



Early developmental, temperamental and educational problems in ‘substance use disorder’ patients with and without ADHD. Does ADHD make a difference?



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ABSTRACT

Introduction: The prevalence of ADHD among patients with substance use disorder (SUD) is substantial. This study addressed the following research questions: Are early developmental, temperamental and educational problems overrepresented among SUD patients with ADHD compared to SUD patients without ADHD? Do this comorbid group receive early help for their ADHD, and are there signs of self-medicating with illicit central stimulants?

Method: An international, multi-centre cross-sectional study was carried out involving seven European countries, with 1205 patients in treatment for SUD. The mean age was 40 years and 27% of the sample was female. All participants were interviewed with the Mini International Neuropsychiatric Interview Plus and the Conners' Adult ADHD Diagnostic Interview for DSM-IV.

Results: SUD patients with ADHD ($n = 196$; 16.3% of the total sample) had a significantly slower infant development than SUD patients without ADHD ($n = 1,009$; 83.4%), had greater problems controlling their temperament, and had lower educational attainment. Only 24 (12%) of the current ADHD positive patients had been diagnosed and treated during childhood and/or adolescence. Finally, SUD patients with ADHD were more likely to have

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central stimulants or cannabis as their primary substance of abuse, whereas alcohol use was more likely to be the primary substance of abuse in SUD patients without ADHD.

Conclusion: The results emphasize the importance of early identification of ADHD and targeted interventions in the health and school system, as well as in the addiction field.

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1. Introduction

Studies in the general population have shown a prevalence of adult ADHD of 3–5%. However, among persons with a substance use disorder (SUD) the prevalence rate is significantly higher (Kessler et al., 2006). A meta-analysis of treatment seeking SUD patients reported an overall prevalence of adult ADHD of 23% (van Emmerik-van Oortmerssen et al., 2012). However, prevalence rates vary greatly in different studies, due to the variation in measurement methods and patient characteristics, including age, country and primary substance of abuse. In a recent international, multi-centre study applying the same assessment methods in all participants from treatment centres in 10 countries, the prevalence of adult ADHD in treatment seeking SUD patients still ranged from 6% to 33% with an average of 14% (van de Glind et al., 2013), suggesting that health care organization, treatment setting and patient characteristics play an important role in the attraction of ADHD patients to addiction treatment centres.

According to the diagnostic criteria for ADHD, the first symptoms need to be already present in early childhood, before 7 years of age in DSM-IV and before 12 years in DSM-5 (APA, 2013) with evidence of functional impairment in multiple settings. A recent study showed that high school students with ADHD were significantly more likely to repeat a grade even after adjusting for all other variables, indicating the importance of early identification of ADHD to help mitigate adverse educational outcomes (Fried et al., in press). Early difficulties known to be associated with ADHD may be of particular relevance in the development of SUD. In a study comparing a group of ADHD-only patients with a group of patients with SUD and ADHD, the latter group had significantly higher rates of comorbid oppositional defiant disorder and conduct disorder, difficult temperamental traits (obstinacy, bad temper, impulsive behaviour), maladaptive behaviours at school, familial SUD history, childhood maltreatment, and severe childhood ADHD symptoms (Nogueira et al., 2011).

The present study focuses on ADHD-associated difficulties and childhood vulnerability among treatment seeking SUD patients with and without ADHD. The data are obtained from the international multicentre study on ADHD, presented in detail in a paper by van de Glind et al. (2013). In this paper, we try to answer the following questions: (1) to what extent do treatment seeking SUD patients with adult ADHD, compared to those without adult ADHD, have a delayed infant development, more temperamental problems and more difficulties at school?; (2) how many of those treatment seeking SUD patients with adult ADHD were recognized and treated as such as a child, and which kind of treatment did they receive?; and (3) what are the main substances currently used in treatment seeking SUD patients with and without adult ADHD, and is the use of central stimulants, like amphetamine, metamphetamine and cocaine, overrepresented in the group with adult ADHD, suggesting the presence of self-medication?

