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## **The association between depressive mood and ischemic heart disease: a twin study**

**Running title:** Mood and ischemic heart disease in twins

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**ABSTRACT**

*Objective:* Individuals with mood disorders have increased risk of cardiovascular disease. The aims of this study were to evaluate if the risk of cardiovascular disease in individuals with mood disorder could be explained by shared genetic and early environmental factors.

*Methods:* We included 6,714 Danish middle and old aged twins from two large population-based studies. Cox proportional hazards regression was used to perform individual-level and intra-pair analyses of the association between self-reported depression symptomatology scores and register-based diagnoses of ischemic heart disease.

*Results:* Higher depression symptomatology scores (both total, affective and somatic) were associated with higher incidence of ischemic heart disease after multivariable adjustment in individual-level analyses. In intra-pair analyses, this association was similar but with slightly larger confidence intervals. There was no interaction with gender and no major differences between mono- or dizygotic twins. Within twin pairs, the twin scoring highest on depressive symptoms developed ischemic heart disease more often or earlier than the lower scoring twin. A sensitivity analysis including a 2-year time lag of depression symptomatology to limit the risk of reverse causality showed similar results.

*Conclusion:* Genetic factors and early life environment do not seem to explain the association between depressive mood and ischemic heart disease.

## **KEYWORDS**

Depressive mood, ischemic heart disease, twin study

## **SIGNIFICANT OUTCOMES**

- The well-known association between depression and ischemic heart disease also exists within twin pairs
- Genetic and shared early environmental factors did not seem to explain the association between depressive mood and ischemic heart diseases in middle and old age.

## **LIMITATIONS**

- Power limitations in the intra-pair analyses which limited stratification on gender or zygosity status.
- Lack of information on potential early life confounders such as childhood health and social relations may have biased the results.
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## **INTRODUCTION**

Mood disorders, including depression, are common mental illnesses and globally more than 300 million people suffer from depression<sup>1</sup>. Furthermore, depression is a leading cause of disability worldwide and a major risk factor for somatic diseases<sup>2-5</sup>.

Most notably, individuals with mood disorders have increased risk of cardiovascular disease, which has been reported in several studies including two large meta-analyses<sup>6,7</sup>. In the latest meta-analysis including only prospective studies, it was estimated that individuals with depression have approximately 30% higher risk of cardiovascular disease than individuals without depression<sup>6</sup>. One apparent explanation for this association is that adults with mood disorders have a more unhealthy lifestyle<sup>8</sup>. However, the association persists in studies, which have controlled for several lifestyle and socio-economic factors<sup>6</sup>.

Another possible explanation behind the relationship between cardiovascular disease and depression is shared genes or early environmental factors<sup>9</sup>. A recent large systematic review of genome-wide and candidate gene studies reported 24 potential pleiotropic genes that are likely to be shared between individuals with mood disorders and cardiometabolic diseases<sup>10</sup>. Furthermore, theories on the importance of the fetal period and early life environment suggest that these periods are crucial for an individual's subsequent risk of adult disease including both cardiovascular disease and depression<sup>11</sup>. Consequently, early factors such as growth restriction during the fetal period could be potential confounders of the association between mood disorders and cardiovascular disease<sup>12</sup>.

Sibling and family studies have often been used to provide evidence for the role of genetics, but also to account for confounding by unmeasured family-level risk factors<sup>13</sup>. Twin studies are even more powerful since twins compared to siblings also share intrauterine environment and more similar family circumstances, which can be accounted for by testing associations within twin pairs. One often applied method is the discordant twin-pair design<sup>14</sup>. The idea of this method is to examine whether twins who are discordant regarding an exposure will have different risk of an outcome in intra-pair analyses compared to individual-level analyses, hence, independent of shared genes and early environment.

#### *Aims of the study*

We used two large population-based twin cohorts to investigate: 1) whether the association between depressive mood and ischemic heart disease was present in individual-level analyses, that is, in a standard cohort analysis treating each twin as individuals; 2) whether a potential association could

be replicated in intra-pair analyses of twin pairs i.e. after adjusting for genetic factors and shared environment; and 3) whether the twin with the highest depression symptomatology score more often developed ischemic heart disease in groups of twin pairs with larger intra-pair differences in depression symptomatology scores. This altogether provides information on whether a potential association between mood and ischemic heart disease is explained by genes or early environment.

## **METHODS**

### *Study participants*

We used data on Danish twins included in two large population-based twin studies: the study of Middle-Aged Danish Twins (MADT)<sup>15</sup> and the Longitudinal Study on Aging Danish Twins (LSADT)<sup>16</sup>.

The MADT includes a random sample of twins identified in the Civil Registration System and in the Danish Twin Registry in 1998. The twins were born between 1931 and 1952 and alive in 1998 (at ages 46-67 years). Of eligible twins, 4,314 (83%) completed a baseline interview. LSADT was initiated in 1995 and includes Danish twins aged 75 years or older residing in Denmark by January 1995. The twins were born between 1892 and 1919 and identified by the local clergy who reported twin births where both twins had survived to the age of 6 years in their parishes. Among all eligible twins, 2,400 (71%) completed a baseline interview without missing information on study date. The interview typically took place at the participants' home by one of approximately 100 interviewers. Interviewers completed a detailed training program two months prior to survey administration and different interviewers interviewed the two members of intact twin pairs independently. Both MADT and LSADT included similar questionnaires on socio-demographic factors, health and diseases, life style factors along with physical and cognitive tests.

