlands. Taken together, our findings provide support for the notion that risk factors may have a stronger association with depression when their occurrence is least expected.

We expected childhood abuse and personality to have a stronger association with depression in younger ages, because of their established association with early-onset MDD.(4-6) We found childhood abuse to be an age-dependent risk factor indeed showing the strongest association with depression in younger ages, but even in old age childhood abuse was still associated with depression. This finding is in line with previous research showing that childhood abuse is also associated with late-onset depression.(39) However, we found personality to be an age-independent risk factor, displaying similar associations

with depression in all ages. As personality has previously been shown to affect depression treatment outcomes,(40) it is important to note that personality is associated with depression across the lifespan, despite its associations with early-onset depression.(4-6)

We found lifestyle factors to be equally associated with depression across the life span. Although few studies have investigated age-specific associations between lifestyle and depression, another study also demonstrated that physical activity was associated with depression in women of all ages.(41)

This study is the first to examine a variety of risk factors associated with depression within one large sample covering the entire adult lifespan. In addition, we used clinical DSM-IV diagnoses to establish presence of MDD, and we were able to study a wide range of well-established risk factors. Further, in order to limit the number of chance findings, we only considered risk factors to be age-dependent when they showed an interaction effect with age consistently for having an MDD diagnosis as well as depression severity. A limitation of this study is the cross-sectional design, preventing us from studying associations between risk factors and depression onset. This way, temporality cannot be established, leaving it unclear whether risk factors preceded or occurred due to depression. The cross-sectional design also complicates the ability to distinguish age effects from birth cohort effects. Also, the age categories used in this study were arbitrary. One could argue that differences exist, for example, within the group of persons aged 60 and above and comparing more than three age groups might be ideal to observe age differences in more detail. However, because the number of old persons in this study is somewhat lower compared to the number of younger persons, dividing the sample into quartiles or quintiles would still cause all persons aged 61 and above and 63 and above respectively to be placed into the same age category. It is important to emphasize that since all age cut-offs have a partly arbitrary nature, we also included analyses with continuous age which basically confirms that age differences found in the impact of risk factors are not simply dependent on the choice of specific age cut-offs. Another limitation is that for some risk factors in our study, associations with older age may have been underestimated due to a healthy survivor effect. For example, those who suffered the most severe consequences of childhood abuse may not have survived until old age and may therefore not be included in our study. Further, our measure of socio-economic status

only included years of education and household income, which may be seen as a somewhat narrow definition of the concept. Future studies could broaden this definition in order to make sure no relevant characteristics are missed. Finally, especially the oldest subjects may have shown age-dependent recall bias, as in older age, it may be hard to remember the exact nature of childhood abuse as well as feelings of past depression.

In order to efficiently target risk factors with regard to depression prevention across the lifespan, a measure incorporating both the occurrence of risk factors as well as the strength of the association between risk factors and MDD could be helpful. In our study, we were unable to include such measure as these measures often require population prevalences of risk factors and incidence rates for outcome measures. Also, additional longitudinal research into age-specific risk factors for depression could help create risk profiles or prediction models in order to establish common combinations of risk factors strongly associated with depression onset across the lifespan. With regard to the current findings, clinicians should note especially that risk factors thought to have a large impact on depression in certain ages due to their likelihood to occur, may be equally or even more important at other ages.

To conclude, this study confirmed a wide range of well-established risk factors for depression and showed that these risk factors are relevant across the *entire* adult lifespan for both MDD as well as for severity of depressive symptoms. For specific risk factors (low income, and the health factors higher BMI, pain and the number of chronic diseases), we found evidence that associations with depression were stronger in the age group where occurrence was least expected and thus 'off-time'.