2. Method

2.1. Study design and recruitment of patients

A cross-sectional design was applied in a number of treatment centres from seven European countries: Sweden, Norway, Netherlands, Switzerland, France, Spain and Hungary (van de Glind et al., 2013). The project was approved by each country's or institute's related ethical

research committee, and the participation was voluntary. The addiction centres involved offered inpatient and/or outpatient treatment for various substance use disorders, and the patients were invited to participate. Exclusion criteria were substance intoxication, acute psychiatric crisis such as psychosis or manic episodes, limited literacy or cognitive impairment, unwillingness to sign informed consent, or other practical problems. The participating patients gave their written informed consent. The diagnostic stage of the study was preferably performed while patients were abstinent but exceptions were made based on the clinician's judgement, since full sustained abstinence as a study requirement would have most likely led to high non-participation rates and limited generalizability. As there is no information on the level of substance use at the time of interview, there is no information on the percentage of abstinent patients versus non-abstinent patients.

2.2. Instruments

The Mini International Neuropsychiatric Interview (M.I.N.I.) Plus, version 5.0.0 (Sheehan et al., 1998) was used to assess DSM-IV substance use disorders and the primary substances currently used, as well as other current mental health problems, such as episodes of mood disorders and antisocial personality disorder.

The Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID; Epstein, Johnson, & Conners, 2001), a semi-structured interview, was used for the diagnosis of adult ADHD. CAADID (Part II) includes a thorough assessment of the DSM-IV criteria for adult ADHD including a) number of symptoms, b) age of onset, c) pervasiveness, d) impairment and e) symptoms that cannot be explained by another psychiatric disorder. The CAADID has good psychometric properties and, and Kappa statistics for individual symptoms of inattention and hyperactivity-impulsivity were in the fair to good range for current report and retrospective childhood report (Epstein & Kollin, 2006). The CAADID is based on DSM-IV criteria, but the diagnostic algorithm was adapted to make the findings suitable for DSM-5. The differences between DSM-IV and DSM-5 in this sample are minimal (van de Glind et al., 2013). Ideally, the self-report should be supplemented by collateral information, but it was difficult to obtain such information from childhood, home or school due to the many dissolved families and broken relationships.

In addition, the CAADID (Part I) deals with the important psychological and social difficulties in childhood and adolescence associated with ADHD, including delayed infant development, problems controlling temper, educational difficulties, and indicators of professional help for ADHD and ADHD-associated problems during childhood and/or adolescence. A problem score was calculated for each problem area based on the number of affirmative answers in CAADID, indicating problem severity. The following CAADID sections were selected for the study:

2.2.1. Delayed infant development

This includes developmental milestones in childhood, such as walking, talking, and toilet training (4 questions: index range 0–4).

2.2.2. Temperamental problems in infancy and early childhood

This includes rage, anxiety, behavioural problems, clumsiness, eating and sleep problems (13 questions: index range 0–13).

2.2.3. School-related difficulties

This includes repeated grades, learning disabilities, extra tuition, expulsion from school, underachievement in primary school (15 questions: index range 0–15), and in middle/high school (16 questions: index range 0–16).

2.2.4. Early diagnosis and professional help

The patients were also asked whether they received a diagnosis of ADHD as a child, and whether they received any professional help from a counsellor, psychologist or psychiatrist as a child or adolescent, and for what kind of difficulties. The patients' drug taking history was also recorded.

In addition, the patient's current substance use was assessed, including use of alcohol, opiates, central stimulants, cannabis and other substances. Many of the patients in the study were polydrug abusers, but for the purpose of the current study only the most frequently used drug was selected for the analysis.

2.3. Statistics

Cross tabulation and chi-square statistics were used in relation to prior diagnosis and treatment. Because of lack of homogeneity of variance between the two patient groups, non-parametric *U*-tests for independent samples were used for all between group comparisons. For the non-parametric tests, effect size estimates were based on *Z* values ($r = Z/\sqrt{N}$), indicating the variance explained by the analysed effect. According to Cohen, a small effect is equivalent to 0.1, a moderate effect to 0.3 and a large effect to 0.5 (Cohen, 1992). The number of patients included in the different analyses varied depending on the degree of completion of the various parts of CAADID, although the overall completion rate was good. Due to large differences in sample sizes between the two groups, *U*-tests were also performed on randomized samples based on 20% of the SUD patients without adult ADHD and 100% of the SUD patients with adult ADHD, to make the number of patients similar for the two groups. All computations were made using the statistical programme SPSS 22 (IBM Corp, 2013).

