Original Article

Bidirectional Associations Between Asthma and Types of Mental Disorders

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What is already known about this topic? Asthma and mental disorders frequently co-occur. Most existing studies on the associations between asthma and mental disorders report relatively restricted types of mental disorders and very often investigate associations in one direction.

What does this article add to our knowledge? In this population-based cohort study comprising 5,053,471 individuals, we found bidirectional associations for 10 bidirectional mental disorder–asthma pairs, for instance, schizophrenia, mood disorders, neurotic disorders, eating disorders, personality disorders, and developmental disorders.

How does this study impact current management guidelines? Our findings may be of clinical importance in reducing diagnostic delay and improving the management of both disorder types.

BACKGROUND: Asthma and mental disorders frequently co-occur. Studies of their comorbidity have generally focused on associations related to a subset of mental disorders.

OBJECTIVE: To estimate bidirectional associations between asthma and 10 broad types of mental disorders.

METHODS: In a population-based cohort study, including all individuals born in Denmark between 1955 and 2011 (N = 5,053,471), we considered diagnoses of comorbid mental disorders among those with asthma, and vice versa, between 2000 and 2016. We used Cox regression models to calculate overall and time-dependent hazard ratios for mental disorder–asthma pairs and competing-risks survival analyses to estimate absolute risks.

RESULTS: Altogether, 376,756 individuals were identified as having an incident mental disorder and 364,063 incident asthma during follow-up. An increased risk was seen for all bidirectional mental disorder–asthma pairs. Following an asthma diagnosis, adjusted hazard ratios for different subsequent mental disorders ranged from 1.75 (95% CI, 1.64-1.87) for organic disorders to 2.75 (95% CI, 2.69-2.81) for personality disorders. Following a prior mental disorder diagnosis, hazard ratios for asthma ranged from 1.06 (95% CI, 1.00-1.12) for developmental disorders to 2.33 (95% CI, 2.28-2.39) for substance use disorders. Risks varied with time since prior disorder diagnosis but remained elevated. Cumulative incidence of (1) asthma after a mental disorder and (2) a mental disorder after asthma was higher in those with prior disorders than in matched reference groups.

CONCLUSIONS: Our findings provide evidence of bidirectional associations between asthma and each of the mental disorder types, suggesting possible shared etiological factors or pathophysiologic processes. **© 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;■:■-■)**

Key words: *Asthma; Mental disorder; Comorbidity; Epidemiology; Register-based research*

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Abbreviations used
HR- hazard ratio

INTRODUCTION

Asthma and mental disorders are among the most prevalent chronic diseases worldwide, co-occurring more often than expected by chance.[1-6] Patients with asthma have higher rates of mental disorders.[1,2] Similarly, patients suffering from mental disorders are at increased risk for asthma.[1,2,6,7] The comorbidity between asthma and mental disorders leads to substantially reduced health-related quality of life and imposes significant public health burdens.[8]

A growing number of population-based epidemiological studies report associations between asthma and mental disorders.[1-5,9-11] However, the focus has primarily been on mood and anxiety disorders,[1,2,4,5,9-11] with 2 studies on attention deficit/hyperactivity disorder and autism spectrum disorders showing associations with later asthma.[3,12] Furthermore, studies often investigated associations in 1 direction or lifetime-ever associations,[3-5,9-12] precluding assessment of temporal ordering. Two studies examined the associations bidirectionally, reporting an increased risk of subsequent asthma in those with depression and anxiety disorders and vice versa.[1,2] Studies have mainly conveyed relative risks, seldom providing information on the cumulative incidence of subsequent disorders. It remains elusive whether the bidirectional associations with asthma are specific to depression and anxiety disorders, but large sample sizes are needed to consider less common mental disorders. Moreover, the prevalence of specific mental disorders differs between males and females,[13] as does asthma prevalence.[14] However, sex-specific associations have rarely been explored. Addressing these research gaps will further research into mechanisms and inform clinical guidelines regarding early identification and treatment of comorbidities.

We undertook a longitudinal study using administrative data in Denmark to provide a comprehensive compilation of bidirectional associations between asthma and mental disorders, considering 10 diagnostic groups of mental disorders. In addition, we calculated bidirectional sex-specific pairwise measures of both relative risks and cumulative incidence between asthma and mental disorders. Relative risks provide an estimate of how much more (or less) a later disorder of interest occurred in individuals with a prior disorder of interest (the exposed group), compared with individuals without the prior disorder (the unexposed group), whereas cumulative incidence provides the proportion of people who develop subsequent disorders over a specified time, and can be a more useful metric for understanding how many individuals actually have a later disorder, aiding in the understanding of the public health impact of the exposure. With a common outcome, an exposure that leads to a small increase in relative risk could produce many more cases; however, for a rare disorder, even with a big impact on relative risk, an exposure may result in only a small number of additional cases. Both measures are needed for a complete picture.

METHODS

Study population

Using the Danish Civil Registration System,[15] we identified all 5,053,471 individuals born in Denmark between 1955 and 2011, residing in the country at the start of the follow-up period (January 1, 2000, or their first birthday, whichever occurred later). The start of the follow-up on this date allowed for a "washout" period of at least 5 years (1995-1999) to identify prevalent mental disorders or asthma using both hospital contacts (including outpatient visits)[16,17] and prescriptions[18] (see Table E1 in this article's Online Repository at www.jaci-inpractice.org), ensuring only incident cases diagnosed during the observation period were included.

Study design

We conducted a population-based cohort study using data from Danish nationwide registers[15-19] (see Online Repository text in this article's Online Repository at www.jaci-inpractice.org). All Danish residents are assigned a unique 10-digit number in the Danish Civil Registration System, enabling individual-level linkage between registers. We examined associations between asthma and mental disorders considering the temporal order, that is, the risk of receiving a specific type of mental disorder diagnosis (in this case, the later disorder) among persons with asthma (in this case, the prior disorder), and vice versa. The study was approved by the Danish Data Protection Agency. By Danish law, no informed consent is required for a register-based study based on anonymized data.

Ascertainment of mental disorders

Mental disorders were defined as any clinical diagnosis recorded in the Psychiatric Central Research Register. Diagnosis dates were defined as the date of first hospital contact (inpatient, outpatient, or emergency room visit). We assessed 10 broad types of mental disorders based on *International Classification of Diseases, Tenth Revision* diagnostic research criteria subchapter F categories (F00-F09, F10-F19, etc), and corresponding diagnoses in *International Classification of Diseases, Eighth Revision* (Table E1).

Ascertainment of asthma

In line with our previous research,[20,21] we considered an individual to have asthma if they fulfilled at least *1* of the following 3 criteria:

1. At least 1 hospital contact for asthma (*International Classification of Diseases, Eighth Revision* code 493 and *International Classification of Diseases, Tenth Revision* codes J45 and J46) in the Danish National Patient Registry;
2. At least 2 prescriptions for asthma medication within 1 year in the National Prescription Registry (Anatomical Therapeutic Chemical codes: inhaled β2-agonists [R03AC02-04, -12, and -13], inhaled glucocorticoids/corticosteroids [R03BA01, -02, and -05], fixed-dose combination of inhaled β2-agonists and glucocorticoids [R03AK06 and -07], and leukotriene receptor antagonists [R03DC03]);
3. Diagnosis of asthma recorded as the cause of death in the Cause of Death Register.

The diagnosis date of asthma was defined as the date of the first prescription for asthma medication, the first hospital contact for asthma, or the date of death from asthma, whichever occurred first. We defined and identified asthma after age 5 years because an accurate diagnosis of asthma in younger children is challenging.[22]

Statistical analysis

We adopted our analysis from our previous study on the association between mental disorders and general medical conditions.[23] Although this study examined "chronic pulmonary disorders," including asthma, its broad focus meant it did not fractionate out the disorder.

To estimate the association between a prior and later disorder, follow-up started on January 1, 2000, or at the minimum age at which a person might develop the later disorder (5 years for asthma; see Table E1 for mental disorders), whichever came later. Follow-up ended at the first occurrence of the following events: diagnosis of the later disorder, death, emigration, or December 31, 2016. Our analyses focused on incident cases of the later disorder, developed in the period 2000 to 2016. Individuals who had received a diagnosis of a particular later disorder of interest before this observation period were considered prevalent cases and excluded from the analyses of this particular disorder. Persons who had not received a diagnosis of the prior disorder before follow-up were considered unexposed at the start of follow-up; if they received a diagnosis during follow-up, they were considered exposed from the date of the first diagnosis of the prior disorder. The sample sizes for each later disorder are presented in Table E2 in this article's Online Repository at www.jaci-inpractice.org. For example, for mood disorders as a later disorder, 18,489 persons were excluded from the analysis because they received a diagnosis before follow-up.

We compared the risk of diagnosis with a later disorder between those exposed and unexposed to each prior disorder. We calculated 3 results for each of the 10 bidirectional mental disorder—asthma pairs: (1) overall hazard ratios (HRs), (2) lagged HRs, and (3) cumulative incidence. Overall, HRs provide a measure of relative risk of the later disorder in those with the prior disorder compared with those without the prior disorder over the entire follow-up period, whereas lagged HRs break up the follow-up period to ascertain relative risk at different periods after the diagnosis of the prior disorder. Cumulative incidence shows the proportion of people with the prior disorder who are diagnosed with the later disorder of interest over time. All the analyses described below were also repeated, stratified by sex, to see whether the associations differed between males and females.

Overall HRs. The overall HRs were calculated, with their 95% CIs for 10 bidirectional mental disorders—asthma pairs, using Cox proportional hazards regression models with age as the underlying time scale. All analyses were adjusted for sex and calendar time. In addition, we adjusted for other mental disorders occurring before the prior disorder of interest as a time-varying variable; that is, when mood disorder was the prior disorder of interest, as an example, we adjusted for all other mental disorder diagnoses that occurred before the diagnosis of mood disorder. They were considered to have no other mental disorders until they received a diagnosis, after which they were considered to have other mental disorders.

Lagged HRs. We further investigated whether the associations differed depending on time since the diagnosis of the prior disorder (ie, time-dependent HRs) by analyzing 7 periods after the prior diagnosis: 0 to 6 months, more than 6 months to 12 months, more than 1 year to 2 years, more than 2 years to 5 years, more than 5 years to 10 years, more than 10 years to 15 years, and more than 15 years.

Cumulative incidence. We estimated the cumulative incidence of diagnosis with a later disorder after receiving a diagnosis of a prior disorder as the number of incident cases of the later disorder divided by the total number of individuals in the population at risk, using the Aalen-Johansen estimator (competing-risks survival analyses). For each index individual with a prior disorder of interest, up to 5 birthdate- (±90 days) and sex-matched individuals who had not been diagnosed with the prior disorder at or before the age at which the index individuals received the diagnosis were randomly selected from the entire study population. They were selected randomly after using the Stata "*rangejoin*" function.

Sensitivity analysis

The symptoms and medication treatment of asthma often overlap with chronic obstructive pulmonary disease and heart failure in the elderly.[24] Therefore, we repeated our analyses in individuals younger than 40 years, because these diagnoses are uncommon before this age.[24] Individuals born during the period 1960 to 2011 were included in the analyses and censored when they reached 40 years.

Asthma is a complex and multifaceted disease, and age of onset is often used to distinguish different asthma phenotypes.[22] To estimate whether associations were different when asthma diagnoses were limited to child and adolescent-onset asthma (<20 years, abbreviated as early-onset asthma hereafter), we also calculated the relative risk of later asthma in individuals younger than 20 years. Furthermore, we calculated the relative risks of later mental disorders in individuals with a prior diagnosis of early-onset asthma compared with individuals without a diagnosis of early-onset asthma.

RESULTS

Of 5,053,471 individuals included in the study, 52.1% were male and 75.2% were Danish (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). During a maximum of 76.1 million person-years at risk (depending on the pair of disorders of interest), 364,063 individuals were identified as having incident asthma as a later disorder (73.9% defined by prescription data and 26.1% by diagnosis or cause of death) and 376,756 having an incident mental disorder as a later disorder. The numbers of cases of each mental disorder and asthma during follow-up are presented in Table E2. To aid the readers, the associations between asthma and mood disorders (in both directions) are presented as an example in the Online Repository text in this article's Online Repository at www.jaci-inpractice.org.

Prior asthma—later mental disorders

There were 69,992 individuals who were ascertained to have asthma followed by an incident mental disorder.

Overall HRs. The risk of receiving a subsequent diagnosis for each mental disorder of interest was elevated; for instance, by 93% for mood disorders (HR, 1.93; 95% CI, 1.90-1.96), 92% for neurotic disorders (HR, 1.92; 95% CI, 1.90-1.94), and 85% for developmental disorders (HR, 1.85; 95% CI, 1.79-1.92) (Figure 1). HRs ranged from 1.75 (95% CI, 1.64- 1.87) for later organic disorders to 2.75 (95% CI, 2.69-2.81) for later personality disorders.

