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# Attention-Deficit/Hyperactivity Disorder and Late-Life Cognitive Impairment

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**IMPORTANCE** Attention-deficit/hyperactivity disorder (ADHD) affects tens to hundreds of millions of adults worldwide, and preliminary evidence suggests it may be associated with increased risk of mild cognitive impairment (MCI) and dementia. However, concerns regarding diagnostic ascertainment and residual confounding remain.

**OBJECTIVE** To investigate the association of ADHD with incident cognitive impairment, defined as MCI or dementia, using electronic health record (EHR) diagnoses and genetic liability measured using genome-wide ADHD polygenic risk score (ADHD PRS) in the same individuals.

**DESIGN, SETTING, AND PARTICIPANTS** This cohort study used data from the US All of Us Research Program (enrollment May 6, 2018, to October 1, 2023; EHR data from January 4, 1985, to October 1, 2023; mean [SD] follow-up 10.26 [6.75] years). A total of 187 341 participants aged 50 years and older with available EHR and genomic data were included. Data were analyzed from October 2025 to July 2026.

**EXPOSURES** ADHD diagnosis and ADHD PRS.

**MAIN OUTCOMES AND MEASURES** Incident MCI or dementia.

**RESULTS** Among 187 341 participants (mean [SD] age, 56.41 [7.88] years; 107 266 [57%] female), 3026 (1.6%) had ADHD. Among participants with ADHD, 203 (6.7%) developed cognitive impairment, compared with 6259 (3.4%) among those without ADHD. In adjusted Cox models, ADHD was associated with a more than 4-fold higher hazard of cognitive impairment (hazard ratio [HR], 4.60; 95% CI, 3.99-5.29; $P < .001$). Adjustments for comorbidities, educational attainment, and health care utilization attenuated but did not eliminate the association. Similarly, ADHD PRS was associated with incident cognitive impairment (highest vs lowest quintile: HR, 1.35; 95% CI, 1.25-1.46; $P < .001$). Among participants who developed cognitive impairment, comorbid ADHD diagnosis was associated with a nearly 2-fold higher odds of suboptimal mental health (odds ratio [OR], 1.69; 95% CI, 1.18–2.39; $P = .01$), quality of life (OR, 1.66; 95% CI, 1.14-2.39; $P = .02$), social satisfaction (OR, 2.39; 95% CI, 1.69–3.37; $P < .001$), and 20% higher health care utilization (incidence rate ratio, 1.20; 95% CI, 1.09–1.34; $P = .003$), suggesting greater care burden beyond the elevated incidence risk.

**CONCLUSIONS AND RELEVANCE** In this cohort study, convergent clinical and genetic evidence revealed ADHD was associated with a markedly increased risk of late-life cognitive impairment. Among those who develop cognitive impairment, an ADHD diagnosis was associated with worse health outcomes and greater health care utilization, supporting the need for targeted monitoring and integrated care in this population.

Supplemental content

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Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by pervasive and impairing symptoms of inattention, hyperactivity-impulsivity, or both.[1] Although historically viewed as restricted to childhood, ADHD is now recognized as a lifelong disorder that can persist across the lifespan, with population estimates suggesting a prevalence of approximately 1% among adults older than 60 years.[2] As populations age globally, the absolute number of older adults living with ADHD is expected to increase.[3] However, ADHD remains relatively underinvestigated in later life compared with younger age groups.[4]

Of particular interest is the potential association between ADHD and late-life incidence of cognitive impairment. Emerging epidemiologic evidence suggests that ADHD may be associated with an increased risk of mild cognitive impairment (MCI) and dementia.[5-12] Alongside studies based on clinical diagnoses, recent research suggests an association between the ADHD polygenic risk score (ADHD PRS),[13] a probabilistic estimate of ADHD risk based on population-level DNA association,[14] and cognitive decline in older age.[15] If ADHD contributes to risk of cognitive impairment, clarifying this relationship could have implications for risk stratification and prevention efforts.

Despite accumulating evidence, important limitations constrain the interpretation and generalizability of studies linking ADHD to MCI and dementia. Most reports rely solely on electronic health records (EHRs) to ascertain ADHD diagnosis, which may reflect differential health care access and use, clinician recognition, and documentation practices, potentially introducing bias.[16] Additionally, adjustment for confounders has varied across studies.[5-12] Beyond risk of MCI and dementia, ADHD has been associated with worse perceived health,[17] greater functional burden,[18] and increased health care utilization.[19] However, whether ADHD is associated with these outcomes among older adults with MCI or dementia remains unclear. These gaps motivate further investigation in diverse cohorts and approaches that expand EHR diagnoses with additional information, such as the ADHD PRS. To our knowledge, no prior study has evaluated whether EHR-documented ADHD and ADHD PRS provide complementary information about risk for MCI and dementia or examined self-reported health status and health care utilization among these individuals.

Therefore, this study had the following aims: (1) to investigate the association between ADHD diagnosis and incident MCI or dementia in a large, diverse sample from the All of Us Research Program while evaluating potential confounders; (2) to complement EHR-based ADHD ascertainment by analyzing genetic liability to ADHD using an ADHD PRS; and (3) to examine whether ADHD is associated with worse self-reported health status and health care utilization among individuals with cognitive impairment.

### Key Points

**Question** Are diagnosis and polygenic risk of attention-deficit/hyperactivity disorder (ADHD) associated with increased risk of late-life cognitive impairment?

**Findings** In this cohort study of 187 341 adults from the All of Us Research Program with electronic health records and genomic data, ADHD was also associated with a higher hazard of incident mild cognitive impairment or dementia, and a higher ADHD polygenic risk score was associated with an increased risk.

**Meaning** ADHD, whether identified clinically or genetically, is associated with greater risk for late-life cognitive impairment.

## Methods

### Study Design and Population

This retrospective cohort study used data from the All of Us Research Program[20,21] (controlled tier version 8 [C2024Q3R8], cutoff date October 1, 2023), and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[22] All participants provided written informed consent, and protocols were reviewed by the institutional review board of the All of Us Research Program. As the dataset was fully deidentified and investigators had no access to information permitting reidentification of participants, the present study was determined not to be human subjects research according to federal guidelines.

