Attention-deficit/hyperactivity disorder and Alzheimer’s disease and any dementia: A multi-generation cohort study in Sweden

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Abstract

Introduction: We examined the extent to which attention-deficit/hyperactivity disorder (ADHD), a neurodevelopmental disorder, is linked with Alzheimer’s disease (AD) and any dementia, neurodegenerative diseases, across generations.

Methods: A nationwide cohort born between 1980 and 2001 (index persons) were linked to their biological relatives (parents, grandparents, uncles/aunts) using Swedish national registers. We used Cox models to examine the cross-generation associations.

Results: Among relatives of 2,132,929 index persons, 3042 parents, 171,732 grandparents, and 1369 uncles/aunts had a diagnosis of AD. Parents of individuals with ADHD had an increased risk of AD (hazard ratio 1.55, 95% confidence interval 1.26–1.89). The associations attenuated but remained elevated in grandparents and uncles/aunts. The association for early-onset AD was stronger than late-onset AD. Similar results were observed for any dementia.

Discussion: ADHD is associated with AD and any dementia across generations. The associations attenuated with decreasing genetic relatedness, suggesting shared familial risk between ADHD and AD.

KEYWORDS
Alzheimer’s disease, dementia, epidemiology, family design, neurodevelopmental disorder

1 INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder, characterized by impairing levels of poor sustained attention, impaired impulse control, and hyperactivity.1 Follow-up studies have shown that the disorder often persists into adulthood, affecting 3% of adults worldwide.2,3 Alzheimer’s disease (AD) is a neurodegenerative disease characterized by aging-related progressive deterioration in cognition and ability for independent living, and it is the most common subtype of dementia. A meta-analytic study estimated that the age-standardized prevalence of dementia in those aged 60 and above ranged from 5% to 7% worldwide.4 With the life expectancy of individuals getting longer, dementia represents an increasing public health concern.5

Very few studies, with limited sample size, have explored the association between ADHD and AD, and conflicting results exist.6–8 An ecologic study using state-level hospitalization discharge data from the United States found that antecedent ADHD significantly predicted AD with incidence rate increased 15%.6 On the other hand, a case-control study interviewing individuals from a medical insurance...
group in Buenos Aires, Argentina, suggested that prior ADHD was not associated with AD (non-significant increased odds 10%). Similar non-significant results were found in a retrospective matched-cohort study using Taiwan’s Health Insurance Research Database. So far, there are no large-scale longitudinal studies that have explored the potential association, as such a study would require very long follow-up from diagnoses of ADHD, which was not commonly diagnosed until recent decades, to diagnoses of AD in older age. Even though the magnitude of the association between these two conditions remains unclear, a few potential mechanisms may explain an observed association. First, ADHD could increase the risk of late-life dementia through adverse health outcomes of ADHD. A review of meta-analyses identified seven modifiable risk factors associated with dementia, including diabetes mellitus, midlife hypertension, physical inactivity, depression, smoking, and low educational attainment; each of these risk factors has been shown to be a consequence of ADHD. Second, adult ADHD may mimic cognitive symptoms of AD (including loss of memory and inattention) as studies have suggested that ADHD is not adequately and accurately identified in clinics in the context of late-life cognitive disorders. Third, ADHD and AD may share genetic risk, as both ADHD and AD are highly heritable and complex disorders. So far, the largest genome-wide association studies (GWAS) have failed to detect any genetic overlap between ADHD and AD, yet the result is inconclusive as the genetic variants discovered so far only explained a relatively small proportion of the heritability.

As ADHD has only been commonly diagnosed in recent decades and follow-up data of diagnosed individuals into later life is limited, we performed a longitudinal multi-generation study to explore the cross-generation (i.e., parents, grandparents, and uncles/aunts) familial co-aggregation of ADHD with AD and any dementia, using data from the linkage of Swedish national registers.