Lagged HRs

For HRs over time, patterns varied for different subsequent mental disorders but remained elevated during the study period (Figure 2; see Table E4 in this article's Online Repository at www.jaci-inpractice.org). For example, the risk of a subsequent diagnosis of substance use disorders or mood disorders stayed fairly constant as time passed since the asthma diagnosis was

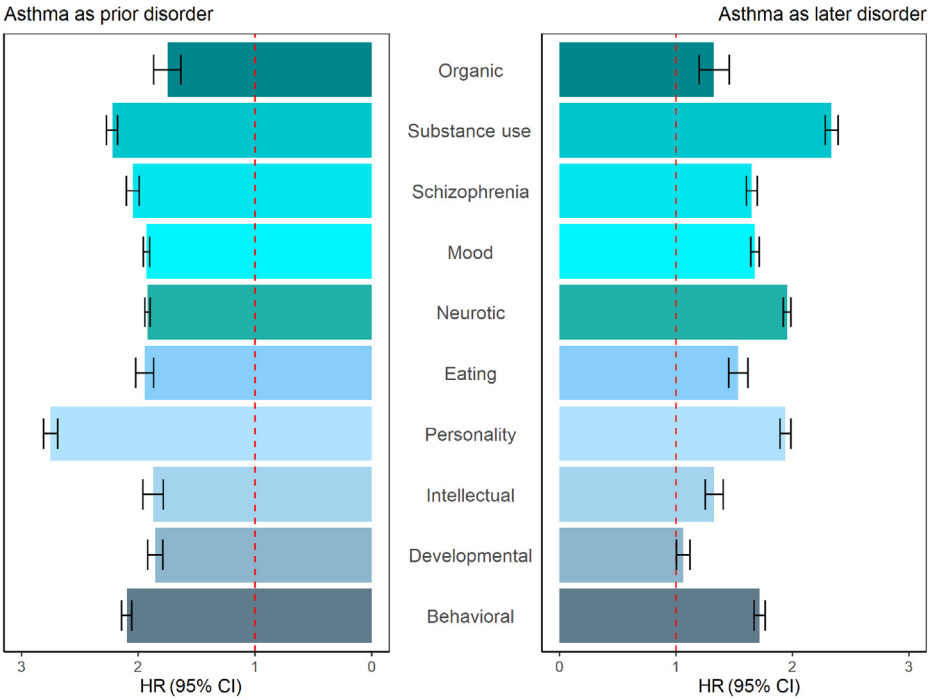

FIGURE 1. Bidirectional HRs for asthma and mental disorders, all persons. On the left side of the graph, HRs are shown for subsequent diagnoses of each mental disorder type* in those with prior diagnosis of asthma, compared with those without. On the right side of the graph, HRs are shown for subsequent diagnosis of asthma among those with prior diagnoses of each mental disorder type, compared with those without. *More information about the mental disorder groups can be found in Table E1; however, we provide some example diagnoses within each group here. Organic disorders include dementia in Alzheimer disease; Substance use disorders include use of alcohol or cannabis; Schizophrenia and related disorders include schizophrenia; Mood disorders include bipolar disorder and depressive disorders; Neurotic disorders include anxiety disorders and phobias; Eating disorders include anorexia nervosa; Personality disorders include paranoid personality disorders; Intellectual disabilities include mild to profound mental retardation; Developmental disorders include autism spectrum disorders; and Behavioral disorders include attention deficit/hyperactivity disorder.

made. The risk of later personality disorders, developmental disorders, or behavioral disorders rose over time, whereas that of neurotic disorders decreased.

Cumulative incidence. Within 15 years of follow-up among those with prior asthma, mental disorder diagnoses varied between 0.07 per 100 persons for later organic disorders and 6.08 per 100 persons for later neurotic disorders, which were higher than in the matched reference group (Figure 3).

Prior mental disorders—later asthma

There were 62,186 persons who were ascertained to have a mental disorder followed by incident asthma.

Overall HRs. The risk of receiving a subsequent asthma diagnosis was elevated. For instance, the HR was 1.68 (95% CI, 1.64-1.71) for prior mood disorders and 1.95 (95% CI, 1.92-1.99) for prior neurotic disorders. Associations were smaller compared with those when asthma was the prior disorder (Figure 1), with HRs ranging from 1.06 (95% CI, 1.00-1.12) for prior developmental disorders to 2.33 (95% CI, 2.28-2.39) for prior substance use disorders.

Lagged HRs. For some prior mental disorders, the risk of a subsequent asthma diagnosis rose slowly over time, for example, substance use or schizophrenia (Figure 4; see Table E4). However, for others, risks remained fairly stable, for example, for personality disorders, developmental disorders, or mood disorders.

Cumulative incidence. Within 15 years of an initial mental disorder diagnosis, the number of individuals with an asthma diagnosis varied between 8.0 per 100 persons for prior developmental disorders and 14.3 per 100 persons for prior personality disorders. Cumulative incidence was higher in those with a prior mental disorder than in the matched reference group (Figure 5).

Sex-specific bidirectional associations

Following asthma, the HRs for later mental disorders were generally larger in females than in males, except for organic disorders, mood disorders, and eating disorders. For those with a prior mental disorder, the HRs for asthma were slightly larger in females than in males, except for organic disorders and developmental disorders (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Sex-specific time-dependent

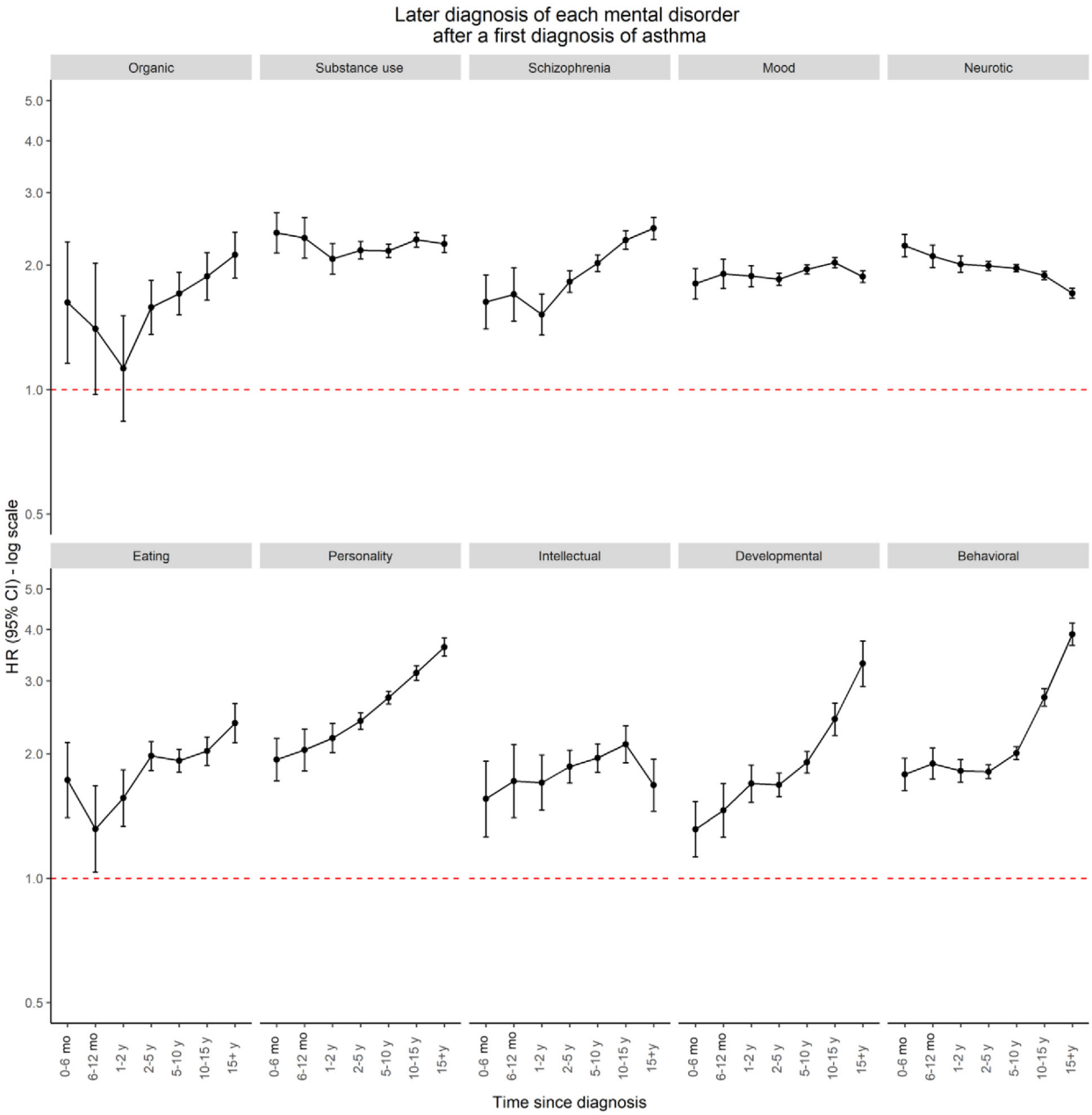

FIGURE 2. Lagged HRs for later mental disorder diagnoses in those with prior diagnoses of asthma, compared with those without, all persons.

HRs are shown in Figures E2 and E3 and Table E4 in this article's Online Repository at www.jaci-inpractice.org, and cumulative incidences for later mental disorders following asthma and for later asthma following mental disorders are shown in Figures E4 and E5.

Sensitivity analyses

When we repeated our analyses, including only those individuals who were younger than 40 years, the study population included 4,619,177 persons, followed up for 52.1 million person-years. The HRs in the sensitivity analysis were similar to those in the primary analysis (see Figure E6 in this article's Online Repository at www.jaci-inpractice.org). Bidirectional associations for early-onset asthma are shown in Figure E7 in this article's Online Repository at www.jaci-inpractice.org. We found bidirectional associations between 10 broad types of mental disorders and early-onset asthma, as observed in the main analysis, although the magnitude of the associations varied slightly.

DISCUSSION

In this population-based cohort study comprising more than 5 million individuals, we found that those with asthma were at higher risks of mental disorders compared with those with no

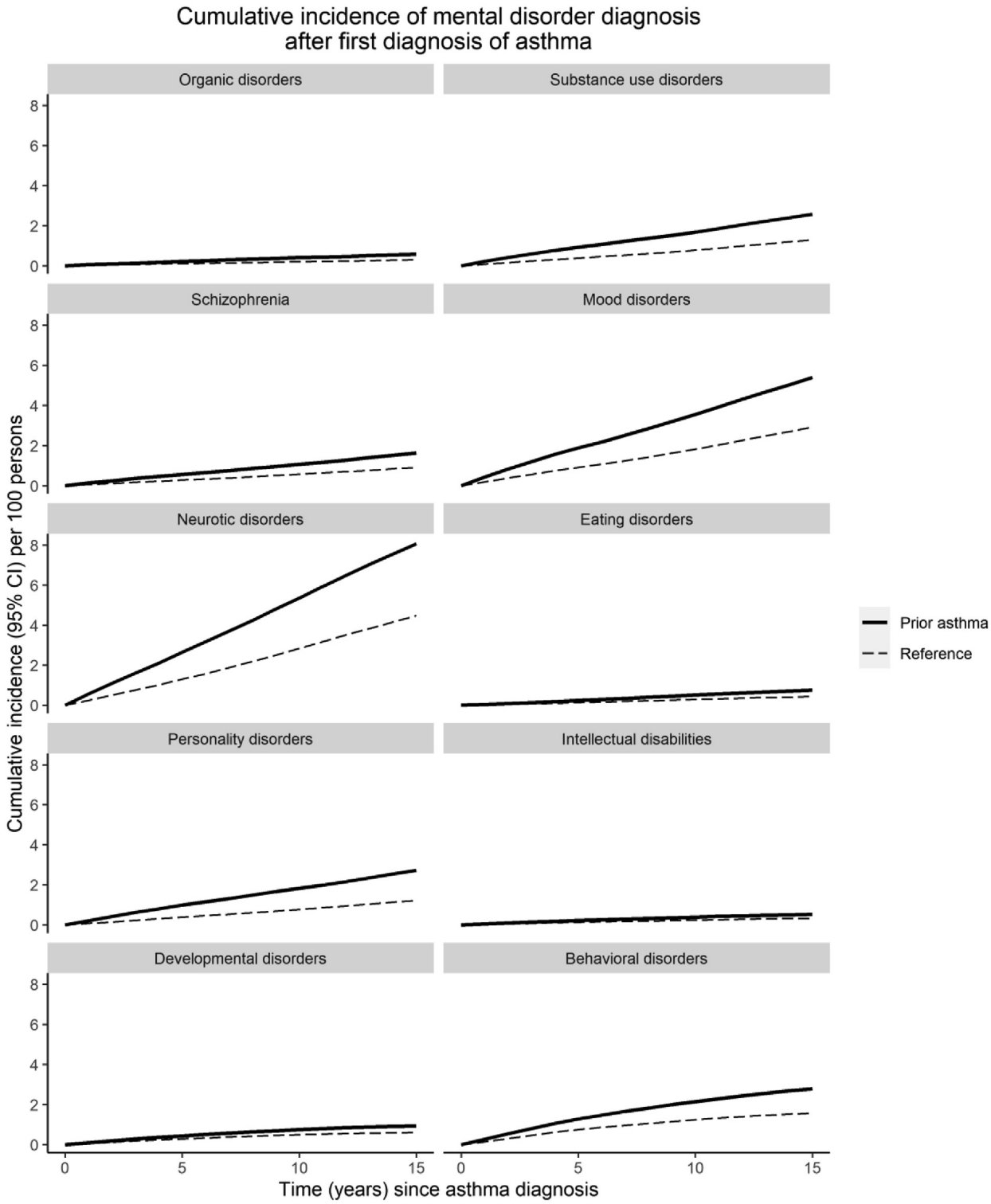

FIGURE 3. Cumulative incidence for prior asthma and later mental disorders, all persons.The cumulative incidence per 100 persons of receiving a diagnosis of each later mental disorder of interest after a diagnosis of asthma. Shaded gray areas around the lines for those with the prior asthma diagnosis represent 95% CIs (in some panels, where CIs are very narrow, obscured by the estimates line). The horizontal axes show the time since first diagnosis of asthma. The vertical axes show the cumulative incidence per 100 persons (and 95% CI). The reference group was selected randomly after using the Stata "*rangejoin*" function: for each index individual with a prior disorder of interest, up to 5 birthdate- (±90 days) and sex-matched individuals who had not been diagnosed with the prior disorder at or before the age at which the index individuals received the diagnosis were randomly selected from the entire study population.

