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Do early-life eating habits predict later autistic traits? Results from a population-based study

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ABSTRACT

Eating problems are common among children with Autism Spectrum Disorder (ASD), but it is unknown to what extent infant eating behavior is associated with later autistic traits. As eating behavior is currently not included in ASD screening instruments, it is important to evaluate whether infant eating behavior predicts later autistic traits and might therefore be used to enhance the early detection of ASD. We investigated the association of breastfeeding and eating behavior during infancy with later autistic traits in the population-based Generation R cohort. We included 3546 mother-child dyads with maternal reports on feeding and eating at age two months and autistic traits at six years. Eating behavior was assessed with seven items on specific eating habits and the Social Responsiveness Scale was used to evaluate autistic traits. Covariates included child sex, and maternal psychopathology and autistic traits. Linear regression analyses showed that being formula fed at two months was associated with a higher autistic trait score at six years (adjusted $B=0.07$; 95% CI: 0.00-0.14). Children who were drinking only small quantities (adjusted $B=0.17$, 95%CI: 0.04-0.30) and were hungry/not satisfied (adjusted $B=0.23$, 95%CI: 0.08-0.39) at age two months also had a higher autistic traits score at age six years. We found no interactions with sex or breastfeeding. This study shows that eating behavior during infancy is related with autistic traits in childhood. Although the associations were fairly small, these findings suggest that early-life eating problems might be relevant for early detection of ASD and a potential addition to ASD-specific screening instruments.

Keywords

Breastfeeding, eating behavior, autism spectrum disorder, autistic traits, infancy, general population

INTRODUCTION

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder that is present from early life onwards. It is characterized by persistent deficiencies in communication and social interaction, and restricted, repetitive patterns of behaviors, interests and activities. Although several symptoms are already present in the early developmental period, some symptoms manifest itself only later in life.¹ ASD can be reliably diagnosed as young as 24 months,² but the current mean age at diagnosis ranges from 38 to 120 months.³ There is an urgency to identifying children with ASD, as particularly early interventions can improve language and cognitive abilities⁴ and result in better long-term outcomes across the school age years⁵ compared to interventions at a later stage.

Detection of the earliest signs of ASD can enhance timely identification and diagnosis, which then permits early treatment to achieve the most optimal long-term outcomes for children with ASD. There are several widely used instruments available for ASD screening. The Modified Checklist for Autism in Toddlers (M-CHAT(R/F))^{6,7} is currently the most commonly used screening instrument.⁸ Other instruments like the Social Communication Questionnaire (SCQ)⁹ and the Early Screening of Autistic Traits Questionnaire (ESAT/CoSoS in Dutch)¹⁰ are also frequently used. These screening instruments focus primarily on ASD deficiencies described in the DSM-5 criteria, but also include items specific to other ASD-related deficiencies like having an unusual response to sensory stimuli.^{6,9,10} Although eating problems are often seen among children with ASD, they are currently not included in ASD screening instruments.

Eating problems –like severe or prolonged picky eating and food neophobia (fear of new/unknown foods)– are seen in 46-89% of children with ASD¹¹ compared to 6-50% of children in the general population.¹² Food neophobia is two to three times more common in children with ASD than in non-ASD children.¹³ In previous studies in the general population, we also identified eating problems in early childhood as a possible early sign of ASD.¹⁴ While eating problems may already be expressed early in life, to our knowledge there are no studies on the association of eating behavior in infancy with ASD, except for research on breastfeeding.¹⁵

Absence of breastfeeding has been examined as a risk factor for ASD numerous times. A recent meta-analysis indicated that breastfeeding may protect against developing ASD and suggests genetic factors, content of breastmilk, and skin-to-skin contact as potential causal pathways for this protective effect.¹⁵ However, eating problems can also complicate breastfeeding, with unsuccessful breastfeeding thus potentially being indicative of other eating problems seen in children with ASD. Current research calls for prospective studies to confirm the suspected protective effect of breastfeeding on the development of ASD.¹⁵

We investigated the association between eating behavior in infancy, differentiated into breastfeeding and feeding habits, with later autistic traits in a prospective, population-based cohort. Knowing whether infant eating behavior predicts later autistic traits could be useful to enhance screening for autism at an early stage. We hypothesize that breastfeeding is associated with fewer autistic traits in later childhood, while problematic eating behaviors in infants is prospectively associated with a higher autistic traits score.

