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Family burden of hospital-managed pediatric atopic dermatitis: A nationwide registry-based study

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Declaration of interests:

Dr. Vittrup has received salary from funding associated with this study from Sanofi and Regeneron Pharmaceuticals, Inc. **Dr. Andersen** has received research funding from AP Møller Foundation and the Kgl Hofbundtmager Aage Bang Foundation**. Dr. Droitcourt** has received honoraria from Sanofi-Genzyme. **Dr. Skov** has been a paid speaker for AbbVie, Eli Lilly, Novartis, and LEO Pharma, and has been a consultant or has served on Advisory Boards with AbbVie, Janssen Cilag, Novartis, Eli Lilly, LEO Pharma, UCB, Almirall, and Sanofi. She has served as an investigator for AbbVie, Sanofi, Janssen Cilag, Boehringer Ingelheim, AstraZenica, Eli Lilly, Novartis, Regeneron, and LEO Pharma, and has received research and educational grants from Novartis, Sanofi, Janssen Cilag, and LEO Pharma. **Dr. Egeberg** has received research funding from Pfizer, Eli Lilly, the Danish National Psoriasis Foundation, and the Kgl Hofbundtmager Aage Bang Foundation, and honoraria as consultant and/or speaker from AbbVie, Almirall, Leo Pharma, Samsung Bioepis Co., Ltd., Pfizer, Eli Lilly and Company, Novartis, Galderma, Dermavant, Bristol-Myers Squibb, Mylan, UCB, and Janssen Pharmaceuticals. **Dr. Thyssen** has attended advisory boards for Sanofi-Genzyme, Regeneron, LEO Pharma, Union Therapeutics, Pfizer, AbbVie and Eli Lilly & Co, and received speaker honorarium from LEO Pharma, Regeneron, Abbvie and Sanofi-Genzyme, and been an investigator for Sanofi-Genzyme, Eli Lilly & Co, LEO Pharma, Pfizer and

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Abstract

Background: Parents of children with atopic dermatitis (AD) report reduced quality of life and higher stress level, which could increase risk of psychiatric and pain disorders, and medication use.

Methods: By use of Danish national registries, we identified family members of all first-born Danish children born between January 1st, 1995 and December 31st, 2013 with a hospital diagnosis of AD, matched them 1:10 with family members of children without AD, and followed the cohorts over time.

Results: Mothers of children with hospital-managed AD had higher risk of filling a prescription for medications for depression, anxiety, pain and sleep problems, and of consulting a psychologist, but most associations disappeared after full adjustment. Siblings had higher risk of receiving a diagnosis for adjustment disorder, and fathers showed increased risk of filling a prescription for pain medication and of divorce, in crude but not adjusted models.

Conclusions: The increased risk of study endpoints seen in mothers of children with hospital-managed AD was not explained by pediatric AD alone. Rather, the total burden in these families including parent and child morbidity and socioeconomic resources seem to explain these observations. The burden in families of children with AD may potentially affect the overall management of their child's AD.

Key words: atopic dermatitis, depression, drug prescriptions, family, mental disorders, mothers, pain disorder.

Key message

We showed specific impact on mothers of children with hospital-managed AD, exhibiting increased risk of filling a prescription for medications for depression, anxiety, pain and sleep problems, and of consulting a psychologist. Fewer outcomes were associated with being a father or sibling of a child with hospital-managed AD. Results indicated that various child and parental

sociodemographic and morbidity factors, rather than AD alone, constituted important explanations for the increased burden in the families.

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Introduction

Atopic dermatitis (AD) is a common chronic and relapsing inflammatory skin condition. Children with AD suffer from pruritus and interrupted sleep and require intense daily care with emollients and topical medication[1].

Caring for a child with AD can be a burdensome task. Time spent on daily AD treatment and parental hours of nightly sleep loss due to AD have been estimated to 2-3 hours and 1-2 hours, respectively, depending on AD severity. Surprisingly, the negative impact on families is significantly higher in those with AD children than those with children who have type 1 diabetes[2]. Parents of children with AD also report feelings of guilt, resentment and helplessness[3,4] as well as increased stress levels[1,5], and reduced quality of life[6].

While the body of evidence on AD and parental stress and sleep loss is significant, it is unclear whether this leads to increased morbidity and medication use in parents of children with AD. Most studies have investigated the reverse association on e.g. prenatal mental problems and development of AD in the offspring[7,8] or used self-reported information on investigated outcomes[3,9]. We hypothesized, that disease-associated stress in families could potentially result in increased risk of psychiatric or pain disorders and medication use,[10–12] could negatively affect spousal relationships and reduce the attention to siblings[6].