### *Exposure: depression symptomatology scores*

Current depressive mood symptoms during the baseline interview (for MADT in 1998 and for LSADT in 1995) were assessed using an adaptation of the depression section of the Cambridge Mental Disorders of the Elderly Examination (CAMDEX), which is a structured interview schedule for the diagnosis and measurement of dementia<sup>17</sup>. To differentiate from dementia, CAMDEX includes 21 depression items, which were supplemented by additional 11 items to provide a more

comprehensive assessment of affective state<sup>18</sup>. This scale does not evaluate presence of depression but rather depressive mood symptoms, and it consists of a two-factor structure including both depressed affect and lack of well-being (9-item affective symptom score) and neurovegetative symptoms related to psychomotor slowing and cognitive difficulties (8-item somatic symptom score)<sup>19</sup>. The total depression scale has high internal consistency reliability ( $\alpha > 0.85$ )<sup>16</sup>. The scale is shown in Supplementary Table 1 and further information on the CAMDEX scale explained in detail elsewhere<sup>18,19</sup>.

#### *Outcome: Ischemic heart disease*

Ischemic heart disease was defined according to the International Classification of Disease 10<sup>th</sup> edition (ICD-10) codes I20-25 or ICD8 codes 410-414 in the National Danish Patient Register<sup>20</sup> and followed from study entry until end of 2011. The National Danish Patient Register covers all hospital admissions since 1977 and since 1995 also outpatient hospital clinics and emergency room contacts.

#### *Baseline covariates*

Interview information on self-reported smoking status (never smoker; former smoker; current smoker), number of alcoholic drinks per week categorized into four groups (non-drinkers; no. of drinks in the lowest, middle or highest tertile), and self-reported medically treated hypertension or diabetes was included. We included variables of self-reported hypertension and diabetes since many patients with these conditions are treated in general practice or by private specialists. Thus, using register-based information from the National Patient Registry may underestimate the presence of these diseases. Finally, body mass index (BMI) was calculated from measured weight in kg divided by height in meters squared and categorized into tertiles.

#### *Statistical methods*

Stata version 15 (StataCorp, College Station, TX) was used for all statistical analyses. Missing values in the variables from the pooled cohorts were imputed using multiple imputations based on age and gender as the variables were assumed to be missing completely at random (Supplementary Table 2). Study aims were tested in different subpopulations of the entire twin population, described in Figure 1.

We studied the first aim in the “main twin population” including 6,464 individuals using Cox proportional hazards regressions to calculate hazard ratios (HR) with 95% confidence intervals (CI). In these analyses, individuals without information on depression symptomatology scores (N=250) as well as individuals with a diagnosis of ischemic heart disease before study entry (N=548) were excluded. To maximize power, the cohorts were pooled before analysis. As no clinical cut points to the depression score exist, the depression symptomatology score was categorized into tertiles (quartiles showed similar results but with lower power in the intra-pair analyses). Individuals were followed for diagnoses of ischemic heart disease from study entry (the date of study participation) and until first diagnosis of ischemic heart disease, death, emigration or end of follow-up (December 31<sup>st</sup>, 2011), whichever came first. Age was the underlying timescale of the Cox proportional hazard model, because age is assumed to be more strongly associated with the risk of developing ischemic heart disease than follow-up time in these analyses. This means that the estimated hazard ratios are based on comparisons between individuals with the same age and the estimates are, thus, adjusted for age. The proportional hazards assumption was tested by calculating Schoenfeld residuals and graphically by plotting  $-\log(-\log(\text{survival}))$  vs.  $\log(\text{follow-up time})$ . No violations were found. The models were adjusted for cohort, gender, smoke status, alcohol use, BMI, hypertension, diabetes and calendar year. To account for the interdependence of observations within twins in the standard cohort analyses, we added a cluster to the models. We conducted models for both the total depression score, the affective symptom score and the somatic symptom score.

The second aim was tested in individuals with their co-twin present in the cohort (“complete twin pair population”, N=4,600 pairs) and analyses were repeated for 1) the entire cohort with twins as individuals in a cohort analyses and 2) within twin pair (intra-pair analyses) in which twin pair match id was included as a stratum variable. The intra-pair analysis was performed to adjust for shared genetics and early environment. This was done by including a variable identifying membership of a twin pair as a stratum variable fixing the baseline hazard within twins but allowing the baseline hazard to differ between individuals who were not twins. Thus, the hazard ratios were estimated conditional on the twin-level intercept, which allows comparisons within twins that ensure adjustments for shared familial factors that may confound the relationship between depression and ischemic heart disease. Furthermore, as a supplementary analysis we performed the inter- and intra-pair analyses in separately in mono- and dizygotic twins. For these analyses, we excluded twins without a co-twin present, twin pairs with unknown zygosity or

opposite dizygotic twin pairs (as risk of both depression and ischemic heart disease may vary between men and women), which left 1,642 monozygotic and 1,688 same-sex dizygotic twins for analysis.