METHOD

Data source

This study uses data from the Generation R Study, a population-based, longitudinal cohort study from the fetal stage onwards; the cohort is based in Rotterdam, the Netherlands. In short, all pregnant women living in Rotterdam, with an expected delivery date between April 2002 and January 2006, were invited to participate in the study (participation rate: 61%). The Generation R study design and population has been described in detail.¹⁶ Written informed consent was obtained from all participants. The study was approved by the Medical Ethical Committee of the Erasmus Medical Center, Rotterdam.

Participants

Our study population includes all parents of 6625 children who gave consent for participation in the postnatal phase of the Generation R study (Figure 5.1). We excluded children with missing data on eating behavior ($n = 1779$) or breastfeeding ($n = 69$) at two months and those without information on autistic traits at 6 years ($n = 1231$). This resulted in a study sample of 3546 mother-child dyads.

Measures

Breastfeeding

Information about feeding mode was obtained by a maternal postal questionnaire when children were two months old. We assessed if infants were breastfed (yes/no) and whether they received breastfeeding only, a combination of breast- and formula feeding, or formula feeding only at the time the questionnaire was filled out.

Eating behavior

Eating behavior at age two months was assessed in the same maternal questionnaire using seven single items related to eating and feeding difficulties. These assessed relatively common difficulties and behavior, and were partly based on previous studies that also used single items on infant

feeding.^{17,18} Parents (mostly mothers, 93.7%) responded; they were asked if their infant exhibited one or more of the following feeding habits: 'Drinks slowly', 'Drinks only small quantities', 'Drinks very greedily', 'Is hungry or not satisfied', 'Spits up a lot,' Regurgitates mouthfuls of food' and 'Refuses breastfeeding'. Response options were Yes or No.

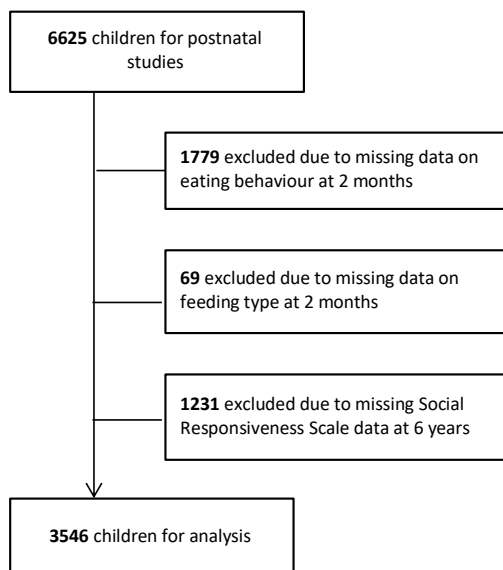


Figure 5.1 Flow diagram of the study population

Autistic traits

Autistic traits were assessed using maternal reports of the validated Social Responsiveness Scale (SRS)¹⁹ when children were six years old. The SRS is an autism screening questionnaire providing a quantitative measure of (sub)clinical autistic traits related to social cognition and communication. The psychometric properties are good, including a test-retest reliability of 0.88 and a two-year stability correlation of 0.83.²⁰ The original questionnaire was reduced to an 18-item shortened SRS to minimize subject burden, with selected items encompassing all DSM-IV autism domains. The shortening was done in consultation with the SRS test developer, as described previously.²¹ Our SRS short form consists of the Social Cognition (5 items), Social Communication (8 items) and Mannerism (5 items) subscales. Items assessed traits in the past three months and were scored on a 4-point scale (not true, sometimes true, often true, almost always true). The 18-item shortened SRS shows high correlations of 0.93-0.99 with the full scale, as described in Blanken et al.²² Diagnostic validity studies comparing the SRS with the Autism Diagnostic Interview- Revised (ADI-R) and Autism Diagnostic Observation Scale (ADOS) found acceptable sensitivity and specificity rates of 70-80%.²³

To identify children with an ASD diagnosis, we examined medical records using a multifaceted screening procedure.²⁴ First, cut-off scores for the SRS were used to identify children with elevated ASD traits. Second, to rule out false-negatives, children scoring in the top 15% of the total score of the Child Behavior Checklist (CBCL/1½-5)²⁵ at age six years were then screened using the 40-item Social Communication Questionnaire (SCQ), as reported by a parent.²⁶ Additionally, psychiatric diagnoses and treatment were routinely assessed at all contact moments between ages 6–9 years (health center visits and questionnaires). If children scored positive in one or more of these three information sources, the medical records at their general practitioners were examined. If an ASD diagnosis was confirmed through the medical records, the child was considered to be a clinically confirmed case of ASD.