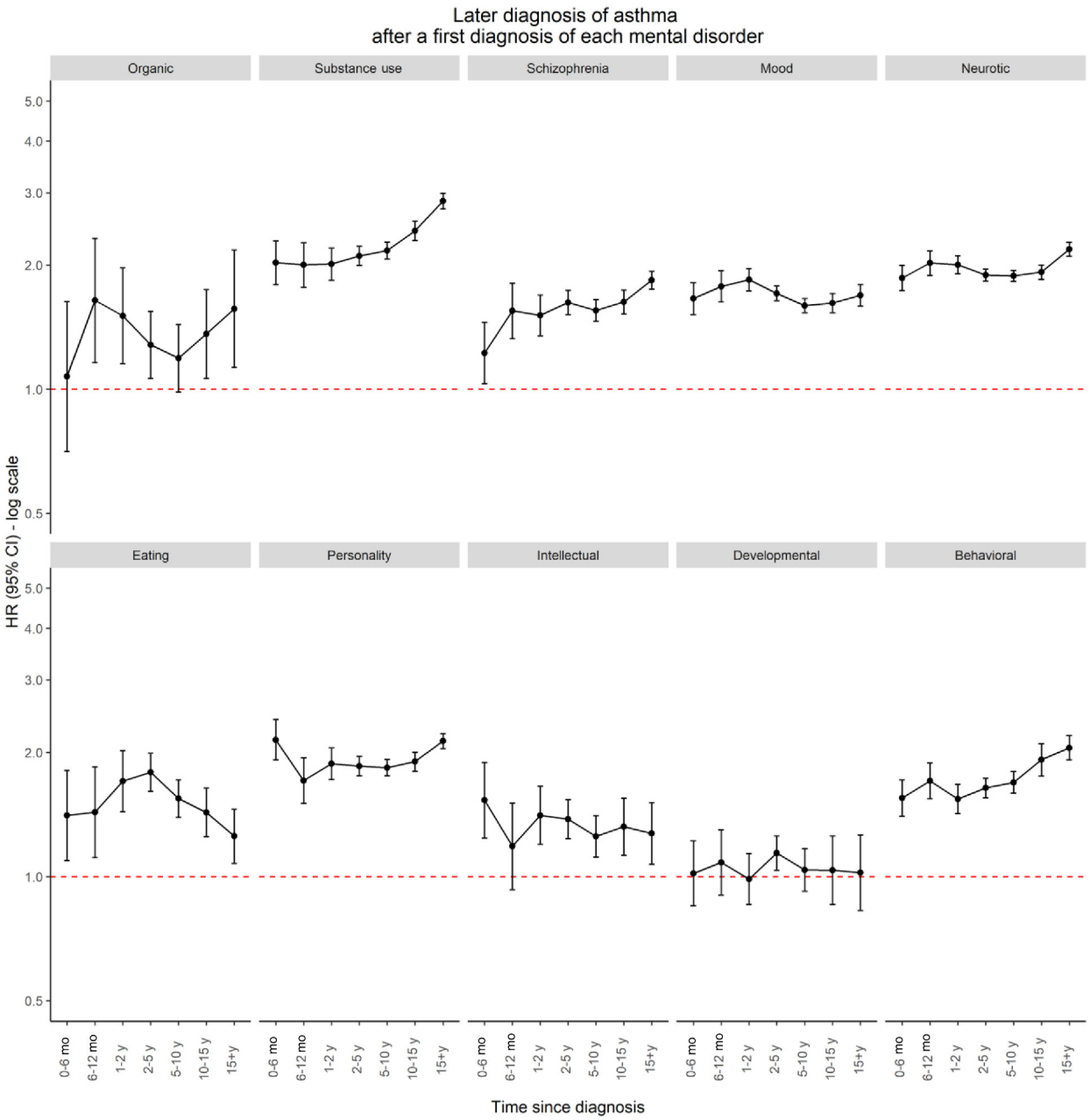

FIGURE 4. Lagged HRs for later asthma diagnoses in those with prior diagnoses of each mental disorder, compared with those without, all persons.

asthma and vice versa. The extent of the increase in risk varied by type of mental disorder, which disorder was diagnosed first, and the time since the prior disorder. Slightly stronger associations were generally observed for females.

Our results suggest robust links between asthma and 10 broad types of mental disorders. Stronger associations were observed when asthma was the prior disorder (rather than the later disorder). This may be attributable to the differences in age at onset for asthma and mental disorders, with asthma often diagnosed at a younger age.[25,26] Our findings of increased risk of subsequent asthma in patients with mental disorders (HRs of 1.06-2.33) align with but expand upon previous research.[1-5,9-11] We found a slightly increased risk of later asthma (1.06; 95% CI, 1.00-1.12) following a diagnosis of developmental disorders, but the increased risk was observed only 2 to 5 years after the diagnosis. This finding differs from that of a cross-sectional study based on parental-reported asthma and developmental disorders (odds ratio, 1.68; 95% CI, 1.07- 2.63); however, the estimate from the cross-sectional study may be a combination of bidirectional asthma and mental disorder effects.[12] In our study, in which we

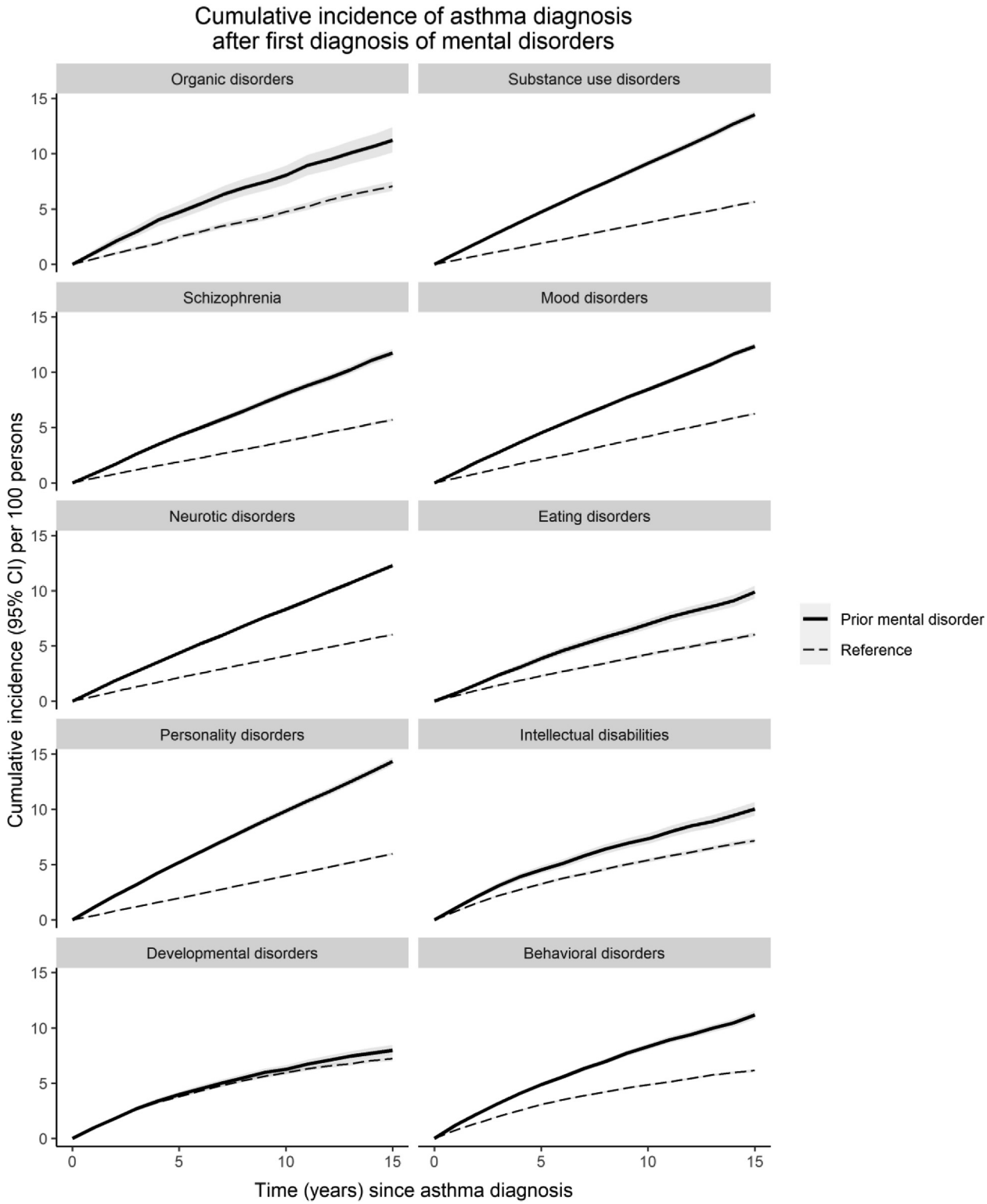

FIGURE 5. Cumulative incidence for prior mental disorders and later asthma, all persons, all ages. The cumulative incidence per 100 persons of receiving an asthma diagnosis, after a diagnosis of a prior mental disorder of interest. Shaded gray areas around the lines for those with the prior diagnosis of a mental disorder represent 95% CIs (in some panels, where CIs are very narrow, obscured by the estimates line). The horizontal axes show the time since first diagnosis of the prior mental disorder. The vertical axes show the cumulative incidence per 100 persons (and 95% CI). The reference group was selected randomly after using the Stata "*rangejoin*" function: for each index individual with a prior disorder of interest, up to 5 birthdate- (±90 days) and sex-matched individuals who had not been diagnosed with the prior disorder at or before the age at which the index individuals received the diagnosis were randomly selected from the entire study population.

examined the association in each direction, we did observe a higher risk of developmental disorders after a prior diagnosis of asthma (HR, 1.85; 95% CI, 1.79-1.92).

Our findings regarding prior asthma and later mental disorders are consistent with those of 2 recent population-based studies,[1,2] albeit our HR for depression (1.93; 95% CI, 1.90-1.96) was slightly higher than 1.35 (95% CI, 1.31-1.40) reported by Choi et al,[1] possibly due to different study populations and disorder definitions. This is in contrast to a meta-analysis of 7 prospective studies that suggested no increased risk for later depression.[7]

The mechanisms linking asthma and mental disorders remain unclear. One possible explanation is shared pathophysiological pathways, for example, inflammatory responses.[27] Asthma is a chronic inflammatory disorder with a well-established link with several anti-inflammatory cytokines, such as IL-13 and IL-4.[28] Similarly, increased inflammatory cytokines and relevant receptors in the peripheral blood—cerebrospinal fluid have been reported in patients with mental disorders.[27] Second, patients with asthma often suffer from wheezing, shortness of breath, chest tightness, and cough. Fear of asthma episodes may cause stress for some individuals and lead to an increased risk of anxiety and mood disorders. Moreover, some antiasthma medications, such as inhaled or systematic corticosteroids, may have anxiogenic properties, and overuse of antiasthma medications may trigger or exacerbate depression and anxiety symptoms.[29] Third, mental disorders and asthma share common environmental risk factors such as air pollution and smoking, psychosocial risk factors such as stress, and genetic factors.[30,31] Genetic contributions to immune system pathways that are important in the genetic architecture of asthma[32] are also linked to some mental disorders such as depression.[33] A statistically significant genetic correlation of 0.17 has been reported between asthma and depression in a study of Swedish adults.[34]

We found that the size and the pattern of lagged HRs varied by mental disorder type. In previous studies,[23,35] HRs were observed to be highest in the years immediately after diagnosis of the prior disorder, which has been postulated to partly be due to Berkson's bias.[36] However, this does not seem to be the case across all asthma and mental disorder pairs, possibly due to differences in typical age of onset and different specialties focusing on these disorders. For some later disorders, an increase in the HRs was observed, for instance, schizophrenia, developmental disorders, and behavioral disorders. This may be related to the treatment of asthma among these patients. In the present study, slightly more pronounced associations were seen in females than in males. We speculate that it may be in part attributable to dissimilarities in health-seeking behaviors. Women use more medical care services than do men,[37] and, among those with mental disorders, women are more likely than men to be diagnosed and treated.[38] Moreover, sex-dependent effects on genes related to neuronal development and immune functions[39] may contribute to the sex-specific associations observed in our study.

