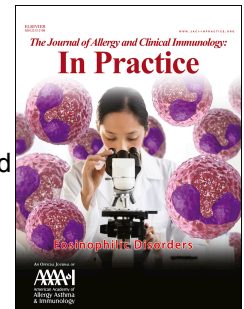


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Alopecia Areata is Associated with Atopic Diathesis; Results from a Population-Based Study of 51,561 Patients

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Title: Alopecia Areata is Associated with Atopic Diathesis;

Results from a Population-Based Study of 51,561 Patients

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Abstract

Background: Evidence of Th1/interferon (IFN) γ over-activation as major pathogenic driver somewhat conflicts with data supporting robust allergic background in alopecia areata (AA) patients. Previous investigations of immunologic dysregulations show both Th1 and Th2-related markers are over-expressed in AA. Clinical correlations in large populations may shed light on the immune pathways most likely to result in the clinical phenotype of AA.

Objective: To investigate the atopic comorbidities among patients with AA in a large, population-based study.

Methods: This is a cross-sectional retrospective study of AA patients and a matched comparison group, analyzing the associations between AA and four atopic comorbidities: asthma, atopic dermatitis (AD), allergic rhinitis, and allergic conjunctivitis. Chi-square and t-tests were used for univariate analysis, and logistic regression model was used for multivariate analysis. The study was performed utilizing the computerized database of Clalit Health Services ensuring 4.4 million subjects.

Results: The study population includes 51,561 AA patients and 51,410 matched control subjects. The prevalence of asthma (7.8% vs. 6.5%; OR 1.22; 95%CI 1.17-1.28, $p < 0.001$), AD (3.9% vs. 2.6%; OR 1.55; 95%CI 1.44-1.66, $p < 0.001$), allergic rhinitis (16.0% vs. 12.8%; OR 1.29; 95%CI 1.25-1.34, $p < 0.001$), and allergic conjunctivitis (23.5% vs. 19.6%; OR 1.27; 95%CI 1.23-1.30, $p < 0.001$) was significantly higher among patients with AA as compared to matched control subjects. AA patients also had significantly higher probability to have more than one atopic comorbidity, with increasing OR as the number of concomitant atopic conditions increases.

Conclusion: Our analysis supports the previous literature and provides strong generalizability of significant atopy in AA patients, suggesting Th2 pathogenicity in AA, and challenging the traditional view of AA as a single axis, Th1-centered disease.

Highlights box - no longer than 35 words in each

- What is already known about this topic? There is conflicting evidence for both Th1/interferon (IFN) γ and Th2-related markers as drivers of the inflammatory process of alopecia areata (AA).
- What is already known about this topic? AA patients had significant atopic associations as compared to a matched control group, in line with previous, smaller-scale publications. These findings lend weight to the concept of Th2-skewing in AA.
- What is already known about this topic? Our study reinforces a rationale for Th2-targeting approaches in patients with AA.

Key words: Alopecia areata, population based, atopic dermatitis, asthma, allergic rhinitis, allergic conjunctivitis, comorbidities, atopy, big data.

Abbreviations used:

AA: Alopecia areata

AD: Atopic dermatitis

CHS: Clalit Health Services

CI: Confidence interval

OR: Odds ratio

Introduction

Alopecia areata (AA) is a common dermatologic disease, affecting up to 2% of the population, and is characterized by non-scarring hair loss.¹⁻³ Clinical presentations range from patchy, circumscribed hair loss to alopecia totalis or universalis (complete loss of scalp hair or scalp and body hair, respectively).³ Despite significant emotional and psychosocial distress for patients and their families,⁴ AA has no definitive, safe, and effective treatment,⁵⁻⁸ and the incomplete understanding of AA pathogenesis hinders further therapeutic developments.^{9,10} While consensus exists for the hair follicle immune privilege disruption as a trigger of hair follicle immune attack,¹¹ the immune pathways driving the inflammatory response resulting in hair loss are not yet fully elucidated. Traditionally, Th1/interferon/IFN γ -related cytokines and chemokines have been viewed as chief players in AA initiation and maintenance, as supported by animal models.^{12,13} The newly introduced Janus kinase/JAK inhibitors were also shown to downregulate Th1/IFN γ and associated markers, along with other immune axes, such as Th2 coupled with up-regulations of hair keratins.¹⁴⁻¹⁶ Moreover, dysregulations of Th1/IFN γ , Th2, IL-9, PDE4, and Th17/IL-23 were found in several human and in mouse AA studies.^{12,17,18} Increasing evidence for a possible role of Th2 immune pathway in AA is supported by the high levels of Th2-related cytokines (e.g. IL-4, IL-5, IL-10) in skin and serum of AA patients, as well as findings of eosinophilia and elevated IgE levels in blood from AA patients.^{17,19-21} Moreover, genetic studies have identified polymorphisms in filaggrin, IL-4, and IL-13 (key players of the Th2 pathway) in AA patients, and associated filaggrin mutations with AA severity.^{19,22,23}