Covariates

We included several child and family covariates based on previous studies.^{14,22,27} Information about sex, birth weight and gestational age at birth was obtained from midwife- and hospital registries. Maternal age, educational level and ethnicity were obtained by postal questionnaire. We used the Brief Symptom Inventory (BSI) to assess maternal psychopathology during pregnancy. The BSI is a validated 53-item self-reported questionnaire assessing diverse psychiatric problems.²⁸ We also used the Autism-Spectrum Quotient (AQ-short) to assess maternal autistic traits. Although this questionnaire was distributed when the children were 9 years old, we assumed that maternal autistic traits were fairly stable across adulthood. The AQ-short is a 28-item self-report assessing autistic traits on the scales ‘social behavioral difficulties’ and ‘fascination for numbers/patterns’, which sum into a total score (minimum=28, maximum= 112). A cut-off score of >65 is suggested for a quick screening of autistic traits in a clinical setting.²⁹

Statistical analyses

First, separate linear regressions were conducted to evaluate the relationship between breastfeeding at two months and autistic traits at six years. Three models were evaluated: model 1 was an unadjusted model, model 2 included the covariates maternal age, education and psychopathology, and model 3 additionally included measures of maternal autistic traits. Only covariates that altered the unadjusted beta by more than 10% were included in model 2. Maternal autistic traits were included to demonstrate the possible influence of a familial predisposition for ASD. We also tested sex interactions and finally evaluated the association between breastfeeding at two months and clinically confirmed ASD diagnosis by logistic regression.

In a second set of analyses, linear regressions were conducted to evaluate the relationship between eating behavior at two months and autistic traits at six years, with separate regressions for each type

of eating behavior. The same three adjusted and unadjusted models were evaluated for each eating behavior, using a similar method to that described above. We tested for possible interactions of sex with eating behavior, as well as for breastfeeding with eating behavior.

Table 5.1 General characteristics of parent-child dyads from Generation R cohort (n = 3546)

	Percentage or median ^a	% missing
Child characteristics		
Sex		0.0
Girl, %	51.0	
Age at assessment (months)		
Feeding and eating behavior	2.8 (0.4 to 6.0)	7.4
Social Responsiveness Scale	71.8 (58.7 to 106.8)	0.0
Gestational age at birth	40.1 (27.1 to 43.4)	0.0
Birth weight (grams)	3480 (780 to 5610)	0.0
Breastfeeding at 2 months		
Yes, %	68.8	0.0
Breastfeeding type at 2 months		
Breastfeeding only, %	41.2	
Breastfeeding & formula feeding, %	27.7	
Formula feeding only, %	31.2	
Eating behavior at 2 months		
Drinks slowly, %	13.9	0.0
Drinks only small quantities, %	6.0	0.0
Drinks very greedily, %	39.1	0.0
Is hungry or not satisfied, %	3.9	0.0
Spits up a lot, %	12.2	0.0
Regurgitates mouthfuls of feed, %	32.0	0.0
Refuses to breastfeed, %	1.7	0.0
Autistic traits at 6 years	0.2 (0.0 to 2.5)	0.0
Maternal characteristics		
Age at intake (years)	31.9 (15.3 to 45.4)	0.0
Ethnicity		
Dutch, %	68.0	
Other, %	31.9	
Education		
Higher vocational education/university, %	59.5	2.7
Lower vocational education, %	26.0	
Less than high school, %	11.8	
Psychopathology score	0.1 (0.0 to 2.7)	15.9
Autism traits score	50.0 (28.0 to 84.0)	32.1

^a Values are percentages for categorical variables and medians (range) for continuous non-normally distributed variables.

We estimated missing values on confounders (ranging from 0% missing for sex to 32.1 % for maternal autistic traits) using multiple imputation techniques. All variables included in the analyses were used

to estimate the missing values.³⁰ Regressions were conducted on the imputed data and reported estimates are the pooled results of 30 imputed datasets. All statistical analyses were performed with SPSS 21.

