

Association of Childhood Atopic Dermatitis With Atopic and Nonatopic Multimorbidity

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Background: Little is known about the impact of multimorbidity in childhood atopic dermatitis (AD).

Objective: We sought to determine the likelihood and predictors of chronic disease multimorbidity in childhood AD.

Methods: Data were examined for children (<18 years) in the 1996–2015 Medical Expenditure Panel Survey, an annual, representative sample of United States households. Multimorbidity was assessed using Charlson Comorbidity Index (CCI), Healthcare Utilization Project Chronic Comorbidity Indicator (HCUP-CCI) and frequency of atopic comorbidities.

Results: Young children with mild-moderate and severe AD, and adolescents with mild-moderate AD had higher CCI scores. Similarly, young children and adolescents with mild-moderate and severe AD had increased HCUP-CCI scores. Children with AD and atopic disease had higher CCI and HCUP-CCI scores than children with either alone. Young children and adolescents with mild-moderate and severe AD had more atopic comorbidities.

Conclusions: Pediatric AD is associated with increased atopic and non-atopic multimorbidity. Comorbid atopic disease may identify a subset of children with AD who particularly benefit from enhanced screening and management of multimorbidity.

Atopic dermatitis (AD) or eczema is a chronic, pruritic condition that affects an estimated 13% of US children.¹ In previous studies, childhood AD was found to be associated with numerous individual comorbidities,² including depression,³ extracutaneous infection,⁴ cardiovascular risk factors,^{5,6} and poorer quality of life.^{1,7} In particular, more severe AD is associated with even higher rates of asthma, atopic disease (such as hay fever, food allergy, and eosinophilic esophagitis), and impaired sleep.¹ Many of these comorbidities co-occur in patients, a phenomenon called multimorbidity.

Multimorbidity is particularly important because it is associated with higher health care costs, poorer quality of life, and increased mortality, compared with individual comorbidities.⁸

Previous studies showed increased multimorbidity in adults with AD.^{9,10} However, little is known about the rates of multimorbidity in pediatric AD. Understanding the role of multimorbidity has significant clinical ramifications for the evaluation and management of children with AD and improving clinical decision making. We hypothesized that pediatric AD is associated with atopic and nonatopic multimorbidity, particularly among those with severe AD. In addition, we hypothesized that children with AD and 1 or more comorbid atopic diseases or mental health disorders have even higher rates of multimorbidity than those with AD alone. In the present study, we examined the association of childhood AD with multimorbidity.

METHODS

Data Source

Data were analyzed from the 1996–2015 Medical Expenditure Panel Survey (MEPS), a cross-sectional, representative survey of approximately 15,000 US households conducted annually by the Agency for Healthcare Research and Quality. Computer-assisted personal interviewing technology was utilized. Interviews were conducted in English or Spanish. Data in the MEPS included sociodemographic characteristics, clinical diagnoses and procedure codes, and details on person-level functional status.

The complex survey structure and sample weights provided by MEPS allowed for representative estimates of the US civilian

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J.I.S. had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

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noninstitutionalized population.¹¹ This study was approved by the Northwestern University Institutional Review Board. The study protocol and analysis were conducted in accordance with all the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.¹²

Identification of AD

This study examined children (age <18 years) with AD. Children with a diagnosis of AD were identified by *International Classification of Diseases, Ninth Edition, Clinical Modification* (ICD-9-CM) codes 691 and 692. Clinical diagnoses reflected in interview transcripts were translated into ICD-9-CM codes by professional coders.

No clinician-reported (eg, eczema area and severity index) or patient-reported (eg, patient-oriented eczema measure) measures of AD severity were included in MEPS. Therefore, children with AD were determined to have severe disease if they had been prescribed high-potency topical corticosteroids or systemic therapy (azathioprine, cyclosporine, methotrexate, mycophenolate, and systemic corticosteroids) for AD, consistent with the severity stratification method in previous studies.^{10,13} All other children with AD without these prescriptions were considered to have mild-moderate AD. Prescribed medications were recorded in MEPS using National Drug Codes assigned by the US Food and Drug Administration. The National Drug Codes for each medication were identified by querying the US Food and Drug Administration directory.

