Title: Descriptives and genetic correlates of eating disorder diagnostic transitions and

presumed remission in the Danish registry.

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Abstract

Objective. Eating disorders (EDs) are serious psychiatric disorders with an estimated 3.3

million healthy life-years lost worldwide yearly. Understanding the course of illness,

diagnostic transitions and remission, and their associated genetic correlates could inform

both ED etiology and treatment. The authors investigated occurrences of ED transitions and

presumed remission and their genetic correlates as captured by polygenic scores (PGSs) in a

large Danish register-based cohort. **Methods.** The sample compromised of 10,565

individuals with a diagnosis of anorexia nervosa (AN), bulimia nervosa (BN), or eating

disorder not otherwise specified (EDNOS) with at least two registered hospital contacts

between 1995 and 2018. Based on medical records, occurrence of diagnostic transitions and

periods of presumed remission were identified. Associations between 422 PGS and

diagnostic transitions and presumed remission were evaluated using Cox proportional

hazard models. **Results.** A minority of ED cases (14.1%-23.1%) experienced a diagnostic

transition. Presumed remission ranged between 86.9%-89.8%. Higher (one SD increase) PGS

for major depressive disorder and multisite chronic pain were positively associated with

transitioning from AN to either BN or EDNOS. Higher PGS on a measure of body fat

percentage and financial difficulties were positively associated with presumed remission

from AN. Higher PGS for mood swings was positively associated with presumed remission

from EDNOS whereas higher PGS for health rating showed the opposite. **Conclusions.** The

authors found that most ED patients did not experience diagnostic transitions but were

more likely to experience a period of presumed remission. Both diagnostic transitions and

presumed remission have significant polygenic component.

Introduction

Eating disorders (EDs) are serious psychiatric disorders which can have a complicated course of illness characterized by diagnostic transition from one ED to another, and eventually remission for some patients (1–6). Annually, it is estimated that 3.3 million healthy life years are lost worldwide due to anorexia nervosa (AN), bulimia nervosa (BN), and eating disorder not otherwise specified (EDNOS) (7). Studies have reported varying frequencies of diagnostic transitions across EDs. For instance, some case-cohort and clinical studies found that the transition from AN to BN occurs in 13%-54% of cases, and from BN to AN in 7%-27% of cases (1–3,6). However, a large Swedish population register study (8) reported much lower transition probabilities (2%) from AN to BN and vice versa, with the transition to EDNOS occurring in 17%-24% of AN cases and in 18%-22% of BN cases (3,8). Estimates of ED remission also differ in the literature, ranging from 27%-78% for AN cases, 40%-83% for BN cases, and about 49% of EDNOS cases in studies with a minimum follow-up of 6 years (2,5,8). These differences could be due to variations in study design, assessment methods, or follow-up time.

It is unclear what factors determine a patient's risk of transitioning from one ED to another or their duration of illness. Previous research suggests that greater experience of psychopathology (e.g., anxiety) may increase the likelihood of transition from AN to BN (1,6,9). Anthropometric factors such as body mass index (BMI) may also play a role as individuals who transition from AN to BN tend to have higher current, past minimum, and past maximum BMIs compared to those who do not transition (9). Similarly, higher BMI and traits such as premorbid perfectionism, state anxiety, and trait anxiety are associated with lower occurrence of ED remission (10–12).

One interesting approach to understanding biological factors that may influence ED

transition and remission is to explore genetic factors that contribute to the risk of EDs

(4,13). Most genome-wide association studies (GWAS) of EDs have focused on AN (14–17)

and have not examined genetic factors influencing diagnostic transition or remission.

Polygenic scores (PGSs) offer a powerful method to leverage the small-to-moderate effect

sizes of common single nucleotide polymorphisms (SNPs) identified in a GWAS into a single

continuous score that surpasses the explanatory power of individual SNPs (4). This approach

has been successful in exploring the genetic relationship between traits by associating the

PGS for one trait (e.g., BMI) with a phenotypic measurement of another trait (18).