This registry-based nationwide study investigated whether parents and siblings of children with AD had increased occurrence of psychiatric or pain disorders, medication use, consultations with psychologist or psychiatrists, divorce, or suicide.

Methods

Data sources

Danish national registries linked via a unique personal identification number. In this study we bridge data from the Civil Registration System[13], the Danish National Patient Registry[14], the Danish National Prescription Registry[15], the Danish National Health Service Register[16], the National Causes of Death Registry[17] and the Income Statistics Register[18]. Please see Supplementary Appendix 1 and Supplemental Table 1 for further information.

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Study context

Danish children with AD are initially seen, diagnosed and treated by their general practitioner (GP). The GP can refer patients to a dermatologist if needed, but most Danish AD patients will be followed solely by their GP. Referral to a dermatology hospital department can be initiated by either the GP, dermatologist, allergist or pediatrician and is predominantly for the minority of patients with severe or persistent AD.

Source population

The index children comprised all first-born children, born in Denmark between January 1st, 1995 and December 31st, 2013.

Exposure

From this index population, we identified all children managed with AD (either in- or outpatient) by a hospital physician between January 1st, 1995 and December 31st, 2013.

Study participants

Mothers, fathers and siblings of a child with AD were identified and each matched with ten non-AD family members (family members without a first-born child/older sibling with a hospital diagnostic code of AD) from the general population (Fig 1). For parents, matching was done by birth date (index child) and age at birth of index child (family member). For siblings, we matched on sex (family member), birth date (index child) and age difference (between sibling and index child). Date of AD diagnosis (index child) served as index date for both the AD parents and their ten reference individuals. For siblings, index date was the last of AD diagnosis date (index child) and birth date (family member). Family members were followed until the first of either December 31st, 2018; 18th birthday (index child); death (index child or family member); emigration (family member); or occurrence of an outcome. We required all family members to be resident in Denmark at least two years before index date to ensure adequate time for recording of history of covariates (please see later).

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Outcomes

The outcomes included a hospital diagnosis of depression, anxiety, adjustment disorders, substance abuse or self-harming behavior, a recorded suicide, a filled prescription for antidepressants or anxiolytics, a consultation with a psychiatrist or psychologist, a diagnosis of migraine, other headache syndromes, fibromyalgia, a filled prescription for pain-, sleep- or migraine medication. For parents, divorce was further included as an outcome for those being married at index.

Other variables

Atopic disease (family member) was defined as an International Classification of Diseases 10th revision (ICD-10) diagnostic code of AD/asthma/hay fever/food allergy within two years before index date to study end and was modelled as a time-updated covariate. Atopic comorbidity (index child) was defined as either a diagnosis of asthma/hay fever/food allergy, or minimum two filled prescriptions of drugs for obstructive airway diseases or nasal anti-allergic agents. Please see Supplemental Appendix 1 for further information. Psychiatric disease (index child) was defined as an ICD-10 diagnostic code of depression/anxiety/attention deficit hyperactivity disorder/autism spectrum disorder in the study period and was modelled as a time-updated covariate. Socio-economic status (family member) was determined based on household income at index date and the study population was divided into quintiles. History of outcome (family member) was defined as a diagnostic/prescription/specialty code of that specific outcome until two years before the index date. Having a later child/sibling with AD (family member) was defined as having a subsequently child/younger sibling with a diagnostic code of AD.

Statistical analyses

All analyses were done separately for each family member class (mother, father and sibling).

Summary statistics were generated and expressed as mean and standard deviation (SD) for normally distributed variables, median and interquartile range for non-normally distributed continuous variables and frequencies for categorical. Chi-square tests were performed to compare differences between groups.

Family members with a recent event of outcome, defined as the presence of a diagnostic/prescription/specialty code for that outcome within two years before the index date were excluded in that specific analysis (not regarding suicide and divorce). Reference family members to an excluded AD family member were also excluded.

Number of events, total follow-up time, incidence rate (IR) and 95% confidence interval (CI) were calculated for each outcome.

Cox regression models were conducted to estimate adjusted hazard ratios (HR). Model 1 was adjusted for sex (family member), age at index (family member), atopic disease (family member), psychiatric disease (index child), socioeconomic status (family member), having a later AD child/sibling (family member), and history of outcome (family member). Model 2 was further adjusted for atopic comorbidity (index child). Analyses for divorce were further adjusted for length of marriage at index. The proportional hazards assumption was graphically assessed using log-log plots.

In a sensitivity analysis, we investigated the impact on older siblings of children with hospital-managed AD, by using second-born children as index children, and then identifying their older sibling. Older siblings were followed until the first of either December 31st, 2018, 18th birthday (family member), death (index child or family member), emigration (family member), or occurrence of an endpoint. All other inclusion criteria and covariates were similar to the main analyses.