Consistent with previous studies,[7,8] we included participants aged 50 years and older at cohort entry (**Figure 1**). Cohort entry was defined as the date at which the participant reached 50 years of age or the start of their EHR observation window, whichever occurred later. We excluded participants without EHR and genomic data, with MCI or dementia at or before cohort entry, ADHD diagnosed after MCI or dementia onset, missing demographic information, sex at birth other than male or female, and age greater than 95 years at entry or greater than 100 years at censoring, to limit potential selective survival bias at extreme ages. Follow-up continued until the earliest of cognitive impairment diagnosis, death, or the end of the EHR observation window.

### Ascertainment of Diagnoses

ADHD and cognitive impairment were ascertained from EHR using validated algorithms[23] requiring multiple diagnoses or medication records on separate occasions. See details in the eMethods in Supplement 1 and in eTables 2 and 3 in Supplement 2.

### Genomic Data and ADHD PRS Calculation

All of Us Research Program genomic data processing and quality control have been described previously.[21] We applied additional variant- and sample-level quality control. ADHD PRSs were calculated from the most recent genome-wide association study[24] using PRSice version 2.3.5[25] under an additive model. Further details are provided in the eMethods in Supplement 1.

### Covariates

Covariates included sex at birth (male or female), self-identified race and ethnicity, calendar year of cohort entry, and *APOE* ε4 carrier status. Sex at birth, race, and ethnicity were self-reported by participants at enrollment using



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Figure 1. Study Flow Diagram

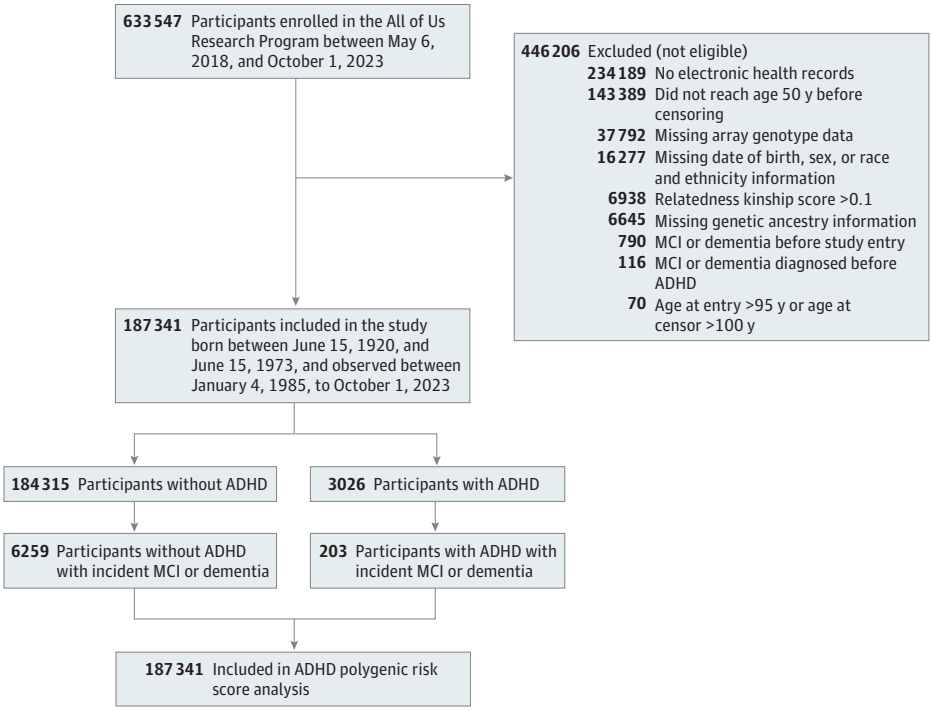



Diagram of study cohort selection, exclusion, and follow-up from the All of Us Research Program. All 187 341 participants were included in attention-deficit/hyperactivity disorder (ADHD) polygenic risk score analyses. MCI indicates mild cognitive impairment.

response options predefined by the All of Us Research Program.[26] Race and ethnicity were included because ADHD diagnosis, cognitive impairment, and health care access can differ across racial and ethnic groups. Participants were grouped as Hispanic or Latino, non-Hispanic Black or African American, non-Hispanic White, or other (non-Hispanic Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Middle Eastern or North African, multiple races, and unspecified).

We assessed somatic comorbidities using the Charlson comorbidities (eMethods in Supplement 1) and summary indices[27] derived from EHR data over a 5-year period preceding cohort entry.[28,29] Neuropsychiatric comorbidities were ascertained from EHR records at any time preceding cohort entry and included depression, anxiety disorder, substance use disorder, bipolar disorder, schizophrenia, and other developmental disorders (eTable 7 in Supplement 1).

## Self-Reported Health and Health Care Utilization

Self-reported health status was assessed using the All of Us Research Program Overall Health survey after MCI or dementia diagnosis (eMethods in Supplement 1). Health care utilization was measured as the number of emergency department, inpatient, outpatient, and total visits.

## Statistical Analysis

Cox proportional hazards models estimated the hazard ratios (HRs) and 95% CIs for the association between ADHD and ADHD PRS and incident MCI or dementia. Models used age as the underlying timescale with delayed entry (left truncation) to account for varying ages at cohort entry.[30] Proportional hazards assumption was assessed using Schoenfeld residuals. Covariate balance across groups was assessed using absolute standardized mean differences (|SMDs|).[31]

In primary analyses, ADHD was modeled as a time-varying exposure,[8] meaning pre-entry diagnoses were assigned effect from cohort entry, and postentry diagnoses from the diagnosis date. We fitted additional models with covariate adjustments: (1) adjusted for sex, race, ethnicity, *APOE* ε4 carrier status, and cohort entry year; (2) additionally adjusted for somatic comorbidities; or (3) additionally adjusted for neuropsychiatric comorbidities. For PRS analyses, ADHD PRS was categorized into 3 risk categories: low (quintile 1), intermediate (quintiles 2-4), and high (quintile 5).[32] Models followed the same sequential adjustment approach, with race and ethnicity omitted because genetic ancestry was accounted for by residualizing the ADHD PRS. Sensitivity analyses assessed robustness of findings (eMethods in Supplement 1).