Finally, we included all twin pairs with data on depression score of whom at least one twin had a diagnosis of ischemic heart disease ("IHS twin pair subpopulation", N=1,412). For these analyses, the depression symptomatology scores were used on a continuous scale and as their distribution was slightly positively skewed, the scores were log<sub>2</sub>-transformed. The reason for using log<sub>2</sub> transformation instead of using the natural logarithm was that log<sub>2</sub> transformation is easier to interpret clinically, as one step on a log<sub>2</sub> transformed scale means a doubling of the actual values. After exclusion of twins with the same depression symptomatology score, we calculated the difference in depression symptomatology scores within each twin pair and this intra-pair difference was categorized into five groups based on the size of the difference (a difference of 1; 2-3; 4-5; 6-8; 9-27). In each group, the proportion of pairs in which ischemic heart disease occurred first in the twin with the highest depression score was calculated and we further calculated a non-parametric test for trend across groups. In 130 twin pairs ("both IHS twin pair subpopulation", N=260), both twins had a diagnosis of ischemic heart disease, and in these twins, we calculated the number of days between diagnoses and performed a linear regression predicting number of days as a function of the depression score. The assumptions of the linear regression were tested graphically after calculation of residuals and no violations were found.

In sensitivity analyses, we explored potential reverse causation (i.e. that undiagnosed symptoms of heart disease before study entry could lead to a lower mood score at examination) by lagging follow up 2 years after study entry. Individuals who had a diagnosis of ischemic heart disease (N=138) or who died or emigrated (N=257) during the first 2 years after study entry were excluded in these analyses. Analyses of the association between mood and ischemic heart disease within the first 2 years after study entry were not possible due to few outcomes and violation of the proportional hazard assumption. In further sensitivity analyses, interactions between the three depression symptomatology scores and gender were tested by including interaction terms into the separate models. The interactions were tested using a likelihood ratio test.

## RESULTS

A total of 2,400 and 4,314 individual twins were included from LSADT and MADT, respectively. Baseline characteristics based on tertiles of depression scores are shown in Table 1. Of the twins,

2,208 (32.9 %) were monozygotic twins. The mean age was 65.8 years and 54.5 % were women. During follow-up, 369 (20%) twins in LSADT and 507 (13%) twins in MADT were diagnosed with ischemic heart disease. The mean follow-up was 10.8 years (range 0.01-17.9 years).

#### *Association between depression symptomatology scores and ischemic heart disease in individual level analyses*

In the “main twin population”, those with a depression score in the two highest tertile had a 27% higher HR of ischemic heart disease compared to those with a score in the lowest tertile (HR<sub>3rd tertile</sub> (95 % CI 1.07-1.51)) after adjustment for all covariates (Figure 2). When examining the affective and somatic symptom score, those with a score in especially the highest tertile similarly had a 25% (95% CI 1.03-1.53) and 35% (95% CI: 1.12-1.62) higher HR of ischemic heart disease, respectively. For all scores, the risk estimates were slightly higher when only adjusting for gender and cohort (Figure 2).

#### *Association between depression symptomatology scores and ischemic heart disease within twin pairs (intra-pair analysis)*

Intra-pair analyses of the 2,300 complete twin pairs in the “complete twin pair population” showed associations between all three types of depression symptomatology scores and ischemic heart disease similar to the main findings (Figure 2). Those in the highest tertile of the total depression score had a 64% higher HR of ischemic heart disease (CI 95%: 0.97-2.76), while the corresponding HRs for the affective and somatic score were 2.08 (CI 95%: 1.18-3.67) and 1.59 (CI 95%: 0.87-2.91) (Figure 2). When we examined mono- and same-sex dizygotic twins separately, the analyses showed slightly larger hazard ratios in the intra-pair analyses of both mono- and dizygotic twins but with estimates similar to in the entire twin cohort (Supplementary Table 3). When examining the affective symptom score as the exposure, the hazard ratios increased in the intra-pair analyses of monozygotic twins, while they decreased in dizygotic twins. Opposite for the somatic symptom scale as the exposure, the hazard ratios decreased in intra-pair analyses in monozygotic twins, while they decreased in dizygotic twins. However, all estimates were imprecisely estimated with wide confidence intervals, which limits the certainty of the results.

*Difference in depression score and ischemic heart disease*

In the “IHS twin pair subpopulation”, the intra-pair difference in depression symptomatology scores ranged between 0 and 27. There was a tendency that in the groups of twin pairs with greater differences in depression scores, it was more often the twin with the highest depression score who experienced the diagnosis of ischemic heart disease compared to the co-twin with the lower depression score. Yet, the trend test was not significant ( $p=0.14$ ) (Figure 3).