Few preliminary epidemiological studies and meta-analyses have shown a higher prevalence of atopic diseases, such as atopic dermatitis (AD), asthma, and allergic rhinitis (commonly driven by Th2-skewing) in patients with AA, hinting towards a shared

immunological background in these conditions.^{3,24-28} Last, the therapeutic armamentarium available for patients with atopic conditions, including AD, is rapidly expanding,²⁹ and it is thus important to further understand the associations between these conditions and AA.

We investigated the association between AA and Th2-related diseases in a uniquely large and detailed database from Israel, in which patients have long-term follow-up of various health-related systems. We opted to complement previous data suggesting Th2 skewing in AA patients. To the best of our knowledge, this is the largest population-based study investigating the atopic comorbidities of AA patients, encompassing more than 4.4 million patients.

Methods

Study design and setting

The current study was designed as a cross-sectional retrospective study utilizing information from the Clalit Health Services (CHS) database. CHS is the largest health maintenance organization in Israel, serving a population of approximately 4,400,000 as for 2017. CHS has a comprehensive computerized database with incessant real-time input from medical, administrative, and pharmaceutical computerized operating systems that enables data collection for epidemiological studies. The validity of diagnoses in this dataset, which are based on reports from both hospital and primary care physicians and specialists, was proven highly reliable⁹. A chronic disease register is gathered from these data sources and continuously updated and validated through algorithmic checks⁹. The current study was approved by the institutional ethical board of Ben-Gurion University and CHS.

Study population and covariates

All medical records of CHS enrollees were screened for the diagnosis of AA, and data on prevalent cases of AA was retrieved. The diagnosis of AA was based on the documentation of an AA-specific diagnostic code registered by a board-certified dermatologist. A comparison group of individuals without AA was selected through 1:1 matching based on age, sex, ethnicity, and primary care practice. The control group was randomly selected from the list of CHS enrollees' frequency-matched to cases, excluding case patients with AA. Age matching was grounded on the exact year of birth (1-year strata).

Other covariates in the analysis included: comorbid conditions as determined using Charlson comorbidity index,¹⁰ a weighted index used to categorize the degree of comorbidity of a patient by taking into account the number and seriousness of comorbid conditions. This validated method has been shown to be a robust predictor of mortality and it correlates positively with a fatal outcome.¹⁰ Socioeconomic status was defined according to the poverty index of the patient's residence area as defined during the 2008 National Census. The population was divided into 3 categories according to their poverty index (low, intermediate, and high)¹¹. Data on ethnicity was based on the address of the patient's primary care clinic. The vast majority of the Arab population in Israel resides in highly homogenous Arab towns and villages. Patients affiliated to healthcare facilities in these towns are designated as belonging to the "Arab Sector". Thus, primary care clinic location represents a relatively precise measure of the ethnicity of patients in Israel.

Statistical analysis

The distribution of sociodemographic and clinical features was compared between case and control subjects using chi-square test for sex and socioeconomic status, and t-test for age. Conditional logistic regression was then used to calculate adjusted odds ratio (OR), and 95%

confidence interval (CI), to compare cases and controls with respect to the presence of atopic comorbidities. All statistical analyses were performed using SPSS software, version 23 (SPSS, Chicago, IL, USA).