Due to the high numbers of comparisons and subsequent risk of type I errors, Bonferroni adjustment was used for regression analyses, and p-values <0.00069 were considered statistically significant (Alpha level [0.05] divided by 72 comparisons).

Data management and statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, U.S.A.) and Stata/MP version 15 (StataCorp, College Station, TX, U.S.A.).

This study was approved by the Danish Data Protection Agency (journal number VD-2018-286).

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Results

A total of 5,976 mothers of children with AD, 54,927 non-AD mothers, 5,846 fathers of children with AD, 53,647 non-AD fathers, 6,053 younger siblings of children with AD and 59,489 younger non-AD siblings were included (Fig 1 and Table 1). In both groups, mean maternal age (SD) at index was 31.3 (5.7) years and 33.5 (6.0) years for fathers. The median age (IQR) for siblings at index was 0.0 (0.0-1.1) years. More non-AD family members had Denmark as their country of origin, most pronounced among siblings (86.8% vs. 92.1%, p<0.0001). Slightly more parents of children with hospital-managed AD were in the lowest socioeconomic group compared to non-AD parents (e.g. mothers 21.5% vs. 19.8%, p=0.026). More AD mothers than non-AD mothers had a history of psychiatric outcomes (21.4% vs. 18.7%, p<0.0001) and pain or sleep outcomes (22.8% vs. 20.4%, p<0.0001). For fathers, an equal occurrence of previous psychiatric outcomes (12.7% vs. 12.0%, p=0.095) was found, but a higher proportion of fathers of children with hospital-managed AD had previous pain or sleep outcomes (16.6% vs. 15.2%, p=0.006). Siblings had similar previous occurrences of psychiatric (0.7% vs. 0.5%, p=0.067) and pain or sleep outcomes (both 0.6%, p=0.435). All AD family members had higher occurrence of own atopic disease at index than non-AD family members (2.7% vs. 0.9%, 0.9% vs. 0.5%, 1.2% vs. 0.5%, for mothers, fathers and siblings, respectively, p<0.0001 for all).

For parents of children with hospital-managed AD, IRs per 10,000 person-years were generally higher for most psychiatric, pain, sleep and marital outcomes than non-AD parents (Supplemental Table 2-3). For younger siblings, IRs were similar in the two groups (Supplemental Table 4).

In cox regression models AD mothers (Figs 2-3) showed a slightly increased risk of psychotropic (HR 1.17; 95%CI 1.10-1.24 and 1.22; 95%CI 1.12-1.32, for antidepressants and anxiolytics respectively), pain (HR 1.18; 95%CI 1.13-1.22), migraine (HR 1.16; 95%CI 1.08-1.26) and sleep (HR 1.17; 95%CI 1.09-1.26) medication use, and of seeing a psychologist (HR 1.15; 95%CI 1.09-1.23), which remained significant in the adjusted model (model 1). Only a slightly higher occurrence of opioid use (fully adjusted HR 1.11; 95%CI 1.05-1.18) was seen after further adjusting the model for index child's atopic comorbidities (model 2). Fathers of children with hospital-managed AD(Figs 2-3) had a slightly increased risk of filling a prescription for pain medication (HR 1.08;

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95%CI 1.04-1.14) and of experiencing a divorce (HR 1.16; 95%CI 1.07-1.26) compared to non-AD fathers, however, all associations became non-significant when adjusting the model. Younger AD siblings (Figs 2-3) showed higher risk of receiving a diagnosis for adjustment disorders (HR 1.94; 95%CI 1.36-2.77), which was eliminated in the adjusted models. Absolute event numbers for especially siblings and absolute risks were generally low or moderate, and the excess risk seen in parents of children with hospital-managed AD was less than 8 and 4 events per year per 1,000 AD mothers and fathers, respectively.

In a sensitivity analysis on older siblings, a total of 4,240 older AD siblings and 40,918 older non-AD siblings were included. Median age (IQR) at index was 4.8 years (3.62-6.93). No increased occurrence of any of the examined outcomes was seen, when comparing older AD-siblings to older siblings of non-AD children (data not shown).

Discussion

MAIN FINDINGS

Mothers of Danish children with hospital-managed AD had an increased risk of filling a prescription for medications for depression, anxiety, pain and sleep problems, and of consulting a psychologist compared to non-AD mothers, whereas fewer outcomes were associated with being a father or sibling of a child with hospital-managed AD. Most associations became insignificant in adjusted models, indicating that the index child's coexistence of other atopic diseases, as well as various parental sociodemographic and morbidity factors, constituted important explanations for the increased burden in the families.