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Table 1. Occurrence (in frequencies or means and standard deviations) of depression risk factors per age category, and linear associations between risk factors and age

	Age categories					Age continuous[a]			
	18-39 (n=787)	40-59 (n=852)	60+ (n=576)	test value(df)	p	B	SE	t(df)	p
Socio-economic status									
Education, in years, M (SD)	12.25 (3.1)	11.92 (3.5)	11.22 (3.5)	F=16.06(2, 2212)	**<.001**	-0.55	0.11	-5.10(2214)	**<.001**
Income, in 1000 Euros, M (SD)	2.02 (1.06)	2.38 (1.17)	2.28 (1.13)	F=2.57(2, 2173)	**<.001**	1.84	0.32	5.84(2175)	**<.001**
Life stressors									
Childhood abuse index, M (SD)	1.35 (2.00)	1.85 (2.27)	1.49 (2.10)	F=12.18(2, 2203)	**<.001**	0.29	0.17	1.72(2205)	.09
Recent negative life events, M (SD)	2.81 (1.83)	2.48 (1.69)	1.75 (1.36)	F=68.61(2, 2207)	**<.001**	-2.26	0.21	-11.02(2209)	**<.001**
Personality									
Big Five									
Neuroticism, M (SD)	37.52 (10.09)	36.20 (10.16)	34.46 (9.64)	F=14.98(2, 2158)	**<.001**	-0.20	0.04	-5.59(2160)	**<.001**
Agreeableness, M (SD)	43.58 (5.41)	43.78 (5.24)	44.14 (5.54)	F=1.77(2, 2152)	**<.001**	0.17	0.07	2.57(2154)	**.01**
Openness, M (SD)	38.08 (6.14)	37.80 (5.89)	31.47 (6.12)	F=233.22(2, 2152)	**<.001**	-0.94	0.05	-18.50(2154)	**<.001**

Conscientiousness, M (SD)	40.77 (6.67)	41.74 (6.83)	39.04 (6.41)	F=27.29(2, 2155)	**<.001**	-0.16	0.05	-3.01(2157)	**.003**
Extraversion, M (SD)	37.55 (8.04)	35.64 (7.71)	36.16 (7.39)	F=12.76(2, 2156)	**<.001**	-0.19	0.05	-4.06(2158)	**<.001**
Mastery, M (SD)	17.44 (4.71)	16.62 (5.07)	16.64 (5.14)	F=5.74(2, 932)	**.003**	-0.25	0.08	-3.17(1934)	**.002**
Social functioning									
Not having a partner, %	37.2	27.1	38.2	X=26.17(2)	**<.001**	-0.07	0.77	-0.09(2214)	.93
Loneliness, M (SD)	4.03 (3.72)	4.95 (3.88)	5.06 (3.80)	F=14.11(2, 1949)	**<.001**	0.47	0.10	4.71(1951)	**<.001**
Small social network, %	48.2	58.0	49.5	X=18.06(2)	**<.001**	0.87	0.72	1.20(2184)	.23
Social support, M (SD)	28.14 (12.92)	25.75 (13.52)	24.32 (13.59)	F=13.97(2,2137)	**<.001**	-0.11	0.03	-4.19(2138)	**<.001**
Lifestyle									
Number of alcoholic drinks per week, M (SD)	5.40 (8.43)	8.14 (11.22)	5.87 (8.19)	F=18.74(2, 2175)	**<.001**	.04	0.04	1.18(2177)	.24
Physical activity, in 1000 MET-minutes, M (SD)	3.55 (2.98)	3.64 (3.35)	3.01 (2.87)	F=7.59(2, 2085)	**.001**	-0.57	0.12	-4.74(2087)	**<.001**
Smoking, %	36.9	35.7	21.8	X=40.93(2)	**<.001**	-	0.71	-6.10(2204)	**<.001**

						4.67				
Health										
Pain, M (SD)	1.55 (1.03)	1.79 (1.15)	1.72 (1.20)	F=9.45(2, 2207)	**<.001**	1.09	0.32	3.43(2209)	**.001**
Body Mass Index, M (SD)	24.41 (5.01)	26.52 (5.17)	26.61 (4.47)	F=47.82(2, 2210)	**<.001**	0.64	0.07	9.09(2212)	**<.001**
Number of chronic diseases, M (SD)	0.33 (0.61)	0.79 (0.97)	1.43 (1.20)	F=231.11(2, 221)	**<.001**	7.30	0.32	23.04(2213)	**<.001**
Outcome measures									
MDD diagnosis, %	62.8	65.0	66.5	X=2.12(2)	.35	1.41	0.76	1.87(2214)	.06
Severity of depressive symptoms, M (SD)	22.69 (15.55)	24.90 (16.13)	23.35 (15.41)	F=4.20(2, 2179)	**.02**	.03	0.02	1.40(2181)	.16