Multimorbidity

Multimorbidity burden was first assessed using the Charlson Comorbidity Index (CCI), a scoring system developed to assess 1-year mortality.¹⁴ Charlson Comorbidity Index allows for patient comparison based on ICD diagnostic codes. Specifically, we used the version adapted for use with administrative databases.^{15,16} Weighted scores¹⁻⁶ were assigned to 17 different medical diagnoses (ie, myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, ulcer disease, mild and severe liver disease, hemiplegia, renal disease, diabetes, tumor, leukemia, lymphoma, and metastatic solid tumor) based on strength of association with mortality. A total index was calculated as the summation of the weighted scores, such that a higher score indicates greater comorbidity burden. Charlson Comorbidity Index is not calibrated for children but provides valuable insight into multimorbidity of conditions specifically associated with 1-year mortality.

Multimorbidity was also identified using a comprehensive list of ICD-9-CM codes determined by a panel of general pediatricians to constitute pediatric chronic conditions.¹⁷ This list was later adapted by the AHRQ to comprise the Healthcare Cost and Utilization Project–Chronic Comorbidity Indicator (HCUP-CCI). Briefly, the Clinical Classification Software developed by the AHRQ was used to aggregate diagnoses into clinically homogeneous groups and determine the number of unique chronic comorbidities. The total number of unique conditions was the HCUP-CCI score.

The ICD-9-CM codes were used to identify atopic multimorbidity, including sinusitis, rhinitis, allergic rhinitis, nasal polyps, conjunctivitis, asthma, chronic bronchitis, allergic alveolitis, anaphylaxis, angioedema, urticaria, and eosinophilic esophagitis.

Statistical Analysis

Summary statistics were generated to describe the sociodemographics of those children with versus without AD. Weighted frequencies, prevalences, and 95% confidence intervals (CIs) of number of chronic conditions were reported among those with mild-moderate or severe AD versus no AD. Weighted frequencies, prevalences, and 95% CIs of sociodemographics were reported among those with versus without AD. Rao-Scott χ^2 tests were used to evaluate the association of sociodemographics with AD. The most common CCI and HCUP-CCI comorbidities were identified.

Weighted frequency and prevalence of AD were overall estimated for children 11 years or younger and older than 11 years and those with mild or severe AD. Linear regression models were constructed with CCI or HCUP-CCI scores or with the number of atopic comorbidities as dependent variables and severity of AD as the independent variables. Models included sex as a covariable. Least squares mean (LSM) and 95% CI of CCI and HCUP-CCI scores were estimated. Two-way interactions of AD with depression, anxiety, or atopic disease (yes/no) were examined to determine if these comorbidities were particularly associated with multimorbidity.

All statistical analyses were performed using survey weights, strata, and clustering to generate nationally representative estimates in SAS (version 9.4; SAS Institute, Cary, NC). Complete case analysis was performed. The Benjamini and Hochberg method was used to minimize the false discovery rate ($k = 62$); adjusted P values are presented. A 2-sided adjusted P value of less than 0.05 was considered statistically significant.

RESULTS

Population Characteristics

There were 135,272 (weighted frequency: 1,156,240,349) children in the 1996–2015 MEPS, of which 4385 (weighted: 38,817,925) had a reported diagnosis of AD. Atopic dermatitis was associated with age, race/ethnicity, US census region, and type of insurance coverage (Rao-Scott χ^2 test, $P \leq 0.002$) (Supplemental Table 1, <http://links.lww.com/DER/A41>).

CCI Scores

In young children (aged ≤ 11 years), the CCI scores were significantly higher in those with mild-moderate AD (multivariable survey linear regression; LSM, 0.13 vs 0.10; adjusted β [95% CI], 0.03 [0.01–0.05]; $P = 0.0009$) and severe AD (0.21 vs 0.10; 0.11 [0.05–0.17]; $P = 0.0004$) compared with those without AD. However, in adolescents, the mean CCI scores were significantly increased in those with mild-moderate AD (0.17 vs 0.12; 0.05

[0.01–0.09]; $P = 0.04$) and not significantly higher in those with severe AD (0.17 vs 0.12; 0.05 [–0.05–0.14]; $P = 0.34$) compared with those without AD. Overall, diagnosis of AD was associated with higher CCI scores, similar to other common chronic disorders, including acne, asthma, anxiety, and depression (Fig. 1).