For self-reported health and health care utilization outcomes among participants who developed MCI or dementia, logistic regression models estimated ORs for self-reported health status (suboptimal vs adequate), and negative binomial regression models estimated incidence rate ratios for health care utilization (eMethods in Supplement 1).

Statistical tests were 2-sided, with $P < .05$ considered significant. Analyses were conducted using R version 4.3.0 (R Foundation) in the All of Us Research Program Researcher Workbench. Data were analyzed from October 2025 to July 2026.



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## Results

A total of 187 341 participants (mean [SD] age at cohort entry, 56.41 [7.88] years; 107 266 [57%] female and 80 075 [43%] male) were included in our retrospective cohort analysis (Figure 1; **Table 1**). Participants were followed up for a mean (SD) of 10.26 (6.75) years, with a maximum of 38.73 years. Age at first available EHR record varied substantially across participants (eTable 5 in Supplement 1). The cohort was racially and ethnically diverse, including Hispanic or Latino (25 429 [13.6%]), non-Hispanic Black or African American (32 474 [17.3%]), non-Hispanic White (115 320 [61.6%]), and other (14 118 [7.5%]) participants. The overall prevalence of diagnosed ADHD was 1.6% (3026 individuals). The mean (SD) age at first recorded ADHD diagnosis, which does not necessarily correspond to the age at first diagnosis, was 53.30 (9.71) years (eTable 6 in Supplement 1). Individuals with ADHD entered the cohort at a younger age than those without and had a higher burden of somatic and neuropsychiatric comorbid conditions. Participants stratified by ADHD PRS showed similar values across most characteristics. Notable exceptions were the prevalence of several neuropsychiatric comorbid conditions, including substance use disorder (|SMD|, 0.15), depression (|SMD|, 0.11), and anxiety disorder (|SMD|, 0.11), all of which showed a graded increase from the lowest to the highest PRS category (Table 1). *APOE* ε4 carrier status was similar across all groups, regardless of ADHD diagnosis or ADHD PRS.

### ADHD and Incident Cognitive Impairment

The mean follow-up duration was similar among individuals with and without ADHD (|SMD|, 0.05) (Table 1), as well as across ADHD PRS categories (|SMD|, 0.11). During follow-up, 6462 participants (3.4%) received a diagnosis of cognitive impairment (MCI or dementia). Among participants with ADHD, 203 (6.7%) developed cognitive impairment vs 6259 (3.4%) among those without ADHD. Incidence rates of cognitive impairment were 8.96 and 3.29 per 1000 person-years among participants with and without ADHD, respectively. Cumulative incidence was higher in participants with ADHD, with divergence emerging early and widening with age (**Figure 2**A). A similar pattern was observed across ADHD PRS categories, with incidence rates of 3.04 and 3.67 per 1000 person-years in the low and high categories, respectively (Figure 2B).

In adjusted Cox models, ADHD was associated with a more than 4-fold higher hazard of developing MCI or dementia (HR, 4.60; 95% CI, 3.99-5.29; $P < .001$) (**Figure 3**A). Further adjustment for somatic comorbidities marginally attenuated the association (HR, 4.04; 95% CI, 3.50-4.66; $P < .001$), whereas adjustment for neuropsychiatric comorbidities yielded a more conservative but still substantial estimate (HR, 3.19; 95% CI, 2.76-3.68; $P < .001$). In subgroup analyses, this association was consistent across strata of sex (male: HR, 4.05; 95% CI, 3.29-4.99; female: HR, 5.15; 95% CI, 4.25-6.23; interaction $P = .15$), race and ethnicity (non-Hispanic White: HR, 4.83; 95% CI, 4.15-5.62; non-Hispanic Black or African American: HR, 6.12; 95% CI, 3.37-11.11; Hispanic: HR, 2.48; 95% CI, 1.11-5.55; other: HR, 2.80; 95% CI, 1.44-5.43; interaction $P = .11$), and APOE ε4 status (carriers: HR, 3.98; 95% CI, 3.02-5.23; noncarriers: HR, 4.84; 95% CI, 4.11-5.70; interaction $P = .13$).

Higher ADHD PRS was also associated with an increased hazard of MCI or dementia. Participants in the high ADHD PRS category showed a 35% higher hazard compared with those in the low category (adjusted HR, 1.35; 95% CI, 1.25-1.46; $P < .001$), and this estimate remained stable after adjustment for somatic or neuropsychiatric comorbidities (Figure 3B). This association was consistent across strata of sex (male: HR, 1.40; 95% CI, 1.25-1.56; female: HR, 1.32; 95% CI, 1.18-1.47; interaction $P = .41$) and *APOE* ε4 status (carriers: HR, 1.38; 95% CI, 1.20-1.58; noncarriers: HR, 1.34; 95% CI, 1.22-1.47; interaction $P = .85$). In genetic ancestry-stratified analyses, statistically significant associations were observed among participants of European (HR, 1.38; 95% CI, 1.26-1.50; $P < .001$) and African (HR, 1.29; 95% CI, 1.03-1.61; $P = .02$) ancestry.

### Sensitivity Analyses

Results were consistent when treating ADHD as a fixed exposure from cohort entry or restricting to ADHD diagnoses before entry only, restricting to individuals entering the cohort at age of 60 years or older, excluding MCI cases, excluding individuals with any neuropsychiatric comorbidities before cohort entry, or restricting the outcome to MCI only (ADHD HR, 3.83; 95% CI, 3.27-4.47; ADHD PRS HR, 1.21; 95% CI, 1.11-1.33; all $P < .001$) or dementia only (ADHD HR, 3.07; 95% CI, 2.12-4.44; ADHD PRS HR, 1.62, 95% CI, 1.40-1.89; all $P < .001$) (eTable 9 in Supplement 1). In a 1:2 matched cohort in which ADHD and comparison individuals were balanced on age, sex, race, ethnicity, cohort entry year, *APOE* ε4 status, somatic and neuropsychiatric comorbidities, and health care utilization, the association was attenuated but remained significant (ADHD HR, 2.26; 95% CI, 1.75-2.92; $P < .001$). Competing risk models accounting for death yielded similar results (ADHD subdistribution HR [sHR], 4.30; 95% CI, 3.73-4.97; $P < .001$; ADHD PRS sHR, 1.19; 95% CI, 1.12-1.26; $P < .001$). A fully adjusted model incorporating sex, race, ethnicity, cohort entry year, *APOE* ε4 status, somatic and neuropsychiatric comorbidities, health care utilization, educational attainment, and lifetime smoking history yielded consistent results (ADHD HR, 3.08; 95% CI, 2.66-3.58; ADHD PRS HR, 1.30; 95% CI, 1.21-1.41; all $P < .001$).