Therefore, the aims of our study were two-fold: (i) quantify occurrences of ED

transitions and remission; and (ii) investigate whether diagnostic transitions and ED

remission are associated with PGSs of various complex traits in a nationwide sample of

treatment-seeking individuals in Denmark (19).

Methods and Materials

Study population

Using data from the Danish National Patient Register (NPR) (20) and the Psychiatric Central

Research Register (PCRR) (21), the study population comprised individuals: (i) born in

Denmark between May 1, 1981 and December 31, 2009; (ii) who were alive and living in

Denmark at their 6th birthday; (iii) who received an International Classification of Diseases,

10th edition (ICD-10) primary or secondary diagnosis for AN (F50.0, F50.1), BN (F50.2, F50.3),

or EDNOS (F50.8, F50.9) on or after their 6th birthday; (iv) for whom genotype data were

available; (v) who had at least two registered ED-related hospital contacts between 1995

and 2018 after the age of 6 years. Genotype data for EDNOS cases without any other

lifetime ED diagnosis were obtained from the iPSYCH2015 case-cohort sample (also

including the iPSYCH2012 case cohort) (19,22), for AN cases from the Danish branch of the

Anorexia Nervosa Genetics Initiative (ANGI-DK) (23), and for BN cases from the Danish

branch of the Eating Disorders Genetics Initiative (EDGI-DK) (24). In total, we included

10,565 individuals with EDs, with their first recorded diagnosis being: AN, n = 6,901; BN, n =

1,417; EDNOS, n = 2,247. Each individual was followed up until December 31, 2018. Sex

information was obtained from the NPR and PCRR. Sex is assigned at birth; however, each

individual over the age of 18 years can legally change their sex information in the registers

based on their gender identity. Therefore, from here onwards we report on gender.

Ancestry was based on genetic information and was determined by calculating robust

Mahalanobis (squared) distances using the first two genomic principal components. This

approach relies on the fact that the Danish population is fairly homogenous (22) and

calculating robust distance captures individuals with an European ancestry.

Outcome data

ED episodes. From the inpatient and outpatient hospital contacts in the NPR and the PCRR,

we defined distinct ED episodes for each individual (for detailed information, see

Supplemental Methods and **Figure S1**). First, we combined patient records into distinct

hospital contacts. We further merged contacts into ED episodes (i.e., a time period in which

an individual had a diagnosis of an ED). The merging of records into contacts and episodes

resulted in three possible ED episodes: AN; BN; or EDNOS. We also included an episode of

presumed remission; individuals that were contact free regarding their ED for at least 2

years.

Time to diagnostic transition. Based on the defined ED episodes, we first grouped

individuals by their first ED diagnosis. Second, we defined a diagnostic transition as an

individual receiving another ED diagnosis in a subsequent ED episode. Time to diagnostic

transition was calculated as the difference between the beginning of the first ED episode

and the beginning of the episode in which the individual received a different ED diagnosis.

Time to presumed remission. Time to presumed remission was calculated as the time

difference between the moment the person is at risk for presumed remission (two years

following the start of the first episode) and the date the individual met the above-

mentioned criteria for presumed remission.

Genetic data

Genotyping. Dried blood spot samples were obtained through routine screening for

congenital disorders from nearly all Danish newborns after 1981 and stored at the Danish

Newborn Screening Biobank (25). Genotyping of the DNA extracted from the blood spot

samples was carried out and described elsewhere (19,22,23,25). This study was approved by

the Danish Data Protection Agency, the Danish Scientific Ethics Committee, the Danish

Health Data Authority, and the Danish Newborn Screening Biobank Steering. The Danish

Scientific Ethics Committee, in accordance with Danish legislation, has, for this study,

waived the need for informed consent in biomedical research based on existing biobanks

(19).