Results

Our study population comprised of 51,561 patients with AA and 51,410 age- and sex-matched control subjects. The mean age ($\pm$ standard deviation/SD) of patients with AA was 34.1 ± 17.1 , which is identical to that of control subjects at the date of enrollment. Overall, 20,476 (39.7%) of AA patients were females and a similar proportion was documented among controls. No significant differences in ethnic background and socioeconomic status were noted between the two groups. Comorbidity rates, measured by the Charlson comorbidity index, were comparable between the two groups, with 1,352 (2.6%) AA patients and 1,354 (2.6%) control subjects experiencing severe comorbidities. The mean body mass index (BMI) was lower among patients with AA (**Table 1**).

We evaluated the presence of four atopic conditions (AD, asthma, allergic rhinitis, and allergic conjunctivitis) among AA patients and control groups. **Table 2** demonstrates the proportions of AA patients and controls with atopic comorbidities stratified by sex and age category. The prevalence of asthma (7.8% vs. 6.5%; $p < 0.001$), AD (3.9% vs. 2.6%; $p < 0.001$), allergic rhinitis (16.0% vs. 12.8%; $p < 0.001$), and allergic conjunctivitis (23.5% vs. 19.6%; $p < 0.001$) was significantly higher among patients with AA as compared to matched control subjects. In both AA and controls, the highest prevalence of both AD and Allergic conjunctivitis was reported in patients younger than 20 years of age. **Table 3** presents the results of univariate and logistic regression models, and summarizes ORs for atopic conditions in patients with AA

and controls across the entire study sample. Among included atopic diseases, AD demonstrated the strongest association with AA (OR, 1.55; 95% CI, 1.44-1.66). A milder, but still statistically significant increase, was observed in the odds of asthma (OR, 1.22; 95% CI, 1.17–1.28), allergic rhinitis (OR, 1.29; 95% CI, 1.25–1.34), and allergic conjunctivitis (OR, 1.27; 95% CI, 1.23–1.30) among patients with AA relative to control subjects. In a multivariate logistic regression model, adjustment for age, sex, ethnicity, socioeconomic status, and comorbidities did not interfere with any of the aforementioned significant associations (**Table 3**).

We compared the characteristics of patients with AA presenting with comorbid atopic diseases relative to patients with isolated AA (**Table 4**). Patients with comorbid asthma and AD presented with their AA at a significantly earlier age, whereas patients with comorbid allergic rhinitis developed AA at an older age. An overwhelming male preponderance was observed among patients with AA and comorbid allergic rhinitis, whereas a slighter female predominance emerged among patients with AA and comorbid AD and allergic conjunctivitis. Notably, patients with AA and comorbid allergic rhinitis, AD and, to a lesser extent, allergic conjunctivitis were less frequently exposed to cigarette smoking (**Table 4**).

Lastly, we investigated the association between having one or more atopic comorbidities in AA patients as compared to controls. The prevalence of at least a single atopic comorbidity was greater among patients with AA as compared to control subjects (39.5% vs. 32.9%, respectively; OR, 1.33; 95% CI, 1.30–1.37; $p < 0.001$). The prevalence of two or more (≥ 2) concomitant atopic conditions was significantly higher among AA patients than controls (10.1% vs. 7.5%, respectively; OR, 1.39; 95% CI, 1.34–1.46; $p < 0.001$). When the probability of having three or more (≥ 3) concomitant atopic conditions was compared, even a more robust association was revealed (1.5% vs. 1.0%, respectively; OR, 1.54; 95% CI, 1.37–1.72; $p < 0.001$). All the

aforementioned associations were robust to a multivariate analysis adjusting for age, sex, ethnicity, socioeconomic status, and comorbidities (**Table 5**).

Discussion

Various comorbidities been reported in patients with AA, including psychological, autoimmune, and atopic diseases.^{24-26,30,31} However, the association between AA and atopic diseases has been evaluated in small cohorts.²⁴⁻²⁸ In the current population-based study, we investigated the prevalence of atopic comorbidities in 51,561 patients with AA and 51,410 matched controls, to better characterize these associations. Of all four atopic comorbidities included in this study, the most robust association of AA was with concomitant AD. The most prevalent atopic disease in the entire cohort was allergic conjunctivitis, similar to previous publications,³² and AA was also significantly associated with this condition, although to a lesser extent in comparison with.