To further address potential reverse causation, we required progressively longer minimum intervals (1 to 10 years) between ADHD diagnosis and cognitive impairment onset (eTable 10 in Supplement 1). The association attenuated as the interval lengthened but remained significant at intervals up to 8 years (HR, 1.44; 95% CI, 1.12-1.86; $P = .005$). It became nonsignificant at 9 years (HR, 1.28; 95% CI, 0.98-1.68; $P = .07$), by which point 150 ADHD–cognitive impairment cases (74%) were reclassified, reducing statistical power.

### Self-Reported Health and Health Care Utilization

Among participants who developed cognitive impairment (n = 6462 for utilization outcomes; approximately 4180 for survey outcomes), comorbid ADHD was significantly associated with worse outcomes across multiple domains (**Table 2**). ADHD was associated with significantly higher odds of suboptimal self-reported mental health (OR, 1.69; 95% CI,



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Table 1. Characteristics of the Study Cohort

| Characteristic | Overall (N = 187 341) | ADHD diagnosis | | | ADHD PRS | | | |
|---|---|---|---|---|---|---|---|---|
| | | No ADHD (n = 184 315) | ADHD (n = 3026) | \|SMD\| | Low (n = 37 469) | Intermediate (n = 112 404) | High (n = 37 468) | \|SMD\|[a] |
| Incident MCI or dementia, No. (%) | 6462 (3.4) | 6259 (3.4) | 203 (6.7) | 0.15 | 1219 (3.3) | 3871 (3.4) | 1372 (3.7) | 0.02 |
| Age at cohort entry, mean (SD), y | 56.41 (7.88) | 56.47 (7.90) | 52.49 (4.93) | 0.61 | 56.83 (8.13) | 56.36 (7.84) | 56.13 (7.72) | 0.09 |
| Follow-up duration, mean (SD), y | 10.26 (6.75) | 10.26 (6.74) | 10.59 (6.80) | 0.05 | 10.72 (6.94) | 10.21 (6.72) | 9.99 (6.59) | 0.11 |
| Sex, No. (%) | | | | | | | | |
| Male | 80 075 (42.7) | 78 915 (42.8) | 1160 (38.3) | 0.09 | 16 636 (44.4) | 48 014 (42.7) | 15 425 (41.2) | 0.07 |
| Female | 107 266 (57.3) | 105 400 (57.2) | 1866 (61.7) | | 20 833 (55.6) | 64 390 (57.3) | 22 043 (58.8) | |
| Race and ethnicity, No. (%) | | | | | | | | |
| Hispanic | 25 429 (13.6) | 25 236 (13.7) | 193 (6.4) | 0.52 | 4281 (11.4) | 15 594 (13.9) | 5554 (14.8) | 0.17 |
| Non-Hispanic Black or African American | 32 474 (17.3) | 32 322 (17.5) | 152 (5.0) | | 5628 (15.0) | 21 576 (19.2) | 5270 (14.1) | |
| Non-Hispanic White | 115 320 (61.6) | 112 856 (61.2) | 2464 (81.4) | | 25 228 (67.3) | 66 447 (59.1) | 23 645 (63.1) | |
| Other[b] | 14 118 (7.5) | 13 901 (7.5) | 217 (7.2) | | 2332 (6.2) | 8787 (7.8) | 2999 (8.0) | |
| *APOE* ε4 status, No. (%) | | | | | | | | |
| Noncarrier | 137 017 (73.1) | 134 728 (73.1) | 2289 (75.6) | 0.06 | 27 428 (73.2) | 81 882 (72.8) | 27 707 (73.9) | 0.02 |
| Carrier | 50 324 (26.9) | 49 587 (26.9) | 737 (24.4) | | 10 041 (26.8) | 30 522 (27.2) | 9761 (26.1) | |
| Education attainment, No. (%) | | | | | | | | |
| No college degree | 95 702 (51.1) | 94 377 (51.2) | 1325 (43.8) | 0.17 | 16 038 (42.8) | 58 041 (51.6) | 21 623 (57.7) | 0.31 |
| College degree or higher | 87 677 (46.8) | 86 015 (46.7) | 1662 (54.9) | | 20 798 (55.5) | 51 864 (46.1) | 15 015 (40.1) | |
| Unknown, refused to answer or missing | 3962 (2.1) | 3923 (2.1) | 39 (1.3) | | 633 (1.7) | 2499 (2.2) | 830 (2.2) | |
| Smoked ≥100 cigarettes in lifetime, No. (%) | | | | | | | | |
| Yes | 82 103 (43.8) | 80 626 (43.7) | 1477 (48.8) | 0.1 | 14 480 (38.6) | 49 205 (43.8) | 18 418 (49.2) | 0.22 |
| No | 100 946 (53.9) | 99 468 (54.0) | 1478 (48.8) | | 22 164 (59.2) | 60 623 (53.9) | 18 159 (48.5) | |
| Unknown, refused to answer or missing | 4292 (2.3) | 4221 (2.3) | 71 (2.3) | | 825 (2.2) | 2576 (2.3) | 891 (2.4) | |
| Charlson Comorbidity Index, mean (SD) | 0.25 (0.93) | 0.24 (0.92) | 0.57 (1.35) | 0.28 | 0.21 (0.85) | 0.25 (0.93) | 0.29 (1.01) | 0.09 |
| Myocardial infarction, No. (%) | 1233 (0.7) | 1194 (0.6) | 39 (1.3) | 0.07 | 188 (0.5) | 747 (0.7) | 298 (0.8) | 0.04 |
| Congestive heart failure, No. (%) | 1955 (1.0) | 1908 (1.0) | 47 (1.6) | 0.05 | 342 (0.9) | 1177 (1.0) | 436 (1.2) | 0.02 |
| Peripheral vascular disease, No. (%) | 1458 (0.8) | 1406 (0.8) | 52 (1.7) | 0.09 | 239 (0.6) | 877 (0.8) | 342 (0.9) | 0.03 |
| Cerebrovascular disease, No. (%) | 1901 (1.0) | 1827 (1.0) | 74 (2.4) | 0.11 | 296 (0.8) | 1176 (1.0) | 429 (1.1) | 0.04 |
| Chronic pulmonary disease, No. (%) | 10 452 (5.6) | 9963 (5.4) | 489 (16.2) | 0.35 | 1702 (4.5) | 6267 (5.6) | 2483 (6.6) | 0.09 |
| Rheumatic disease, No. (%) | 2067 (1.1) | 1990 (1.1) | 77 (2.5) | 0.11 | 366 (1.0) | 1239 (1.1) | 462 (1.2) | 0.02 |
| Peptic ulcer disease, No. (%) | 910 (0.5) | 868 (0.5) | 42 (1.4) | 0.1 | 152 (0.4) | 535 (0.5) | 223 (0.6) | 0.03 |
| Liver disease, No. (%) | 4499 (2.4) | 4306 (2.3) | 193 (6.4) | 0.19 | 725 (1.9) | 2668 (2.4) | 1106 (3.0) | 0.06 |
| Diabetes without complications, No. (%) | 6242 (3.3) | 6063 (3.3) | 179 (5.9) | 0.13 | 1013 (2.7) | 3761 (3.3) | 1468 (3.9) | 0.07 |
| Diabetes with complications, No. (%) | 2754 (1.5) | 2677 (1.5) | 77 (2.5) | 0.08 | 440 (1.2) | 1689 (1.5) | 625 (1.7) | 0.04 |
| Hemiplegia or paraplegia, No. (%) | 563 (0.3) | Not reported[c] | Not reported[c] | NA | 104 (0.3) | 317 (0.3) | 142 (0.4) | 0.02 |
| Kidney disease, No. (%) | 2121 (1.1) | 2069 (1.1) | 52 (1.7) | 0.05 | 393 (1.0) | 1243 (1.1) | 485 (1.3) | 0.02 |
| Cancer, No. (%) | 3174 (1.7) | 3065 (1.7) | 109 (3.6) | 0.12 | 622 (1.7) | 1894 (1.7) | 658 (1.8) | 0.01 |
| Metastatic solid tumor, No. (%) | 703 (0.4) | 682 (0.4) | 21 (0.7) | 0.04 | 118 (0.3) | 418 (0.4) | 167 (0.4) | 0.02 |
| AIDS/HIV, No. (%) | 1015 (0.5) | 980 (0.5) | 35 (1.2) | 0.07 | 144 (0.4) | 626 (0.6) | 245 (0.7) | 0.04 |
| Head injuries, No. (%) | 1147 (0.6) | 1074 (0.6) | 73 (2.4) | 0.15 | 222 (0.6) | 685 (0.6) | 240 (0.6) | 0.01 |
| Depression, No. (%) | 15 179 (8.1) | 14 186 (7.7) | 993 (32.8) | 0.66 | 2491 (6.6) | 9042 (8.0) | 3646 (9.7) | 0.11 |
| Anxiety disorder, No. (%) | 12 858 (6.9) | 11 994 (6.5) | 864 (28.6) | 0.61 | 2077 (5.5) | 7669 (6.8) | 3112 (8.3) | 0.11 |
| Substance use disorder, No. (%) | 11 944 (6.4) | 11 415 (6.2) | 529 (17.5) | 0.35 | 1661 (4.4) | 7233 (6.4) | 3050 (8.1) | 0.15 |