PGSs calculations. PGSs were calculated for ED cases with genetic data (n cases = 10,565)

using LDpred2 (26) for 940 traits and with the meta-PRS (27) approach for 6 traits (i.e.,

attention deficit hyperactivity disorder [ADHD], AN, autism spectrum disorder, bipolar

disorder, major depression, and schizophrenia). We performed pre-filtering on 940

LDpred2-calculated PGSs (e.g., duplicates and highly correlated PGSs; for details see

Supplemental Methods and **Figure S2**). After filtering, a total of 422 PGSs remained for

analyses and were standardized (**Table S1**).

Statistical analyses

We tested the association between PGSs (one at a time) and our outcome measures using

Cox proportional hazard models. We did not exclude individuals based on genetic ancestry

and instead controlled for population stratification using the first five genomic principal

components as covariates in the Cox regression models. We did not include transitions from

BN to AN or EDNOS or from EDNOS to AN or BN in our PGS analysis due to the infrequent

occurrence of these transitions in our sample (**Table 1**). We estimated hazard ratios with

95% confidence intervals for each outcome for one SD increase in the PGS. We corrected for

the number of PGSs tested (n = 422) by calculating the number of effective tests using the

meff() function (PoolR package) on the genetic correlation matrix of the selected 422 PGS

applying the Galwey method (28). The number of effective tests was estimated to be 317,

therefore the threshold for multiple testing was set at $\alpha < 1.57 \times 10^{-4}$.

Results

Sample description

Demographics. We included a total of 10,565 (92.6% women; 85.5% European ancestry) individuals with genotype and ED diagnostic data in our analyses (**Table 1**): 6,901 individuals with AN, 1,417 individuals with BN, and 2,247 individuals with EDNOS as their first episode. The mean age at first diagnosis for AN, BN, and EDNOS in our sample were 17.3 (standard deviation [SD] = 4.1), 20.9 (SD = 4.3), and 18.7 (SD = 5.1) years, respectively. The mean follow-up time was 8.9 years (SD = 5.2).

Transitions. Among individuals with AN as their first episode, 14.1% transitioned to another ED with such transition taking an average time of 4.5 years (**Table 1**). The transition from AN to BN occurred in 5.4% of individuals, with an average time to transition of 4.5 years. A higher percentage of individuals with AN (9.7%) transitioned to EDNOS, with a mean time to transition of 4.7 years. Among individuals with BN as their first episode, 21.8% individuals transitioned to AN or EDNOS: specifically, 11.6% transitioned to AN and 12.3% transitioned to EDNOS, with an average transition time of 4 years and 4.6 years, respectively. Individuals presenting with EDNOS as their first episode showed the highest transitions; 23.1% of the individuals transitioned to AN or BN with a mean transition time of 2.7 years. More EDNOS cases transitioned to AN (17.8%) than to BN (6.8%).

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Table 1: Descriptive statistics of the sample by first eating disorder diagnosis presentation

	Total sample (n = 10,565)		AN as first episode (n = 6,901)		BN as first episode (n = 1,417)		EDNOS as first episode (n = 2,247)	
Binary descriptives	n	%	n	%	n	%	n	%
Gender, women	9,784	92.6	6,425	93.1	1,381	97.5	1,978	88.0
European ancestry	9,037	85.5	5,952	86.2	1,201	84.8	1,884	83.8
Transition to BN			370	5.4			153	6.8
Transition to EDNOS			661	9.6	175	12.3		
Transition to AN					165	11.6	404	17.8
Transition to BN or EDNOS			968	14.1				
Transition to AN or EDNOS					309	21.8		
Transition to AN or BN							521	23.1
Presumed remission	9,273	87.7	5,999	86.9	1,273	89.8	2,001	89.0
Relapsed from presumed remission	1,585	15.0	970	14.0	290	20.5	325	14.5
Continuous descriptives	mean	sd	mean	sd	mean	sd	mean	sd
Age at first diagnosis in years	18.1	4.5	17.3	4.1	20.9	4.3	18.7	5.1
Follow-up time in years	8.9	5.2	9.0	5.4	9.1	4.9	8.2	4.9
Time to transition to BN in years			4.5	3.3			3.6	3.1
Time to transition to EDNOS in years			4.7	3.8	4.6	3.6		
Time to transition to AN in years					4.0	3.4	2.6	2.5
Time to transition to BN or EDNOS in years			4.5	3.5				
Time to transition to AN or EDNOS in years					4.0	3.2		
Time to transition to AN or BN in years							2.7	2.7
Time to presumed remission in years	1.6	1.8	1.7	1.9	1.7	1.76	1.2	1.6
Duration presumed remission in years	5.3	4.7	5.4	4.9	4.9	4.3	5.0	4.3

