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ORIGINAL ARTICLE

Metabolic status is not associated with job stress in individuals with obesity: the ELSA-Brasil baseline

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Abstract
Purpose Job stress has proven to be a relevant cause of stress for adults, but its effect on the development of metabolic alterations in individuals with obesity is still poorly explored. We aimed to investigate the association between job stress and metabolically unhealthy obesity (MUO) phenotype in participants with obesity at the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) baseline assessment.
Methods This study analyzed data collected at the baseline examination between 2008 and 2010. A total of 2371 individuals with obesity were included. Two metabolic phenotypes were characterized based on the US National Health and Nutrition Examination Survey criteria. The job stress scale was based on the Brazilian version of the Swedish Demand-Control-Support Questionnaire. The association between job stress domains and MUO phenotype was assessed by binary logistic models.
Results In our sample, 1297 (54.7%) participants were women, mean age was 49.6 ± 7.1 years and 1696 (71.5%) had MUO. Low skill discretion was associated with MUO after adjustment for age, sex and race. However, in fully-adjusted models, the MUO phenotype was not associated with high job demand (odds ratio [OR] = 1.05; 95% confidence interval [95%CI] 0.82–1.35), low skill discretion (OR = 1.26; 95%CI 0.95–1.68), low decision authority (OR = 0.94; 95%CI 0.70–1.25) nor low social support (OR = 0.93; 95%CI 0.71–1.20).
Conclusion We found a significant association between low skill discretion and an adverse metabolic profile in models adjusted for age, sex and race. No associations were significant between job stress domains and the metabolic profile of individuals with obesity in full models.

Keywords Epidemiology · Job stress · Metabolically unhealthy obesity · Metabolic abnormalities · Cross-sectional

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Introduction

Obesity is a global epidemic and one of the most neglected public health problems according to the World Health Organization (WHO). The year 2000 started with over 300 million adults with obesity worldwide (World Health Organization 2013). In 2016, the Global Health Observatory data showed that 11% of men and 15% of women had obesity, which stands for more than half billion people (World Health Organization 2019). Obesity has been on the rise not only in several high-income countries, but also in many middle- and low-income countries (Stanaway et al. 2018).

Over the last decade, two metabolic phenotypes in individuals with obesity have been described: metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUO) (Ahima and Lazar 2013). No consensus has been reached on the definition of these metabolic profile, but the latter has been characterized by the presence of metabolic and cardiovascular comorbidities, such as high blood pressure and insulin resistance. Individuals with MUO may be at a higher risk of all-cause mortality when compared to people with MUO, i.e., without significant obesity-related metabolic abnormalities (Rey-López et al. 2014; Cho et al. 2019).

Modern life stress may lead to visceral fat accumulation and the low-grade inflammatory state that accompany the growth of obesity epidemics. Some authors suggest that chronic stress may be associated with MUO-related changes, such as high blood pressure (Liu et al. 2017; Ushakov et al. 2017) and glucose levels (Kyrou and Tsigos 2009; Kelly and Ismail 2015), which may be a mechanism to explain the higher incidence of cardiovascular diseases in individuals exposed to psychosocial stress (Kivimäki et al. 2012).

In particular, the workplace is a substantial source of stress for many individuals. Previous studies have indicated the role of work-related stress as a risk factor for the adoption of an unhealthy lifestyle (Heikkilä et al. 2013), which, in turn, may lead to an increase in abdominal and general obesity (Ishizaki et al. 2008; Brunner et al. 2007). Although the association between job stress and obesity has been described, the effect of work-related stress on the development of metabolic alterations in individuals with obesity is still poorly explored. This may be at least partially explained by the lack of a single, standardized definition of which parameters and cutoff values should be used to characterize metabolic health, as well as different strategies to measure and conceptualize job stress.

The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) is a large multicentric study in Brazil, with a high proportion (22.9%) (Schmidt et al. 2015) of individuals with obesity. Data from this sample may contribute to current knowledge about the association between job stress and the metabolic profile of individuals with obesity. We hypothesized that individuals with obesity exposed to high job stress have higher risk to develop metabolically unhealthy obesity compared to those exposed to low job stress in ELSA-Brasil baseline assessment.