In the “both IHS twin pair sub population” of 130 twin pairs we found that the twin with the highest depression score was most likely to have ischemic heart disease first. We also found that a higher intra-pair difference in depression symptomatology scores was associated with a greater time span between the time of ischemic heart diagnoses (coef -152 days/score (95% CI -273,-32)) (Figure 4).

*Sensitivity analysis*

In the analysis with a 2-year lagged follow-up start, risk estimates for ischemic heart disease were similar to the main findings (Supplementary Figure 1). Furthermore, in the main twin population, we found no interaction between gender and total depression symptomatology scores ( $p$ -interaction=0.88), affective depression score ( $p$ -interaction=0.76), or somatic depression score ( $p$ -interaction=0.56), respectively. The risk estimates for the association estimated separately in men and women were similar (albeit with larger confidence intervals) to both the individual level analysis and the intra-pair analyses (data not shown).

**DISCUSSION**

In this twin study, higher depression symptomatology scores (both total, affective and somatic) were associated with higher incidence of ischemic heart disease after adjustment for demographics, life-style and health-related factors. The findings were similar in intra-pair analyses, however, with less precision of the estimates illustrated by slightly larger confidence intervals. Thus, only the association between a higher affective symptom score and ischemic heart disease reached statistical significance in the intra-pair analyses. The sensitivity analyses with 2-year lagged follow-up start support that reverse causation does not explain our results. Gender did not modify the detected associations and no major differences in mono- or dizygotic twins were detected. Further, there was a tendency, though insignificant, that in twin pairs with greater difference in depression scores, the twin with the highest score more often also experienced a diagnosis with ischemic heart disease.

Finally, in twin pairs where both twins had ischemic heart disease, larger differences in depression symptomatology scores between the twins were associated with greater time span between the twins' diagnoses of ischemic heart disease.

### *Interpretation of our results*

Testing our first hypothesis, we replicated the association between depressive mood and risk of ischemic heart disease in an individual-based analysis. The association is well-known, but only few previous twin studies have been performed. One Vietnamese study (N=2,731 twin pairs) published in 2003 showed that depression was associated with coronary heart disease in a cross-sectional design and concluded that the co-occurrence was explained by common genetic factors<sup>21</sup>. Another larger Swedish study (N=15,284 twin pairs) from 2009 concluded that an association between depression and coronary heart disease was present. The findings were strongest the first year after depression and was only partly explained by genetic factors, mainly in women and in younger men<sup>22</sup>.

Testing our second hypothesis, we found that in intra-pair analyses, the association was similar or slightly higher, but the estimates were imprecise. As twins share genes and early environment, the intra-pair analyses should theoretically match and thus account for shared genetics and early environment. The results of the intra-pair analyses suggested that the association between mood and ischemic heart disease was not a result of shared genetics or early environment. If the association was explained by shared genetics or early environment, we would have expected an attenuation of the risk estimated. Thus, the association may be explained by other factors such as later environmental factors, which was also reported in older Swedish male twins<sup>22</sup>. Unfortunately, we were not able to test the gender differences found in the previous Swedish study due to lack of power. In the main analyses, we found no interaction with gender. It is possible that shared genetics and early environmental factors play a more prominent role in younger individuals, whereas in older individuals, later environmental effects are more important. It is also possible that geriatric depressive symptoms lead to coronary heart disease through other factors. Thus, it has been suggested that antidepressant medication, especially selective serotonin reuptake inhibitors use could lead to ischemic heart disease, even though this has been questioned in a recent large cohort study<sup>23</sup>. Other explanations include dysfunction of the hypothalamus-hypophysis-adrenal cortex axis, chronic inflammation or endothelial dysregulation<sup>24,25</sup> and recently hypotheses of epigenetic changes or mitochondrial dysfunction have emerged as common pathophysiological pathways

linking depression and cardiovascular disease<sup>26</sup>. In support of this, it has previously been suggested that the co-morbidity of depression and cardiovascular disease is more related to a somatic depression type<sup>27</sup>. A recent meta-analysis suggested that especially somatic depressive symptoms were associated with cardiovascular outcomes in individuals with preexisting cardiovascular disease<sup>28</sup>. In the main analyses, we used both an affective and a somatic symptom score and found that both scores were associated with risk of ischemic heart disease. Yet in intra-pair analyses, we found that only the affective symptom score was significantly associated with ischemic heart disease suggesting that affective symptoms are associated with ischemic heart disease independent of genetic factors and early environment.

Finally, testing our third hypothesis, we found that higher difference in depression score was associated with ischemic heart disease more often occurred in the twin with the highest score. In analyses in which both twins had ischemic heart disease, a dose-response relationship between degree of difference in depression symptomatology and time of ischemic heart disease was detected. Specifically, there was a tendency that the twin with the highest depression score received the diagnosis of ischemic heart disease earlier than the other twin in the pairs with higher differences in depression scores. This could support that depressive mood somehow independent of shared genetic factors or early environment increases the risk of ischemic heart disease.