2 METHODS

2.1 Data sources

We used data from the linkage of several Swedish nationwide registers through unique personal identification numbers. (1) The Medical Birth Register contains information on all births in Sweden since 1973 and pregnancy related factors; (2) the Swedish Total Population Register covers demographic information on all Swedish inhabitants since 1968; (3) the Multi-generation Register contains information on biological and adoptive relationships on individuals living in Sweden since 1961; (4) the National Patient Register (NPR) contains data on inpatient diagnoses since 1973 and outpatient diagnoses since 2001 based on the International Classification of Diseases (ICD) in its seventh (ICD-7: before 1969), eighth (ICD-8: 1969–1986), ninth (ICD-9: 1987–1996), and tenth (ICD-10: since 1997) revisions; (5) the Cause of Death Register (CDR) contains information on all deaths since 1952 (complete coverage since 1961) based on ICD codes, including underlying and contributing causes of death; (6) the Prescribed Drug Register contains information on all prescribed medications dispensed at pharmacies in Sweden since July 2005, with drug identity defined using Anatomical Therapeutic Chemical (ATC) codes; and (7) the Migration Register records all migration in and out of Sweden.

2.2 Study population

We identified all individuals born in Sweden between 1980 and 2001. We excluded stillbirths, individuals missing key demographic information, and individuals who died or migrated before their 12th birthday, by linking to the Total Population Register, Medical Birth Register, Migration Register, and CDR, respectively. Each individual (referred

HIGHLIGHTS

- This study suggests that attention-deficit hyperactivity disorder (ADHD) is associated with Alzheimer’s disease (AD) and any dementia across generations.
- The associations attenuated with decreasing genetic relatedness (parents > grandparents and uncles/aunts), suggesting shared familial risk between ADHD and AD.
- The increased familial risk for early-onset AD, associated with ADHD, was higher than that for late-onset AD.

RESEARCH IN CONTEXT

1. Systematic review: The authors searched titles and abstracts indexed on PubMed. Only a few studies with limited sample size have investigated the association between attention-deficit/hyperactivity disorder (ADHD) and Alzheimer’s disease (AD). Findings of available studies are inconsistent.
2. Interpretation: In a large population-based study, we found that ADHD is associated with AD and any dementia across generations. The associations attenuated with decreasing genetic relatedness (parents > grandparents and uncles/aunts), suggesting shared familial risk between ADHD and AD. The increased familial risk for early-onset AD, associated with ADHD, was higher than that for late-onset AD.
3. Future directions: Research on underlying risk factors contributing to both ADHD and AD are warranted, including molecular genetic and family studies aiming to identify attributing pleiotropic genetic variants and family-wide environmental risk factors. Our study calls attention to advancing the understanding of ADHD and cognitive decline in older age, and, if verified, warrants investigation of treatment of ADHD to prevent or delay the development of neurodegenerative diseases in individuals with ADHD and their family members.
TABLE 1 Descriptive characteristics of the three relative cohorts

| Type of individuals | Variables                                | Overall          | Female           | Male            |
|---------------------|------------------------------------------|------------------|------------------|-----------------|
| Index persons       | No. of index persons                     | 2,132,929        | 1,037,385        | 1,095,544       |
|                     | Age, median (IQR)a                        | 23 (18–28)       | 23 (18–28)       | 23 (18–28)      |
|                     | ADHD, no. (%)                             | 68,379 (3.21)    | 24,226 (2.34)    | 44,153 (4.03)   |
|                     | Onset age of ADHD, median (IQR)           | 16 (12–20)       | 18 (14–22)       | 15 (11–19)      |
| Parents             | No. of parents                            | 2,293,961        | 1,146,865        | 1,147,096       |
|                     | Age, median (IQR)a                        | 53 (47–59)       | 51 (46–58)       | 54 (48–61)      |
|                     | Alzheimer’s disease, no. (%)              | 3042 (0.13)      | 980 (0.09)       | 2062 (0.18)     |
|                     | Onset age of Alzheimer’s disease, median (IQR)b | 61 (56–67)    | 57 (53–62)       | 63 (57–70)      |
|                     | Onset age of any dementia, median (IQR)b  | 59 (54–65)       | 56 (52–60)       | 61 (56–67)      |
| Grandparents        | No. of grandparents                       | 2,518,669        | 1,275,202        | 1,243,467       |
|                     | Age, median (IQR)a                        | 82 (72–91)       | 80 (71–90)       | 83 (73–93)      |
|                     | Alzheimer’s disease, no. (%)              | 171,732 (6.82)   | 99,454 (7.80)    | 72,278 (5.81)   |
|                     | Any dementia, no. (%)                     | 197,843 (7.86)   | 111,584 (8.75)   | 86,259 (6.94)   |
|                     | Onset age of Alzheimer’s disease, median (IQR)b | 78 (73–83)    | 79 (74–83)       | 78 (73–82)      |
|                     | Onset age of any dementia, median (IQR)b  | 77 (71–81)       | 77 (72–82)       | 76 (70–80)      |
| Uncles/aunts        | No. of uncles/aunts                       | 933,263          | 475,793          | 457,470         |
|                     | Age, median (IQR)a                        | 53 (47–60)       | 53 (47–60)       | 53 (47–60)      |
|                     | Alzheimer’s disease, no. (%)              | 1369 (0.15)      | 743 (0.16)       | 626 (0.14)      |
|                     | Any dementia, no. (%)                     | 1697 (0.18)      | 852 (0.18)       | 845 (0.18)      |
|                     | Onset age of Alzheimer’s disease, median (IQR)b | 62 (57–67)    | 62 (56–66)       | 62 (57–67)      |
|                     | Onset age of any dementia, median (IQR)b  | 60 (55–65)       | 60 (55–64)       | 60 (55–65)      |