(continued)



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Table 1. Characteristics of the Study Cohort (continued)

| Characteristic | Overall (N = 187 341) | ADHD diagnosis | | | ADHD PRS | | | |
|---|---|---|---|---|---|---|---|---|
| | | No ADHD (n = 184 315) | ADHD (n = 3026) | \|SMD\| | Low (n = 37 469) | Intermediate (n = 112 404) | High (n = 37 468) | \|SMD\|[a] |
| Bipolar disorder, No. (%) | 3123 (1.7) | 2843 (1.5) | 280 (9.3) | 0.35 | 413 (1.1) | 1853 (1.6) | 857 (2.3) | 0.09 |
| Schizophrenia, No. (%) | 1541 (0.8) | 1467 (0.8) | 74 (2.4) | 0.13 | 242 (0.6) | 933 (0.8) | 366 (1.0) | 0.04 |
| Other developmental disorders, No. (%) | 310 (0.2) | 270 (0.1) | 40 (1.3) | 0.14 | 53 (0.1) | 189 (0.2) | 68 (0.2) | 0.01 |
| Health care visits (1 y prior cohort entry), mean (SD) | 2.83 (9.17) | 2.72 (8.93) | 9.13 (17.60) | 0.46 | 2.53 (8.46) | 2.85 (9.19) | 3.06 (9.78) | 0.06 |

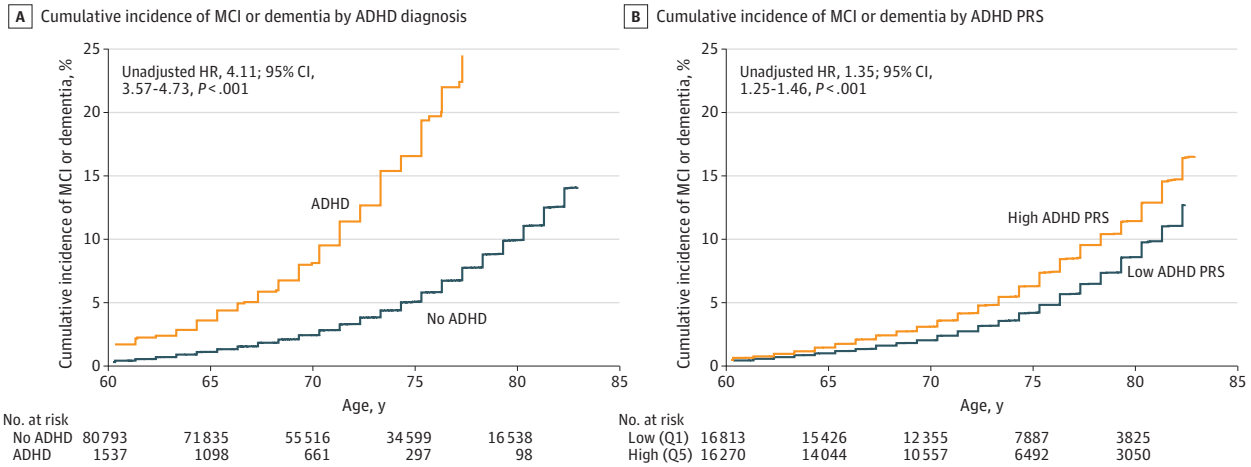
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; *APOE*, apolipoprotein E; MCI, mild cognitive impairment; NA, not applicable; SMD, standardized mean difference.