#### *Strengths and limitations*

The strengths of this study are the inclusion of both affective and somatic depression symptomatology scores as well as lifestyle factors and self-reported disease. Furthermore, due to the Danish health registers all individuals were followed for more than 10 years for hospital diagnoses of ischemic heart disease, death or emigration. The diagnostic validity of the diagnoses of acute coronary symptom in the National Patient Registry is high, with a positive predictive value of 65.5% and 81.9% for acute myocardial infarction alone<sup>29</sup> but potentially lower for angina pectoris. Another study examining the validity of cardiovascular disease in the Danish registers reported an agreement of 74.2% between diagnoses in the registers and validation by an adjudication committee in patients discharged alive<sup>30</sup>. However, any misclassification is likely to be random and might thus only lead to an underestimation of the associations. The twin pair design allowed us to control for shared genetic factors and early environmental factors. However, despite the relatively large sample of twins, the intra-pair analyses suffered from limited power, which resulted in slightly imprecise point estimates and did not allow us to stratify on gender or zygosity without losing power leading

to imprecisely measured estimates. Furthermore, we cannot fully exclude reverse causation. Atherosclerotic cardiovascular disease starts many years before it is diagnosed, and we only delayed our entry two years. However, the risk estimates were similar in the analyses with a two-year follow-up lag, but we cannot exclude that it would have been different if we could have extended this time even further. Other limitations to the design include the assumption that twins share the same genes and early life environment. Only monozygotic twins share 100% of their genes, whereas dizygotic twins only share 50% and only one third of our cohort were monozygotic twins. However, compared to some monozygotic twins, dizygotic twins have a similar intrauterine environment, whereas monozygotic twins who share chorion and/or amnion may have an asymmetrical distribution of nutritional supply and thus a different intrauterine environment<sup>31</sup>. Furthermore, despite growing up together, other factors such as difference in childhood health and social relations may affect the twins during their early life<sup>32</sup>; factors we had no information on. Consequently, despite aiming to reduce the risk of shared genes or early environment through intra-pair twin design, the risk of residual confounding cannot be excluded. Another limitation could be that twins may not be representative of the general population. However, numerous studies have found that twins after infancy are similar to the general population in terms of health, disease and survival<sup>33,34</sup>.

In conclusion, this study of 6,714 twins and a total of 2,559 twin pairs, we found that depressive mood (both total, affective and somatic symptomology scores) at baseline were associated with higher incidence of ischemic heart disease in both inter- and intra-pair analysis. This suggest that shared genetic factors and shared early life environment do not explain the association between depressive mood and ischemic heart disease in middle- and old age.

#### **CONFLICTS OF INTEREST**

All authors report no conflicts of interest.

#### **DATA AVAILABILITY**

The data that support the findings of this study are available from Statistics Denmark. Restrictions apply to the availability of these data, which were used under license for this study. Data are

available from Statistics Denmark with the permission of the scientific board of the Danish Twin Registry<sup>35</sup>.

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## TABLES

**Table 1. Baseline characteristics based on depression scores in MADT and LSADT.**

Variable	CAMDEX total depression score			
	Lowest tertile	Middle tertile	Highest tertile	Missing
Number (%)	2570 (38)	1962 (29)	1932 (29)	250 (4)
Age, median (IQR)	66.6 (60.9-79.2)	58.7 (51.4-66.7)	58.0 (52.9-77.6)	84.5 (80.0-88.5)
Women, N (%)	1312 (51)	1051 (54)	1130 (58)	165 (66)
Smoking status, N (%)				
Never smoker	931 (36)	714 (36)	713 (37)	106 (42)
Former smoker	778 (30)	548 (28)	468 (24)	85 (34)
Current smoker	861 (34)	700 (36)	751 (39)	59 (24)
Alcohol use, N (%)				
Non-drinkers	458 (18)	347 (18)	485 (25)	127 (51)
Lowest tertile of drinkers	812 (32)	601 (31)	545 (28)	47 (19)
Middle tertile of drinkers	672 (26)	509 (26)	414 (21)	41 (16)

Highest tertile of drinkers	628 (24)	505 (26)	488 (25)	35 (14)
Body mass index, median (IQR)	25 (22-27)	25 (22-27)	24 (22-27)	23 (20-26)
Self-reported hypertension, N (%)	496 (19)	334 (17)	350 (18)	37 (15)
Self-reported diabetes, N (%)	122 (5)	94 (5)	108 (6)	24 (10)
Self-reported depression	232 (9)	209 (11)	385 (20)	43 (20)

Based on 4314 Middle Age Danish twins (MADT study) and 2400 twins in the Longitudinal Study of Aging Danish Twins (LSADT study). CAMDEX = Cambridge Mental Disorders of the Elderly Examination. IQR = interquartile range.