AN, anorexia nervosa; BN, bulimia nervosa; EDNOS, eating disorder not otherwise specified; SD, standard deviation.
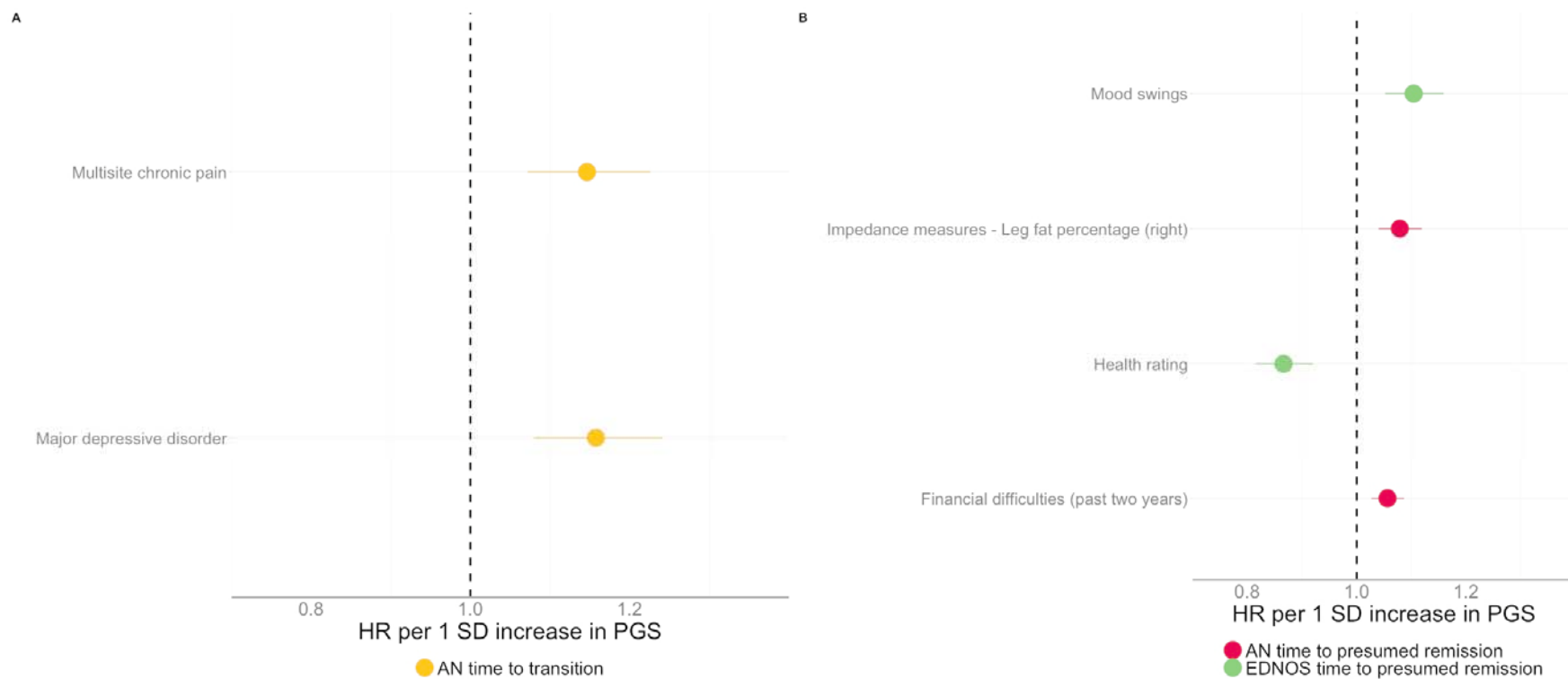
Figure 1: Associations between polygenic scores (PGS) and eating disorder (ED) diagnostic transition and remission. Depicted are the associations that remained significant after correcting for multiple hypothesis testing. Associations are depicted in hazard ratios (HR) per one standard deviation (SD) increase in the PGS with dots representing the HR point estimate and the line depicting the 95% confidence interval **A.** Associations of PGS with transitioning from AN to BN or EDNOS. **B.** Associations of PGS with ED presumed remission.