Methods

Study design

The present cross-sectional study used data obtained at the baseline of ELSA-Brasil. Briefly, ELSA-Brasil is an ongoing prospective cohort study that aims to investigate the development and risk factors for the progression of cardiovascular diseases and diabetes mellitus. During the ELSA-Brasil study recruitment, all active or retired employees from six universities and research institutes in Brazil, aged 35–74 years were eligible for the study. Exclusion criteria were current or recent (< 4 months prior to the first interview) pregnancy, intention to quit working at the institution in the near future, severe cognitive or communication impairment, and, if retired, residence outside of a study center's corresponding metropolitan area. Baseline assessment occurred from August 2008 and December 2010 and enrolled 15,105 participants (12,096 active workers). Further details about the study design, selection criteria, and recruitment methods were described elsewhere (Aquino et al. 2012; Schmidt et al. 2015).

Study sample

For the purpose of this study, 2704 participants who were active workers at the baseline, with obesity according to WHO criteria (BMI $\geq$ 30 kg/m^2) were eligible. Exclusion criteria included previous myocardium infarction, stroke, or myocardial revascularization ($n = 83$); a C-reactive protein level of more than 10 mg/L ($n = 214$); and missing data for any of the study parameters ($n = 36$). A total of 2371 individuals were included in the analyses. Among ELSA-Brasil participants there were non-skilled workers as janitors and gardeners; clerical or technician workers, as those involved in most administrative affairs and support activities, as information technology professionals, and graduation-required jobs, as health care workers and university faculty. In our sample, 799 (33.7%) participants were non-skilled workers, 914 (38.5%) clerical or technician workers and 658 (27.8%) had graduation-required jobs. When the job stress questionnaire was applied, the mean time working in the same institution was 20.3 years. The mean time performing the same functions was 14.1 years; 1862 (78.5%) were performing the same functions for at least 5 years and 1491 (62.9%) were performing the same functions for 10 years or more.

Job stress variables

The job stress scale was based on the validated Brazilian version (Alves et al. 2004) of the Swedish Demand-Control-Support Questionnaire (DCSQ), which was developed with reference to the Job Content Questionnaire (Karasek 1979). The job stress scale was considered reliable and highly consistent with the Job Content Questionnaire, as also shown in other studies (Griep et al. 2009; Santos et al. 2014). The DCSQ included three domains: psychological job demands, social support, and job control (Chungkham et al. 2013) (Supplementary data 1).

Job demand included five items on time and speed to perform tasks, as well as the existence of conflicts between different demands, each of them were presented on a Likert-type scale (1–4), varying between "often" and "never/almost never". Social support was related to the opinion and support of colleagues and supervisors, each of the six items were presented on a Likert-type scale (1–4) varying between "strongly agree" and "strongly disagree".

In this study, we adopted the strategy suggested in the article by Chungkham et al. (2013). In that article, a factor analysis showed that the job control domain is composed by two subdomains (skill discretion and decision authority), which are not strongly correlated. In addition, that analysis suggested the question about repetitive work should be removed. This alternative strategy by Chungkham et al. has been adopted elsewhere (Theorell et al. 2016, Fandiño-Losada et al. 2013), and is a counterpoint to the classic Karasek's model (Karasek 1979), which combines demand and control, categorizing job stress perception as low strain (low demand and high control), passive (low demand and low control), active (high demand and high control) and high strain (high demand and low control) jobs, according to a cutoff at job demand and control median scores. As a corollary, Karasek's model considers job control as a single domain. To enhance comparability, in some sensitivity analyses, we used the classic Karasek's model for demand-control interaction.

Definition of metabolic status

Data used in the present article were collected using structured questionnaires, clinical and laboratory examinations (Aquino et al. 2012). The anthropometric parameters were measured using calibrated equipment and standard techniques (Mill et al. 2013). Weight (kg) and height (cm) were measured using Toledo scales (to the nearest 100 g) and a stadiometer (accuracy of 0.1 cm), respectively. Participants were barefoot, wearing light clothes, and standing straight with the head level. Waist circumference (mid-point between lowest rib and iliac crest) was measured by inelastic tapes (cm) and the average of two measures was used in the analyses. Resting blood pressure was measured three times in the seated position after a five-minute rest, and the mean value between the second and third measurements was considered in the analyses.