INTERPRETATION

Maternal prenatal psychiatric problems have been suggested as a risk factor for AD in the offspring[7,8], but few studies have examined the reverse relationship between child AD and psychiatric symptoms in the mother. Studies have found mothers of AD infants to be more depressive/hopeless and more anxious/overprotective[9], marked depressed mood in 10% of AD mothers[19] and twofold increased depression scores compared to mothers of asthmatic children[3]. While mothers of children with hospital-managed AD in our study exhibited greater risk of filling a prescription for psychotropic, sleep or pain medication and of seeing a psychologist, no

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association was found with hospital-diagnoses of psychiatric or pain disorders, suggesting maternal symptoms to be mild or transient and not leading to specialist-hospital care.

Psychosocial consequences of being the father of an AD child, has been very sparsely investigated. We found, fathers of children with hospital-managed AD to be less impacted by their child's disease than the mother, supported by previous research showing no significant difference in depression scores when comparing fathers of AD and asthmatic children[3], but contradicted by a recently published study finding fathers of children with AD to be more impacted than mothers by their child's AD[20]. Increased risk of pain medication use, and divorce was observed in our study. Marital issues in relation to stress, tiredness, lack of intimacy and financial strain from being parents of an AD child has previously been described[21].

The particular parental focus on the affected child may decrease attention to siblings. A Swedish twin study showed that if one twin had eczema, the other twin was at risk of having depression or anxiety regardless of their own atopic status[22]. And 63% of siblings have been reported losing sleep due to their AD sibling's skin condition[23]. Due to a very limited number of some events in the sibling analyses, estimates must be assessed with great caution as even small changes in event numbers could alter the results. We only identified an association with a diagnosis of adjustment disorders, which disappeared in adjusted models. The conflicting results in relation to the Swedish study is probably due to different collection of outcome information (screening questionnaire vs. ICD-10 diagnosis).

Positive associations were eliminated when adjusting the models for e.g. socioeconomic status and previous morbidity. This observation suggests that the increased burden in families of children with hospital-managed AD can be ascribed not only to the index child's AD, but more importantly to the total morbidity burden, parental health status and possible vulnerability. Many of the maternal associations became non-significant when adjusting the models for index child's atopic comorbidity. The concern regarding this adjustment is, that AD, hay fever, food allergy and allergic asthma may be seen as belonging to the same disease spectrum as they share the same type 2 inflammation and very often co-exist as the atopic triad[24]. A holistic disease understanding would argue against adjustment, since doing so can potentially interfere with measuring the true effect of AD.

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The specific impact on the mother, could be explained by AD affecting children from a very young age, where the mother is normally the primary caregiver. Further, mothers generally rate their child's AD as more severe and the impact on the child's quality of life worse than fathers, though the differences are not statistically significant[25]. Father's quality of life is affected by the child's AD, but a more significant influence is seen in mothers[26].

Successful management of pediatric AD improves sleep and daytime functioning in both children and parents, and the effect is maintained over time[27]. The strongest predictor of adherence to skin-care treatment is a satisfactory doctor-patient (mother) relationship[19], why we must not neglect the importance of building a strong caregiver alliance and offer supportive initiatives. The clinician must try to identify the familial milieu and align with, maybe especially, the mother's situation and expectations. Support and educational programs for AD families may reduce AD-related stress, anxiety, helplessness and disease severity, and have a positive effect on AD families' quality of life and coping[6]. In Danish hospitals, longer consultations, translators and eczema schools are offered to all parents, which could explain the weak risk estimates.

STRENGTHS AND LIMITATIONS

Our ability to combine complete national registries and to crosslink family information is unique. The definition of index child's AD has been validated[28]. Systematic studies validating the psychiatric diagnoses do not exist, however, validation of selected diagnoses, e.g. depression, has been carried out with satisfactory results in this registry[29–31]. The AD study population consists only of family members of AD children seen at a hospital department, where AD families are offered a wide range of educational programs and support, why results cannot necessarily be generalized to other populations seen outside the hospital system or at hospitals with different approaches. Including only hospital-managed AD could cause selection of patients with more severe or persistent disease. However, other factors than disease severity are important, such as ethnicity since families may need more time and translation of information, specific parental demands (e.g. for eczema schools that are only given by hospitals and target all families including those with children who have mild disease), or children who are referred to rule out differential diagnoses or perform patch test. Children from homes with psychiatric challenges could be more prone to receiving a hospital diagnostic code of AD due to e.g. problems complying with

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treatment, supporting a reverse causal pathway. Bonferroni adjustment is a conservative tool to correct for multiple testing, why we might have increased the risk of type 2 errors. For some outcomes, especially regarding siblings, absolute event numbers were low, reducing the precision of the estimates as well as the absolute risk of these events. Further, the magnitude of associations was relatively small, and we cannot rule out that findings could be due to AD families having increased contact with the health care system and thereby receiving earlier diagnoses and treatment of investigated outcomes. Residual confounding is a possible explanation for some of our results, and though we e.g. attempted to adjust for socio-economic status, the available information may not be sufficient to describe resources in the families.