Future studies on mental disorders and asthma comorbidity are warranted to provide more information on several areas. One example would be to unveil the mechanisms by which asthma and mental disorder are comorbid. It would also be useful to see whether the results can be replicated in a data set that includes primary care diagnoses to observe whether similar associations are found. In addition, future studies could consider more specific diagnoses. For example, to consider bipolar disorder and mood disorder separately. Repeating the analyses for bipolar disorder (*International Classification of Diseases, Tenth Revision* codes F30-F31) and major depression (F32-F33) indicated some notable differences (eg, an HR of 2.24 for bipolar disorder and 1.92 for major depression). A narrower focus may provide more information on mental disorders and allow for more relevant covariates or a more specific exposure window to be considered.

Strengths and limitations

Our study describes the bidirectional associations in a large, representative population with negligible sample attrition attributable to complete follow-up via administrative data. Information on mental disorders and asthma was independently collected, minimizing information bias. Our study also has limitations. First, asthma was ascertained using data on hospital diagnoses, causes of death, and prescription medications. We do not hold information on diagnoses from general practitioners. Antiasthma medications, such as short-acting beta-2 agonists, can be prescribed for chronic obstructive pulmonary disease in individuals 40 years and older.[24] In addition, similarities in the symptoms between asthma and heart failure exist. Individuals without asthma might have been misclassified as having asthma. The associations differed slightly but remained robust when restricted to individuals younger than 40 years, among whom chronic obstructive pulmonary disease and heart failure would be rare. Second, we defined mental disorders by hospital contact only. We lack information on mental illnesses diagnosed by general practitioners, which would have omitted less severe cases treated only in general practice. Furthermore, we have no information on undiagnosed cases. Because the severity of mental disorders may also relate to the strength of the associations, our findings may not be generalized to mild to moderate mental disorders. The lack of diagnosis data from general practitioners also affects ascertainment of asthma. Individuals could be classified as having asthma through diagnosis only if they received a diagnosis in a hospital setting. This is mitigated by the use of prescription data; however, as noted above, this is not without limitations. Moreover, we have determined onset using the first diagnosis or treatment, but disorders may have onset/present before diagnosis or treatment initiation. Therefore, the observed bidirectional associations reflect the temporal order of diagnosis/treatment rather than onset. Third, we do not have detailed information on disorder severity. Therefore, we could not determine whether a prior disorder triggers the development or exacerbates a subsequent disorder, resulting in treatment. Fourth, the current selection of confounders (sex, age, and mental disorder comorbidity) may be considered too narrow to infer causality; however, this is valid as a descriptive and keeps with our previous studies on comorbidity[13,23] and we retain the confounder selection for comparability and interpretation. Lastly, all residents in Denmark have universal and free access to health care systems. Therefore, our findings may not necessarily be generalizable to countries with distinct welfare systems.

Clinical implications

Our findings may have important clinical and public health implications. Mental disorders and asthma are often diagnosed and treated by different clinicians, and consequently, delayed

diagnosis of subsequent disorders is unavoidable. Awareness of the bidirectional associations may help reduce diagnostic delays. Moreover, the relationship between asthma and mental disorders is complex, and they should not be treated in isolation. Having severe asthma may exacerbate symptoms of depression and anxiety or even trigger panic attacks.[1,2] In turn, some mental disorders are associated with poor adherence to medical treatment, leading to undesirable treatment outcomes.[40] Therefore, early identification and good management of both disorder types are key. Psychiatrists and respiratory specialists should be aware of the potential associations between asthma and mental disorders and coordinate treatment of these conditions when they coexist.

CONCLUSIONS

This longitudinal population study provides a comprehensive compilation of the comorbidity between asthma and various mental disorders, presenting relative risks and cumulative incidence for the associations in both directions. In line with but expanding on other studies, we found universal bidirectional associations between asthma and 10 types of mental disorders. Our findings may be of clinical importance in reducing diagnostic delay and improving the management of both disorder types.

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ONLINE RESPOSITORY

BRIEF INTRODUCTION OF DANISH NATIONAL REGISTERS USED IN THIS STUDY

All Danish residents are assigned a unique 10-digit number in the Danish Civil Registration System.[E1] The Civil Registration System was established in 1968, holding information on birthdate, sex, and vital status.[E1] The personal number allows individual-level linkage between registers. The National Patient Register contains information on inpatient visits since 1977, and outpatients and emergency room visits since 1995.[E2] The Psychiatric Central Research Register holds information on inpatient treatment for mental disorders since 1969, and emergency room visits and outpatient treatments since 1995.[E3] The Cause of Death Register includes information on date, manner, and causes of all deaths among Danish residents dying in Denmark since 1970. Diagnoses and deaths were recorded using the *International Classification of Diseases, Eighth Revision* before 1994 and the *International Classification of Diseases, Tenth Revision* from 1994 onwards.[E4] The National Prescription Registry includes records on the Anatomical Therapeutic Chemical classification codes and the dispensing date of all prescriptions dispensed in Denmark since 1995.[E5]

ASSOCIATIONS OBSERVED FOR ASTHMA AND MOOD DISORDERS

Prior asthma—later mood disorders

For mood disorders, 18,489 persons were excluded from the study population because they had a mood disorder diagnosis before follow-up began (January 1, 2000, or at age 10 years, the minimum age at which a person might develop mood disorders, whichever came later). The remaining 4,658,924 were considered as "at risk" of an incident mood disorder and were included in the analysis. Of these, 130,578 were diagnosed with a mood disorder for the first time during the follow-up period (from the start of follow-up until a diagnosis of mood disorder, death, emigration, or December 31, 2016, whichever came first).

The risk of receiving a diagnosis of a mood disorder for those with asthma, compared with those who did not have asthma, was increased by 93% (HR, 1.93; 95% CI, 1.90-1.96) (Figure 1 and Table E4). Sex-specific estimates were 1.94 (95% CI, 1.90-1.99) for males and 1.92 (95% CI, 1.89-1.99) for females (Figure E1 and Table E4).

With respect to the pattern of HRs over time since the onset of asthma (lagged HR, Figure 2 and Table E4), the highest HR for mood disorders was seen at 10 to 15 years following an asthma diagnosis (2.02; 95% CI, 1.97-2.09), but did not change greatly over time. For females, a similar pattern was observed; however, for males, the risk of a mood disorder was most elevated in the first 0 to 6 months after an asthma diagnosis (2.09; 95% CI, 1.80-2.41), after which the increase in risk was slightly lower (Figure E2 and Table E4).

Five years after a diagnosis of asthma, 1.88% (95% CI, 1.83%-1.93%) had been diagnosed with a mood disorder. By 10 years, this had increased to 3.55% (95% CI, 3.49%-3.61%), and by 15 years, to 5.38% (95% CI, 5.30%-5.46%). In the matched reference group, mood disorders at 5, 10, and 15 years had been diagnosed in 0.91% (95% CI, 0.89%-0.92%), 1.82% (95% CI, 1.80%-1.84%), and 2.91% (95% CI, 2.88%-2.93%), respectively (Figure 3).

Prior mood disorders—later asthma

For asthma, 192,737 persons were excluded from the study population because they had a diagnosis of asthma before follow-up began (January 1, 2000, or at age 5 years, the minimum age at which a person might develop asthma, whichever came later). The remaining 4,841,117 were considered as "at risk" of incident asthma and were included in the analysis. Of these, 364,063 were ascertained to have asthma for the first time during the follow-up period (from the start of follow-up until an asthma diagnosis, death, emigration, or December 31, 2016, whichever came first).

The risk of asthma for those diagnosed with a mood disorder, compared with those who were not diagnosed with a mood disorder, was increased by 68% (HR, 1.68; 95% CI, 1.64-1.71) (Figure 1 and Table E4). Sex-specific estimates were 1.61 (95% CI, 1.55-1.67) for males and 1.71 (95% CI, 1.67-1.75) for females (Figure E1 and Table E4).

With respect to the pattern of HRs over time since the onset of the prior disorder (lagged HR, Figure 4 and Table E4), the highest HR for asthma was seen at 1 to 2 years following a mood disorder diagnosis (1.84; 95% CI, 1.73-1.96). For females, a similar pattern was observed; however, for males, the risk of asthma was most elevated 15+ years after an asthma diagnosis (1.81; 95% CI, 1.63-2.00) (Figure E3 and Table E4).

Five years after a diagnosis of a mood disorder, 4.51% (95% CI, 4.38%-4.64%) had been ascertained to have asthma. By 10 years, this had increased to 8.45% (95% CI, 8.25%-8.65%), and by 15 years, to 12.35% (95% CI, 12.07%-12.64%). In the matched reference group, mood disorders at 5, 10, and 15 years had been diagnosed in 2.13% (95% CI, 2.09%-2.17%), 4.19% (95% CI, 4.13%-4.26%), and 6.26% (95% CI, 6.17%-6.35%), respectively (Figure 5).

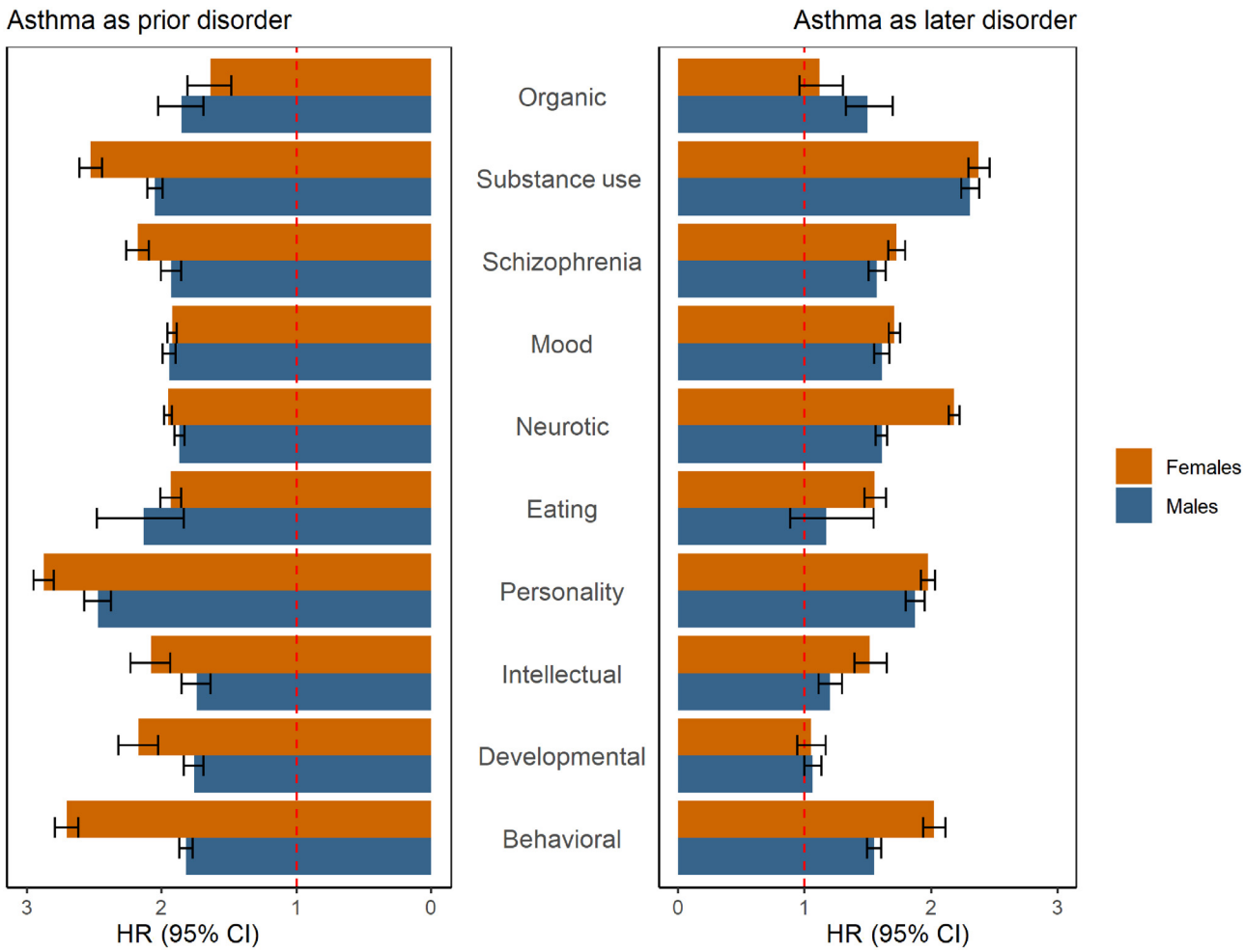

FIGURE E1. Bidirectional HRs for asthma and mental disorders, sex-specific. On the left side of the graph, HRs are shown for subsequent diagnoses of each mental disorder type in males (blue) and females (orange) with prior diagnoses of asthma, compared with those without. On the right side of the graph, HRs are shown for subsequent diagnoses of asthma among males (blue) and females (orange) with prior diagnoses of each mental disorder type, compared with those without.