All laboratory tests were performed at the ELSA-Brasil center in São Paulo (Fedeli et al. 2013). Blood samples were collected after 12 h of nocturnal fasting. From these samples, fasting plasma glucose (FPG) and insulin tests were obtained and the homeostasis model assessment-insulin resistance (HOMA-IR) index was calculated according to the formula [(FPG (mg/dl) × 0.0555) × (fasting plasma insulin (mIU/L)/22.5)] (Matthews et al. 1985). FPG was determined by the hexokinase method (enzymatic colorimetric). Insulin was calculated using the immunoenzymatic assay (ADVIA Centaur Siemens, Deerfield, IL). Total cholesterol was determined by the oxidase method (enzymatic colorimetric) and high-density cholesterol (HDL-c) through homogeneous colorimetrics without precipitation, both of which using an ADVIA 1200 Siemens system (Deerfield, IL). Triglycerides (TG) were computed by glycerolphosphate peroxidase. Low-density cholesterol (LDL-c) was calculated by the Friedewald Equation, when TG ≤ 400 mg/dL, or determined by the homogeneous enzymatic colorimetric method without precipitation (ADVIA 1200 Siemens system), when TG > 400 mg/dL. The C-reactive protein (CRP) was determined by immunochemistry through nephelometry (nephelometer BNII, Dade Behring; Siemens).

The main metabolic profile classification used in this study was based on the Third National Health and Nutrition Examination Survey (NHANES) criteria for anthropometric–metabolic profiles (Supplementary Table 1). Our main analyses classified individuals with two or more alterations in NHANES criteria as MUO. To enhance comparability to the multiple criteria found in literature to define metabolic health in individuals with obesity, in some analyses we also adopted the National Cholesterol Education Program—Adult Treatment Panel III (NCEP—ATP III) criteria (Supplementary Table 2), defining MUO as having three or more altered parameters (Rey-Lopez et al. 2014; Diniz et al. 2016).

Other variables

Sex, age, race/skin color, educational level, marital status, and smoking status were self-reported. Smoking status was classified into never, past, and current smokers. Physical activity at leisure was verified through the International Physical Activity Questionnaire (IPAQ). Physical activity was categorized as poor (not practicing physical activity), intermediate (practicing less than the cut-offs defined for ideal physical activity), or ideal (≥ 150 min of moderate activity, ≥ 75 min of vigorous or ≥ 150 min of moderate or vigorous activity per week). Mental health data were collected through the Portuguese version of the Clinical Interview Schedule-Revised (CIS-R) (Chor et al. 2013).

Statistical analysis

Categorical variables were expressed as absolute counts and proportions and were compared using Chi-square tests. Normally distributed continuous variables were expressed as means ± SD or medians (interquartile range) and compared using the Student *T* test or ANOVA. Non-normally distributed continuous variables were expressed in median (interquartile range) and compared using the Wilcoxon or Kruskal–Wallis test.

The association between job stress domains and MUO phenotype was evaluated using binary logistic models. The job stress domains were separately included as independent variables in each of the models. Models are presented as follows: (1) crude; (2) adjusted for age, sex, and race/skin color; and (3) adjusted for age, sex, race/skin color, educational level, marital status, smoking, physical activity level, CIS-R score, and BMI. We also present the odds ratios and *p* values for the association between MUO and each of the confounders included in full models. These estimates are presented both for bivariate (single independent variable) and full models. In addition, we present the same models using as the main independent variable the demand-control categories as defined by Karasek's model. Statistical significance level was set at 0.05. The statistical software R version 3.1.2 was used for the analyses.

Results

Sample characteristics stratified by metabolic obesity phenotype are summarized in Table 1. Participants were predominately middle-aged (mean age of 49.6 ± 7.1) and white (46.7%). Approximately half were female (54.7%) and almost two-thirds were living with a partner (66.4%). The frequency of use of antihypertensive, hypoglycemic, and lipid lowering agents were 38.3%, 11.1%, and 12.5%, respectively. The prevalence of MUO, according to NHANES criteria, was 71.5% (95% confidence interval [95% CI] 69.7–73.3). In the bivariate analyses, higher age, male gender, lower educational level, smoking, and higher BMI were statistically associated with an unhealthy metabolic profile. We present further details in sample characteristics, by sex and according to both metabolic profile criteria in Supplemental Table 3 (NHANES criteria) and Supplemental Table 4 (NCEP—ATP III criteria). Mean job stress scores were 13.4 ± 2.9 for demand, 10.5 ± 1.7 for skill discretion, 5.7 ± 1.7 for decision authority, and 19.7 ± 3.4 for social support (Table 2). Supplementary Tables 5 (NHANES criteria) and 6 presents (NCEP—ATP III criteria) job stress scores according to metabolic profile and sex.