Significant 2-way statistical interactions were observed between AD and 1 or more comorbid atopic diseases as predictors of higher CCI score ($P = 0.0004$). Atopic dermatitis and 1 or more comorbid atopic diseases were associated with increased LSMs of CCI scores (0.28) compared with children with AD (0.06) or atopic disease (0.22) alone (both $P < 0.0001$; Fig. 2). Surprisingly, no significant interactions were observed for AD with depression ($P = 0.69$) or anxiety ($P = 0.10$) as predictors of higher CCI scores.

The most common CCI diagnoses were chronic pulmonary disease (13.3% [11.8%–14.7%]) and diabetes (0.3% [0.0%–0.7%]) in children with AD.

HCUP-CCI Comorbidity Scores

In models adjusted for sex, HCUP-CCI scores were significantly increased in young children with mild-moderate AD (LSM, 0.44 vs 0.31; adjusted β [95% CI], 0.13 [0.09–0.16]; $P < 0.0001$) and severe AD (0.56 vs 0.31; 0.25 [0.12–0.37]; $P = 0.0002$). Comorbidity burden was significantly increased in adolescents with mild-moderate AD (0.53 vs 0.38; 0.15 [0.05–0.24]; $P = 0.002$) and in adolescents with severe AD (0.60 vs 0.38; 0.22 [0.04–0.41]; $P = 0.03$) (Table 1). Children with AD had increased HCUP-CCI scores, similar to other common chronic disorders, including psoriasis and asthma (Fig. 1).

Moreover, there were significant 2-way statistical interactions between AD and 1 or more comorbid atopic diseases as predictors of HCUP-CCI scores ($P < 0.0001$). Children with AD and 1 or more comorbid atopic diseases had higher overall HCUP-CCI scores (0.83) than with either AD (0.12) or 1 or more atopic diseases (0.59) alone (both $P < 0.0001$, Fig. 2). There were no significant

interactions of AD with depression ($P = 0.87$) or anxiety ($P = 0.23$) as predictors of HCUP-CCI scores.

The most frequent HCUP-CCI diagnoses among children with AD were allergic rhinitis (15.8% [14.2%–17.4%]), asthma (13.3% [11.8%–14.7%]), and disease of the esophagus (2.1% [1.5%–2.7%]) (Supplemental Table 2, <http://links.lww.com/DER/A42>).

Atopic Multimorbidity

In young children, mild-moderate AD (LSM, 0.79 vs 0.64; adjusted β [95% CI], 0.14 [0.09–0.19]; $P < 0.0001$) and severe AD (0.88 vs 0.64; 0.24 [0.08–0.41]; $P = 0.005$) had significantly more atopic comorbidities. Similarly, in adolescents, mild-moderate AD (0.58 vs 0.51; 0.08 [0.01–0.15]; $P = 0.05$) and severe AD (0.78 vs 0.51; 0.28 [0.07–0.48]; $P = 0.01$) were associated with increased atopic comorbidities. Young children with AD had more atopic comorbidities than did adolescents with AD (0.79 vs 0.61; 0.18 [0.10–0.26]; $P < 0.0001$). Moreover, children with mild-moderate or severe AD had numerically more atopic comorbidities than children with psoriasis, acne, anxiety, depression, or without AD (Fig. 1).

Comparison of Comorbidity Profiles

There was notable overlap in children with AD and high comorbidity burden (≥ 2) as measured by CCI and HCUP-CCI scores and number of atopic comorbidities (Fig. 3). Of those with a high comorbidity burden for any of the 3 scores, 2.8% (95% CI, 2.0%–3.6%) had high CCI, 48.3% (44.4%–52.3%) had high HCUP-CCI, and 84.8% (82.1%–87.5%) had atopic disease burden; 0.8% (0.1%–1.5%) had both high CCI and HCUP-CCI burden, 0.4% (0.0%–0.8%) had high CCI and atopic disease burden, and 34.7% (31.1%–38.8%) had high HCUP-CCI and atopic disease burden. Moreover, 0.2% (0.0%–0.5%) of children with AD had high CCI, HCUP-CCI, and atopic disease burden.