3. Results

A total of 1205 SUD patients were included: 196 (16.3%) with adult ADHD (SUD + ADHD) and 1009 (83.7%) without adult ADHD (SUD-ADHD) according to DSM-5. Table 1 shows the number of patients from each country, the percentage of women and mean age. The percentage of women varied from 18% in the Netherlands to 34% in Switzerland (Pearson chi square = 16.0, $p = .013$), and the mean age varied from 36.8 years in France to 43.0 years in Hungary ($F = 11.8$, $p < .001$). The primary substances of abuse in the sample were alcohol (55%), followed by cannabis (11%), heroin (10%), cocaine (9%), amphetamine (6%), addictive medicines (e.g. opioids, benzodiazepines; 4%), illegal methadone (1%) and "other substances" (3%).

Table 1
Countries of origin, number of patients, percentage women and mean age.

Country	Number and percentage of total	Percentage females	Mean age/SD
Sweden	165/13.7%	31%	42.6/11.6
Norway	175/14.5%	31%	37.6/10.8
Netherlands	125/10.4%	18%	40.7/10.1
Switzerland	152/12.6%	34%	42.5/10.8
France	154/12.8%	27%	36.8/10.7
Spain	220/18.3%	21%	37.1/9.7
Hungary	214/17.8%	25%	43.0/12.2
Total sample	$N = 1205$	27%	40/11.2

3.1. Infant development

SUD + ADHD patients were significantly slower in the development of basic skills such as walking, talking, toilet training, as well as reading (Table 2); ($U = 70753$, $p < 0.001$, $r = 0.15$). Similar results were obtained in the analysis with a 20% random selection of patients from SUD-ADHD group ($U = 6902$, $p = 0.008$, $r = 0.16$).

3.2. Difficult temperament

SUD + ADHD patients scored significantly higher than SUD-ADHD patients on temperamental difficulties ($U = 35594$, $p < 0.001$, $r = 0.38$) with similar results when using the 20% random selection of SUD-ADHD patients ($U = 6902$, $p < 0.001$, $r = 0.45$). The SUD + ADHD patients reported struggling more with difficulties related to rage, anxiety, behavioural problems, clumsiness, eating and sleeping.

3.3. Problems at school

The SUD + ADHD group also had significantly more school related difficulties, both at primary school level ($U = 42121$, $p < 0.001$, $r = 0.34$) and at middle/high school level ($U = 35643$, $p < 0.001$, $r = 0.34$) with similar results when using the 20% random selection of SUD-ADHD patients (primary school level: $U = 9013$, $p < 0.001$, $r = 0.45$; middle/high school level: $U = 7899$, $p < 0.001$, $r = 0.45$). The SUD + ADHD group were substantially more likely to have struggled, with reading and writing, had extra tuition, and experienced labelling and expulsion from school than SUD-ADHD patients.

3.3.1. Gender

There were no significant gender effects within the SUD + ADHD group regarding infant development, difficult temperament or school problems. There was, however, a significant effect within the SUD-ADHD group for difficulties at elementary school, where boys had a slightly higher score than girls ($U = 80900$, $p < 0.001$, $r = 0.06$).

3.4. Early diagnosis and professional help

Among the 196 SUD + ADHD patients, 24 patients (12.2%) were diagnosed with ADHD as a child or adolescent, whereas the remaining 172 patients (87.8%) had never been diagnosed with ADHD before the study. In the SUD-ADHD group, 50 patients (5.0%) had been diagnosed with ADHD as a child. In the SUD + ADHD group, significantly more patients had seen a counsellor, psychologist or psychiatrist as a child than in the SUD-ADHD group: SUD + ADHD 47% vs. SUD-ADHD 24% (Fischer exact probability test $p < .001$). Among the reasons for seeking professional help, either through their parents or school, were behavioural problems and acting out, difficulty concentrating, hyperactivity, depression, various forms of trauma and abuse, as well as truancy.

Seventeen percent of the SUD + ADHD group and 8% of the SUD-ADHD group had taken medication for ADHD or for another mental health problem as a child (Fisher exact probability test $p < 0.001$). Among the medications that were mentioned were central stimulants such as immediate release methylphenidate and OROS methylphenidate, but also other medications such as antidepressants, sleeping pills and tranquilizers. Fifteen patients received ADHD medication as a child: 8 from the SUD + ADHD group (4.0%) and 7 from the SUD-ADHD group (0.7%), including 3 patients (0.3%) with childhood ADHD-only (i.e. not adult ADHD).