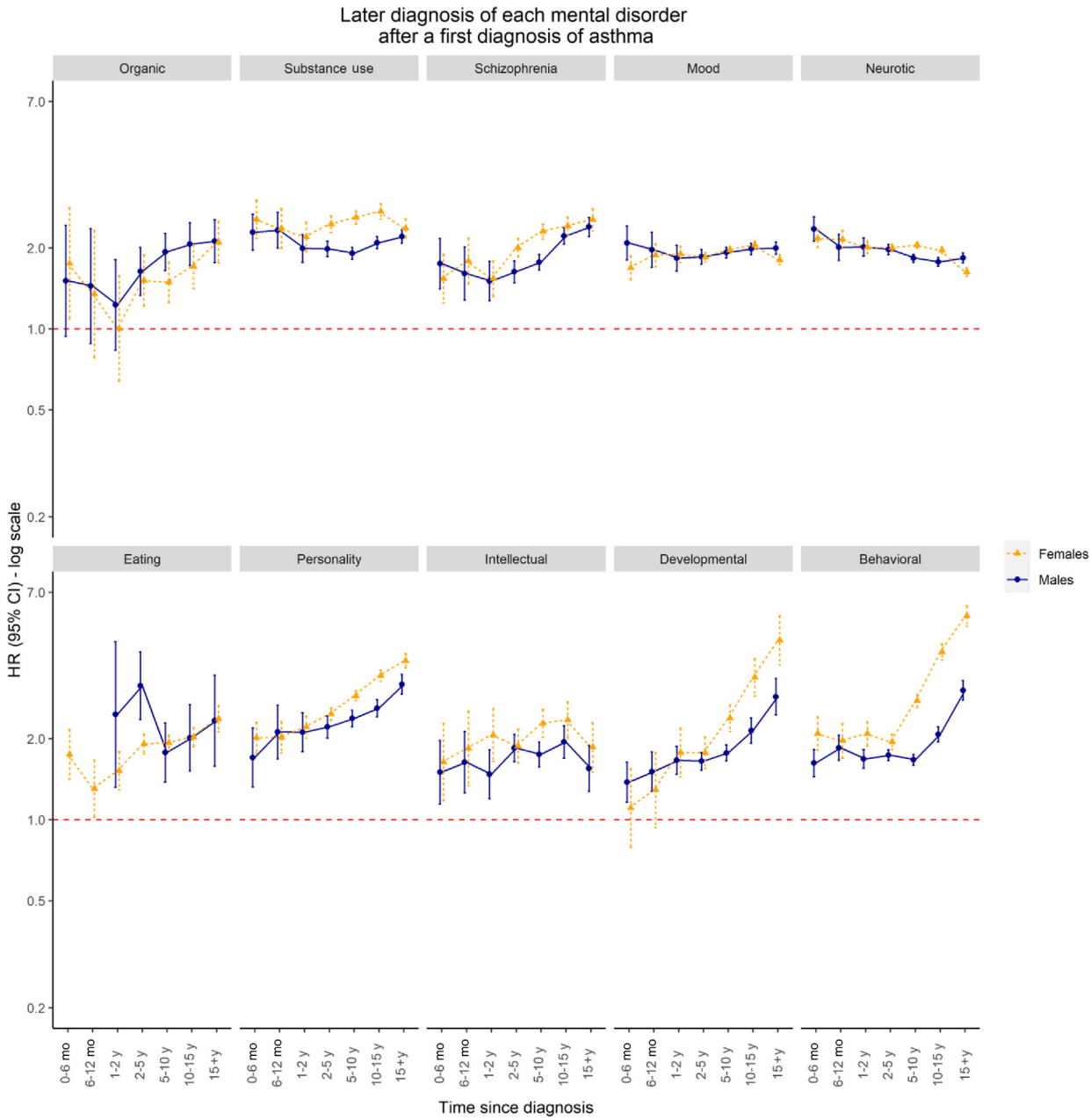

FIGURE E2. Lagged HRs for later mental disorder diagnoses in those with prior diagnoses of asthma, compared with those without, sex-specific.

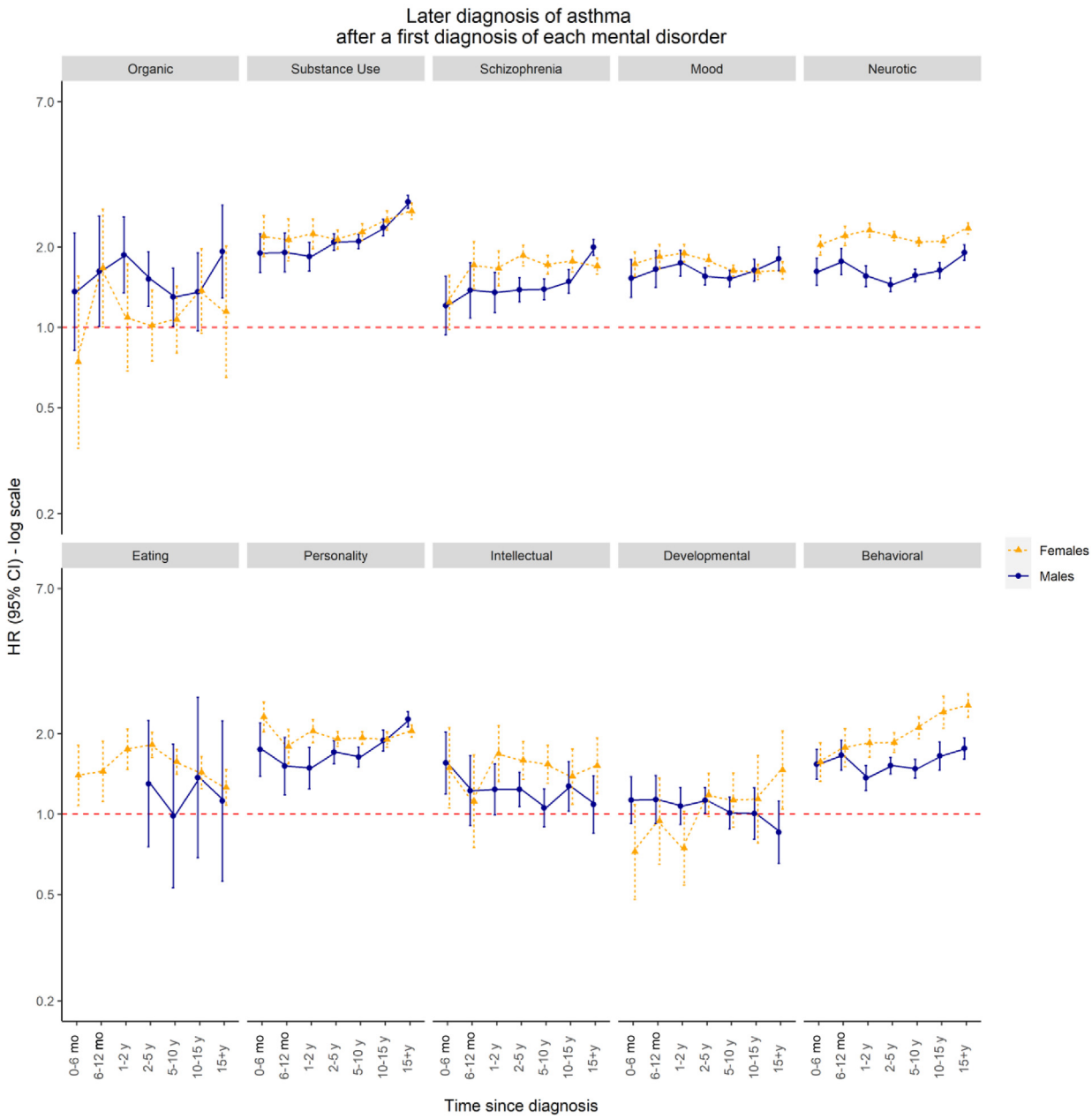

FIGURE E3. Lagged HRs for later asthma diagnoses in those with prior diagnoses of mental disorders, compared with those without, sex-specific.

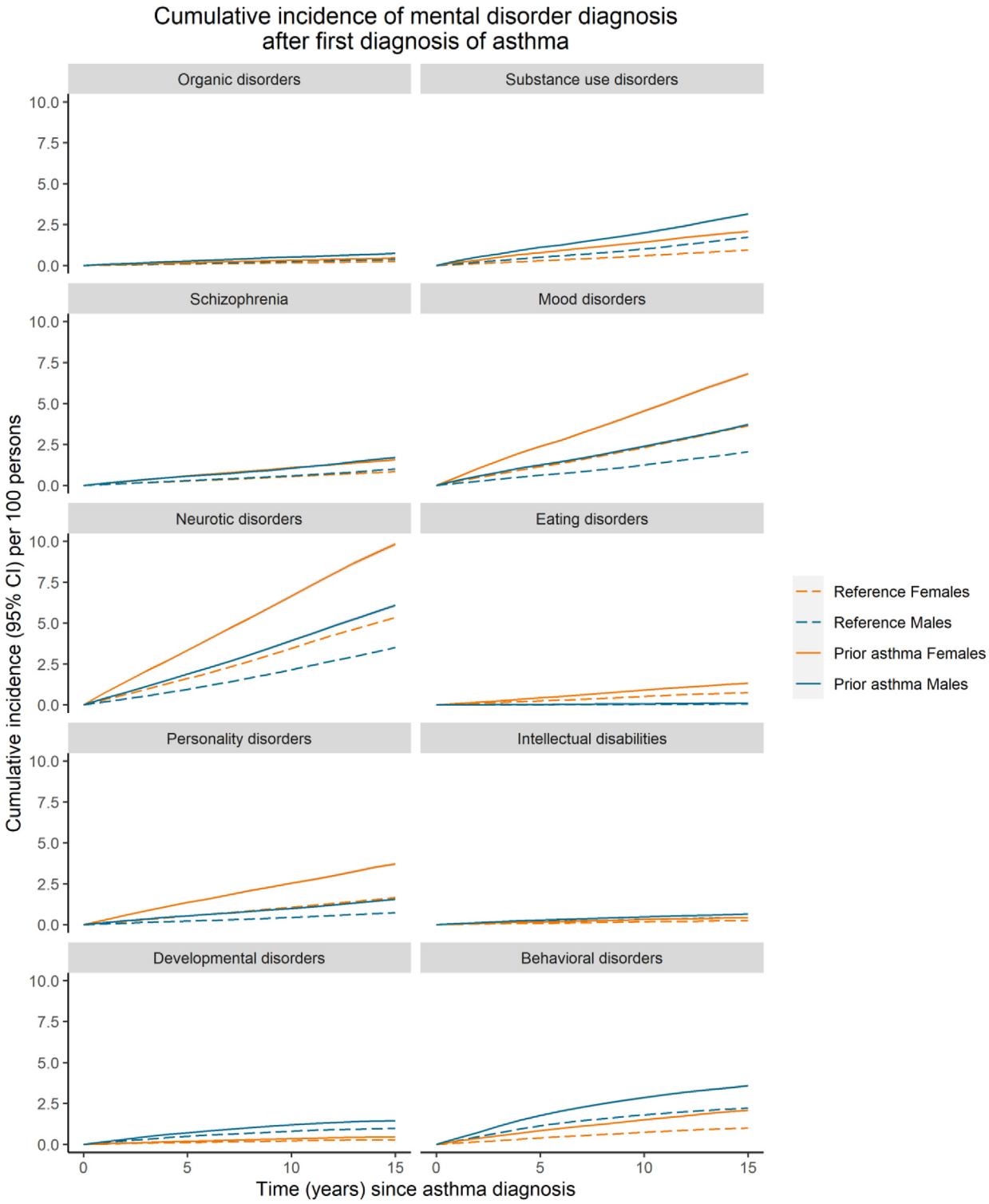

FIGURE E4. Cumulative incidences for prior asthma and later mental disorders, sex-specific. The cumulative incidence per 100 persons of receiving a diagnosis of each later mental disorder of interest, after a diagnosis of the prior diagnosis of asthma, for females (orange, dashed line) and males (blue, solid line). Shaded gray areas around the lines for those with the prior asthma diagnosis represent 95% CIs (in some panels obscured by the estimates line). In addition, in some cases, the line for females is obscured by the line for males. The horizontal axes show the time since first diagnosis of asthma. The vertical axes show the cumulative incidence per 100 persons (and 95% CI).