Presumed remission. Regardless of ED diagnosis at first episode, 87.7% of individuals experienced a period of presumed remission with a mean time to presumed remission of 1.6 years (SD = 1.8; **Table 1**) with an average duration of the presumed remission period of 5.3 years (SD = 4.7). Presumed remission occurred in 86.9% of individuals with AN as first episode, with a mean time to presumed remission of 1.7 years (SD = 1.9). Among individuals with BN as first episode, 89.8% experienced a period of presumed remission with a mean time to presumed remission of 1.7 years (SD = 1.7). Of the individuals with EDNOS as their first episode, 89.0% experienced a period of presumed remission with a mean time to remission of 1.2 years (SD = 1.6). A minority (15%) of the cases experienced an ED diagnosis following a period of presumed remission; relapse was highest (20.8%) among those with BN diagnosis as their first episode.

Association of PGSs with transition from AN to BN or EDNOS

Higher major depressive disorder (MDD) and higher multisite chronic pain PGS were significantly associated with a 15% greater hazard of transitioning from AN to BN or EDNOS, respectively (**Figure 1A;** see **Table S2** for full results).

Association of PGSs with time to presumed remission

Higher (one SD) PGS of a body fat percentage measure (i.e., leg fat percentage) was associated with an 8% greater hazard for presumed remission from AN (**Figure 1B; Table S3-S5**). In AN individuals, higher PGS on financial difficulties was also associated with a 5%

greater hazard for presumed remission. Regarding EDNOS, each one SD increase in the PGS

of overall health rating corresponded with a 12% lower hazard for presumed remission

while a higher PGS on mood swings was associated with a 10% increased hazard for

presumed remission.

Discussion

In this Danish nationwide population study, we examined 10,565 individuals with EDs over
an average follow-up time of 9 years. Overall, the occurrence of transitions (ranging
between 5.4%-23.1%) in our sample fall on the lower end of previous estimates (1–3,6). For
example, in a study in which AN cases were followed weekly, about a third of all AN cases
transitioned to BN in a period of 7 years (2); their transition estimate is much higher
compared to ours (5.4%). However, our estimate of transitions are more comparable to
another registry-based study that found similar estimates that ranged between 2%-24% (8).
There could be several explanations for our lower estimates of transitions. It could be that
diagnostic transitions might occur in-between hospital visits and are therefore likely missed
in register-based research. It is also possible that patients seek treatment elsewhere (e.g.,
private practice that is not recorded in the registries we utilized) or decide to no longer
pursue further treatment. Despite differences in estimate of threshold ED transitions across
studies, the general pattern to emerge is that diagnostic stability is the norm and if
transitions do occur they often happen within the first five years of Illness (1–3,6,8).