[a] For ADHD PRS, |SMD| are computed comparing high (quintile 5) vs low (quintile 1) categories.

[b] Includes non-Hispanic Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Middle Eastern or North African, multiple races, and unspecified.

[c] Per the All of Us Data and Statistics Dissemination Policy, participant counts of 20 or fewer, and values that would enable their derivation, are not reported.

Figure 2. Cumulative Incidence Curves Showing Mild Cognitive Impairment (MCI) or Dementia by Attention-Deficit/Hyperactivity Disorder (ADHD) Diagnosis and ADHD Polygenic Risk Score (PRS)




A, Cumulative incidence of MCI or dementia by ADHD diagnosis (ADHD vs no ADHD). B, Cumulative incidence of MCI or dementia by ADHD PRS (low [quintile 1; Q1] vs high [quintile 5; Q5]). Hazard ratios (HRs) and *P* values from unadjusted Cox proportional hazards models.

1.18-2.39; adjusted *P* = .01), quality of life (OR, 1.66; 95% CI, 1.14-2.39; adjusted *P* = .02), and social satisfaction (OR, 2.39; 95% CI, 1.69-3.37; adjusted *P* < .001). No significant differences were observed for general or physical health. In the year following cognitive impairment diagnosis, ADHD was associated with 34% higher outpatient visit rates (incidence rate ratio [IRR], 1.34; 95% CI, 1.15-1.56; adjusted *P* = .001) and 20% higher total health care utilization (IRR, 1.20; 95% CI, 1.09-1.34; adjusted *P* = .003), even after adjustment for prediagnosis visit rates. Emergency department and inpatient visits did not differ significantly by ADHD diagnosis. Conversely, higher ADHD PRS was associated with higher emergency department visit rates (IRR, 1.42; 95% CI, 1.15-1.75; adjusted *P* = .005).

## Discussion

This cohort study evaluated the association between ADHD and incident cognitive impairment in a large, diverse sample from the All of Us Research Program, addressing key limitations from prior research by complementing EHR-based ADHD ascertainment with independent genetic evidence (ADHD PRS), adjusting for a broader range of confounders (including *APOE* ε4 carrier status and health care utilization), and examining associated mental health and health care outcomes among older adults with MCI or dementia and comorbid ADHD. ADHD diagnosis was associated with a higher risk of subsequent cognitive impairment, and this association remained across multiple sensitivity analyses. Analyses leveraging genomic data from the same study population provided convergent evidence, with higher ADHD PRS also associated with increased risk of cognitive impairment. Finally, among individuals with cognitive impairment, comorbid ADHD was associated with worse self-reported mental health, quality of life, social satisfaction, and higher health care utilization.

Our findings align with and expand a growing literature supporting an association between ADHD and increased risk of MCI and dementia. Studies using population-based health claims databases from Taiwan,[5] Sweden,[7] Israel,[8] and Germany[9] have reported elevated risk estimates that are

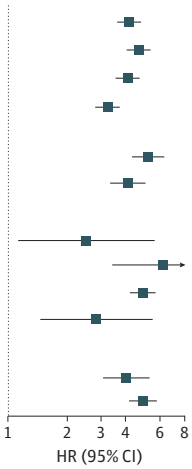


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**Figure 3. Forest Plots Showing Association of Attention-Deficit/Hyperactivity Disorder (ADHD) Diagnosis and ADHD Polygenic Risk Score (PRS) With Incident Mild Cognitive Impairment (MCI) or Dementia**

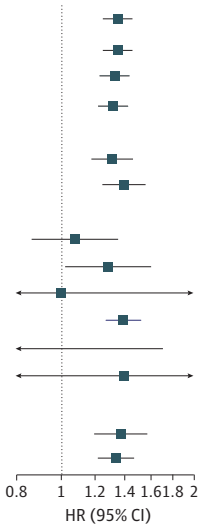
A Association of ADHD diagnosis with incidence of MCI or dementia

| Model or subgroup | No. | HR (95% CI) | *P* value | *P* value for interaction |
|---|---|---|---|---|
| Main models | | | | |
| Unadjusted | 187 341 | 4.11 (3.57-4.73) | <.001 | |
| Adjusted[a] | 187 341 | 4.60 (3.99-5.29) | <.001 | |
| Somatic comorbidities[a] | 187 341 | 4.04 (3.50-4.66) | <.001 | NA |
| Neuropsychiatric comorbidities[a] | 187 341 | 3.19 (2.76-3.68) | <.001 | |
| Stratified by sex[a] | | | | |
| Female | 107 266 | 5.15 (4.25-6.23) | <.001 | .15 |
| Male | 80 075 | 4.05 (3.29-4.99) | <.001 | |
| Stratified by race and ethnicity[a] | | | | |
| Hispanic | 25 429 | 2.48 (1.11-5.55) | .03 | |
| Non-Hispanic Black or African American | 32 474 | 6.12 (3.37-11.11) | <.001 | .11 |
| Non-Hispanic White | 115 320 | 4.83 (4.15-5.62) | <.001 | |
| Other | 14 118 | 2.80 (1.44-5.43) | .002 | |
| Stratified by *APOE* ε4 status[a] | | | | |
| Carrier | 50 324 | 3.98 (3.02-5.23) | <.001 | .13 |
| Noncarrier | 137 017 | 4.84 (4.11-5.70) | <.001 | |