Table 3 shows the results from logistic regression models for the association between job stress domains and MUO. In crude models, low skill discretion was positively associated with MUO (odds ratio [OR] = 1.40, 95% CI 1.09–1.79), and low social support was inversely associated with MUO (OR = 0.70, 95% CI 0.56–0.89). After adjustment for age, sex, and race/skin color, the clearest association (including a dose–response pattern) was between low skill discretion scores and MUO (OR = 1.52, 95% CI 1.18–1.97).

Table 1 Characteristics of metabolically healthy and metabolically unhealthy individuals with obesity, according to NHANES criteria

	MHO (*N* = 675)	MUO (*N* = 1696)	Total (*N* = 2371)
Age (mean ± SD)	47.8 ± 6.9	50.3 ± 7.1	49.6 ± 7.1
Race/skin color			
White	310 (46.3%)	786 (46.9%)	1096 (46.7%)
Brown	178 (26.6%)	501 (29.9%)	679 (28.9%)
Black	167 (24.9%)	338 (20.2%)	505 (21.5%)
Other	15 (2.2%)	52 (3.1%)	67 (2.9%)
Educational level			
Up to incomplete high school	50 (7.4%)	273 (16.1%)	323 (13.6%)
High school	276 (40.9%)	684 (40.3%)	960 (40.5%)
College or above	349 (51.7%)	739 (43.6%)	1088 (45.9%)
Living with partner	415 (61.5%)	1159 (68.3%)	1574 (66.4%)
Smoking status			
Never smokers	447 (66.2%)	881 (51.9%)	1328 (56.0%)
Past smokers	164 (24.3%)	606 (35.7%)	770 (32.5%)
Current smokers	64 (9.5%)	209 (12.3%)	273 (11.5%)
Leisure time physical activity			
Poor	459 (68.9%)	1189 (71.2%)	1648 (70.5%)
Intermediate	76 (11.4%)	195 (11.7%)	271 (11.6%)
Ideal	131 (19.7%)	287 (17.2%)	418 (17.9%)
CIS-R score (mean ± SD)	9.9 ± 8.7	9.4 ± 8.7	9.6 ± 8.7
BMI, kg/m^2 (mean ± SD)	32.9 ± 2.8	33.7 ± 3.4	33.5 ± 3.3
Waist circumference, cm	101.7 ± 9.0	107.3 ± 9.8	105.7 ± 9.9

NHANES National Health and Nutrition Examination Survey, *MHO* metabolically healthy obesity. *MUO* metabolically unhealthy obesity, *CIS-R* clinical interview scheduled-revised, *BMI* body mass index

Table 2 Job stress domains (continuous and classified in tertiles) according to metabolic profile and sex according to NHANES criteria

	MHO (*N* = 675)	MUO (*N* = 1696)	Total (*N* = 2371)
Demand (mean ± SD)	13.5 ± 2.8	13.4 ± 2.9	13.4 ± 2.9
Low	236 (35.0%)	617 (36.4%)	853 (36.0%)
Medium	253 (37.5%)	644 (38.0%)	897 (37.8%)
High	186 (27.6%)	435 (25.6%)	621 (26.2%)
Skill discretion (mean ± SD)	10.7 ± 1.6	10.5 ± 1.7	10.5 ± 1.7
Low	126 (18.7%)	392 (23.1%)	518 (21.8%)
Medium	274 (40.6%)	691 (40.7%)	965 (40.7%)
High	275 (40.7%)	613 (36.1%)	888 (37.5%)
Decision authority (mean ± SD)	5.7 ± 1.6	5.6 ± 1.7	5.7 ± 1.7
Low	281 (41.6%)	735 (43.3%)	1016 (42.9%)
Medium	296 (43.9%)	669 (39.4%)	965 (40.7%)
High	98 (14.5%)	292 (17.2%)	390 (16.4%)
Social support (mean ± SD)	19.6 ± 3.2	19.8 ± 3.4	19.7 ± 3.4
Low	303 (44.9%)	707 (41.7%)	1010 (42.6%)
Medium	238 (35.3%)	545 (32.1%)	783 (33.0%)
High	134 (19.9%)	444 (26.2%)	578 (24.4%)