Table 2. Main effects and interaction effects between risk factors of depression and age on the presence of an MDD diagnosis and severity of depressive symptoms

	MDD diagnosis				Severity of depressive symptoms							
	Model 1: Risk factor		Model 2: Risk*age interaction[a]		Model 1: Risk factor				Model 2: Risk*age interaction[a]			
	OR (95% CI)	p	OR (95% CI)	P	B	SE	t(df)	p	B	SE	t(df)	p
Socio-economic status												
Education (in years)	0.89 (0.86-0.91)	**<.001**	1.00 (0.98-1.01)	.55	-1.14	0.10	-11.66(2181)	**<.001**	0.07	0.06	1.16(2181)	.25
Income (per 1000 Euros)	0.67 (0.62-0.73)	**<.001**	0.94 (0.89-0.98)	**.01**	-3.33	0.30	-11.28(2143)	**<.001**	-0.78	0.18	-4.45(2143)	**<.001**
Life stressors												
Childhood abuse index (score)	1.60 (1.50-1.71)	**<.001**	0.95 (0.91-0.99)	**.01**	2.89	0.15	19.80(2172)	**<.001**	-0.25	0.10	-2.61(2172)	**.01**
Number of recent negative life events	1.28 (1.20-1.35)	**<.001**	0.99 (0.96-1.03)	.72	1.86	0.20	9.37(2176)	**<.001**	0.03	0.13	0.21(2176)	.83
Personality												
Neuroticism (score)	1.32 (1.29-	**<.001**	1.00 (0.99-	.84	1.26	0.02	61.14(2154)	**<.001**	0.01	0.01	0.78(2154)	.43

	1.35)		1.01)									
Agreeableness (score)	0.90 (0.89-0.92)	**<.001**	1.01 (1.00-1.02)	.07	-1.02	0.06	-16.85(2149)	**<.001**	0.08	0.04	2.30(2149)	**.02**
Openness (score)	0.99 (0.97-1.00)	.08	0.99 (0.98-1.00)	**.02**	-0.21	0.06	-3.83(2149)	**<.001**	0.03	0.03	0.82(2149)	.41
Conscientiousness (score)	0.86 (0.84-0.87)	**<.001**	1.00 (0.99-1.01)	.69	-1.03	0.05	-22.81(2152)	**<.001**	-0.004	0.03	0.14(2152)	.89
Extraversion (score)	0.81 (0.80-0.83)	**<.001**	1.01 (1.00-1.02)	.22	-1.28	0.03	-37.97(2152)	**<.001**	0.02	0.02	0.99(2152)	.32
Mastery	0.65 (0.63-0.68)	**<.001**	1.01 (0.99-1.04)	.23	-2.29	0.05	-46.81(1926)	**<.001**	0.06	0.03	2.06(1926)	**.04**
Social functioning												
Not having a partner (yes versus no)	1.85 (1.52-2.24)	**<.001**	1.11 (0.99-1.24)	.07	4.11	0.71	5.79(2181)	**<.001**	0.40	0.40	0.99(2181)	.32
Loneliness (score)	1.52 (1.46-1.58)	**<.001**	1.00 (0.98-1.02)	.98	2.47	0.08	33.04(1943)	**<.001**	-0.10	0.04	-2.27(1943)	**.02**
Small social network (yes versus no)	3.77 (3.13-4.54)	**<.001**	0.99 (0.88-1.11)	.83	10.81	0.63	17.05(2177)	**<.001**	-0.83	0.38	-2.21(2180)	**.03**
Social support (score)	0.98 (0.97-	**<.001**	1.00 (1.00-	.31	-0.24	0.03	-9.38 (2132)	**<.001**	0.03	0.02	2.17(2131)	**.03**