Presumed remission was very likely in our sample; depending on the diagnosis of the
first episode, between 86.9%-89.0% of the individuals experienced a period of presumed
remission with only a minority (14.0%-20.5%) of the individuals experiencing relapse
suggesting that this is a relatively stable state. The frequency of presumed remission in our
study was comparable to partial recovery frequencies (78.4%-82.8%) reported in a
longitudinal study of ED (2), suggesting that our definition likely reflects individuals that are
on their way to recovery. However, our estimates for presumed remission are much higher
compared to the only other register-based study on this topic that reported remission to

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vary between 23%-36% (8). The definition of remission in the other register-based study

was defined as instances in which an ED diagnosis was no longer coded in the register at an

assessment visit whereas ours was based on being contact free regarding ED for at least 2

years. The discrepancy in result is likely due to these differing operationalizations of a

remission phenotype and might suggest that our estimates for presumed remission is an

overestimation. However, the overall conclusion regarding remission in our study and those

of the other register-based study (8) remain the same; remission is a more likely outcome

than diagnostic transitions and remission is a fairly stable state.

Regarding our PGS analysis of transitions from AN to BN or EDNOS; higher PGS for MDD

and multisite chronic pain (a phenotype defined as the sum of the number of body sites at

which an individual reported chronic pain that lasted at least 3 months) corresponded with

a 15% greater hazard of transitioning. Associations between AN and depression are well

established with some of the shared etiology likely due to shared genomics; MDD is

genetically positively correlated (r_g = 0.28, SE = 0.07, p = 8.95 × 10^{-5}) with AN caseness

(16,29,30). Our finding adds to the literature of AN and MDD and suggest that alleles that

underlie MDD can also influence the course of AN. Along similar lines, multisite chronic pain

is reported to be genetically negatively correlated (r_g = -0.06, SE = 0.03, p = 0.047) with AN

(31). ED disturbances are elevated in patients with chronic pain, and findings from a

longitudinal study show that adolescents with an ED are more likely to experience frequent

or persistent pain (32). Furthermore, studies suggest that pain sensitivity may be decreased

in individuals with AN and BN compared to non-ED controls (33–35). This change in pain

perception is likely not due to deficits in interoception (sense of the physiological condition

of the body (36)), which are implicated in both AN and BN (37). A recent study found no

evidence for a mediation effect for interoception in the association between pain

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experience and EDs, which suggests that pain perception in AN may be altered through a

different physiological system (37). One possible shared biological process that might

explain the co-occurrence of chronic pain and ED could be central sensitization: a state in

which the central nervous system responsiveness is increased to internal and external

conditions, which is a process that is dysregulated in both conditions (32).

Regarding our PGS analysis and remission, higher PGS on a body fat measure (leg fat

percentage) was associated with presumed remission from AN. This finding is of

considerable relevance etiologically as the maintenance of low BMI and persistence of

dietary restriction are unique and biologically challenging symptom profiles. How some

individuals maintain a low BMI throughout their course of illness versus conceding

biologically to increased caloric intake and weight gain may indeed rest in genetic

susceptibility to both anthropometric and metabolic traits. Our findings suggest that those

that harbor genetic variants that increases their bodyweight might counter the symptom

profile (i.e., maintaining a low body weight) of AN and hence they contribute to presumed

remission. We also report that higher PGS on financial difficulties was associated with

remission from AN. Several longitudinal studies have implicated higher parental SES and

increased risk of developing AN (38,40). Furthermore, AN is reported to be positively

genetically correlated (r_g = 0.20 - 0.27) with several measures of educational attainment and

a recent PGS study found that higher AN PGS is associated with higher SES in parents of AN

cases (16,39). Our findings are likely captures the SES component of financial difficulties and

might suggest that SES additionally plays a role in the course of AN.