RESULTS

Non-response analyses

We compared the characteristics of participating mother-child dyads ($n = 3546$) with those excluded from the study due to missing data on determinants or outcome ($n = 3079$). Data were more often missing in mothers who were younger, had a lower education level, were of non-Dutch ethnicity, and who had higher psychopathology and autistic traits scores (all p -values $< .01$). Excluded children had a lower birth weight, were more often boys, and more often received no breastfeeding than included children (all p -values $< .01$).

Sample characteristics

Child and maternal characteristics of the study sample are presented in Table 5.1. In total, 51.0% of children were girls and 68.8% received breastfeeding at two months. More than two-thirds (68.0%) of the mothers had a Dutch background. The study sample included 50 children (1.4%) who had a GP-confirmed diagnosis of ASD. Of the mothers, 5.9% showed elevated levels of autistic traits (AQ-short score > 65).

Prospective relationship between breastfeeding and autistic traits

Table 5.2 shows that receiving formula feeding at two months was associated with a higher autistic traits score at six years (confounder adjusted $B = 0.07$; 95% CI: 0.00 to 0.14) than when receiving breastfeeding.

Particularly receiving only formula feeding was associated with a higher autistic traits score at six years (confounder adjusted $B = 0.08$; 95% CI: 0.00 to 0.15), while receiving mixed formula and breastfeeding was not significantly associated with autistic traits score. Adjustment for maternal age, education and psychopathology led to a change in the association between breastfeeding and autistic traits of more than 10%, while the additional inclusion of maternal autistic traits in the model did not notably affect this association. We found no interactions of breastfeeding and sex on autistic traits.

Sensitivity analyses showed that children who were breastfed at two months did not differ in their odds of a later ASD diagnosis, compared with children who were not breastfed (OR = 0.81; 95% CI: 0.44 to 1.48, $p = 0.50$).

Table 5.2 Prospective association between breastfeeding and child autistic traits (n = 3546)

	B for SRS total score at six years (95% CI)		
	Model 1	Model 2	Model 3
Breastfeeding at 2 months (reference response=yes)	0.15 (0.02;0.22)**	0.07 (0.00;0.14)*	0.07 (0.00;0.14)*
Type of feeding at 2 months			
Breastfeeding only	Reference	Reference	Reference
Breastfeeding & formula feeding	0.05 (-0.02;0.13)	0.03 (-0.05;0.10)	0.02 (-0.05;0.09)
Formula feeding only	0.17 (0.10;0.24)**	0.08 (0.01;0.16)*	0.08 (0.00;0.15)*

Model 1: unadjusted

Model 2: adjusted for maternal age, education and psychopathology

Model 3: adjusted for maternal age, education, psychopathology and autistic traits

Note: We found no significant interaction with sex.

**p<.01, *p<.05

Prospective relationship between eating behavior and autistic traits

Table 5.3 indicates that infants who drank only small quantities at two months had a higher autistic traits score at six years (confounder adjusted B = 0.17; 95% CI: 0.04 to 0.30) compared to infants who did not drink small quantities. Results further show that the infant eating behavior '*being hungry or not being satisfied*' at two months was associated with later autistic traits (confounder adjusted B = 0.23; 95% CI: 0.08 to 0.39). The inclusion of maternal autistic traits in the models did not notably affect the association between infant eating behavior and later autistic traits. The other eating behaviors were not associated with later autistic traits. No interaction of sex or breastfeeding with eating behavior was found.

Table 5.3 Prospective association between infant eating behavior and child autistic traits (n = 3546)

Eating behavior at age 2 months (reference response=no)	B for SRS total score at six years (95% CI)		
	Model 1	Model 2	Model 3
Drinks slowly	0.12 (0.03;0.21)*	0.07 (-0.01;0.16)	0.06 (-0.02;0.15)
Drinks only small quantities	0.28 (0.15-0.40)**	0.20 (0.07-0.33)**	0.17 (0.04;0.30)**
Drinks very greedily	0.03 (-0.04;0.09)	0.00 (-0.06;0.07)	0.01 (-0.05;0.07)
Is hungry or not satisfied	0.40 (0.23-0.56)**	0.24 (0.09;0.40)**	0.23 (0.08;0.39)**
Spits up a lot	0.08 (-0.01;0.18)	0.06 (-0.03;0.16)	0.05 (-0.04;0.14)
Regurgitates mouthfuls of feed	-0.05 (-0.12;0.01)	-0.04 (-0.10;0.03)	-0.03 (-0.10;0.03)
Refuses to breastfeed	0.05 (-0.20;0.29)	0.02 (-0.21;0.26)	-0.00 (-0.23;0.23)

Model 1: unadjusted

Model 2: adjusted for maternal age, education and psychopathology

Model 3: adjusted for maternal age, education, psychopathology and autistic traits

Note: We found no significant interactions between sex or breastfeeding (yes/no) with eating behavior.