## FIGURE LEGENDS

**Figure 1.** The population and sub-populations used to investigate the 3 aims of the study.

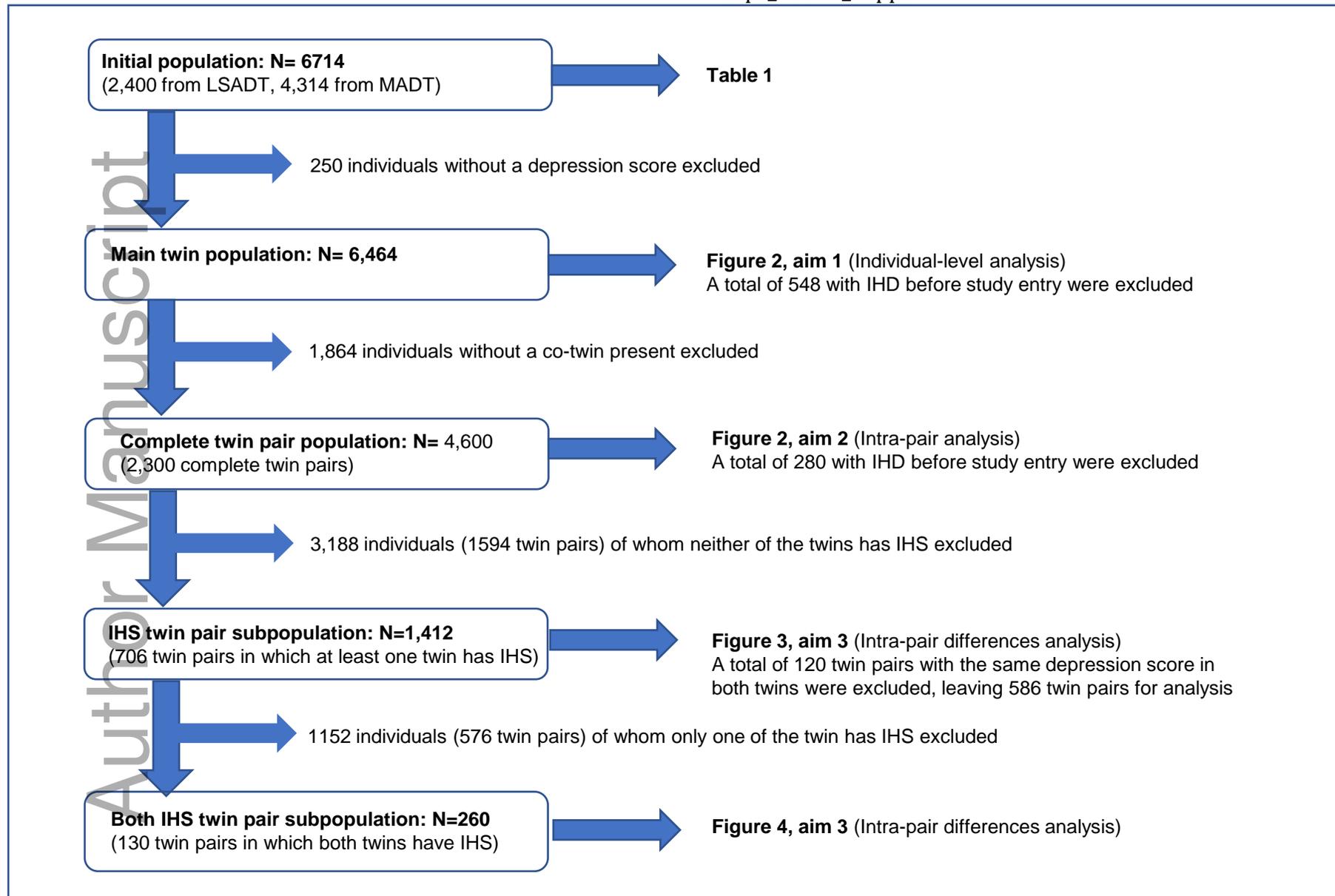
MADT=study of middle-aged Danish twins. LSADT= the longitudinal study on aging Danish twins  
IHS=ischemic heart disease.

**Figure 2.** Risk of ischemic heart disease (IHS) based on depression scores at study entry in twins from the study of middle-aged Danish twins (MADTs) and the longitudinal study on aging Danish twins (LSADT). Multifactorial adjusted is for age (as the underlying time scale), gender, cohort, calendar year, smoke status, alcohol consumption, body mass index, self-reported diabetes and self-reported hypertension. HR= hazard ratio. CI = confidence interval.