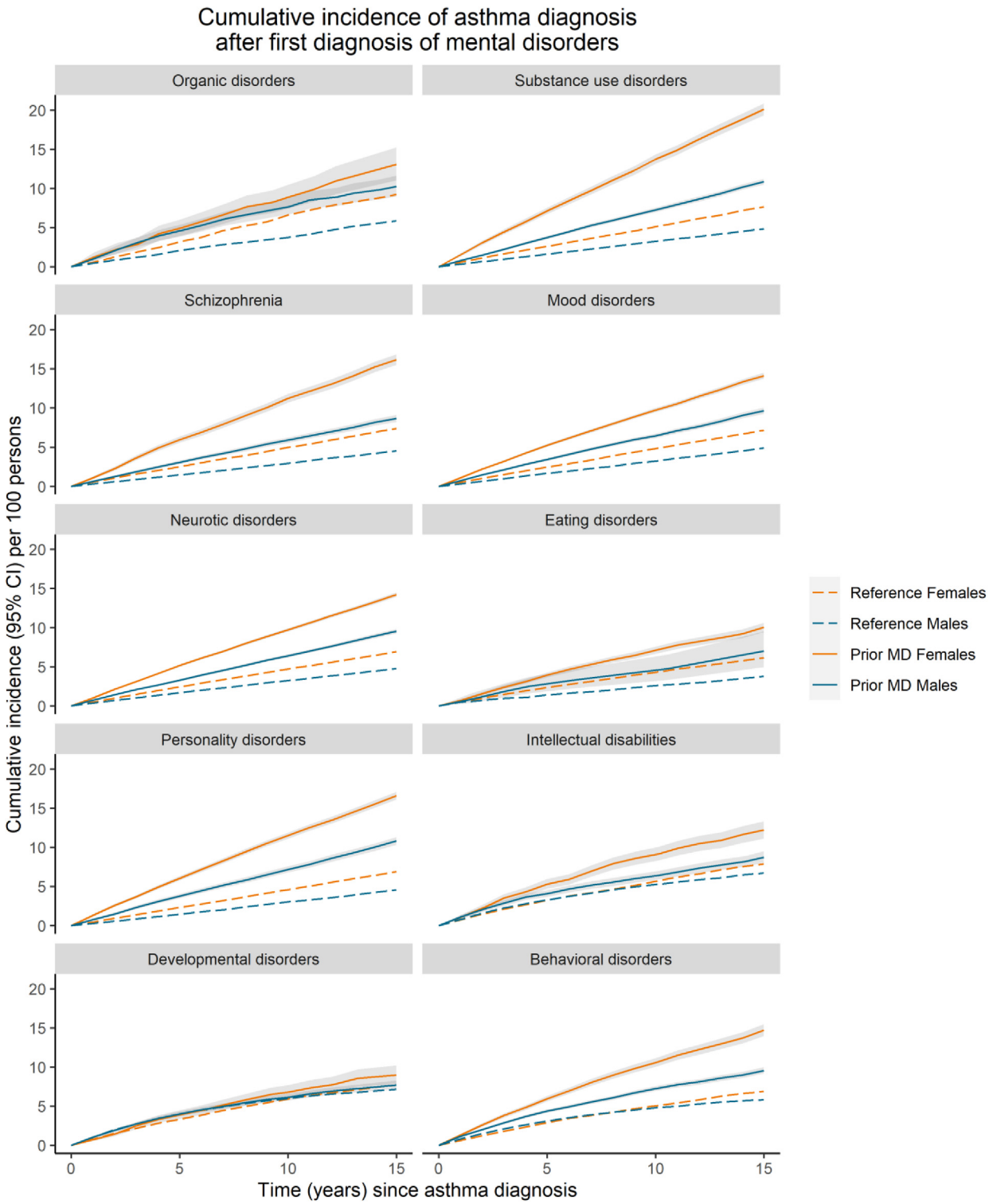

FIGURE E5. Cumulative incidences for prior mental disorders and later asthma, sex-specific. The cumulative incidence per 100 persons of receiving a diagnosis of asthma, after a diagnosis of each prior mental disorder of interest, for females (orange, dashed line) and males (blue, solid line). Shaded gray areas around the lines for those with the prior mental disorder of interest represent 95% CIs (in some panels obscured by the estimates line). The horizontal axes show the time since first diagnosis of the prior mental disorder. The vertical axes show the cumulative incidence per 100 persons (and 95% CI). *MD*, Mental disorder.

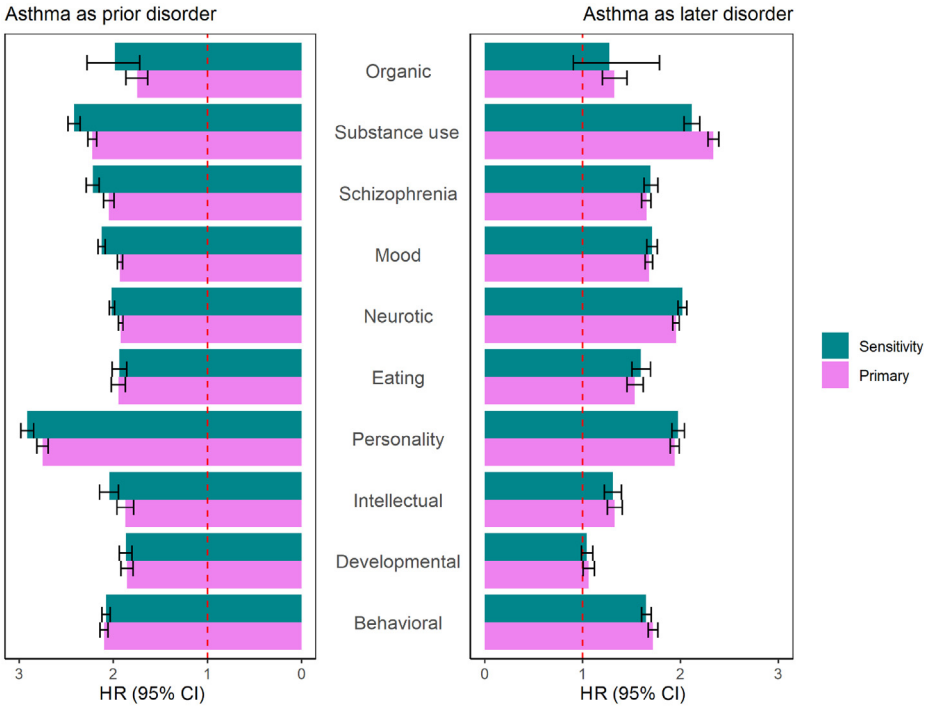

FIGURE E6. Bidirectional HRs for asthma and mental disorders in the primary analysis and sensitivity analysis in individuals younger than 40 years. On the left side of the graph, HRs are shown for subsequent diagnoses of each mental disorder type in those with prior diagnoses of asthma, compared with those without. On the right side of the graph, HRs are shown for subsequent diagnoses of asthma among those with prior diagnoses of each mental disorder type, compared with those without.

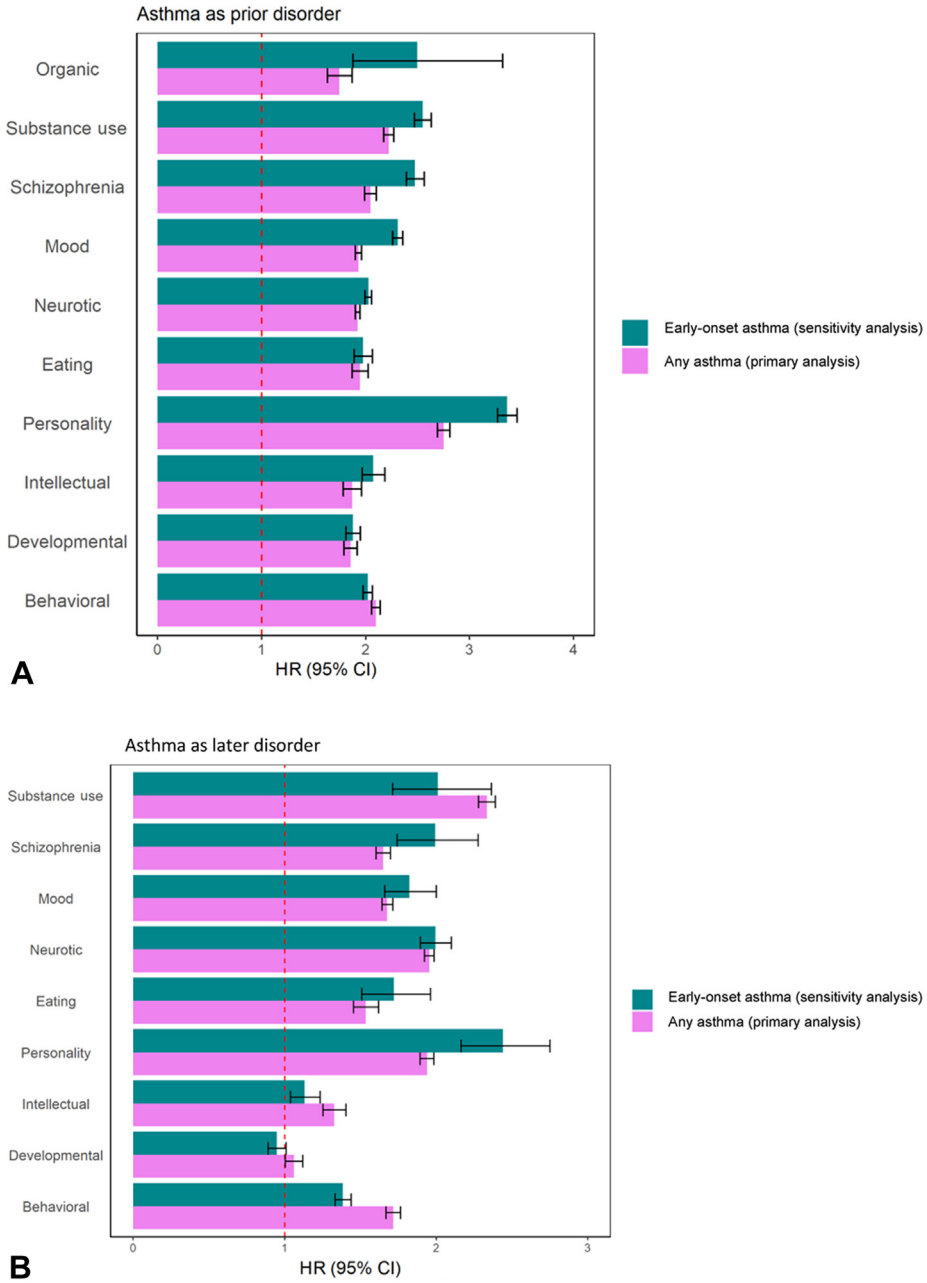

FIGURE E7. HRs for asthma and mental disorders in the primary analysis and sensitivity analysis. (A) Prior asthma. HRs are shown for subsequent diagnoses of each mental disorder type in those with prior diagnoses of asthma, compared with those without. Note that these results are not displayed in the same figures as the results for subsequent childhood asthma diagnoses, due to differences between analyses. (B) Later asthma. HRs are shown for subsequent diagnoses of asthma in those with prior diagnoses of each mental disorder type, compared with those without. Note that these results are not displayed in the same figures as the results for prior childhood asthma diagnoses, due to differences between analyses.

TABLE E1. Diagnostic classification of mental disorders according to the *ICD-10* codes and equivalent *ICD-8* codes

ICD subchapters	Earliest age at onset (y)	*ICD-10* codes	*ICD-8* codes
Organic, including symptomatic, mental disorders Includes dementia in Alzheimer disease, vascular dementia, etc	35	F00-09	290.09, 290.10, 290.11, 290.18, 290.19, 292.x9, 293.x9, 294.x9, 309.x9
Mental and behavioral disorders due to psychoactive substance use Includes use of alcohol, cannabis, cocaine, nicotine, opioids, sedatives, hypnotics, anxiolytics, etc	10	F10-19	291.x9, 294.39, 303.x9, 303.20, 303.28, 303.90, 304.x9
Schizophrenia and related disorders Includes schizophrenia, schizotypal disorders, schizoaffective disorders and other psychotic disorders	10	F20-29	295.x9, 296.89, 297.x9, 298.29-298.99, 299.04, 299.05, 299.09, 301.83
Mood disorders Includes bipolar disorder, depressive disorders, etc	10	F30-39	296.x9 (excluding 296.89), 298.09, 298.19, 300.49, 301.19
Neurotic, stress-related, and somatoform disorders Includes anxiety disorders, phobias, obsessive compulsive disorders, etc	5	F40-48	300.x9 (excluding 300.49), 305.x9, 305.68, 307.99
Eating disorders Includes anorexia nervosa, bulimia nervosa, etc	1	F50	306.50, 306.58, 306.59
Personality disorders Includes paranoid personality disorder, etc	10	F60	301.x9 (excluding 301.19), 301.80, 301.81, 301.82, 301.84
Intellectual disabilities Includes mild to profound mental retardation	1	F70-79	311-315
Developmental disorders Includes autism spectrum disorders	1	F84	299.00, 299.01, 299.02, 299.03
Behavioral disorders Includes attention/deficit hyperactivity disorder, conduct disorders, childhood emotional disorders, etc	1	F90-98	306.x9, 308.0

ICD-8, International Classification of Diseases, Eighth Revision; ICD-10, International Classification of Diseases, Tenth Revision.

TABLE E2. Number of cases of mental disorders and asthma in this study

Diseases	Prevalent cases	Persons at risk*	New cases during follow-up
Any mental disorder	110,767	4,942,704	376,756
Organic disorders	884	2,389,834	6,366
Substance use disorders	24,879	4,652,534	63,002
Schizophrenia	20,990	4,656,423	42,651
Mood disorders	18,489	4,658,924	130,578
Neurotic disorders	42,221	4,991,633	212,055
Eating disorders	4,852	5,048,619	19,992
Personality disorders	28,226	4,649,187	58,403
Intellectual disabilities	3,657	5,049,814	17,248
Development disorders	3,320	5,050,151	31,408
Behavioral disorders	13,630	5,039,841	77,396
Asthma	192,737	4,841,117	364,063

The bold values indicate the overall group.

*The number of persons at risk differs between each type of mental disorder and asthma for 2 reasons: (1) there are different minimum ages at which a person can develop each disorder and only individuals older than the minimum age contributed to the calculation of the risk of later disorder; (2) prevalent cases (ie, people who were diagnosed with the disorder of interest before the start of follow-up) were excluded.