CONCLUSION

Increased risk of psychotropic and other medication use and of seeing a psychologist was seen in mothers of children with AD, but the increased risk did not seem to be explained by pediatric AD alone, but by the total burden in these families including parent and child morbidity and socioeconomic resources. Clinicians should adapt their management, support, expectations and treatment offers to each family, with special focus on the highly burdened ones.

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Table 1. Demographic characteristics of family members of children with atopic dermatitis (AD) and non-AD children

	Mothers			**Fathers**			**Younger siblings**		
	Total	AD children	Non-AD children	Total	AD children	Non-AD children	Total	AD children	Non-AD children
	n = 60,903	n = 5,976	n = 54,927	n = 59,493	n = 5,846	n = 53,647	n = 65,542	n = 6,053	n = 59,489
Sex (male), n (%)							33,647 (51.3)	3,106 (51.3)	30,541 (51.3)
Age at index in years, mean (SD)	31.32 (5.65)	31.29 (5.79)	31.33 (5.63)	33.54 (6.02)	33.55 (6.19)	33.53 (6.00)			
Age at index in years, median (p25, p75)							0 (0-1.11)	0 (0-1.11)	0 (0-1.10)
Country of origin categories (DK), n (%)	55,233 (90.7)	5,264 (88.1)	49,969 (91.0)	54,123 (91.0)	5,200 (88.9)	48,923 (91.2)	60,056 (91.6)	5,256 (86.8)	54,800 (92.1)
Socioeconomic status, n (%)									
Lowest	12,180 (20.0)	1,287 (21.5)	10,893 (19.8)	11,898 (20.0)	1,222 (20.9)	10,676 (19.9)	13,107 (20.0)		
Below average	12,181 (20.0)	1,181 (19.8)	11,000 (20.0)	11,899 (20.0)	1,158 (19.8)	10,741 (20.0)	13,107 (20.0)		
Average	12,181 (20.0)	1,145 (19.2)	11,036 (20.1)	11,899 (20.0)	1,189 (20.3)	10,710 (20.0)	13,107 (20.0)	N/A	
Above average	12,181 (20.0)	1,167 (19.5)	11,014 (20.1)	11,899 (20.0)	1,109 (19.0)	10,790 (20.1)	13,107 (20.0)		
Highest	12,180 (20.0)	1,196 (20.0)	10,984 (20.0)	11,898 (20.0)	1,168 (20.0)	10,730 (20.0)	13,107 (20.0)		
Missing	0 (0.0)			0 (0.0)			7 (0.0)		
Married at index, n (%)	33,431 (54.9)	3,237 (54.2)	30,194 (55.0)	33,266 (55.9)	3,254 (55.7)	30,012 (55.9)			
History of psychiatric outcome, n (%)	11,576 (19.0)	1,278 (21.4)	10,298 (18.7)	7,180 (12.1)	745 (12.7)	6,435 (12.0)	348 (0.5)	42 (0.7)	306 (0.5)
History of pain or sleep disorder, n (%)	12,538 (20.6)	1,360 (22.8)	11,178 (20.4)	9,131 (15.4)	969 (16.6)	8,162 (15.2)	418 (0.6)	34 (0.6)	384 (0.6)
Family member's AD, asthma, hay fever, food allergy at index, n (%)	659 (1.1)	159 (2.7)	500 (0.9)	313 (0.5)	54 (0.9)	259 (0.5)	359 (0.5)	74 (1.2)	285 (0.5)
Index child's asthma, hay fever, food allergy at index, n (%)	3,223 (5.3)	833 (13.9)	2,390 (4.4)	3,094 (5.2)	812 (13.9)	2,282 (4.3)	5,657 (8.6)	1,987 (32.8)	3,710 (6.2)
Index child's depression, anxiety, ADHD, ASD at index, n (%)	96 (0.2)	23 (0.4)	73 (0.1)	98 (0.2)	23 (0.4)	75 (0.1)	129 (0.2)	26 (0.4)	103 (0.2)

AD = atopic dermatitis; n = number; p25 = 25th percentile; p75 = 75th percentile; SD = standard deviation, DK = Denmark, ADHD = Attention deficit hyperactivity disorder, ASD = autism spectrum disorder, 'History of' = a diagnostic/prescription/specialty code until two years before the index date, psychiatric outcomes include diagnosis of depression, anxiety, adjustment disorders, substance abuse or self-harming behavior, prescription of antidepressants or anxiolytics, consulting a psychiatrist or psychologist, pain or sleep disorder include a diagnosis of migraine, other headache syndromes, fibromyalgia, or filling a prescription of migraine, sleep or pain medication.