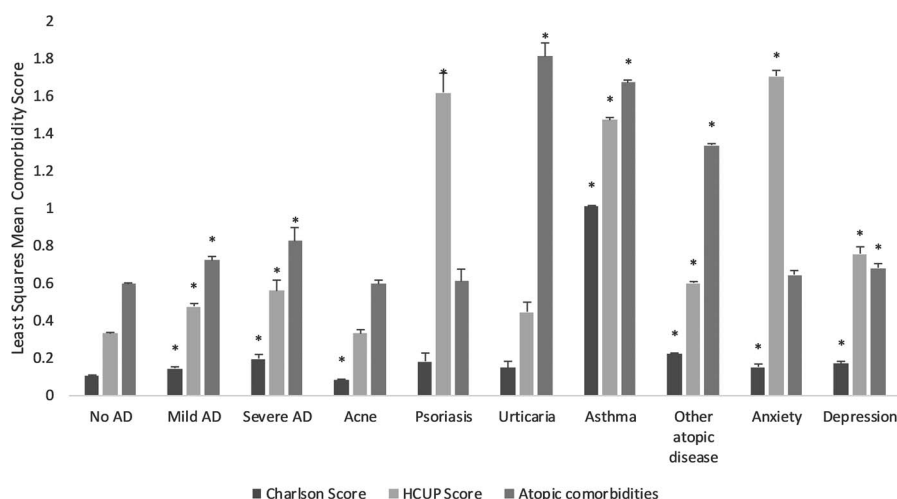


Figure 1. Charlson Comorbidity Index, HCUP-CCI, and atopic comorbidity scores for children with AD and other common chronic conditions. Least squares mean scores adjusted for age and sex are presented. Asterisk indicates significance at $P < 0.05$ level.

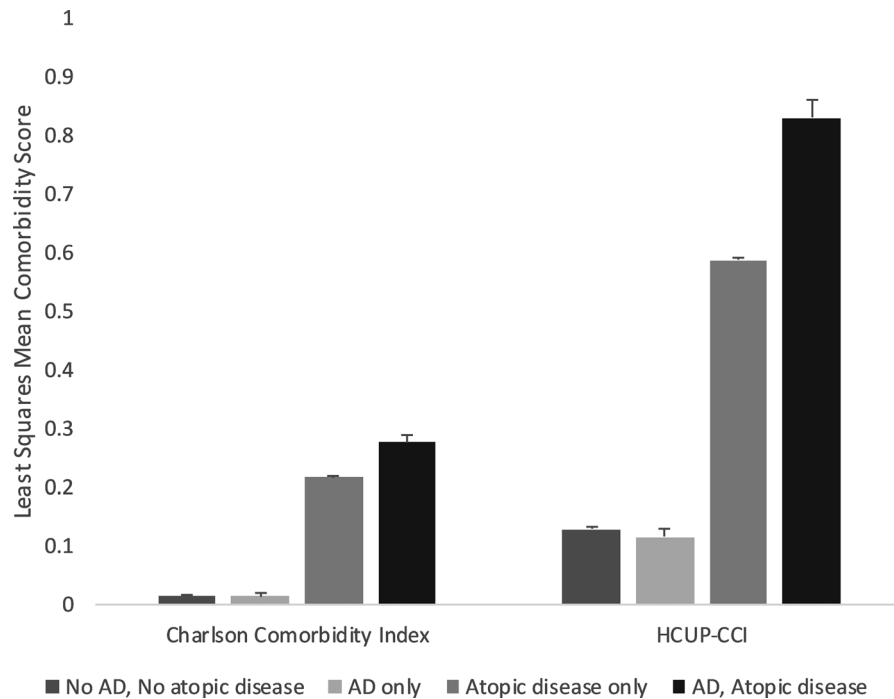


Figure 2. Interactions of AD and atopic disease as predictors of CCI and HCUP-CCI scores. Least squares mean scores adjusted for age and sex are presented.