B Association of ADHD PRS with incidence of MCI or dementia

| Model or subgroup | No. | HR (95% CI) | *P* value | *P* value for interaction |
|---|---|---|---|---|
| Main models | | | | |
| Unadjusted | 187 341 | 1.35 (1.25-1.46) | <.001 | |
| Adjusted[b] | 187 341 | 1.35 (1.25-1.46) | <.001 | |
| Somatic comorbidities[b] | 187 341 | 1.33 (1.23-1.44) | <.001 | NA |
| Neuropsychiatric comorbidities[b] | 187 341 | 1.32 (1.22-1.43) | <.001 | |
| Stratified by sex[b] | | | | |
| Female | 107 266 | 1.32 (1.18-1.47) | <.001 | .41 |
| Male | 80 075 | 1.40 (1.25-1.56) | <.001 | |
| Stratified by genetic ancestry[b] | | | | |
| Admixed American | 24 455 | 1.09 (0.87-1.36) | .47 | |
| African | 36 959 | 1.29 (1.03-1.61) | .02 | |
| East Asian | 2988 | 1.01 (0.38-2.69) | .98 | |
| European | 121 118 | 1.38 (1.26-1.50) | <.001 | .08 |
| Middle Eastern | 488 | 0.48 (0.13-1.71) | .26 | |
| South Asian | 1333 | 1.40 (0.54-3.66) | .49 | |
| Stratified by *APOE* ε4 status[b] | | | | |
| Carrier | 50 324 | 1.38 (1.20-1.58) | <.001 | .85 |
| Noncarrier | 137 017 | 1.34 (1.22-1.47) | <.001 | |




A, Hazard ratios (HRs) for the association between ADHD diagnosis and incident MCI or dementia. B, HRs comparing high vs low ADHD PRS categories and incident MCI or dementia. Panels A and B display main models with sequential covariate adjustment, followed by subgroup analyses stratified by sex, race/ethnicity (panel A) or genetic ancestry (panel B), and *APOE* ε4 carrier status. In subgroup analyses, the stratification variable was not included in model adjustment. For panel B, only the high vs low ADHD PRS comparison is shown for illustrative purposes; statistical models were fitted using all participants across the 3 ADHD PRS categories (low, intermediate, and high).

[a]Adjusted for sex, race, ethnicity, *APOE* ε4 carrier status, and cohort entry year.

[b]Adjusted for sex, *APOE* ε4 carrier status, and cohort entry year. Genetic ancestry principal components are accounted for in PRS residualization.

broadly comparable in magnitude to ours, indicating that the association is not confined to a single health care setting or diagnostic context. Relative to recent case-control work in the All of Us Research Program,[12] we applied a retrospective cohort design with time-to-event analyses, a more stringent diagnostic ascertainment algorithm, and we leveraged genomic data. Studies based solely on EHR for diagnostic ascertainment are susceptible to biases related to health care access, clinician recognition, and changing diagnostic practices over time.[16] Within the same population, the convergence of EHR-based and ADHD PRS findings, 2 independent sources of evidence of ADHD, strengthens confidence in the association.

Notably, the association persisted despite adjustment for variables often considered potential sources of confounding or partial mediation in studies of ADHD and cognitive outcomes, including educational attainment, smoking history, and psychiatric and somatic comorbidities.[33,34] Adjustment for psychiatric comorbidities attenuated but did not eliminate the association, consistent with prior literature,[5,7,12] and the ADHD PRS association likewise remained stable. It also persisted in a propensity score–matched cohort balanced on each individual neuropsychiatric condition and in a sensitivity analysis restricted to participants without any history of neuropsychiatric comorbidity at cohort entry. Estimates attenuated progressively as more confounders were addressed, with the matched analyses yielding the most conservative values, likely through more complete balancing of confounders, including health care utilization, than covariate adjustment alone. That a substantial association persisted under this most



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Table 2. Association Between Attention-Deficit/Hyperactivity Disorder (ADHD) and Self-Reported Health Status and Health Care Resource Utilization After Mild Cognitive Impairment (MCI) or Dementia Diagnosis

| Outcome | ADHD diagnosis[a] | | ADHD-PRS[a] | | No. |
|---|---|---|---|---|---|
| | OR/IRR (95% CI)[b] | Adjusted *P* value[c] | OR/IRR (95% CI)[b] | Adjusted *P* value[c] | |
| Suboptimal self-reported health status[d] | | | | | |
| General health | 1.05 (0.73-1.49) | .84 | 1.11 (0.91-1.36) | .39 | 4185 |
| Mental health | 1.69 (1.18-2.39) | .01 | 1.14 (0.91-1.42) | .35 | 4182 |
| Physical health | 1.31 (0.93-1.85) | .20 | 1.27 (1.04-1.56) | .05 | 4171 |
| Quality of life | 1.66 (1.14-2.39) | .02 | 1.30 (1.02-1.66) | .07 | 4167 |
| Social satisfaction | 2.39 (1.69-3.37) | <.001 | 1.26 (1.00-1.60) | .11 | 4179 |
| Health care utilization 1 y after diagnosis[e] | | | | | |
| ED visits | 0.91 (0.63-1.33) | .67 | 1.42 (1.15-1.75) | .005 | 6462 |
| Inpatient visits | 1.34 (0.93-1.99) | .20 | 0.99 (0.80-1.22) | .90 | 6462 |
| Outpatient visits | 1.34 (1.15-1.56) | .001 | 1.06 (0.98-1.16) | .22 | 6462 |
| Total visits | 1.20 (1.09-1.34) | .003 | 1.02 (0.96-1.08) | .67 | 6462 |

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ED, emergency department; IRR, incidence rate ratio; MCI, mild cognitive impairment; OR, odds ratio.

[a] All models adjusted for age, sex, race, ethnicity, Charlson Comorbidity Index, and presence of any neuropsychiatric comorbidity. In ADHD PRS, race and ethnicity were omitted because genetic ancestry principal components were accounted for in PRS residualization. For ADHD PRS, only the high vs low risk comparison is shown for illustrative purposes; statistical models were fitted using all participants across the 3 categories (low, intermediate, and high).

[b] ORs from logistic regression models are reported for suboptimal self-reported health status outcomes. IRRs from negative binomial regression is reported for health care utilization and medication burden outcomes.

[c] *P* values adjusted for false discovery rate using the Benjamini-Hochberg procedure across all reported outcomes. Significance level: <.05.

[d] Models were additionally adjusted for time from MCI or dementia diagnosis to survey date.