3.5. Primary substance of abuse

In the SUD + ADHD group, 61% reported illicit drugs as their primary substance, as compared to 41% in the SUD-ADHD group (Fisher exact probability test $p < 0.001$). Table 3 shows the very different distribution of the various primary substances being used in the two patient groups

Table 2

Problem area, mean scores and differences between SUD patients with and without adult attention deficit hyperactivity disorder (ADHD).

	SUD + ADHD N = 196			SUD-ADHD N = 1009			U-value	p Value	r
	N	M	SD	N	M	SD			
Infant development (0–4)	181	0.62	0.94	961	0.30	0.59	70753	<.000	0.15
Temperamental (0–13)	182	5.60	2.90	958	2.40	2.50	35594	<.000	0.38
Elementary school (0–15)	184	5.30	3.15	965	2.41	2.73	42121	<.000	0.34
Middle/high school (0–16)	168	5.70	2.84	898	2.95	2.72	35643	<.000	0.34

(Pearson's Chi-square = 53.4, $p < 0.001$) with stimulant use disorder (including amphetamine, methamphetamine and cocaine) and cannabis use disorder much more prevalent in the SUD + ADHD group than in the SUD-ADHD group; stimulant use disorder 29.5% vs. 12.2%; cannabis use disorder 15.5% vs. 9.8%.

4. Discussion

The current study shows a substantial overrepresentation of all childhood and adolescent problems in the SUD + ADHD group, especially more episodes with temperamental outburst, impulsiveness, and impatience, along with poor school performance. The study also clearly shows that surprisingly few SUD patients with ADHD (12%) were diagnosed and treated as a child or adolescent for this disorder. Almost half of the SUD + ADHD patients and one quarter of the SUD-ADHD patients had seen a professional for behavioural problems, impulsivity and acting out, concentration problems, and a number of other psychological symptoms. Only 4% of the SUD + ADHD patients had been treated with a stimulant for childhood ADHD. Finally, SUD + ADHD patients were more likely to have central stimulants or cannabis as their primary substance of abuse, whereas alcohol use was more likely to be the primary substance of abuse in SUD-ADHD patients.

One should bear in mind that these are retrospective data and reliability and validity may be limited by the patients' memory and ability to recall childhood experiences and relevant information from their parents and other close persons. The lack of collateral information from childhood, home or school and the fact that the diagnosis was based solely on information obtained from the patient, this may have led to less accuracy because of poor self-knowledge or under-reporting.

4.1. Infant development and temperamental problems

The SUD + ADHD patients revealed more severe developmental problems such as delay in walking, talking, toilet training and reading. Furthermore, they had significantly more temperamental difficulties than the other group. This result reflects an increased burden in infancy and early childhood regarding rage, anxiety, behavioural problems, clumsiness, and eating problems. These problems have previously been associated with hyperactivity-impulsivity (Chang, Lichtenstein, & Larsson, 2012; Elkins, McGue, & Iacono, 2007). The difficulties are to a large extent highly visible signs often associated with ADHD, but still few of the patients were adequately identified and treated for their ADHD.

Table 3

Primary substance used for SUD patients with and without adult ADHD.

	SUD + ADHD N = 196		SUD-ADHD N = 1009	
	N	%	N	%
Alcohol	71	36.8	594	59.1
Opiates	23	11.9	103	10.2
Central stimulants	57	29.5	123	12.2
Cannabis	30	15.5	98	9.8
Other substances	12	6.2	87	8.7

Pearson's Chi-square = 53.4, $p < 0.001$.

4.2. School experiences

The SUD + ADHD patients had significantly poorer academic achievements such as difficulties in reading, writing and arithmetic, and many had repeated grades, learning disabilities, extra tuition, and expulsion from school. Many of them were probably underachieving at school. However, on the basis of this study it is impossible to say whether their poor school performance was due to environmental or biological/genetic factors, including ADHD. It probably reflects both types of influence. Although ADHD patients show structural and functional brain abnormalities in areas related to executive functions and cognition (Cortese, 2012), psycho-educational interventions for ADHD in school can contribute to improved academic performance and less truancy and drop out from school (DuPaul & Eckert, 1997). The school-based intervention literature suggests that particular attention should be paid to the need for feasible, effective strategies that can be used in general education settings with a variety of age groups with ADHD (DuPaul, 2007).