Counter to our expectations, we found that higher PGS on overall health rating was

negatively associated with remission from EDNOS. It is important to note that about 18% of

the cases with EDNOS transitioned to AN suggesting that these could have been individuals

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that had not yet fulfilled criteria for AN at the time of their first assessment. It is therefore

possible that the PGS on overall health rating captures the characteristics of this subgroup

such as lower body weight and engagement in excessive exercise; both of which have been

previously associated with a measure of overall health rating (41). If shown to true, this

could potentially open a path in which the EDNOS group can be dissected into a more

homogenous group using PGS. Unfortunately, our sample size was not sufficient to pursue

this goal. Lastly, we also report a positive association between higher PGS on mood swings

and remission from EDNOS. Mood swings are highly prevalent in EDNOS patients (43), and it

is therefore likely that the clinical treatment for mood swings takes precedence which might

appear as presumed remission from EDNOS.

The lack of significant associations between most of the tested PGSs and our outcomes

could be due to several reasons. Despite the relatively large sample size, it is possible that

our study lacked power to detect associations between the PGSs and transitioning from AN

to BN or EDNOS, given the infrequent occurrences of these transitions (N cases that

transitioned from AN to BN or EDNOS = 976). Furthermore, it is possible that both AN

transitions and ED remission are largely determined by environmental factors (e.g.,

treatment). Lastly, it is also possible that our transition and remission phenotypes have a

unique genetic architecture that is not best captured by our selection of PGS.

The strengths of this study include its large sample size and the long follow-up period

compared to previous work (1–6). However, findings from this study should be interpreted

in the context of certain limitations. In Denmark, hospital-based treatment is free of charge,

lowering the barrier for individuals to seek treatment (19). However, we cannot rule out

that sociodemographic factors could still have influenced treatment-seeking behavior. The

diagnoses in the registers could have also been impacted by differing registration practices

among hospitals departments and over time which could have impacted our estimates of

diagnostic transition and remission (42). For example, a clinician might assign a diagnosis of

EDNOS as a first diagnosis because threshold AN or BN is still under development. Similarly,

a person with AN might on their way to recovery go through an EDNOS stage. In the

previous examples, the transition to or from EDNOS is likely an artifact of diagnostic

practice. Diagnostic practices when both AN and BN criteria are met can vary between

hospitals as guidelines are not consistent across diagnostic manuals. However, in our work

we have grouped hospital contacts into distinct ED episodes and episodes that are

temporally close were merged into one episode which likely dampened the effects of such

diagnostic practices. We can't rule out that other diagnostic practices could have influenced

our results. Our definition of presumed remission relied on being contact free for at least 24

months and is therefore not a direct measure of remission; hence why we refer to this

phenotype as presumed remission. However, it is important to note that when individuals

entered this period of presumed remission it lasted on average 5.3 years and only a minority

(15%) of cases relapsed suggesting that our definition of presumed remission does

approximate remission. Furthermore, it is important to reiterate that our study might have

missed some diagnostic transitions as they could have occurred between hospital contacts.

Genotyped BN or EDNOS cases were more likely to be included in this study if they had a

lifetime diagnosis of AN or any of the other psychiatric disorders (e.g., schizophrenia,

autism) ascertained for the iPSYCH case-cohort study (19,22). In other words, BN and

EDNOS cases without other lifetime psychiatric diagnoses (included in the iPSYCH case-

cohort study) are not captured in our sample. Therefore, our findings might not be

generalizable to all BN or EDNOS cases. Another limitation is that we are unable to estimate

the extent to which hospital treatment may have impacted observed ED transitions and

remission. For example, treatment for AN could have led to an increased bodyweight and this could have shifted the diagnosis from AN to EDNOS despite the presence of core AN symptoms. The majority of individuals in this study are of European ancestry making the results of this study less generalizable to other non-European populations.

In conclusion, this study supports previous findings that the majority of ED patients do not experience diagnostic transitions and that presumed remission is likely regardless of ED diagnosis. This study highlights potential genetic influences underlying ED transitions and remission but also points towards a possible unique genetic architecture that is not captured by our selection of PGS. Further research on understanding possible environmental influences on ED transitions and remission is warranted as this may give us a deeper understanding of the etiology of EDs and inform tertiary prevention strategies that could lead to improved outcomes.