AA patients with concomitant AD and asthma were associated with an earlier onset of AA, similar to prior reports.^{25,26} This together with the fact that early AA onset is recognized as a risk factor for more recalcitrant disease,³³ potentially support a shared underlying immune dysregulation in the disease burden of AA and the atopic comorbidities. Notably, significantly more AA patients with concomitant AD, allergic rhinitis, and allergic conjunctivitis were non-smokers, theoretically hinting towards an anti-inflammatory, nicotine-mediated effect, as seen in ulcerative colitis and pemphigus.^{34,35} Despite these findings, because the overall hazards of smoking are well known, and lung cancer-related mortality is particularly higher in AA patients,³⁶ smoking cessation recommendations should still be stressed in AA patients.

Since atopic diseases are often manifested concomitantly, a phenomenon referred to as the “atopic march” in the pediatric population,³⁷ we evaluated the OR of patients with AA to have several atopic comorbidities in comparison to patients without AA. We found that patients with AA are more likely to suffer from concomitant atopic comorbidities with increasing OR as the number of concomitant atopic conditions increases.

The mechanisms leading to the clinical manifestations of AA are still elusive, although recent research efforts portray an immune-mediated disease with variable activation of polar cytokine axes, including both Th1 and Th2.¹⁷ Th2 upregulations can be anticipated in patients with concomitant atopic diseases, specifically AD, asthma, and allergic rhinitis patients, in which Th2 pathway pathogenicity has been recently demonstrated by the efficacy of Th2-targeting agents.³⁸⁻⁴⁰ Of note, a large study evaluating scalp of AA patients with and without AD, did not show differences in Th2 activation in AA patients, regardless of their atopic status.¹⁷ Furthermore, in a large genome-wide association study, IL-13 has been the strongest association in AA patients, regardless of concomitant AD.²² The atopic associations in AA patients have led to testing of anti-histamines with beneficial effects in some AA patients, leading to several reports advocating for concomitant antihistamine use together with other treatments in AA patients.⁴¹⁻⁴³

AA management presents significant unmet needs, particularly in patients with moderate to severe hair loss, where intra-lesional and conventional therapeutics have limited applicability and efficacy.^{9,10,44} Due to significant associations between atopic diseases and AA, as well as the increasing evidence of up-regulations of Th2-related products in AA skin and blood,^{17,19-21,45,46} a rationale for possible anti-Th2 approaches emerges in AA patients. This is also supported by few case reports of significant hair regrowth in AA patients with totalis/universalis AA with the

specific Th2 antagonist dupilumab (targeting IL-4 receptor α), given for concomitant AD.⁴⁷⁻⁵⁰ Nevertheless, hair loss with dupilumab has also been documented.⁵¹⁻⁵⁴ The hypothesis of Th2 targeting in AA patients is currently tested in a placebo-controlled trial (*ClinicalTrials.gov* identifier: NCT03359356).

The immune signature of AA is complex, including dysregulations of Th1/IFN γ , Th2, IL-9, PDE4, and IL-23-related cytokines.^{12,17,18} While JAK inhibitors are effective, the long term safety is unknown.⁵⁵ Furthermore, these agents cannot dissect the contribution of specific immune axes to the AA phenotype, due to their wide, non-specific, down-stream suppression. The strong Th2 up-regulation in AA, together with the significant associations with other atopic comorbidities and particularly AD, suggest that the traditional view of AA as a primarily Th1-centered disease, should be expanded. Th2-targeting agents may hold promise in AA, and the relevance of this axis should be revealed through the ongoing and future therapeutic testing with dupilumab and other Th2 targeting agents.

Our study has several limitations. The cross-sectional design does not enable to evaluate a temporal relationship between AA and atopic diseases, so that causal relationship cannot be drawn. Data concerning the severity of AA is not available in CHS registry, as it designed for clinical purposes and not for research purposes. Another drawback of the current study is the lack of direct validation of the diagnosis of AA and atopic comorbidities. Nevertheless, we used stringent rules for diagnosis of AA in our study as we used only diagnoses made by dermatologists. Moreover, previous studies based on the CHS registry have shown that the data is of high reliability and external validity.⁵⁶ A detection bias may stem from the fact that patients with frequent physician contact for one condition may be more likely to have their diagnoses of other conditions recorded. Unfortunately, we were not able to adjust for healthcare utilization in

the current study, and, thus, could not exclude the presence of some sort of a detection or ascertainment bias.