4.3. Diagnosis, medication and substance use

A minority of 12% of the SUD + ADHD group had been identified as having ADHD, but only 4% had received ADHD medication during childhood or adolescence. The fact that so few had been medicated for ADHD suggests the presence of scepticism towards medical treatment for ADHD in children and adolescents.

Almost one third of the SUD + ADHD patients in our study used central stimulants as their primary drug, thus suggesting some sort of self-medication that might have been avoided with proper, early treatment. In a review of relevant literature on individuals with cocaine dependence it was suggested that self-medication, and prescribed psychostimulants may have benefit in restoring dopaminergic function (Mariani, Khantzi, & Levin, 2014). They suggest that psychostimulant treatment of cocaine dependence is consistent with the self-medication hypothesis and is deserving of further study.

Also cannabis was more prevalent in the ADHD group, which is in line with findings in prior research (Charach, Charach, Yeung, Climans, & Lillie, 2011). It has been suggested that cannabis might reduce anxiety (Vorspan, Mehtelli, Dupuy, Bloch, & Lépine, 2015) and restlessness, but is unlikely to help with concentration (Bidwell, Henry, Willcutt, Kinneer, & Ito, 2014). There might be many adults with undiagnosed or untreated ADHD using cannabis who will not be identified because their cannabis use does not cause them to present for treatment.

Apart from the self-medication hypotheses (using substances to decrease ADHD-symptoms and consequences), other possible causes have been explored, such as the route via Oppositional Defiant Disorder/Conduct Disorder and Antisocial Personality Disorder (Flory & Lynam, 2003) and common underlying genetic/neurobiological factors (Arcos-Burgos, Vélez, Solomon, & Muenke, 2012; Ivanov, Schultz, London, & Newcorn, 2008). Regardless of the mechanism underlying the linkage between ADHD and SUD, early treatment of ADHD might have a protective influence on the development of SUD. If so, early detection of ADHD is of major importance for the prevention of SUD development in children and adolescents with this disorder. The factors presented in this paper

appear to be important childhood markers for ADHD and subsequent comorbid SUD and, thus, might help in this early detection.

It has been argued that pharmacological treatment of ADHD with stimulant medication may lower the threshold for future abuse, although to date the evidence regarding the effect of stimulant treatment on the risk of later substance use disorders is mixed. Whilst a recent meta-analytic review concluded that stimulant treatment does not affect the risk for substance use disorders (Humphreys, Eng, & Lee, 2013), subsequently published studies suggest otherwise. A meta-analysis on stimulant treatment of ADHD and its effect on the development of nicotine dependence (Schoenfelder, Faraone, & Kollins, 2014) concluded that there is a significant association between stimulant treatment of ADHD patients and lower smoking rates in these patients. Also, a recent European study showed that stimulant treatment appears to lower the risk of developing substance use disorders in adolescents with ADHD, especially if the treatment is started at a young age (Groenman et al., 2013).

4.4. Conclusions and clinical implications

Based on present knowledge, early diagnosis of ADHD, proper medical and psychological treatment, as well as psycho-education, is of critical importance. Treatment and educational support for youngsters with ADHD is available and may make a major difference in the lives of this group. It may also prevent the development of substance use disorders in late adolescence and adulthood.

Many of the patients have been in contact with health and school services, in conjunction with ADHD associated symptoms, without having been diagnosed with ADHD. Behavioural symptoms such as more temperamental outbursts, impulsiveness, hyperactivity and impatience, along with poor school performance, seem to be associated with subsequent development of a substance use disorder in this group of children with ADHD. It is therefore important that children with such symptoms receive an adequate follow-up and treatment as early as possible so that one can potentially prevent later drug addiction. In order to achieve that goal, more attention and expertise in educational and health agencies in relation to the detection and treatment of ADHD are needed.

The SUD and ADHD patients in this study were offered further assistance. Some have been in individual or group therapy for ADHD with a focus on improving the structure and planning of everyday life, others have received medical attention, and some have received both. It is beyond this article's focus, but it would be interesting to follow them up further. A positive effect of drug therapy in relation to this dual diagnosis group of adults has not been convincingly documented in the research literature, and the need for research on multimodal treatment including both medical (e.g. Konstenius et al., 2014) and psychological approaches (e.g. van Emmerik-van Oortmerssen et al., 2013) is great.