**p<.01, *p<.05

DISCUSSION

This study –in a general population sample– shows that infants who were formula fed, drank only small quantities, or who were often hungry or not satisfied at the age of two months had a higher autistic traits score in childhood at age 6 years.

Breastfeeding

Our results on breastfeeding are in line with previous studies suggesting a negative association between breastfeeding and later ASD.¹⁵ Our study contributes to the clinical findings that breastfeeding is associated with a lower degree of autistic traits at a subclinical level in a large general population sample. Although in our subgroup of children with an ASD diagnosis the association pointed in the same direction, caution is needed in drawing firm conclusions since this result was not significant, mostly likely due to the small number of children with a clinically confirmed ASD diagnosis (n=50).

Although it is often suggested that breastfeeding and ASD are causally linked, these potential causal pathways are still quite hypothetical. Genetic factors may well be implicated since autism has a strong genetic basis, as illustrated by a high concordance rate (64-91%) seen in twin studies.³¹ Moreover, literature indicates that other maternal factors may also play a role in the association between ASD and breastfeeding. Multiple studies indicated that general maternal psychopathology is associated with shorter breastfeeding duration.^{32,33} Also, the broader autism phenotype is related to elevated depressive symptomology³⁴ and socio-affective impairment³⁵ which can negatively affect breastfeeding duration.^{36,37} Nonetheless, our results show that psychopathology and particularly the level of autistic traits of mothers only explain a small part of the association between breastfeeding and later autistic traits in children. This is in line with a previous study indicating that the broader autism phenotype does not fully explain the association between breastfeeding and ASD.³⁸ We should also consider the possibility of residual confounding. For example, maternal under- and over-responsivity to sensory stimuli- which are common in people with ASD (Lai et al. 2011) and influence the duration that women give breastfeeding^{39,40} - were not evaluated in our study.

Also, multiple child factors may contribute to the association between breastfeeding and ASD. Sensory problems that have been found in infants at high risk for ASD⁴¹⁻⁴³ could affect the initiation and/or continuation of breastfeeding, suggesting a reverse causal pathway. This may be due to the fact that breastfeeding provides a richer variation in oral sensory stimulation (taste) compared to formula milk,⁴⁴ because the taste of breastmilk (e.g. bitterness) is affected by the mother's consumption.⁴⁵ Also, compared to other feeding methods, breastfeeding provides more close skin-

to-skin contact⁴⁶ and frequent touch by the mother⁴⁷ which are possibly less pleasant for children with sensory problems. Finally, a dysregulated breastfeeding pattern of endless sucking in children with ASD⁴⁸ may lead to sore nipples and breastfeeding discontinuation.^{49,50}

Eating behavior

The current study showed that specific infant eating problems –particularly *drinking only small quantities* and *being hungry or not satisfied*– were associated with a higher autistic traits score later in childhood. This is in line with our previous study across middle childhood: in that study we found that autistic traits at six years were prospectively associated with elevated levels of picky eating and food responsiveness at ten years in both boys and girls. Among girls only, autistic traits at six years were also associated with elevated levels of emotional over- and undereating at ten years.⁵¹ Our current results add to the literature that the association between eating behavior and autistic traits seems to be present even from very early infancy. It is, however, important to emphasize that, although both studies show a prospective association between eating behavior and autistic traits, based on these findings we cannot draw any conclusions on causality.

There are several possible explanations for the reported association. Drinking only small quantities and being hungry or not satisfied are both linked with appetite self-regulation. Typically developing children show good self-regulation, also in feeding,⁵² but self-regulation difficulties have been reported among children with ASD.^{53,54} It is possible that infant eating problems are an early expression of the self-regulation difficulties typically seen in ASD.