In conclusion, our large-scale study revealed a significant association between AA and several atopic comorbidities (table E1). Future clinical trials should ascertain whether AA can be considered as part of the “atopic” umbrella. Nevertheless, physicians managing patients with AA should be encouraged to evaluate these patients for the presence of atopic manifestations.

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Tables**Table 1-** Descriptive characteristics of the study population

Characteristic	Alopecia areata (n=51,561)	Controls (n=51,410)
Age, years		
Mean±SD	34.1±17.1	34.1±17.0
Median (range)	34.0 (0-99.0)	34.0 (0-99.0)
Male sex, n (%)	31,085 (60.3%)	31,001 (60.3%)
Ethnicity, n (%)		
Jews	34,800 (67.5%)	34,656 (67.4%)
Arabs	16,761 (32.5%)	16,754 (32.6%)
SES, n (%)		
Low	25,218 (48.9%)	25,179 (48.9%)
Intermediate	17,396 (33.7%)	17,328 (33.7%)
High	8,758 (17.0%)	8,720 (17.0%)
Unknown	189 (0.4%)	183 (0.4%)
Charlson comorbidity score, n (%)		
None (0)	42,076 (81.6%)	42,383 (82.4%)
Moderate (1-2)	8,133 (15.8%)	7,673 (14.9%)
Severe (≥3)	1,352 (2.6%)	1,354 (2.6%)
Body mass index (Kg/m ²), Mean±SD	25.5 ± 6.3	25.9 ± 5.6

Abbreviations: n, number; SD, standard deviation; BMI, body mass index; SES, socioeconomic status

Table 2 - Demographic distribution of cases and controls with atopic comorbidities.

	Asthma (n=7,386), n (%)		Atopic dermatitis (n=3,363), n (%)		Allergic rhinitis (n=14,822), n (%)		Allergic conjunctivitis (n=22,199), n (%)	
Character istic	AA (n=51,5 61)	Control (n=51,4 10)	AA (n=51,5 61)	Control (n=51,4 10)	AA (n=51,5 61)	Control (n=51,4 10)	AA (n=51,5 61)	Control (n=51,4 10)
All (n=102,97 1)	4,040 (7.8)	3,346 (6.5)	2,034 (3.9)	1,329 (2.6)	8,230 (16.0)	6,592 (12.8)	12,137 (23.5)	10,062 (19.6)
Male (n=62,086)	2507 (8.1)	2,136 (6.9)	1,094 (3.5)	664 (2.1)	4,763 (15.3)	3,768 (12.2)	6,719 (21.6)	5,445 (17.6)
Female (n=40,885)	1,533 (7.5)	1,210 (5.9)	940 (4.6)	665 (3.3)	3,467 (16.9)	2,824 (13.8)	5,418 (26.5)	4,617 (22.6)

Abbreviations: AA, alopecia areata; n, number. **Bold:** significant value

Table 3 - The association between alopecia areata and atopic comorbidities

Disease	AA (n=51,561), n (%)	Controls (n=51,410), n (%)	OR (95% CI)	Univariate p value	Male-specific OR(95% CI)	Female-specific OR(95% CI)	Adjusted OR (95% CI) ¹
Asthma	4,040 (7.8)	3,346 (6.5)	1.22 (1.17-1.28)	<0.001	1.19 (1.12-1.26)	1.28 (1.19-1.39)	1.24 (0.18-1.31)
Atopic dermatitis	2,034 (3.9)	1,329 (2.6)	1.55 (1.44-1.66)	<0.001	1.67 (1.51-1.84)	1.43 (1.29-1.58)	1.56 (1.45-1.67)
Allergic rhinitis	8,230 (16.0)	6,592 (12.8)	1.29 (1.25-1.34)	<0.001	1.31 (1.25-1.37)	1.27 (1.20-1.34)	1.29 (1.25-1.34)
Allergic conjunctivitis	1,2137 (23.5)	10,062 (19.6)	1.27 (1.23-1.30)	<0.001	1.29 (1.24-1.35)	1.23 (1.18-1.29)	1.27 (1.23-1.31)

Abbreviations: AA, alopecia areata; N, Number; OR, odds ratio; CI, confidence interval. **Bold:** significant value

¹-Multivariate logistic regression model adjusting for age, sex, ethnicity, socioeconomic status, and Charlson comorbidity index.