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Figure legends

Figure 1. Flow diagram of formation of study population.

Having AD: Index child had ICD-10 L20 code between January 1st, 1995 and December 31st, 2013. Remaining population: Index child did not have ICD-10 L20 code between January 1st, 1995 and December 31st, 2013. Matching: by index child's birth date and parent's age at birth of index child (for parents) and family member's sex, index child's birth date and age difference between sibling and index child (for siblings). AD = atopic dermatitis.

Figure 2. Forest plot of crude, adjusted and fully adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for psychiatric diagnoses, suicide and psychotropic medication use comparing family members of atopic dermatitis (AD) children to family members of non-AD children according to family member.

The 'adjusted' model was adjusted for sex (family member), age at index (family member), atopic disease (family member), psychiatric disease (index child), socioeconomic status (family member), having a later AD child/sibling (family member), and history of outcome (family member). The 'fully adjusted' model was further adjusted for atopic comorbidity (index child). Analyses for divorce were further adjusted for length of marriage at index. Significance after Bonferroni correction is marked by *. HR = hazard ratio; CI = confidence interval.

Figure 3. Forest plot of crude, adjusted and fully adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for consultations with a mental health professional, pain disorders, medication use and divorce comparing family members of atopic dermatitis (AD) children to family members of non-AD children according to family member.

The 'adjusted' model was adjusted for sex (family member), age at index (family member), atopic disease (family member), psychiatric disease (index child), socioeconomic status (family member), having a later AD child/sibling (family member), and history of outcome (family member). The 'fully adjusted' model was further adjusted for atopic comorbidity (index child). Analyses for divorce were further adjusted for length of marriage at index. Significance after Bonferroni correction is marked by *. HR = hazard ratio; CI = confidence interval.

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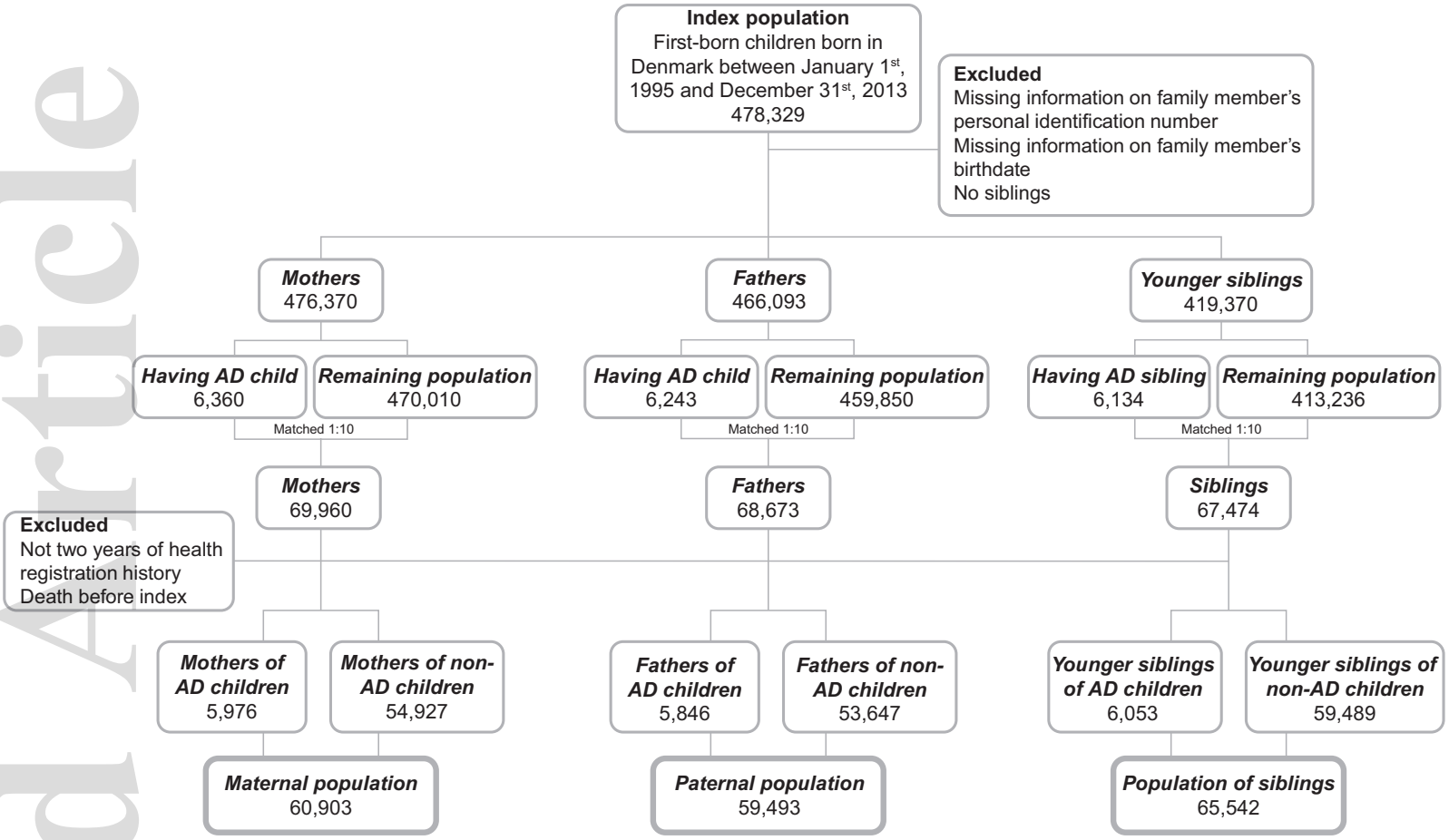