TABLE 1. HCUP-CCI Score Among Children Aged 11 and 12–17 Years With or Without AD

HCUP-CCI	No AD		Mild-Moderate AD		Severe AD	
	Weighted Frequency (Prevalence [95% CI])		Weighted Frequency (Prevalence [95% CI])		Weighted Frequency (Prevalence [95% CI])	
Age ≤ 11 y						
0	561,376,713 (75.6 [75.1–76.1])		18,496,020 (68.1 [65.8–70.5])		1,632,499 (61.0 [54.0–68.0])	
1	142,736,334 (19.2 [18.8–19.7])		6,176,029 (22.7 [20.6–24.9])		707,679 (26.4 [20.4–32.5])	
2	30,709,563 (4.1 [3.9–4.3])		1,954,088 (7.2 [5.8–8.6])		225,722 (8.4 [4.6–12.3])	
≥3	7,888,288 (1.1 [0.9–1.2])		523,944 (1.9 [1.2–2.7])		109,946 (4.1 [1.3–6.9])	
	Mean index (95% CI)	Mean index (95% CI)	Adjusted β (95% CI)	P	Mean index (95% CI)	Adjusted β (95% CI)
	0.31 (0.30–0.32)	0.44 (0.40–0.47)	0.13 (0.09–0.16)	<0.0001	0.56 (0.43–0.68)	0.25 (0.12–0.37)
						0.0002
	Weighted Frequency (Prevalence [95% CI])		Weighted Frequency (Prevalence [95% CI])		Weighted Frequency (Prevalence [95% CI])	
Age 12–17 y						
0	264,943,551 (70.7 [70.0–71.4])		4,990,858 (66.1 [61.8–70.5])		862,195 (59.6 [48.9–70.4])	
1	84,371,485 (22.5 [22.0–23.1])		1,612,225 (21.4 [17.6–25.1])		368,140 (25.5 [16.2–34.8])	
2	19,923,816 (5.3 [5.0–5.6])		625,215 (8.3 [5.8–10.8])		166,097 (11.5 [4.4–18.6])	
≥3	5,472,674 (1.5 [1.3–1.6])		318,135 (4.2 [2.2–6.2])		49,132 (3.4 [0.1–6.7])	
	Mean index (95% CI)	Mean index (95% CI)	Adjusted β (95% CI)	P	Mean index (95% CI)	Adjusted β (95% CI)
	0.38 (0.37–0.39)	0.53 (0.43–0.62)	0.15 (0.05–0.24)	0.003	0.60 (0.42–0.79)	0.22 (0.04–0.41)
						0.03

Boldface indicates statistically significant P values.

DISCUSSION

This study showed that children with AD have increased atopic comorbidity (2 or more atopic comorbidities), as well as nonatopic multimorbidity, as measured by both CCI and HCUP-CCI score indices. This finding was consistent in sensitivity analysis across age and AD severity groups, with the exception of CCI scores in adolescents with severe AD, in which the increase was insignificant, likely due to inadequate sample size. For comparison, asthma was associated with higher score for all 3 multimorbidity scores than AD. Of note, psoriasis was associated with higher HCUP-CCI scores than AD. However, this is attributable in part to the fact that psoriasis is considered a comorbidity in the HCUP-CCI score. In contrast, psoriasis had similar CCI scores as mild AD and severe AD, and fewer atopic comorbidities than AD. However, urticaria was associated with similar CCI and HCUP-CCI scores, but with even higher rates of atopic multimorbidity than AD. These results indicate that AD had a similar burden of atopic and nonatopic multimorbidity as many other inflammatory skin diseases and allergic diseases.

Children with versus without AD were more likely to have atopic and nonatopic multimorbidity. The atopic march to allergic rhinitis and asthma is well documented in a subset of AD patients.¹⁸ Multiple prospective studies have found that early AD is associated with the development^{19,20} and increased severity²¹ of childhood asthma. Moreover, children with AD are 5 times more likely to develop polysensitization.²² These results indicate that AD is associated with increased atopic multimorbidity. Clinicians should be aware of atopic multimorbidity and consider screening for the spectrum of atopic disease in children with AD. Children with AD as well as atopic and/or nonatopic multimorbidity may particularly benefit from management in a multidisciplinary care setting, in order to properly diagnose and treat the comorbidities and address all aspects of their disease.