Abbreviations: AD, Alzheimer’s disease; ADHD, attention-deficit/hyperactivity disorder; IQR, interquartile range.

aThe age of individuals by the end of study.

bTime of disease onset was estimated as 3 years before the first diagnosis, or 5 years before death (primary and contributing causes), whichever came first.

to as index persons) was linked to their biological relatives—parents, grandparents, uncles and aunts—through the Medical Birth Register and Multi-generation Register. All relatives were followed from the date they turned 50 years of age to onset of dementia, date of first migration, date of death, or December 31, 2013 (end of study follow-up), whichever came first. Thus, we generated three cohorts of relatives representing different levels of genetic relatedness: parents who share 50% of their segregating genes with index persons; grandparents who share 25% of their segregating genes with index persons; uncles and aunts who share 25% of their segregating genes with index persons. To ensure the comparability between parents and uncles/aunts cohorts, for each index person we included one uncle/aunt who had at least one child and whose birth date was nearest to that of parents of index persons.

2.3 Identification of ADHD

We used information from the NPR to identify ADHD diagnoses among index persons. In sensitivity analyses, we additionally used information on prescriptions of ADHD medication from the Prescribed Drug Register for case identification (ICD and ATC codes in Table S1 in supporting information). Our approach of using ADHD medication for case identification is consistent with prior research.25,26

2.4 Identification of AD and any dementia

We used validated diagnoses from the NPR and CDR to identify dementia cases among relatives of index persons, including two definitions: AD and any dementia (including AD).27,28 In line with previous studies, time of disease onset was estimated as three years before the first diagnosis (ascertained in the NPR) or 5 years before death (ascertained in the CDR), whichever came first.27–29 In sensitivity analyses, we additionally used information on prescriptions of medications for AD, and the time of disease onset was estimated as the date of the first relevant prescription recorded in the Prescribed Drug Register, in keeping with previous studies.29,30

2.5 Statistical analysis

Cox proportional hazards models were used to examine the association between ADHD and dementia (AD or any dementia) in each of the three relative cohorts (parents, grandparents, and uncles/aunts), with attained age of relatives as the underlying timescale.31–33 The risk of having dementia in relatives of individuals with ADHD was compared to the risk in relatives of individuals without ADHD, and hazard ratios.
(HRs) were estimated with 95% confidence intervals (CIs). Robust standard errors were used to account for non-independence of data due to the repeat of individuals in index person-relative pairs. In adjusted models, HRs were adjusted for birth year of index persons, birth year of relatives, sex of index persons, and sex of relatives. The analyses were further stratified by sex of relatives and sex of index persons.

To test whether the association is moderated by onset age of dementia, HRs were estimated for early-onset dementia (onset before 65 years) and late-onset dementia (onset after 65 years). We fitted a Cox model allowing the HRs to be different for before and after age 65, corresponding to early- and late-onset dementia, in each relative cohort.