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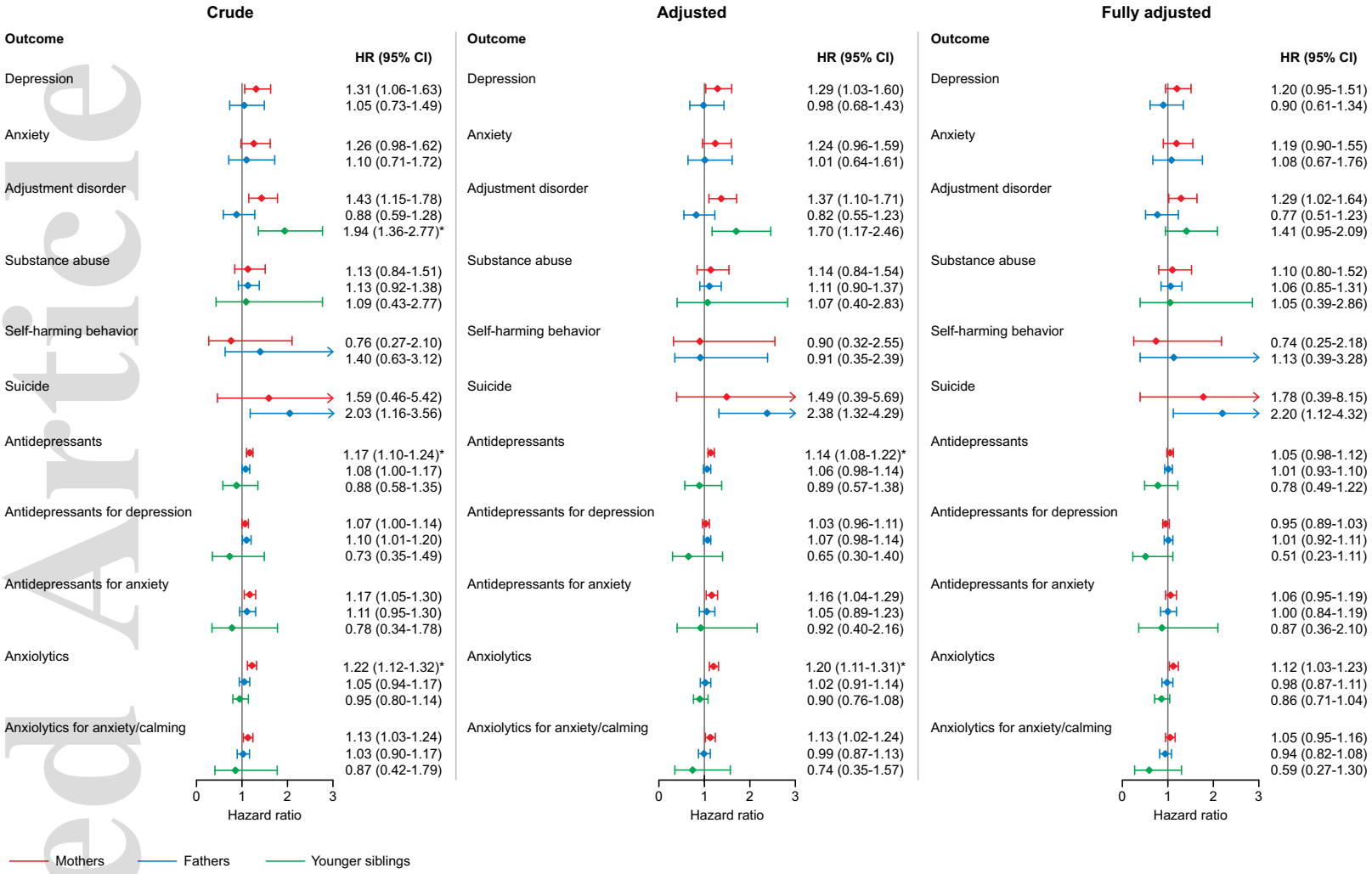