Atopic comorbidities, however, do not fully account for the increased multimorbidity in children with AD. There were significant

2-way interactions such that children with both AD and atopic disease had even higher CCI and HCUP-CCI scores than those with either AD or atopic disease alone. This may be explained in part by atopic disease causing systemic immune activation, leading to other nonatopic and systemic comorbidities.²³ As such, AD patients with comorbid atopic disease seem to comprise a particular patient subset that warrants additional screening and management for atopic and nonatopic multimorbidity. Interestingly, there were no significant 2-way interactions observed for AD with depression or anxiety. Previous studies found such interactions as predictors of lower health utility scores.²⁴ Taken together, these findings suggest that psychiatric comorbidity is associated with more severe AD but may not be associated with additional multimorbidity. Future studies are needed to determine optimal strategies to potentially prevent, screen, and manage multimorbidity in this population.

We examined multiple indicators of multimorbidity because there is currently no criterion standard assessment of multimorbidity in children. Charlson Comorbidity Index was constructed to predict 1-year mortality in adults⁸ and has emerged as the preferred indicator for multimorbidity in adults. However, the HCUP-CCI comprises a list of chronic comorbidities that were determined by pediatricians to be chronic in children.¹⁷ As expected, comorbidity index scores were, as a whole, higher using the HCUP-CCI than using the CCI. Therefore, the CCI likely underestimates the comorbidity burden in children, as it is not calibrated to identify pediatric disorders. Of note, 16% of children with AD had high CCI or HCUP-CCI burden (≥ 2), despite not having any atopic comorbidities. This suggests that AD alone is associated with multimorbidity. However, 35.1% of children with AD and atopic disease had elevated CCI or HCUP-CCI scores, indicating that children with AD and comorbid atopic disease are at particularly increased risk of multimorbidity.

The strengths of this study include the use of a large cohort of children over a 20-year period. Population sampling and survey weights allowed for representative estimates of patient burden in the United States. However, a few limitations merit mention. Information on health conditions was self-reported, and recall bias may

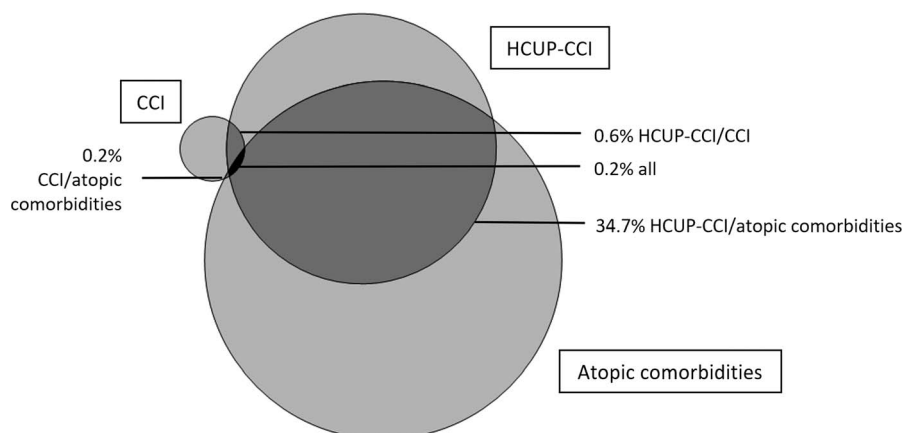


Figure 3. Venn diagram for differences and intersection of high (score ≥ 2) CCI, HCUP-CCI, and atopic comorbidity burden.

partially explain the lower than expected prevalence of AD in our cohort. Data were unavailable on AD severity (eg, eczema area and severity index or scoring), phenotypes, and age at onset. Instead, medication prescribed for the treatment of AD was used as a proxy for AD severity.¹⁰ This approach is based on the “step-up” approach recommended in AD guidelines²⁵ and patients' willingness to use more potent therapies when they have more severe and/or refractory disease. In addition, the cross-sectional design of this study precluded any conclusions about causality. Future longitudinal studies are needed with standardized assessments of AD severity and comorbidities to address these points.

In conclusion, childhood AD is associated with increased multimorbidity. In particular, children with AD and comorbid atopic disease had much greater comorbidity burden. Children with AD and comorbid atopic disease may be candidates for early intervention aimed to prevent and screen for multimorbidity.

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