Sensitivity analyses were performed to examine whether the results were robust with different case and cohort identifications. First, to improve the coverage of ADHD and AD, we additionally used prescriptions of ADHD and AD medications to identify individuals with ADHD or AD. Second, we stratified the estimates by birth year of index persons (1980–1989 and 1990–2001). This was done to assess potential bias due to differences in register coverage and follow-up time for relatives. Third, we additionally adjusted for ADHD status in the relatives in each of the three relative cohorts. If the HRs remain significant after adjustment, the contribution of common familial risk factors to ADHD and AD would be further supported (see further explanation in Figure S2 in supporting information).

Data management was performed using SAS version 9.4 (SAS Institute, Inc.) and all analyses were performed using R version 3.6.1.

3 | RESULTS

We identified 2,224,189 individuals born between 1980 and 2001 from the Medical Birth Register, and 2,132,929 individuals were identified as eligible index persons after applying the exclusion criteria (Figure 1). After linking index persons to their biological relatives, the eligible study cohorts contained 2,293,961 parents, 2,518,669 grandparents, and 933,263 uncles/aunts, which created 4,246,182 index person-parent pairs, 7,548,861 index person-grandparent pairs, and 1,838,520 index person-uncle/aunt pairs. Among the index persons, 68,379 (3.21%) were diagnosed with ADHD (44,153 [4.03%] in men, 24,226 [2.34%] in women, Table 1). The relatives were followed for a median of 8.0 years in parents, 25.0 years in grandparents, and 8.5 years in uncles/aunts. By the end of follow-up, 3042 (0.13%) of parents, 171,732 (6.82%) of grandparents, and 1369 (0.15%) of uncles/aunts had a diagnosis of AD. The numbers for any dementia were 3792 (0.17%) for parents, 197,843 (7.86%) for grandparents, and 1697 (0.18%) for uncles/aunts (Table 1).

Parents of index persons with ADHD had an increased risk of AD compared to the parents of index persons without ADHD (HR 1.55, 95% CI 1.26–1.89; Table 2). The associations attenuated with decreasing genetic relatedness, that is, the association with AD in grandparents attenuated (1.11, 1.08–1.13), and the association in uncles/aunts was similar to grandparents but not statistically significant (1.15, 0.85–1.56). A similar pattern was observed for any dementia with an increased risk in parents (1.34, 1.11–1.63) and grandparents (1.10, 1.08–1.12), and a nonsignificant association in uncles/aunts.
### TABLE 2  Association between ADHD and Alzheimer’s disease and any dementia in three relative cohorts

| Relatives of index persons | No. of event (ADHD = 0) | Person-years (ADHD = 0) | No. of event (ADHD = 1) | Person-years (ADHD = 1) | Crude hazard ratio (95% CI) | Adjusted hazard ratio (95% CI) |
|---------------------------|-------------------------|-------------------------|-------------------------|-------------------------|----------------------------|-------------------------------|
| Alzheimer’s disease       |                         |                         |                         |                         |                            |                               |
| Parents                   | 3569                    | 17,398,062              | 110                     | 365,803                 | 1.51 (1.24–1.85)           | 1.55 (1.26–1.89)             |
| Mother                    | 1128                    | 7,175,475               | 35                      | 141,129                 | 1.66 (1.16–2.38)           | 1.77 (1.23–2.54)             |
| Father                    | 2441                    | 4,338,978               | 75                      | 96,100                  | 1.44 (1.13–1.84)           | 1.46 (1.15–1.86)             |
| Grandparents              | 464,503                 | 163,361,512             | 11,665                  | 4,699,596               | 1.08 (1.06–1.11)           | 1.11 (1.08–1.13)             |
| Grandmother               | 257,621                 | 83,608,787              | 6323                    | 2,392,283               | 1.09 (1.06–1.12)           | 1.12 (1.09–1.16)             |
| Grandfather               | 206,882                 | 79,752,726              | 5342                    | 2,307,313               | 1.08 (1.05–1.11)           | 1.08 (1.05–1.12)             |
| Uncles/aunts              | 1976                    | 8,811,647               | 46                      | 194,967                 | 1.12 (0.83–1.51)           | 1.15 (0.85–1.56)             |
| Aunt                      | 1091                    | 4,472,669               | 25                      | 98,867                  | 1.09 (0.72–1.67)           | 1.13 (0.75–1.72)             |
| Uncle                     | 885                     | 4,338,978               | 21                      | 96,100                  | 1.15 (0.75–1.77)           | 1.18 (0.77–1.82)             |
| Any dementia              |                         |                         |                         |                         |                            |                               |
| Parents                   | 4467                    | 17,384,751              | 120                     | 365,526                 | 1.31 (1.08–1.59)           | 1.34 (1.11–1.63)             |
| Mother                    | 1266                    | 4,469,597               | 32                      | 98,830                  | 1.30 (0.89–1.90)           | 1.45 (1.00–2.13)             |
| Father                    | 3201                    | 4,334,740               | 88                      | 96,017                  | 1.29 (1.03–1.61)           | 1.31 (1.05–1.63)             |
| Grandparents              | 537,135                 | 162,075,129             | 13,590                  | 4,665,588               | 1.05 (1.03–1.07)           | 1.10 (1.08–1.12)             |
| Grandmother               | 289,315                 | 82,952,329              | 7114                    | 2,375,513               | 1.05 (1.03–1.08)           | 1.11 (1.08–1.14)             |
| Grandfather               | 247,820                 | 79,122,800              | 6476                    | 2,290,075               | 1.05 (1.03–1.08)           | 1.08 (1.05–1.11)             |
| Uncles/aunts              | 2452                    | 8,804,337               | 51                      | 194,847                 | 0.98 (0.74–1.30)           | 1.04 (0.79–1.39)             |
| Aunt                      | 1241                    | 4,469,597               | 24                      | 98,830                  | 0.91 (0.59–1.40)           | 0.96 (0.63–1.48)             |
| Uncle                     | 1211                    | 4,338,740               | 27                      | 96,017                  | 1.05 (0.72–1.53)           | 1.13 (0.77–1.65)             |