Role of funding source

The ICASA Foundation (www.adhdandsubstanceabuse.org) developed the IASP study, and arranged with its participating institutes that each of these institutes would seek funding for their regional process and data sampling efforts. The ICASA Network sought funding for the central organization costs. These central costs included:

- Organizing meetings for the network;
- Site visits for training and monitoring (the last author (VdG G) visited all of the institutes at least once, the European institutes were visited twice);
- Building a data base fit for remote data storage at the University of Amsterdam;
- Obtaining the right for use of the CAADID interview;
- Translating the instruments in the necessary languages;

- Cleaning the data;
- Analysing the study results and coordinating publishing;

In the period of development of the study (2005–2010) the ICASA network received unrestricted grants from the following pharmaceutical companies: Janssen Cilag, Eli Lilly and Company, Shire. Since the ICASA Network is a formal foundation (September 2010) it operates independent from pharmaceutical funding. Since then funding was obtained via the following sources:

- Participating institutes;
- The Noaber Foundation;
- The Waterloo Foundation;
- The Augeo Foundation.

The funding companies, institutes and foundations did not have and will not have influence on any aspect of the study, including research questions, data sampling, data management, data analyses and publishing results.

The local institutes report the following funding sources: The Netherlands, Amsterdam: no external funding was obtained. The participating institute, Arkin, paid for the costs involved, and used funding from Fonds NutsOhra for this project.

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G. Van de Glind was on one occasion consultant for Shire, for which he refused payment. In 2013 he received an unrestricted travel grant from Neurotech and he is (unpaid) member of the advisory board of Neurotech.

P.-J. Carpentier received in 2011 fee for speaking at a conference organized by Eli Lilly.

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S. Kaye reports receiving unrestricted travel grants for participation in the World ADHD Federation conference in Berlin (2011) from Shire, Janssen and Eli Lilly.

In the past year, S.V. Faraone received consulting income and/or research support from Shire, Akili Interactive Labs, VAYA Pharma, SynapDx and Alcobra and research support from the National Institutes of Health (NIH). His institution is seeking a patent for the use of sodium–hydrogen exchange inhibitors in the treatment of ADHD. In previous years, he received consulting fees or was on Advisory Boards or participated in continuing medical education programmes sponsored by: Shire, Alcobra, Otsuka, McNeil, Janssen, Novartis, Pfizer and Eli Lilly. He receives royalties from books published by Guilford.

Press: Straight Talk about Your Child's Mental Health and Oxford University.

Press: Schizophrenia: The Facts.

J.A. Ramos-Quiroga was on the speakers' bureau and/or acted as consultant for Eli-Lilly, Janssen-Cilag, Novartis, Shire and Rubió in the last 3 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Janssen-Cilag, Shire, and Eli-Lilly. The ADHD Program chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last 3 years: Eli-Lilly, Janssen-Cilag, Shire, and Rubió.

Z. Demetrovics received reimbursement for participating at a symposia organized by Lundbeck (2011).

G. Dom acted as a paid consultant for Lundbeck and received speakers fee and reimbursement for symposium attendance from GSK, Janssen Ph., Astra-Zeneca, Eli Lilly.

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Contributors

AS, ETHB, FKJ and GvdG wrote the proposal, coordinated the study, were involved in the data management and data analyses, drafted the manuscript and wrote the final version of the manuscript. GVDG, FRL, WvdB, MWJK, PJC, JAR-Q, and AS contributed to the design of the study. MK, KvE-vO, SK, AS, JF, EHTB, FM, GD, ZD, MF, MA, SVF, JAR-Q, SA, RAS, and CB, coordinated the local data collection. MK, KvE-vO, SK, E-TB, SV, MK-F, MF, JAR-Q, SC, and MM collected data. MWJK supervised data analyses on the original IASP data set. AS, ETHB, and FKJ performed data analyses for the current study. AS, ETHB, FKJ, WvdB, and GVDG, were involved in analyses and interpretation of data. AS, ETHB, FKJ, GVDG, MK, MWJK, KvE-vO, PJC, SK, JF, FM, GD, SV, ZD, MF, MA, MM, SVF, JAR-Q, SA, SC, RAS, CB, FRL, and WvdB revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript, agreed on the interpretation of the data, commented on the manuscript.

Conflict of interest

All the authors declare, apart from the funding resources described above, no other conflicts of interest.

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