Delays in the development of early motor skills are also often reported in children with ASD⁵⁵ and can be related to eating behavior problems in infancy. Specific impairment in oral motor function can affect eating behavior by limited bolus control, and/or manipulation and transit of liquids and solids.⁵⁶ while impairments in oral and pharyngeal sensory-motor functioning may also inhibit feeding skills.⁵⁷ Finally, sensory processing deficits are another common problem in children with ASD⁵⁸ and these have been linked to eating problems in ASD.⁵⁹

In contrast to our previous study evaluating the association between eating behavior and autistic traits in middle childhood,⁵¹ we found no sex differences in the current study. This is most likely because sex differences were previously found solely in the association between emotional eating and autistic traits.⁵¹ Emotional eating, however, is mostly shaped by shared environmental factors rather than genetic risk⁶⁰ and develops during childhood. So, potentially emotional eating problems are not yet present in infants, and even if they were present, such eating behavior would be very difficult to assess at a very young age.

Implications

Information on eating problems in infancy can potentially be used by professionals as part of the screening for ASD in the general population. Although most early signs of ASD can only reliably be observed from age 1-2 years onwards, previous research has indicated several possible biological and behavioral markers of ASD in infancy. Research on biological markers found that early brain development⁶¹ may be indicative of ASD as early as six months of age. Furthermore, infant gaze patterns,⁶² reduced looking time,⁶³ less alternating gaze during interaction with adults,⁶⁴ and a decline in eye fixation⁶⁵ have all been identified as early behavioral markers of ASD using eye-tracking techniques.

However, these early biological and behavioral markers require expensive and invasive brain imaging and eye-tracking techniques that cannot be easily used for widespread screening of ASD. Our current results suggest that the addition of certain eating behaviors to ASD-specific screening instruments like the M-CHAT, SCQ and the CoSoS might be helpful in providing a more complete ASD phenotype. Such addition might also enhance the validity, and with that the screening properties, of these instruments. In addition, we suggest the standardized monitoring of infant eating behavior in well-baby clinics to increase the identification of eating and feeding problems by using standardized questionnaires such as the BEBQ or by the inclusion of eating behavior items in developmental screening instruments.

Strengths and limitations

This study has several strengths. First, the large data set enabled us to assess the association between infant eating behavior and autistic traits prospectively and to control for possible confounding factors. We were also able to use validated instruments to assess child (SRS) and maternal (AQ-short) autistic traits in a general population setting, thereby optimizing validity and minimizing measurement bias. However, as infant eating behavior questionnaires, like the Baby Eating Behavior Questionnaire (BEBQ),⁶⁶ were not available when the children in this study were 2 months old, we assessed a limited number of different eating behaviors using unvalidated, single items. Furthermore, we also did not assess the reasons why mothers stopped breastfeeding their child. More detailed information on eating and feeding behaviors could help us to better understand the underlying mechanisms.

Another limitation of our study was that mothers with a higher psychopathology and autistic traits score were more likely to be lost for follow-up. Considering the genetic component in ASD, children with relatively high levels of autistic traits may also have dropped out selectively. Although no data on autistic traits were available for the excluded sample, we expect the effects of drop-out to be fairly small based on results from another large cohort study.⁶⁷ A final limitation was that although

the prevalence of children in this study with an ASD diagnosis (1.4%) was comparable to the prevalence found in the United States (one in 59 children, 1.7%),⁶⁸ the number of children with a confirmed ASD diagnosis in the sample was still small, meaning we had insufficient power to detect statistically significant differences.

Conclusions

Our study shows that infant eating problems and the absence of breastfeeding at two months of age are associated with a higher autistic traits score in later childhood. Although the associations were fairly small, these findings suggest that efforts to detect autism at an early stage might benefit from assessing early-life eating problems, alongside other factors like social interaction deficits. We recommend complementing ASD-specific screening instruments with an assessment of early-life eating habits.

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ETHICAL STATEMENT

Ethics approval and consent to participate Written informed consent was obtained from all participants. The study was approved by the Medical Ethical Committee of the Erasmus Medical Center, Rotterdam.

DECLARATION OF COMPETING INTEREST

PWJ received support from ZonMW (Mental Health Care Research Program, Fellowship 636320005). The authors declare that they have no further competing interest.

AUTHOR'S CONTRIBUTIONS

This study was conceived and designed by MH, WE, MHJH, HH and PJ. Analyses were performed and interpreted by MH, WE and PJ. MH, WE and PJ prepared the draft manuscript with input from IO, MHJH, HH. All authors read and approved the final manuscript.

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