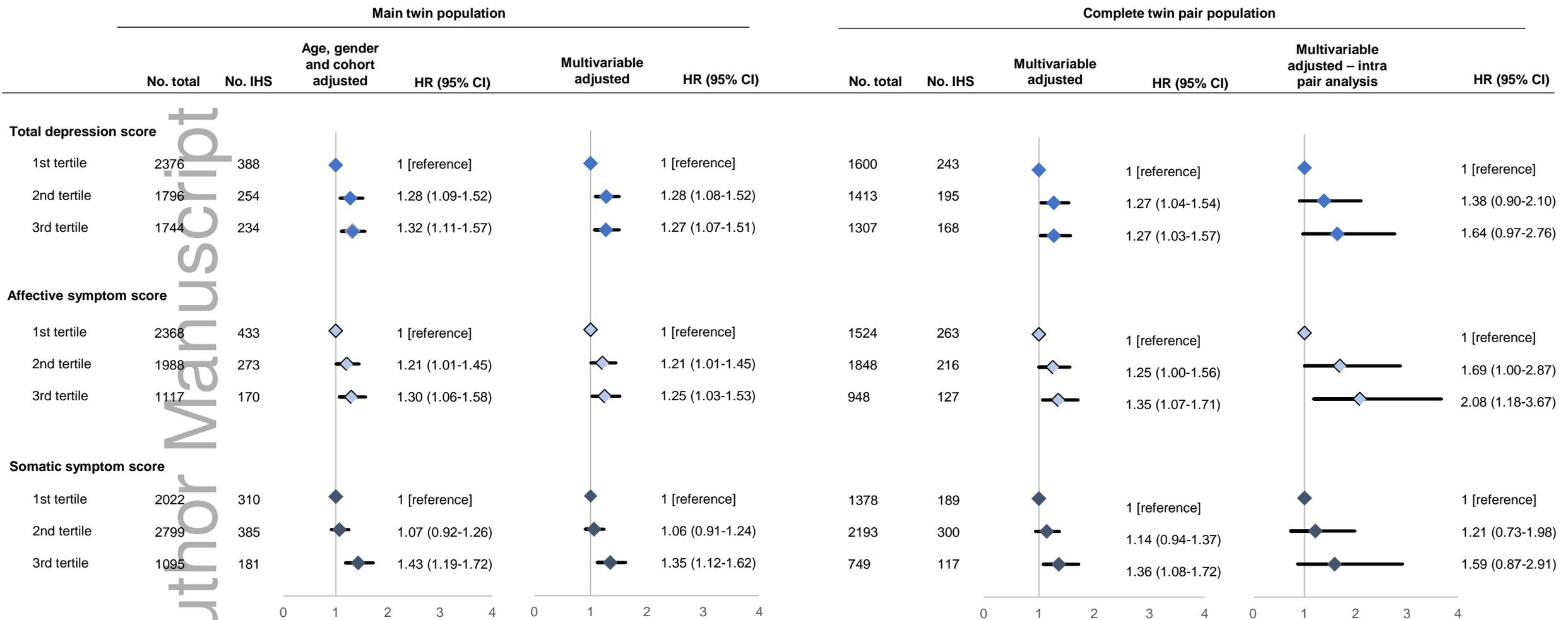
**Figure 3.** Pairs in whom the twin with the highest depression score had a diagnosis with ischemic heart disease (first if both had). Based on 586 twin pair with different depression scores of which at least one twin had a diagnosis of ischemic heart disease.

**Figure 4.** The association between depression symptomatology score difference and time between diagnoses of ischemic heart disease (IHD).

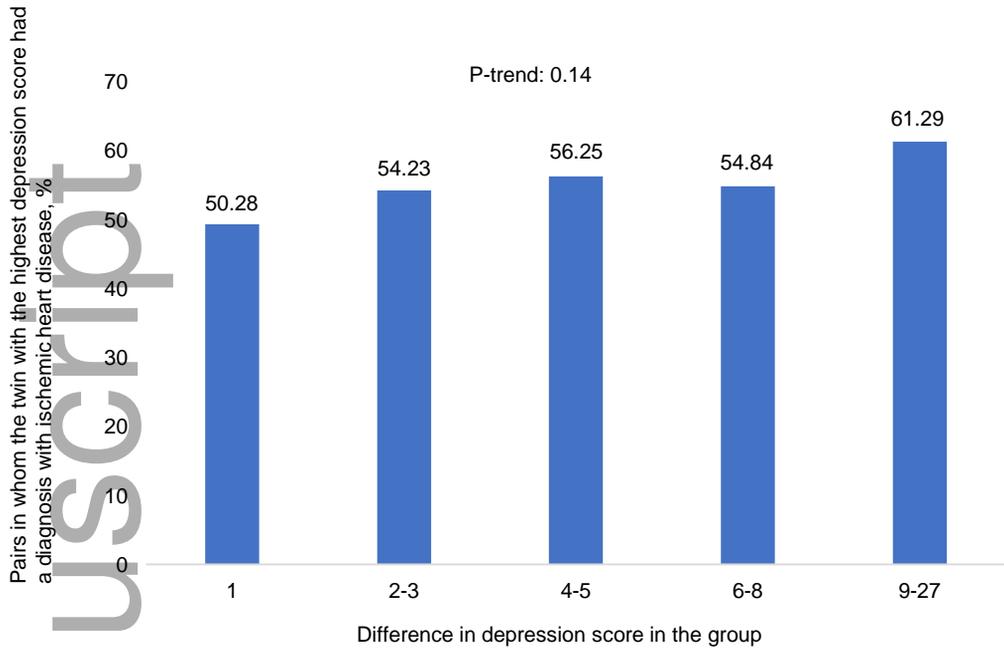
Based on 130 twin pairs in the LSADT and MADT in whom both twins were diagnosed with ischemic heart disease.



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**Figure 1.** The population and subpopulations used to investigate the 3 aims of the study. MADT=study of middle-aged Danish twins. LSADT= the longitudinal study on aging Danish twins IHS=ischemic heart disease.