NHANES National Health and Nutrition Examination Survey, *MHO* metabolically healthy obesity, *MUO* metabolically unhealthy obesity

Table 3 Odds ratios (95% CI) for the association between job stress domains and metabolically unhealthy obesity according to NHANES criteria

	Crude model OR (95% CI)	Adjusted model 1 OR (95% CI)	Adjusted model 2 OR (95% CI)
Demand			
Low	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Medium	0.97 (0.79–1.20)	1.00 (0.81–1.25)	1.00 (0.80–1.25)
High	0.89 (0.71–1.12)	1.00 (0.79–1.27)	1.05 (0.82–1.35)
Skill discretion			
Low	**1.40 (1.09–1.79)**	**1.52 (1.18–1.97)**	1.26 (0.95–1.68)
Medium	1.13 (0.93–1.38)	**1.30 (1.06–1.61)**	1.22 (0.98–1.52)
High	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Decision authority			
Low	0.88 (0.67–1.14)	1.03 (0.78–1.36)	0.94 (0.70–1.25)
Medium	**0.76 (0.58–0.99)**	0.85 (0.64–1.12)	0.84 (0.63–1.11)
High	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Social support			
Low	**0.70 (0.56–0.89)**	0.87 (0.68–1.11)	0.93 (0.71–1.20)
Medium	**0.69 (0.54–0.88)**	0.79 (0.61–1.01)	0.83 (0.64–1.08)
High	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)

Adjusted model 1 is adjusted for age, sex and race/skin color. Adjusted model 2 is adjusted for age, sex, race/skin color, educational level, smoking, leisure physical activity, CIS-R, marital status and BMI

Significant associations at the 5% level are in bold font

After full adjustment, however, the association between low skill discretion scores and MUO were no longer significant ($p = 0.11$). The covariates age, sex, smoking status, educational level and BMI were associated with the MUO phenotype in the bivariate (single independent variable) models and all full models (Supplementary Table 7). Sensitivity analyses were then performed using the NCEP-ATP III criteria (Supplementary Table 8) and Karasek's model classification as the main independent variable (Supplementary Table 9), yielding similar results of no detected association in fully adjusted models.

Discussion

The present study aimed to investigate, in adults with obesity, if high perceived job stress was associated with adverse metabolic profiles, more specifically, with the MUO phenotype. The conceptual basis behind this research question was the existing evidence of a positive association between biological alterations and high job stress (Siegrist and Li 2017), which may be independent of its association with obesity. However, in full-adjusted models, we did not find significant associations between job stress domains (demand, skill discretion, decision authority and social support) and the metabolic profile of individuals with obesity.

A recent systematic review by Watanabe et al. (2018) found a positive association between work-related stress and metabolic syndrome. Considering the results from four articles, the pooled relative risk between job stress and metabolic syndrome was 1.75 (95%CI: 1.09–2.79). However, these articles (Gabarino and Magnavita 2015; Edwards et al. 2012; Chandola et al. 2006; de Bacquer et al. 2009) were not focused on the metabolic profile of individuals with obesity. Additionally, only one of the articles (de Bacquer et al. 2009) had models adjusted for adiposity measurements (weight gain, BMI or waist circumference) at the end of follow-up. Therefore, a plausible main interpretation of their findings is that increasing BMI and/or the development of abdominal obesity may act as mediators for incident metabolic syndrome. Although correlated, our research question differs from these previous studies. For this reason, in addition to restricting the study sample to individuals with obesity ($BMI \geq 30$ kg/m^2), this study sought to minimize a residual confounding effect of BMI by including it as a continuous variable in the full models.

In our sample, individuals with low or medium skill discretion had higher odds of presenting an adverse metabolic profile compared to participants with high skill discretion, in models adjusted for age, sex and race/skin color. Although this association vanished in full-adjusted models, it may not be totally overlooked. A potential effect towards a null association in our study is due to its cross-sectional design, and the possibility of reverse causation. Although it is arguable that people with poor health are more prone to perceive their job as stressful, individuals with more severe diseases may be less prone to be located in stressing positions, specifically in our sample of Brazilian public civil servants. Dismissals and resignations in this setting are much rarer than in the private sector, as these workers have heterogeneous levels of job stability. On the other hand, relocations are usually feasible, a characteristic of the study setting that may have played a role in our negative findings. However, we believe our results may be not excessively influenced by this reverse causation. MUO components are mostly asymptomatic, and we excluded individuals with overt cardiovascular disease from analyses. Moreover, most subjects in our sample were performing the same functions at work for at least 10 years. Although this may not substitute multiple job stress measurements across time, it is arguable that most of the sample had fairly constant levels of job stress in the previous years.