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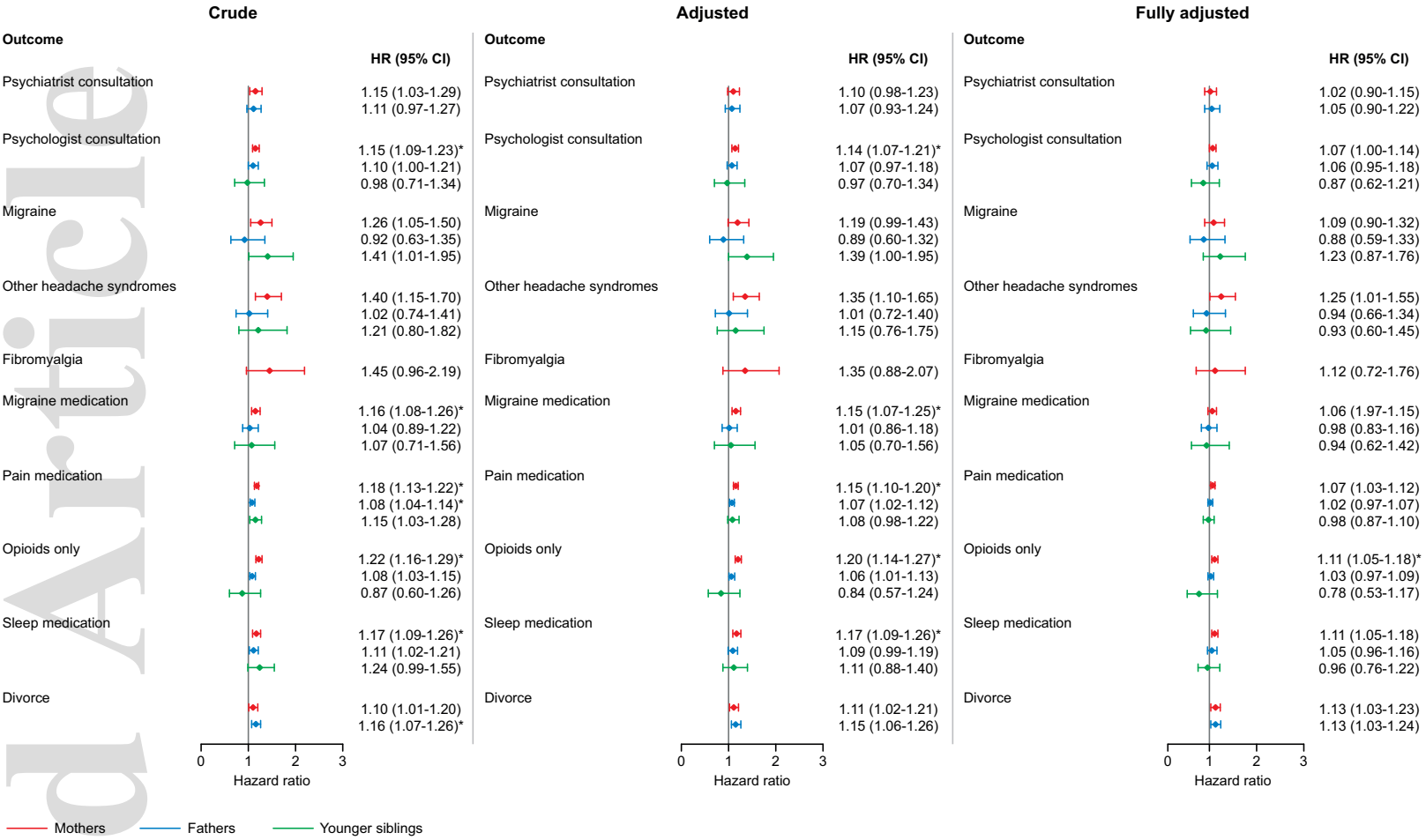

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