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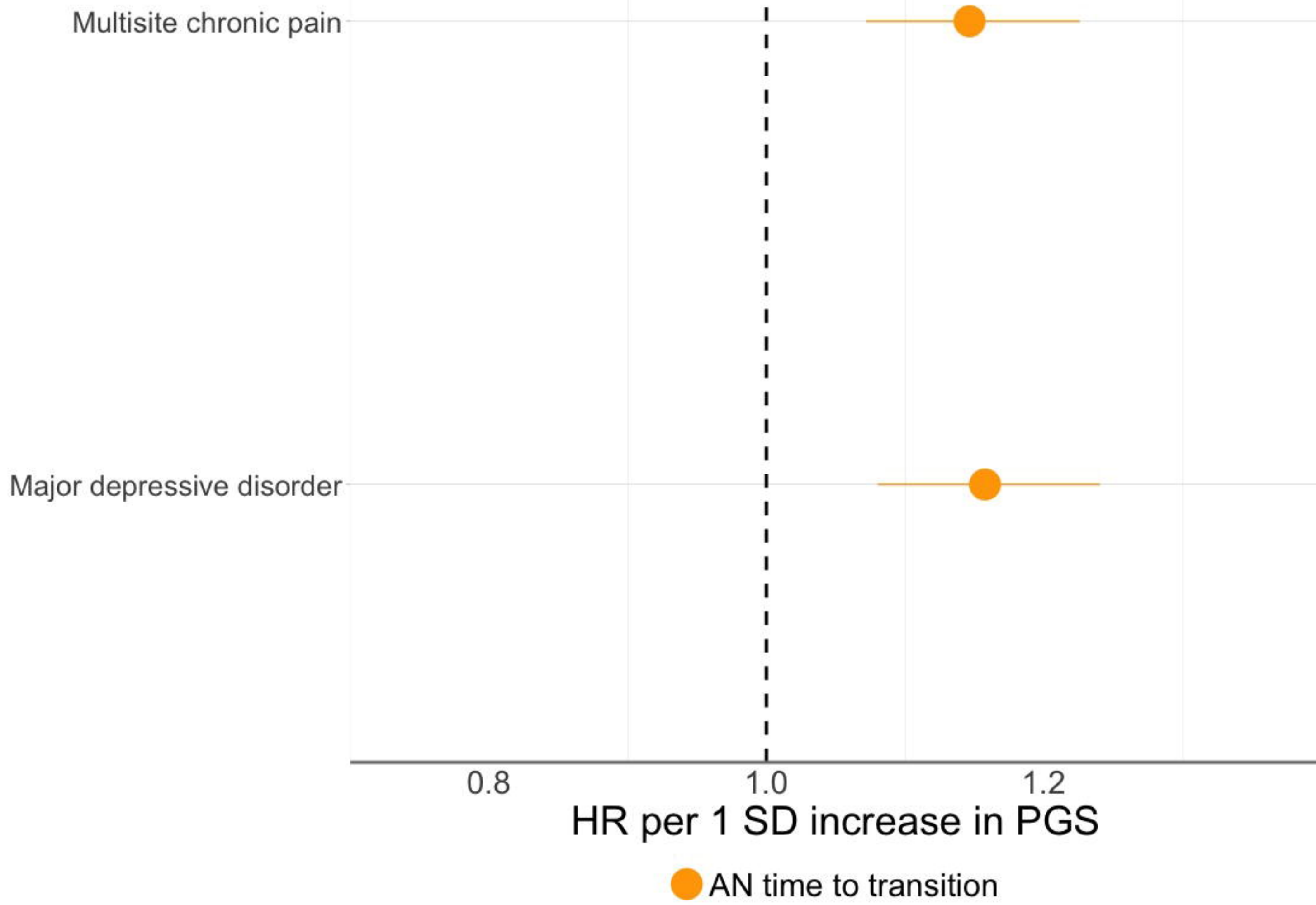interest.

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