TABLE E3. Baseline characteristics of the study population

Characteristics	N	%
Sex		
Male	2,633,782	52.1
Female	2,419,689	47.9
Country of origin		
Denmark	3,802,612	75.2
Outside Denmark	1,250,859	24.8
Education level at start of follow-up*		
Preschool	1,354,009	14.8
Elementary school	749,067	20.8
High school	1,049,473	4.7
Vocational education	238,023	2.0
Higher education	100,594	26.8
Missing	1,562,305	30.9
Civil status at start of follow-up*		
Single	1,508,526	29.9
Cohabiting	943,381	18.7
Civil partnership	3,616	0.1
Married	2,075,698	41.1
Missing	522,250	10.3
Birth year		
1955-1959	501,987	9.9
1960-1969	953,813	18.9
1970-1979	959,866	19.0
1980-1989	987,534	19.5
1990-1999	870,970	17.2
2000-2011	779,301	15.4

*Year 2000 or first birthday, whichever was later.

TABLE E4. HRs for all pairs

			HR (95% CI)		
Exposure	**Outcome**	**Estimate type**	**All**	**Males**	**Females**
Asthma	Organic	Overall HR	1.75 (1.64-1.87)	1.85 (1.69-2.03)	1.64 (1.49-1.81)
Asthma	Organic	Lagged HR 0-6 mo	1.63 (1.16-2.28)	1.51 (0.94-2.43)	1.75 (1.09-2.82)
Asthma	Organic	Lagged HR 6-12 mo	1.40 (0.97-2.02)	1.45 (0.88-2.36)	1.35 (0.78-2.33)
Asthma	Organic	Lagged HR 1-2 y	1.13 (0.84-1.51)	1.23 (0.83-1.81)	1.00 (0.64-1.58)
Asthma	Organic	Lagged HR 2-5 y	1.58 (1.36-1.84)	1.64 (1.33-2.01)	1.51 (1.22-1.88)
Asthma	Organic	Lagged HR 5-10 y	1.71 (1.52-1.92)	1.93 (1.65-2.27)	1.49 (1.25-1.78)
Asthma	Organic	Lagged HR 10-15 y	1.88 (1.65-2.14)	2.07 (1.72-2.48)	1.71 (1.41-2.06)
Asthma	Organic	Lagged HR 15+ y	2.12 (1.86-2.41)	2.12 (1.77-2.55)	2.10 (1.76-2.51)
Asthma	Substance use	Overall HR	2.22 (2.17-2.27)	2.05 (1.99-2.11)	2.53 (2.44-2.61)
Asthma	Substance use	Lagged HR 0-6 mo	2.40 (2.14-2.68)	2.29 (1.96-2.67)	2.55 (2.17-3.01)
Asthma	Substance use	Lagged HR 6-12 mo	2.33 (2.08-2.61)	2.33 (2.00-2.71)	2.36 (1.99-2.80)
Asthma	Substance use	Lagged HR 1-2 y	2.07 (1.90-2.26)	1.99 (1.77-2.24)	2.20 (1.94-2.50)
Asthma	Substance use	Lagged HR 2-5 y	2.17 (2.07-2.28)	1.98 (1.85-2.12)	2.45 (2.29-2.63)
Asthma	Substance use	Lagged HR 5-10 y	2.17 (2.09-2.25)	1.91 (1.82-2.01)	2.59 (2.45-2.75)
Asthma	Substance use	Lagged HR 10-15 y	2.31 (2.21-2.40)	2.09 (1.99-2.21)	2.74 (2.57-2.92)
Asthma	Substance use	Lagged HR 15+ y	2.25 (2.15-2.36)	2.21 (2.08-2.34)	2.37 (2.18-2.57)
Asthma	Schizophrenia	Overall HR	2.05 (1.99-2.10)	1.93 (1.86-2.00)	2.18 (2.10-2.26)
Asthma	Schizophrenia	Lagged HR 0-6 mo	1.63 (1.40-1.89)	1.75 (1.41-2.17)	1.54 (1.25-1.90)
Asthma	Schizophrenia	Lagged HR 6-12 mo	1.70 (1.47-1.97)	1.61 (1.28-2.01)	1.79 (1.47-2.17)
Asthma	Schizophrenia	Lagged HR 1-2 y	1.52 (1.36-1.7)	1.51 (1.27-1.78)	1.54 (1.32-1.79)
Asthma	Schizophrenia	Lagged HR 2-5 y	1.83 (1.72-1.94)	1.63 (1.49-1.79)	2.00 (1.85-2.17)
Asthma	Schizophrenia	Lagged HR 5-10 y	2.02 (1.93-2.12)	1.77 (1.65-1.90)	2.30 (2.16-2.45)
Asthma	Schizophrenia	Lagged HR 10-15 y	2.30 (2.19-2.42)	2.22 (2.07-2.38)	2.42 (2.24-2.61)
Asthma	Schizophrenia	Lagged HR 15+ y	2.46 (2.31-2.61)	2.40 (2.21-2.60)	2.55 (2.32-2.80)
Asthma	Mood	Overall HR	1.93 (1.9-1.96)	1.94 (1.90-1.99)	1.92 (1.89-1.96)
Asthma	Mood	Lagged HR 0-6 mo	1.80 (1.66-1.96)	2.09 (1.80-2.41)	1.69 (1.52-1.87)
Asthma	Mood	Lagged HR 6-12 mo	1.91 (1.76-2.07)	1.97 (1.70-2.29)	1.88 (1.70-2.07)
Asthma	Mood	Lagged HR 1-2 y	1.88 (1.77-1.99)	1.83 (1.64-2.05)	1.90 (1.77-2.04)
Asthma	Mood	Lagged HR 2-5 y	1.85 (1.79-1.91)	1.85 (1.74-1.97)	1.85 (1.77-1.92)
Asthma	Mood	Lagged HR 5-10 y	1.95 (1.90-2.00)	1.92 (1.84-2.01)	1.97 (1.91-2.03)
Asthma	Mood	Lagged HR 10-15 y	2.03 (1.97-2.09)	1.98 (1.89-2.08)	2.05 (1.98-2.12)
Asthma	Mood	Lagged HR 15+ y	1.88 (1.82-1.94)	2.00 (1.90-2.11)	1.81 (1.73-1.88)
Asthma	Neurotic	Overall HR	1.92 (1.90-1.94)	1.87 (1.83-1.91)	1.95 (1.92-1.98)
Asthma	Neurotic	Lagged HR 0-6 mo	2.23 (2.10-2.37)	2.35 (2.12-2.61)	2.17 (2.01-2.34)
Asthma	Neurotic	Lagged HR 6-12 mo	2.10 (1.98-2.24)	2.01 (1.80-2.25)	2.15 (1.99-2.32)
Asthma	Neurotic	Lagged HR 1-2 y	2.01 (1.92-2.11)	2.02 (1.87-2.18)	2.01 (1.90-2.13)
Asthma	Neurotic	Lagged HR 2-5 y	1.99 (1.94-2.05)	1.98 (1.89-2.06)	2.00 (1.94-2.07)
Asthma	Neurotic	Lagged HR 5-10 y	1.97 (1.93-2.01)	1.83 (1.77-1.89)	2.05 (2.00-2.10)
Asthma	Neurotic	Lagged HR 10-15 y	1.89 (1.85-1.93)	1.78 (1.71-1.85)	1.96 (1.91-2.02)
Asthma	Neurotic	Lagged HR 15+ y	1.71 (1.66-1.76)	1.84 (1.76-1.91)	1.63 (1.57-1.69)
Asthma	Eating	Overall HR	1.94 (1.87-2.02)	2.14 (1.84-2.48)	1.93 (1.85-2.01)
Asthma	Eating	Lagged HR 0-6 mo	1.73 (1.40-2.13)	NA	1.75 (1.42-2.16)
Asthma	Eating	Lagged HR 6-12 mo	1.31 (1.03-1.67)	NA	1.30 (1.02-1.67)
Asthma	Eating	Lagged HR 1-2 y	1.56 (1.33-1.83)	2.46 (1.32-4.59)	1.52 (1.29-1.79)
Asthma	Eating	Lagged HR 2-5 y	1.97 (1.82-2.14)	3.15 (2.36-4.21)	1.91 (1.76-2.08)
Asthma	Eating	Lagged HR 5-10 y	1.92 (1.81-2.05)	1.78 (1.38-2.29)	1.93 (1.81−2.06)
Asthma	Eating	Lagged HR 10-15 y	2.03 (1.87-2.19)	2.02 (1.52-2.68)	2.03 (1.87-2.20)
Asthma	Eating	Lagged HR 15+ y	2.37 (2.13-2.64)	2.34 (1.58-3.45)	2.37 (2.12-2.66)
Asthma	Personality	Overall HR	2.75 (2.69-2.81)	2.47 (2.38-2.58)	2.88 (2.80-2.95)
Asthma	Personality	Lagged HR 0-6 mo	1.93 (1.72-2.18)	1.70 (1.32-2.20)	2.02 (1.77-2.31)
Asthma	Personality	Lagged HR 6-12 mo	2.04 (1.82-2.29)	2.12 (1.68-2.67)	2.02 (1.77-2.32)
Asthma	Personality	Lagged HR 1-2 y	2.18 (2.01-2.37)	2.11 (1.79-2.50)	2.21 (2.02-2.43)
Asthma	Personality	Lagged HR 2-5 y	2.40 (2.29-2.51)	2.22 (2.01-2.44)	2.47 (2.34-2.61)

(continued)