Table 4 - Comparison between patients with alopecia areata and atopic comorbidities relative to those with isolated alopecia areata

	AA w/ asthma (n=4,040)	AA w/o asthma (n=47,521)	p value	AA w/ AD (n=2,034)	AA w/o AD (n=49,527)	p value	AA w/ allergic rhinitis (n=8,230)	AA w/o allergic rhinitis (n=43,331)	p value	AA w/ allergic conjunctivitis (n=12,137)	AA w/o allergic conjunctivitis (n=39,424)	p value
Age at AA onset	33.4±17.2	34.1±12.0	0.011	26.5±17.3	34.5±17.0	<0.001	37.0±16.2	34.0±17.0	<0.001	34.0±17.1	34.2±17.1	0.259
F sex, n (%)	1,533 (37.9)	18,943 (39.9)	0.013	940 (46.2)	19,536 (39.4)	<0.001	894 (10.9)	19,582 (45.2)	<0.001	5,418 (44.6)	15,058 (38.2)	<0.001
BMI	25.4 ±5.5	25.3 ± 5.3	0.265	23.7±5.4	25.3±5.3	<0.001	25.4±5.0	25.3±5.3	0.099	25.4±5.3	25.2±5.3	<0.001
Smoking status, n (%)	1,437 (35.6)	16,489 (34.7)	0.249	420 (20.6)	17,506 (35.3)	<0.001	647 (7.9)	17,279 (39.9)	<0.001	3,635 (29.9)	1,4291 (36.2)	<0.001

Abbreviations: AA, alopecia areata; AD, atopic dermatitis; F, female; n, number; BMI, body mass index; w/, with; w/o, without.

Bold: significant value.

Table 5 - The association between alopecia areata and multiple atopic comorbidities

Disease	AA (n=51,561), n (%)	Controls (n=51,410), n (%)	OR (95%CI)	Univariate p value	Male-specific OR(95%CI)	Female- specific OR(95%CI)	Adjusted OR (95%CI)¹
Any atopic comorbidity	20,372 (39.5)	16,931 (32.9)	1.33 (1.30 - 1.37)	<0.001	1.35 (1.31-1.40)	1.31 (1.25-1.36)	1.34 (1.30-1.38)
≥2 concomitant atopic comorbidities	5,232 (10.1)	3,852 (7.5)	1.39 (1.34-1.46)	<0.001	1.40 (1.32-1.49)	1.39 (1.30-1.48)	1.40 (1.34-1.46)
≥3 concomitant atopic comorbidities	772 (1.5)	504 (1.0)	1.54 (1.37-1.72)	<0.001	1.55 (1.33-1.79)	1.52 (1.28-1.81)	1.52 (1.36-1.71)

Abbreviations: AA, alopecia areata; N, Number; OR, odds ratio; CI, confidence interval;

Bold: significant value

1-Multivariate logistic regression model adjusting for age, sex, ethnicity, socioeconomic status, and Charlson comorbidity index.

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Table E1- Distribution of cases and controls with atopic comorbidities stratified by age.

	Asthma (n=7,386), n (%)		Atopic dermatitis (n=3,363), n (%)		Allergic rhinitis (n=14,822), n (%)		Allergic conjunctivitis (n=22,199), n (%)	
	AA (n=51,561)	Control (n=51,410)	AA (n=51,561)	Control (n=51,410)	AA (n=51,561)	Control (n=51,410)	AA (n=51,561)	Control (n=51,410)
Age category (years)								
<20 (n=22960)	967 (8.4)	848 (7.4)	932 (8.1)	695 (6.1)	1,193 (10.4)	948 (8.3)	3,168 (27.6)	2,764 (24.1)
20-39 (n=44002)	1,824 (8.3)	1,526 (6.9)	628 (2.9)	371 (1.7)	3,818 (17.3)	3,143 (14.3)	4,817 (21.9)	3,911 (17.8)
40-59 (n=27307)	877 (6.4)	649 (4.8)	375 (2.7)	200 (1.5)	2,376 (17.4)	1,842 (13.5)	3,053 (22.3)	2,435 (17.9)
≥60 (n=8702)	372 (8.5)	323 (7.5)	99 (2.3)	63 (1.5)	843 (19.3)	659 (15.2)	1,099 (25.2)	952 (22.0)