Note: No. of events and person-years are shown for index person–relative pairs (not individuals); adjusted hazard ratios were derived from Cox proportional models adjusted for birth year of index persons, birth year of relatives, sex of index persons, and sex of relatives. Abbreviation: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval.

The estimates stratified by sex of the relatives showed that mothers of index persons with ADHD had higher risks for AD (1.77, 1.23–2.54) than fathers (1.46, 1.16–1.84), though the difference was not statistically significant (Table 2). Analysis stratified by sex of index person showed similar estimates in parents for male index persons (1.53, 1.18–1.99) and female index persons (1.55, 1.16–2.09; Table S2 in supporting information). When considering age of onset, the risk of having early-onset AD in relatives of index persons with ADHD was higher than the risk of having late-onset AD in relatives of index persons with ADHD (Table 3). In parents, the association with early-onset AD (1.69, 1.34–2.13) was stronger than the association with late-onset AD (1.20, 0.82–1.77). This was also the case with grandparents, that is, the association with early-onset AD (1.27, 1.19–1.36) was stronger than the association with late-onset AD (1.09, 1.07–1.11). Similar patterns were observed in uncles/aunts, and for the associations with any dementia.

Sensitivity analyses further included information on prescribed medications of ADHD and AD for case identification, increased statistical power generated robust results, that is, the coaggregation of ADHD and AD in index person–uncle/aunt pairs became significant (1.28, 1.02–1.61; Table 4). We observed similar results in the subcohorts of index persons born between 1980 and 1989 and between 1990 and 2001, although parents in the subgroup of index persons born between 1990 and 2001 were not significant due to low number of AD cases. Further, the results adjusting for ADHD status of relatives were similar to the main analyses across relative types.

### 4 DISCUSSION

To the best of our knowledge, this is the first study to explore the association of ADHD, a neurodevelopmental disorder, with AD and any dementia, neurodegenerative diseases, across generations. We observed that relatives of individuals with ADHD had an increased risk of developing AD and any dementia compared to relatives of individuals without ADHD. The associations attenuated with decreasing genetic relatedness (parents > grandparents and uncles/aunts). The risk of having early-onset AD associated with ADHD was higher than that for late-onset AD.

The observed familial coaggregation of ADHD in index persons and AD in relatives can be explained by several potential mechanisms or their combination. One mechanism is that the observed familial development for relatives of index persons with and without ADHD are shown in Figure S1 in supporting information.