Some authors argue that MHO is a transient state (Cho et al. 2019), and most individuals will evolve into MUO. However, even if this hypothesis is true, there may be factors that reduce the duration of this transient state, exposing individuals with obesity to the harms of an unhealthy metabolic profile earlier, and for longer time. Identifying these potential triggering factors (as psychosocial stress) may disclose potential interventions for postponing the onset of metabolic disturbances.

This study has some strength. We analyzed data from ELSA-Brasil, a large-scale multicenter cohort study, which applied stringent measures to ensure data quality. In addition, it was performed in large sample of individuals with heterogeneous job profiles from different Brazilian regions, which makes it adequate for studying the associations aimed in this article. Study limitations must be correctly acknowledged as well. Cross-sectional studies do not allow to establish temporal relationships. As presented earlier, this design may be also prone to reverse causation. However, we believe this cross-sectional analysis may contribute to the presenting literature and subsidize future prospective studies, due to the lack of studies that investigate the association between job stress and the metabolic profile of individuals with obesity. Additionally, the cohort studies that analyzed the association between metabolic syndrome and job stress did not present results for individuals with obesity in separate, allowing the comparison between the MUO and MHO phenotypes. In fact, due to their different objectives (compared to ours), two of the largest cohort studies to date evaluating the effect of job stress on metabolic syndrome (Chandola et al. 2006; Gimeno et al. 2010) had a low proportion of individuals with obesity at baseline and even excluded individuals with obesity from some analyses. In our article, we aimed to analyze if individuals with obesity who were exposed to job stress were more prone to have MUO. If this were true, despite the acknowledged limitations, we would expect a positive association to be disclosed in our cross-sectional analysis. The mostly negative findings in our analyses (except for the association with low skill discretion in age, sex and race/skin color-adjusted models) suggests against a real effect of job stress on the metabolic profile of individuals with obesity. Job stress was assessed in a single time point. However, as discussed, most subjects in our sample were performing the same functions at work for 10 years or more, with probably constant levels of job stress during this period. The lack of significant associations in the present study might also be influenced by a possible healthy volunteer bias. People who are healthy or have a perception of a lower level of job stress tend to volunteer to participate in studies, as compared to other groups. It is possible that MHO is a transient state (Cho et al. 2019), and most individuals will evolve into MUO. However, even if this hypothesis is true, studying putative triggering factors, such as stress, for MUO may reveal potential interventions for postponing the onset of metabolic disturbances.

Conclusion

We found a significant positive association between low skill discretion and an adverse metabolic profile in models adjusted for age, sex and race/skin color. However, no positive associations were significant between job stress domains (demand, skill discretion, decision authority and social support) and the metabolic profile of individuals with obesity in full-adjusted models. As our conclusions are limited by our cross-sectional design, we recommend future longitudinal studies in the field. ELSA-Brasil follow-up data will also provide more contributions in this direction.

Author contributions LI: conceptualization, methodology, formal analysis, writing original draft. BHT: conceptualization, methodology, supervision, writing original draft. RHG: conceptualization, investigation, writing (review and editing), supervision, project administration, funding acquisition. MJMF: conceptualization, investigation, writing (review and editing), supervision, project administration, funding acquisition. ACP: methodology, investigation, writing (review and editing). MFSD: conceptualization, investigation, writing (review and editing). PAL: conceptualization, investigation, writing (review and editing), supervision, project administration, funding acquisition. IMB: conceptualization, methodology, investigation, writing (review and editing), supervision, project administration, funding acquisition. ISS: conceptualization, methodology, investigation, data curation, formal analysis, writing original draft writing (review and editing), supervision.

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Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

Ethical approval Institutional Review Boards from all six centers approved the study.

Consent to participate All participants provided written informed consent.

Consent for publication All authors agreed with publication.

Availability of data and material (data transparency) Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author.

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