TABLE E4. *(Continued)*

			HR (95% CI)		
Exposure	**Outcome**	**Estimate type**	**All**	**Males**	**Females**
Asthma	Personality	Lagged HR 5-10 y	2.73 (2.64-2.83)	2.38 (2.22-2.55)	2.89 (2.77-3.01)
Asthma	Personality	Lagged HR 10-15 y	3.13 (3.01-3.27)	2.60 (2.41-2.80)	3.43 (3.27-3.60)
Asthma	Personality	Lagged HR 15+ y	3.62 (3.45-3.81)	3.19 (2.93-3.47)	3.90 (3.67-4.14)
Asthma	Intellectual	Overall HR	1.87 (1.79-1.96)	1.74 (1.64-1.85)	2.08 (1.94-2.23)
Asthma	Intellectual	Lagged HR 0-6 mo	1.55 (1.26-1.92)	1.50 (1.15-1.97)	1.64 (1.18-2.29)
Asthma	Intellectual	Lagged HR 6-12 mo	1.72 (1.40-2.10)	1.64 (1.26-2.13)	1.84 (1.34-2.54)
Asthma	Intellectual	Lagged HR 1-2 y	1.70 (1.46-1.98)	1.48 (1.20-1.82)	2.07 (1.65-2.59)
Asthma	Intellectual	Lagged HR 2-5 y	1.86 (1.70-2.04)	1.85 (1.65-2.08)	1.88 (1.62-2.18)
Asthma	Intellectual	Lagged HR 5-10 y	1.95 (1.80-2.11)	1.75 (1.57-1.94)	2.28 (2.03-2.57)
Asthma	Intellectual	Lagged HR 10-15 y	2.11 (1.90-2.34)	1.95 (1.70-2.23)	2.35 (2.02-2.74)
Asthma	Intellectual	Lagged HR 15+ y	1.68 (1.45-1.94)	1.55 (1.27-1.89)	1.86 (1.51-2.30)
Asthma	Developmental	Overall HR	1.85 (1.79-1.92)	1.76 (1.69-1.83)	2.17 (2.03-2.32)
Asthma	Developmental	Lagged HR 0-6 mo	1.31 (1.13-1.53)	1.38 (1.16-1.64)	1.11 (0.79-1.55)
Asthma	Developmental	Lagged HR 6-12 mo	1.46 (1.26-1.69)	1.51 (1.28-1.79)	1.29 (0.93-1.78)
Asthma	Developmental	Lagged HR 1-2 y	1.69 (1.52-1.88)	1.66 (1.48-1.87)	1.78 (1.44-2.19)
Asthma	Developmental	Lagged HR 2-5 y	1.68 (1.57-1.79)	1.65 (1.53-1.78)	1.77 (1.55-2.03)
Asthma	Developmental	Lagged HR 5-10 y	1.91 (1.80-2.02)	1.77 (1.65-1.90)	2.39 (2.13-2.67)
Asthma	Developmental	Lagged HR 10-15 y	2.42 (2.21-2.65)	2.14 (1.92-2.39)	3.38 (2.89-3.97)
Asthma	Developmental	Lagged HR 15+ y	3.30 (2.91-3.75)	2.87 (2.45-3.35)	4.65 (3.77-5.73)
Asthma	Behavioral	Overall HR	2.10 (2.06-2.14)	1.82 (1.77-1.87)	2.71 (2.62-2.79)
Asthma	Behavioral	Lagged HR 0-6 mo	1.78 (1.63-1.95)	1.63 (1.45-1.82)	2.09 (1.81-2.41)
Asthma	Behavioral	Lagged HR 6-12 mo	1.89 (1.73-2.06)	1.85 (1.67-2.06)	1.97 (1.69-2.28)
Asthma	Behavioral	Lagged HR 1-2 y	1.82 (1.71-1.93)	1.68 (1.56-1.82)	2.09 (1.88-2.32)
Asthma	Behavioral	Lagged HR 2-5 y	1.81 (1.74-1.88)	1.74 (1.66-1.82)	1.95 (1.82-2.08)
Asthma	Behavioral	Lagged HR 5-10 y	2.00 (1.93-2.08)	1.67 (1.60-1.75)	2.77 (2.62-2.92)
Asthma	Behavioral	Lagged HR 10-15 y	2.74 (2.61-2.87)	2.08 (1.95-2.22)	4.21 (3.93-4.51)
Asthma	Behavioral	Lagged HR 15+ y	3.89 (3.66-4.14)	3.03 (2.79-3.30)	5.72 (5.25-6.24)
Organic	Asthma	Overall HR	1.32 (1.2-1.46)	1.50 (1.32-1.69)	1.12 (0.96-1.30)
Organic	Asthma	Lagged HR 0-6 mo	1.07 (0.71-1.63)	1.36 (0.82-2.26)	0.74 (0.35-1.55)
Organic	Asthma	Lagged HR 6-12 mo	1.64 (1.16-2.33)	1.62 (1.01-2.61)	1.67 (1.01-2.77)
Organic	Asthma	Lagged HR 1-2 y	1.51 (1.15-1.97)	1.87 (1.35-2.59)	1.09 (0.69-1.73)
Organic	Asthma	Lagged HR 2-5 y	1.28 (1.06-1.55)	1.52 (1.20-1.92)	1.02 (0.75-1.38)
Organic	Asthma	Lagged HR 5-10 y	1.19 (0.99-1.44)	1.30 (1.01-1.66)	1.07 (0.80-1.43)
Organic	Asthma	Lagged HR 10-15 y	1.36 (1.06-1.75)	1.36 (0.97-1.90)	1.37 (0.95-1.97)
Organic	Asthma	Lagged HR 15+ y	1.57 (1.13-2.18)	1.93 (1.29-2.87)	1.14 (0.65-2.02)
Substance use	Asthma	Overall HR	2.33 (2.28-2.39)	2.31 (2.24-2.38)	2.37 (2.29-2.46)
Substance use	Asthma	Lagged HR 0-6 mo	2.03 (1.80-2.29)	1.90 (1.61-2.24)	2.20 (1.84-2.62)
Substance use	Asthma	Lagged HR 6-12 mo	2.00 (1.77-2.27)	1.91 (1.61-2.26)	2.13 (1.78-2.55)
Substance use	Asthma	Lagged HR 1-2 y	2.01 (1.84-2.20)	1.84 (1.63-2.08)	2.24 (1.97-2.55)
Substance use	Asthma	Lagged HR 2-5 y	2.11 (2.00-2.22)	2.09 (1.95-2.24)	2.13 (1.97-2.31)
Substance use	Asthma	Lagged HR 5-10 y	2.17 (2.07-2.28)	2.10 (1.97-2.23)	2.28 (2.12-2.44)
Substance use	Asthma	Lagged HR 10-15 y	2.42 (2.30-2.56)	2.36 (2.20-2.54)	2.51 (2.31-2.73)
Substance use	Asthma	Lagged HR 15+ y	2.86 (2.74-2.99)	2.95 (2.79-3.12)	2.73 (2.54-2.92)
Schizophrenia	Asthma	Overall HR	1.65 (1.60-1.70)	1.57 (1.51-1.64)	1.73 (1.66-1.79)
Schizophrenia	Asthma	Lagged HR 0-6 mo	1.23 (1.03-1.45)	1.21 (0.94-1.55)	1.24 (0.98-1.57)
Schizophrenia	Asthma	Lagged HR 6-12 mo	1.55 (1.33-1.81)	1.38 (1.08-1.75)	1.71 (1.40-2.10)
Schizophrenia	Asthma	Lagged HR 1-2 y	1.51 (1.35-1.70)	1.35 (1.14-1.61)	1.66 (1.43-1.93)
Schizophrenia	Asthma	Lagged HR 2-5 y	1.63 (1.52-1.74)	1.38 (1.25-1.54)	1.86 (1.70-2.03)
Schizophrenia	Asthma	Lagged HR 5-10 y	1.55 (1.46-1.65)	1.39 (1.27-1.52)	1.72 (1.58-1.86)
Schizophrenia	Asthma	Lagged HR 10-15 y	1.63 (1.52-1.74)	1.49 (1.34-1.64)	1.77 (1.62-1.94)
Schizophrenia	Asthma	Lagged HR 15+ y	1.84 (1.75-1.93)	2.00 (1.87-2.14)	1.70 (1.58-1.82)
Mood	Asthma	Overall HR	1.68 (1.64-1.71)	1.61 (1.55-1.67)	1.71 (1.67-1.75)
Mood	Asthma	Lagged HR 0-6 mo	1.66 (1.52-1.82)	1.53 (1.30-1.80)	1.73 (1.55-1.92)

(continued)

TABLE E4. *(Continued)*

Exposure	Outcome	Estimate type	HR (95% CI) All	HR (95% CI) Males	HR (95% CI) Females
Mood	Asthma	Lagged HR 6-12 mo	1.78 (1.63-1.94)	1.65 (1.41-1.94)	1.84 (1.66-2.04)
Mood	Asthma	Lagged HR 1-2 y	1.84 (1.73-1.96)	1.74 (1.56-1.95)	1.90 (1.76-2.04)
Mood	Asthma	Lagged HR 2-5 y	1.71 (1.64-1.78)	1.55 (1.44-1.67)	1.79 (1.70-1.88)
Mood	Asthma	Lagged HR 5-10 y	1.60 (1.53-1.66)	1.52 (1.42-1.64)	1.63 (1.56-1.71)
Mood	Asthma	Lagged HR 10-15 y	1.62 (1.53-1.71)	1.64 (1.49-1.80)	1.61 (1.51-1.72)
Mood	Asthma	Lagged HR 15+ y	1.69 (1.59-1.80)	1.81 (1.63-2.00)	1.64 (1.52-1.76)
Neurotic	Asthma	Overall HR	1.95 (1.92-1.99)	1.61 (1.56-1.65)	2.18 (2.14-2.22)
Neurotic	Asthma	Lagged HR 0-6 mo	1.86 (1.74-2.00)	1.62 (1.44-1.82)	2.03 (1.87-2.22)
Neurotic	Asthma	Lagged HR 6-12 mo	2.02 (1.89-2.17)	1.77 (1.57-1.98)	2.20 (2.02-2.40)
Neurotic	Asthma	Lagged HR 1-2 y	2.01 (1.91-2.11)	1.56 (1.42-1.70)	2.31 (2.18-2.46)
Neurotic	Asthma	Lagged HR 2-5 y	1.89 (1.83-1.96)	1.44 (1.36-1.53)	2.20 (2.11-2.29)
Neurotic	Asthma	Lagged HR 5-10 y	1.89 (1.83-1.94)	1.57 (1.48-1.65)	2.09 (2.02-2.17)
Neurotic	Asthma	Lagged HR 10-15 y	1.92 (1.85-2.00)	1.64 (1.53-1.75)	2.10 (2.00-2.20)
Neurotic	Asthma	Lagged HR 15+ y	2.19 (2.10-2.27)	1.91 (1.78-2.04)	2.35 (2.24-2.46)
Eating	Asthma	Overall HR	1.53 (1.45-1.62)	1.17 (0.89-1.55)	1.55 (1.47-1.64)
Eating	Asthma	Lagged HR 0-6 mo	1.41 (1.09-1.81)	NA	1.40 (1.08-1.81)
Eating	Asthma	Lagged HR 6-12 mo	1.43 (1.11-1.84)	NA	1.45 (1.12-1.88)
Eating	Asthma	Lagged HR 1-2 y	1.70 (1.44-2.02)	NA	1.75 (1.47-2.08)
Eating	Asthma	Lagged HR 2-5 y	1.79 (1.61-1.99)	1.30 (0.76-2.24)	1.82 (1.63-2.02)
Eating	Asthma	Lagged HR 5-10 y	1.54 (1.39-1.72)	0.99 (0.53-1.83)	1.57 (1.41-1.75)
Eating	Asthma	Lagged HR 10-15 y	1.43 (1.25-1.64)	1.37 (0.69-2.74)	1.43 (1.25-1.64)
Eating	Asthma	Lagged HR 15+ y	1.25 (1.08-1.45)	1.12 (0.56-2.24)	1.26 (1.08-1.47)
Personality	Asthma	Overall HR	1.94 (1.89-1.99)	1.87 (1.80-1.95)	1.97 (1.92-2.03)
Personality	Asthma	Lagged HR 0-6 mo	2.15 (1.92-2.40)	1.75 (1.39-2.20)	2.31 (2.03-2.63)
Personality	Asthma	Lagged HR 6-12 mo	1.71 (1.50-1.94)	1.51 (1.18-1.94)	1.79 (1.54-2.08)
Personality	Asthma	Lagged HR 1-2 y	1.88 (1.72-2.05)	1.49 (1.24-1.78)	2.05 (1.85-2.26)
Personality	Asthma	Lagged HR 2-5 y	1.85 (1.75-1.95)	1.71 (1.55-1.89)	1.92 (1.80-2.04)
Personality	Asthma	Lagged HR 5-10 y	1.84 (1.75-1.92)	1.64 (1.50-1.78)	1.93 (1.83-2.04)
Personality	Asthma	Lagged HR 10-15 y	1.90 (1.80-2.00)	1.89 (1.72-2.07)	1.90 (1.78-2.03)
Personality	Asthma	Lagged HR 15+ y	2.13 (2.04-2.22)	2.27 (2.12-2.42)	2.05 (1.94-2.16)
Intellectual	Asthma	Overall HR	1.33 (1.25-1.40)	1.20 (1.11-1.30)	1.52 (1.39-1.65)
Intellectual	Asthma	Lagged HR 0-6 mo	1.53 (1.24-1.89)	1.56 (1.19-2.03)	1.49 (1.05-2.11)
Intellectual	Asthma	Lagged HR 6-12 mo	1.18 (0.93-1.51)	1.22 (0.90-1.66)	1.12 (0.75-1.67)
Intellectual	Asthma	Lagged HR 1-2 y	1.41 (1.20-1.65)	1.24 (0.99-1.54)	1.68 (1.32-2.14)
Intellectual	Asthma	Lagged HR 2-5 y	1.38 (1.23-1.54)	1.24 (1.07-1.44)	1.59 (1.35-1.87)
Intellectual	Asthma	Lagged HR 5-10 y	1.25 (1.11-1.40)	1.06 (0.90-1.24)	1.54 (1.31-1.81)
Intellectual	Asthma	Lagged HR 10-15 y	1.32 (1.13-1.55)	1.27 (1.03-1.58)	1.38 (1.09-1.76)
Intellectual	Asthma	Lagged HR 15+ y	1.27 (1.07-1.51)	1.09 (0.85-1.39)	1.52 (1.19-1.93)
Developmental	Asthma	Overall HR	1.06 (1.00-1.12)	1.06 (1.00-1.13)	1.05 (0.94-1.17)
Developmental	Asthma	Lagged HR 0-6 mo	1.02 (0.85-1.22)	1.13 (0.92-1.38)	0.72 (0.48-1.09)
Developmental	Asthma	Lagged HR 6-12 mo	1.08 (0.90-1.30)	1.13 (0.92-1.40)	0.94 (0.65-1.36)
Developmental	Asthma	Lagged HR 1-2 y	0.99 (0.86-1.14)	1.07 (0.92-1.26)	0.74 (0.54-1.02)
Developmental	Asthma	Lagged HR 2-5 y	1.14 (1.04-1.25)	1.13 (1.01-1.26)	1.18 (0.98-1.42)
Developmental	Asthma	Lagged HR 5-10 y	1.04 (0.92-1.17)	1.01 (0.88-1.16)	1.13 (0.89-1.42)
Developmental	Asthma	Lagged HR 10-15 y	1.04 (0.86-1.25)	1.00 (0.80-1.25)	1.14 (0.78-1.66)
Developmental	Asthma	Lagged HR 15+ y	1.02 (0.83-1.26)	0.86 (0.65-1.12)	1.46 (1.05-2.05)
Behavioral	Asthma	Overall HR	1.72 (1.67-1.77)	1.55 (1.49-1.61)	2.02 (1.93-2.11)
Behavioral	Asthma	Lagged HR 0-6 mo	1.55 (1.40-1.71)	1.54 (1.35-1.75)	1.57 (1.33-1.85)
Behavioral	Asthma	Lagged HR 6-12 mo	1.71 (1.54-1.89)	1.66 (1.46-1.89)	1.78 (1.51-2.09)
Behavioral	Asthma	Lagged HR 1-2 y	1.54 (1.42-1.67)	1.37 (1.23-1.52)	1.85 (1.63-2.09)
Behavioral	Asthma	Lagged HR 2-5 y	1.64 (1.55-1.73)	1.52 (1.42-1.63)	1.85 (1.70-2.02)
Behavioral	Asthma	Lagged HR 5-10 y	1.69 (1.59-1.80)	1.48 (1.36-1.60)	2.11 (1.92-2.31)
Behavioral	Asthma	Lagged HR 10-15 y	1.92 (1.75-2.10)	1.65 (1.46-1.86)	2.41 (2.10-2.77)
Behavioral	Asthma	Lagged HR 15+ y	2.05 (1.92-2.20)	1.76 (1.61-1.93)	2.55 (2.31-2.82)

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