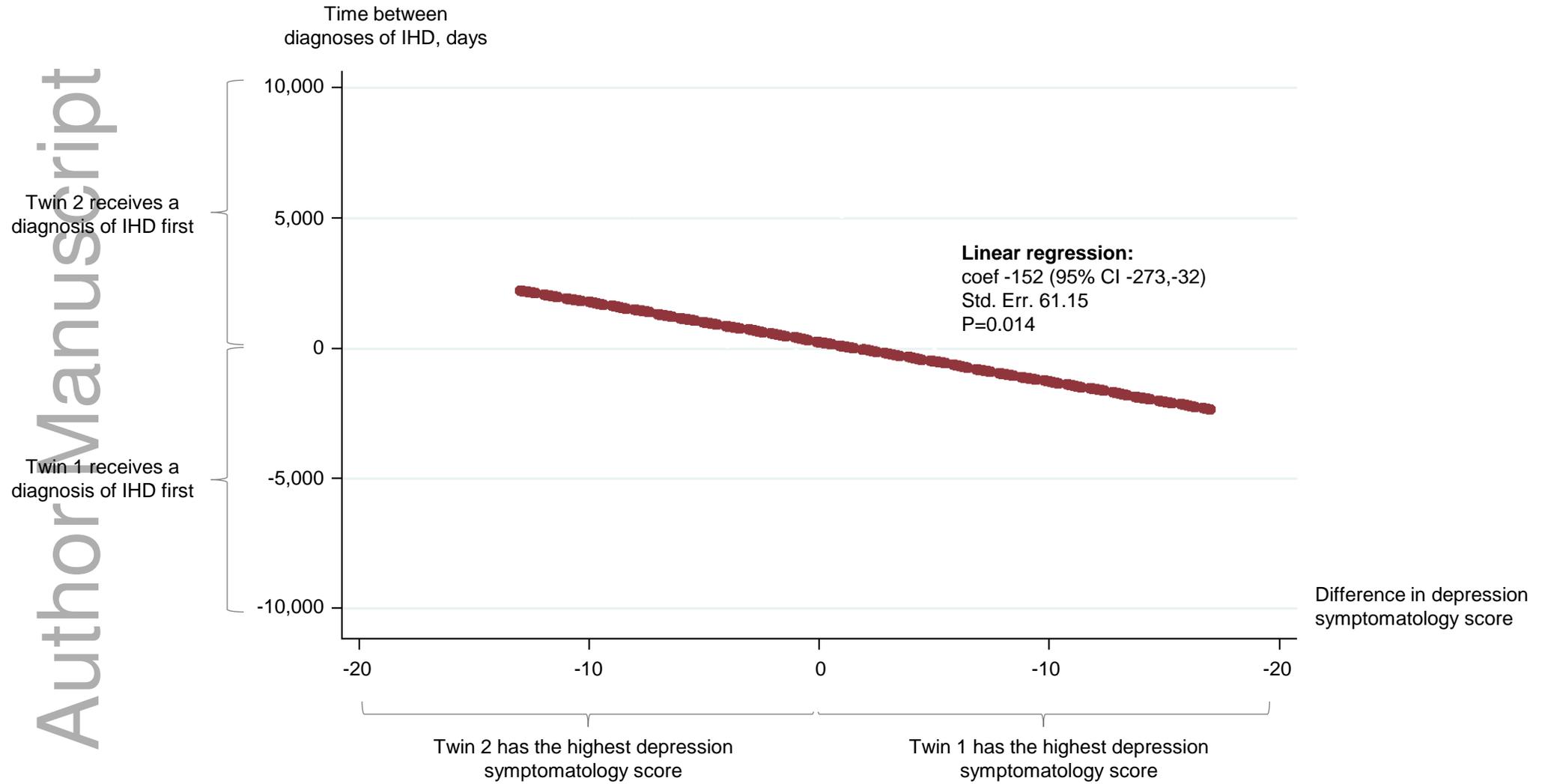


**Figure 2.** Risk of ischemic heart disease (IHS) based on depression scores at study entry in twins from the study of middle-aged Danish twins (MADTs) and the longitudinal study on aging Danish twins (LSADT). Multifactorial adjusted is for age (as the underlying time scale), gender, cohort, calendar year, smoke status, alcohol consumption, body mass index, self-reported diabetes and self-reported hypertension. HR= hazard ratio. CI = confidence interval.



	1	2-3	4-5	6-8	9-27
Number	181	201	80	62	62
Mean difference in score	1.00	2.42	4.39	6.82	12.35
Pairs in whom the twin with the highest score had IHS first	91	109	45	34	38

**Figure 3.** Pairs in whom the twin with the highest depression score had a diagnosis with ischemic heart disease (first if both had). Based on 586 twin pair with different depression scores of which at least one twin had a diagnosis of ischemic heart disease.



**Figure 4.** The association between depression symptomatology score difference and time between diagnoses of ischemic heart disease (IHD).

Based on 130 twin pairs in the LSADT and MADT in whom both twins were diagnosed with ischemic heart disease. Unfortunately, we could not show data for individual pairs as Statistics Denmark prohibit the reporting of five or less individuals in a cell