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### Table 3: Association between ADHD and Alzheimer’s disease and any dementia stratified by onset age of dementia

| Relatives of index persons | Age at onset | No. of event (ADHD = 0) | Person-years (ADHD = 0) | No. of event (ADHD = 1) | Person-years (ADHD = 1) | Adjusted hazard ratio (95% CI) |
|---------------------------|-------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------------|
| **Alzheimer’s disease**   |             |                         |                         |                         |                         |                               |
| Parents                   | Early-onset | 2562                    | 16,574,683              | 85                      | 349,912                 | 1.69 (1.34–2.13)              |
|                           | Late-onset  | 1007                    | 823,379                 | 25                      | 15,892                  | 1.20 (0.82–1.77)              |
| Grandparents              | Early-onset | 29,950                  | 92,295,850              | 1147                    | 2,911,247               | 1.27 (1.19–1.36)              |
|                           | Late-onset  | 434,553                 | 71,065,662              | 10,518                  | 1,788,349               | 1.09 (1.07–1.11)              |
| Uncles/aunts              | Early-onset | 1431                    | 8,239,251               | 34                      | 183,840                 | 1.16 (0.81–1.66)              |
|                           | Late-onset  | 545                     | 572,396                 | 12                      | 11,127                  | 1.13 (0.65–1.98)              |
| **Any dementia**          |             |                         |                         |                         |                         |                               |
| Parents                   | Early-onset | 3489                    | 16,565,847              | 97                      | 349,733                 | 1.40 (1.13–1.74)              |
|                           | Late-onset  | 978                     | 818,904                 | 23                      | 15,793                  | 1.15 (0.77–1.70)              |
| Grandparents              | Early-onset | 51,855                  | 92,199,748              | 2035                    | 2,907,230               | 1.35 (1.29–1.42)              |
|                           | Late-onset  | 485,280                 | 818,904                 | 11,555                  | 15,793                  | 1.06 (1.04–1.08)              |
| Uncles/aunts              | Early-onset | 1971                    | 8,234,383               | 43                      | 183,757                 | 1.09 (0.80–1.48)              |
|                           | Late-onset  | 481                     | 569,953                 | 8                       | 11,090                  | 0.86 (0.44–1.71)              |

Note: No. of events and person-years are shown for index person–relative pairs (not individuals); adjusted hazard ratios were derived from Cox proportional models adjusted for birth year of index persons, birth year of relatives, sex of index persons, and sex of relatives. Abbreviation: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval.

### Table 4: Sensitivity analyses of familial coaggregation between ADHD and Alzheimer’s disease

| Analysis                                                                 | Type of relatives | No. of pairs | No. of events | Adjusted hazard ratio (95% CI) |
|-------------------------------------------------------------------------|-------------------|--------------|--------------|-------------------------------|
| Including medication in addition to diagnosis and cause of death for case identification | Parents           | 4,246,182    | 5951         | 1.44 (1.21–1.71)              |
|                                                                        | Grandparents      | 7,548,861    | 571,025      | 1.09 (1.07–1.11)              |
|                                                                        | Uncles/aunts      | 1,838,520    | 2849         | 1.28 (1.02–1.61)              |
| Subgroup of index persons born 1980–1989                                | Parents           | 1,903,623    | 4128         | 1.56 (1.25–1.96)              |
|                                                                        | Grandparents      | 3,437,638    | 318,249      | 1.08 (1.05–1.11)              |
|                                                                        | Uncles/aunts      | 842,114      | 1755         | 1.10 (0.76–1.58)              |
| Subgroup of index persons born 1990–2001                                | Parents           | 2,342,559    | 982          | 1.48 (0.96–2.28)              |
|                                                                        | Grandparents      | 4,111,223    | 193,608      | 1.13 (1.10–1.16)              |
|                                                                        | Uncles/aunts      | 996,406      | 360          | 1.30 (0.78–2.15)              |
| Additionally adjust for ADHD diagnosis in the relatives of the index person | Parents           | 4,246,182    | 4400         | 1.53 (1.25–1.87)              |
|                                                                        | Grandparents      | 7,548,861    | 510,759      | 1.11 (1.08–1.13)              |
|                                                                        | Uncles/aunts      | 1,838,520    | 2115         | 1.15 (0.85–1.56)              |

Note: No. of events are shown for index person-relative pairs (not individuals); adjusted hazard ratios were derived from Cox proportional models adjusted for the birth year of index persons, the birth year of relatives, sex of index persons, and sex of relatives. Abbreviation: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval.