	0.98)		1.01)									
Lifestyle												
Number of alcoholic drinks per week	0.99 (0.98-1.00)	**.01**	0.99 (0.99-1.00)	.07	-0.09	0.04	-2.63(2173)	**.01**	-0.03	0.03	-1.09(2173)	.28
Physical activity (in 1000 MET-minutes)	0.96 (0.93-0.99)	**.004**	0.98 (0.97-1.00)	.08	-0.57	0.11	-5.13(2076)	**<.001**	-0.08	0.07	-1.18(2076)	.24
Smoking (yes versus no)	2.64 (2.14-3.24)	**<.001**	1.06 (0.93-1.21)	.39	6.86	0.71	9.60(2169)	**<.001**	0.81	0.45	1.82(2168)	.13
Health												
Pain (score)	2.26 (2.03-2.52)	**<.001**	0.94 (0.88-1.00)	**.048**	6.66	0.27	24.98(2176)	**<.001**	-0.73	0.16	-2.27(2176)	**.02**
Body Mass Index (in kg/m²)	1.02 (1.00-1.04)	**.02**	0.98 (0.97-0.99)	**.003**	0.44	0.07	6.40(2179)	**<.001**	-0.12	0.04	-2.85(2179)	**.004**
Number of chronic diseases	1.40 (1.26-1.56)	**<.001**	0.93 (0.87-0.99)	**.02**	3.76	0.36	10.51(2180)	**<.001**	-0.73	0.21	-3.46(2180)	**.001**

Adjusted for age and sex. [a]Age per 10 years.

Table 3. Main effects per age category of risk factors that showed consistent interaction effects with age

	MDD diagnosis		Severity of depressive symptoms			
	OR (95% CI)[a]	P	B	SE	t (df)	p
Income (in 1000 Euros)						
18-39 years	0.73 (0.63-0.84)	**<.001**	-2.10	0.52	-4.00(757)	**<.001**
40-59 years	0.67 (0.59-0.76)	**<.001**	-3.81	0.46	-8.27(837)	**<.001**
60+ years	0.59 (0.50-0.70)	**<.001**	-4.51	0.56	-8.00(547)	**<.001**
Childhood abuse index (score)						
18-39 years	1.89 (1.64-2.18)	**<.001**	3.44	0.25	13.51(765)	**<.001**
40-59 years	1.52 (1.39-1.67)	**<.001**	2.67	0.23	11.61(842)	**<.001**
60+ years	1.52 (1.34-1.73)	**<.001**	2.60	0.29	9.02(563)	**<.001**
Pain (score)						
18-39 years	2.42 (1.96-2.98)	**<.001**	7.19	0.49	14.81(768)	**<.001**
40-59 years	2.31 (1.95-2.74)	**<.001**	6.78	0.43	15.90(844)	**<.001**
60+ years	2.09 (1.73-2.53)	**<.001**	5.86	0.49	12.08(562)	**<.001**
Body Mass Index (in kg/m2)						
18-39 years	1.06 (1.02-1.09)	**<.001**	0.60	0.11	5.32(768)	**<.001**
40-59 years	1.03 (1.00-1.05)	.09	0.44	0.11	4.13(844)	**<.001**
60+ years	0.97 (0.93-1.01)	.13	0.10	0.15	0.65(565)	.51
Number of chronic diseases						
18-39 years	2.26 (1.66-3.07)	**<.001**	5.80	0.89	6.50(768)	**<.001**
40-59 years	1.19 (1.02-1.39)	**.03**	3.22	0.56	5.71(844)	**<.001**
60+ years	1.43 (1.21-1.69)	**<.001**	3.62	0.52	6.99(566)	**<.001**

Adjusted for sex. [a]df = 4.

Table 4. Overview of the combinations between occurrence of risk factors and strength of associations with depression across age groups for risk factors showing significant interaction effects with age

Risk factor	Highest occurrence of risk factor	Stronger association with depression	In line with on-time, off-time hypothesis?[a]
Income	young age	old age	X
Childhood abuse index	middle-age	young age	N/A[b]
Pain	middle-age	young age	X
Body Mass Index	old age	young age	X
Number of chronic diseases	old age	young age	X

[a] This hypothesis is confirmed when a risk factor is more strongly associated with depression in the age group in which occurrence of the risk factor is lowest. [b] Childhood abuse occurred before age 16 for all participants, and therefore cannot have occurred 'on time' or 'off time'.