[e] Models were additionally adjusted for total visits 1 year prior to MCI or dementia diagnosis.

stringent approach argues against confounding as a full explanation, though residual confounding or mediation cannot be excluded.

No clear effect modification by sex or race and ethnicity was observed, though caution is warranted given demographic differences in ADHD recognition.[35,36] The association between ADHD PRS and cognitive decline varied considerably by genetic ancestry, which is not unexpected given that the ADHD PRS was calculated using summary statistics from a genome-wide association study composed predominantly of individuals of European ancestry.[24] We observed no evidence that the association with ADHD differed by *APOE* ε4 status, which is the major genetic risk factor for Alzheimer disease.[37] These findings suggest that ADHD liability contributes to cognitive impairment through pathways that are at least partially distinct from *APOE* ε4-driven risk, consistent with prior work.[15]

A novel finding is that among individuals who developed cognitive impairment, a comorbid ADHD diagnosis was associated with worse mental health, lower social satisfaction, and greater health care utilization, whereas ADHD PRS showed more limited associations with postdiagnosis outcomes, except for higher emergency department visit rates. Although psychiatric comorbidities broadly worsen quality of life and care burden in dementia,[38,39] the specific contribution of ADHD comorbidity to outcomes after cognitive impairment diagnosis has not been examined. The divergence between clinical diagnosis and genetic liability for these outcomes suggests that the full phenotypic expression of ADHD, including its lifelong comorbidities and social outcomes, contributes to postdiagnosis burden in ways that genetic liability alone does not fully capture.

The mechanisms linking ADHD to cognitive decline remain unknown and likely involve multiple interacting processes. One hypothesis is that the ADHD-related liability reflects, in part, reduced cognitive resilience and reserve,[15,40] potentially arising from neurodevelopmental influences on attention and executive function networks.[41] In this framework, lower average baseline cognitive performance observed among individuals with ADHD[42] would increase susceptibility to crossing the clinical threshold for MCI or dementia as neuropathology accumulates. A second hypothesis is that ADHD increases exposure to cumulative risk factors for cognitive impairment, including chronic stress, social adversity, sleep disturbance, physical inactivity, poor diet quality, cardiometabolic risk, injuries, and substance use.[43,44] These pathways are difficult to quantify precisely in retrospective analyses, and disentangling their relative contribution will require longitudinal studies with repeated measurement. However, existing cohorts of individuals with ADHD diagnosed in childhood are only now approaching ages when dementia outcomes can be studied directly.[45] The ADHD-PRS association should also be interpreted cautiously, as it may reflect liability to ADHD and its life-course correlates, shared liability with other psychiatric or neurodevelopmental traits, or broader pleiotropic pathways rather than a direct causal effect on dementia neuropathology.[46]

An association between ADHD and cognitive impairment could have meaningful clinical implications, particularly as rec-



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ognition of ADHD across the lifespan increases and more adults receive diagnoses later in life. A key unanswered question is whether ADHD treatment modifies risk for cognitive impairment. A prior report suggested no elevated dementia risk among older adults with late-life ADHD diagnosis who were being treated with stimulants, though confounding cannot be excluded.[8] We could not address treatment effects here due to limited data on lifetime treatment for ADHD. Notably, among individuals with cognitive impairment, comorbid ADHD was associated with greater support needs, possibly reflecting additive impacts of lifelong executive dysfunction and emerging cognitive decline, underscoring the importance of proactive monitoring and tailored interventions in this population.

### Limitations

Findings from this study should be interpreted considering some limitations. Several features limit causal interpretation. Because this is an observational study, residual confounding cannot be fully excluded. Reverse causation is a particular concern, given the long prodromal phase of dementia[47]; indeed, in lagged analyses, the association attenuated as longer intervals between ADHD diagnosis and cognitive impairment were required, and a contribution from prodromal misattribution cannot be excluded. Differential health care contact could also promote greater ascertainment of cognitive impairment among individuals with ADHD; the association nonetheless persisted after adjustment for and matching on health care utilization. The ADHD-PRS association provides complementary evidence not subject to reverse causation from prodromal cognitive decline, although it does not establish causality as it may reflect shared liability or other pleiotropic pathways. EHR diagnoses may be underascertained or misclassified, limiting identification of ADHD, cognitive impairment, and comorbidities. For most participants, available EHR observation began in midlife or later. Thus, age at first recorded ADHD diagnosis reflects the first ADHD documentation available in the EHR, not necessarily ADHD onset or first clinical diagnosis. ADHD PRS was derived from summary statistics of a genome-wide association study predominantly composed of individuals of European ancestry,[24] limiting its generalizability to other ancestry groups. We could not adequately evaluate the role of ADHD pharmacologic and nonpharmacological treatment in modifying risk, and this remains an important open question for future studies. Selection bias that occurs in volunteer research cohorts like this one may limit generalizability, and the population may not represent the individuals with ADHD commonly found in clinical care. For example, most of the individuals with ADHD were women, contrasting with the broader literature, where ADHD is roughly comparable by sex in adulthood.[48] Similarly, individuals with ADHD had higher educational attainment. Although this finding contrasts with the broader literature linking ADHD to lower educational attainment,[44] prior studies in older populations have reported no differences in education or income between individuals with and without ADHD.[49,50]

## Conclusions

In summary, in this cohort study, ADHD was associated with increased risk of incident MCI or dementia, and this association was observed using both EHR-based diagnoses and complementary genetic liability measures using ADHD PRS. These findings support ADHD as a relevant factor in later-life cognitive health and call for clinical guidelines recommending cognitive monitoring in adults with ADHD, while recognizing that the mechanisms and causal nature of this association remain to be established.

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**Author Contributions:** Drs Bauer-Negrini and Pascoal had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Drs Bauer-Negrini and Leffa are co–first authors.
*Concept and design*: Bauer-Negrini, Leffa, Ferreira, Rohde, Molina, Pascoal.
*Acquisition, analysis, or interpretation of data*: Bauer-Negrini, Leffa, Bellaver, Povala, Medeiros, Lussier, Tudorascu, Cortese, Rohde, Pascoal.
*Drafting of the manuscript*: Bauer-Negrini, Leffa, Rohde, Pascoal.
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*Supervision*: Cortese, Rohde, Molina, Pascoal.

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