Coaggregation is attributable to familial risk factors shared by the two conditions within families, including pleiotropic genetic variants and family-wide environmental factors affecting both conditions. Although the largest GWAS studies on ADHD and AD to date have failed to detect any genetic variant in common,\(^\text{16,17}\) there have been studies suggesting that the genes SORCS2 and SORCS3 may be implicated in both ADHD and AD, with amyloid precursor protein (APP) processing, neuronal development, and plasticity being altered.\(^\text{35,36}\) Furthermore, as common genetic variants only explain a moderate proportion of the heritability of both disorders,\(^\text{16,37}\) it is possible that there exist other
Our study highlights the importance of advancing the understanding of ADHD in older adults. With further triangulation with other studies, ADHD could be considered a potential modifiable risk factor for AD and dementia. A recent meta-analysis found that a considerable number of older adults presented ADHD symptoms, and only less than half of older adults with clinically diagnosed ADHD received treatment. Research has shown that ADHD medications are effective in reducing ADHD symptoms as well as adverse outcomes of ADHD, such as substance abuse, physical injury, and low educational achievement, which are well-documented risk factors for AD. Further studies are warranted to examine whether ADHD medications could alleviate the risk of AD associated with ADHD.

This is, to our knowledge, the first study explored the familial association of ADHD with AD and any dementia using a large population-based sample. The use of multi-generational design enables follow-up from younger elderly to older elderly in different relatives, and provides insight into the genetic and environmental contribution to the associations of ADHD with AD and any dementia. The diagnoses of ADHD and AD were made separately in the index person and relatives, preventing biases from symptom misclassification or preconceptions of patients or clinicians. Our results should also be interpreted in light of several limitations. First, despite the multi-generation design, we were only able to follow most of the parents and uncles/aunts until their sixties; however, the onset of dementia usually peaks around 80 years of age. Nonetheless, results from the subcohort of index persons born between 1980 and 1989 showed similar estimates with those born between 1990 and 2001, suggesting the length of follow-up did not bias the estimates. Second, we were not able to examine the association with specific dementia subtypes other than AD (e.g., vascular dementia, dementia with Lewy bodies, and frontotemporal dementia) due to insufficient statistical power. Future studies are needed to explore whether the associations are differential across subtypes as well as if there exist underlying biological mechanisms specific to associations of certain subtypes. Third, although prior validation studies have reported the diagnoses of dementia in the NPR and CDR with specificity of 99%, the sensitivity is only 63%. Such misclassifications of dementia cases would attenuate the associations toward the null and thus our estimates are likely to be conservative. Nonetheless, we additionally used information on prescriptions for AD in case identification in sensitivity analysis and generated consistent results. Fourth, using anti-dementia drugs for AD case identification in the sensitivity analysis would misclassify some cases, because anti-dementia drugs are also prescribed for other dementias, for example, Lewy body dementia and Parkinson’s disease dementia. However, this misclassification should be nondifferential and not substantially influence the association between ADHD and AD, as Lewy body dementia and Parkinson’s disease dementia constitute only a small proportion of total dementia cases. Finally, although the prevalence of ADHD diagnosis and ADHD medication prescription in Sweden is similar to many European countries, it is lower than other countries, such as the United States, meaning individuals with ADHD in Sweden may represent more severe cases than those countries. Thus, replications in

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other countries are needed to examine to what extent our results generalize to other settings.

5 | CONCLUSIONS

We found that ADHD coaggregated with AD and any dementia within families, and the strength of association attenuated with decreasing degree of genetic relatedness. Molecular genetic and family studies aiming to identify pleiotropic genetic variants and family-wide environmental risk factors contributing to both conditions are warranted. GWAS of ADHD and AD on a larger sample size could provide the potential for unraveling shared genetic mechanisms between the disorders through linkage disequilibrium score regression and network analyses. In addition, our study highlights the importance of advancing the understanding of ADHD and cognitive decline in older age and, if verified, calls for investigation of early-life psychiatric prevention on the development of neurodegenerative diseases in older age.

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CONFLICTS OF INTEREST

EDR has served as a consultant for Shire Sweden AB; HL has served as a speaker for Evolan Pharma and Shire/Takeda and has received research grants from Shire/Takeda, all outside the submitted work. All other authors have no competing interests.

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