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ORIGINAL ARTICLE

The association of atopy with incidence of ischemic heart disease, stroke, and diabetes

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Abstract Allergy is a systemic inflammatory disease that could theoretically affect the risk of cardiovascular disease (CVD) and diabetes through inflammatory pathways or mast cell-induced coronary spasm. Whether allergy is associated with an increased risk of CVD and diabetes is largely unknown. We investigated the association between atopy as assessed by IgE sensitization, a well-accepted biomarker of allergy, and incidence of ischemic heart disease, stroke, and diabetes in five Danish population-based cohorts. A total of 14,849 participants were included in the study. Atopy was defined as serum-specific IgE positivity to inhalant allergens. The Danish National Diabetes Register enabled identification of incident diabetes. Likewise, the Danish Registry of Causes of Death and the Danish National Patient Register provided information on fatal and non-fatal ischemic heart disease and stroke. Data were analyzed by Cox regression analyses with age as underlying time axis and adjusted for study cohort, gender, education, body mass index, alcohol intake, smoking habits, physical activity during leisure time, serum lipids, and blood pressure. The prevalence of atopy was 26.9 % ($n = 3{,}994$). There were 1,170, 817, and 1,063 incident cases of ischemic heart disease, stroke, and diabetes, respectively (median follow-up 11.2 years). The hazard ratios, HRs (95 % confidence intervals, CIs) for atopics versus non-atopics: for ischemic heart disease (HR 1.00, 95 % CI 0.86, 1.16), stroke (HR 1.18, 95 % CI 0.99, 1.41), and diabetes (HR 1.06, 95 % CI 0.91, 1.23). Our results did not support the hypothesis that atopy is associated with higher risk of ischemic heart disease, stroke, or diabetes. However, a small-moderately increased risk cannot be excluded from our data.

Keywords Atopy · Allergy · Diabetes · Stroke · Ischemic heart disease · Cardiovascular disease

Introduction

Ischemic heart disease, stroke, and diabetes are among the leading causes of morbidity and mortality worldwide, and inflammatory mechanisms are known to play a key role in the pathogenesis. Atopy is defined as a familial or personal propensity to develop immunoglobulin E (IgE) antibodies against common environmental allergens [1]. Atopy and the associated allergic diseases, e.g., allergic rhinitis, asthma, and atopic eczema, have been increasing worldwide, particularly in westernized countries [2]. Whether atopy is associated with an increased risk of cardiovascular disease (CVD) and diabetes is largely unknown. Interestingly, mast cells that are the main effector cells in IgE-

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mediated allergic diseases are also shown to be present in increased numbers in atheromatous plaques, mast cell activation contributes to plaque eruption and coronary artery spasm [3, 4], and many mast cell mediators associate with diabetes mellitus [5, 6]. Atopy confers a high risk of developing allergic rhinitis, allergic asthma, food allergies, and atopic eczema. The repeated inflammation, damage, and repair of the tissue characteristic of allergic diseases may also increase the risk of CVD and diabetes.

Results from studies of the association of atopy with CVD and diabetes are still inconclusive. Although some smaller studies, retrospective studies, or subgroup analyses of prospective studies have shown positive associations between atopy and CVD, the relatively few studies so far have failed to establish a consistent association between atopy and CVD [7–10]. Wang et al. [11, 12] found serum total IgE to be positively associated with diabetes status and the risk of pre-diabetes.

New insight into the possible link between atopy and CVD may provide clues for new treatment possibilities. We investigated the association between atopy as assessed by serum-specific IgE positivity against inhalant allergens and the incidence of a registry-based diagnosis of diabetes or fatal and non-fatal ischemic heart disease or stroke according to the International Classification of Diseases (ICD) in five cohorts from the general Danish population. We used the unique Danish registries that allowed us to obtain almost complete follow-up on these outcomes.

Materials and methods

Ethics statement

The recommendations of the Declaration of Helsinki were followed, and the participants gave their informed written consent. The studies were approved by the Danish Data Protection Agency and the Ethics Committee of Copenhagen.

Study populations

We used the five population-based cohort studies, Monica1, Inter99, Health2006, the 1936-cohort, and Allergy98 that included questionnaires, physical examinations, and blood tests. They were recruited from the Danish Central Personal Register as random samples of the population in the southern part of the former Copenhagen County.

The Copenhagen Allergy study that began in 1990 included a group of persons randomly selected from the general population and a selected group of persons with allergic respiratory symptoms (recruited from a random sample of the general population by a screening questionnaire). We used data from the follow-up health examination in 1997–1998 (referred to as 'Allergy98'), where a total of 1,966 persons aged 15–77 years with Danish nationality were invited, and 1,216 (61.9 %) participated [13].

In the Monica1 study conducted in 1982–1984, 4,807 persons at the ages 30, 40, 50, and 60 years old were invited. The participations rate was 79 % giving a total of 3,785 participants [14].

The 1936-cohort consisted of a total of 1,200 randomly selected persons born in 1936 (aged 40 years at the time of the study) invited by letter for a health examination focusing on CVD risk factors. From 1976 to 1977, a total of 1,052 persons were examined (participation rate 87.7 %) [15].

In the Health2006 study, a sample of 7,931 persons with Danish citizenship from 18 to 69 years was invited to a general health examination [16]. A total of 3,471 (43.8 %) persons were examined from 2006 to 2008.

In the Inter99 study from 1999 to 2001, 12,934 persons aged 30–60 years from the general Danish population were invited. A total of 6,784 persons participated, giving a participation rate of 52.5 % [17]. The study was a population-based randomized controlled trial (CT00289237, ClinicalTrials.gov) and investigated the effects of lifestyle intervention on CVD [17].

A total of 15,098 persons from the 5 cohorts had data on atopy measurements (Monica1: 3,481; Inter99: 5,999; Allergy98: 1,186; 1936-cohort: 989; Health2006: 3,443). Of these, a total of 249 persons participated in more than one of the cohorts. They were included in the oldest of the cohorts and excluded from later cohorts. We thus included 14,849 persons in total (Monica1: 3,481; Inter99: 5,961; Allergy98: 1,172; 1936-cohort: 989; Health2006: 3,246) (Supplementary Fig. 1–5).

Assessment of atopy

In the Inter99 study, serum samples were analyzed for specific IgE to mite (*Dermatophagoides [D.] pteronyssinus*), cat, grass, and birch by the IMMULITE 2000 Allergy Immunoassay System [18]. In the Health2006 study, serum samples were analyzed for specific IgE to dust mite (*D. pteronyssinus*), cat, grass, and birch, whereas in the Allergy98 study, serum samples were analyzed for specific IgE to mite (*D. pteronyssinus*), cat, dog, grass, birch, and mugwort. In both the Health2006 and the Allergy98 studies, the ADVIA Centaur sIgE assay (Bayer Corporation, New York, NY, USA) was used [19]. In both the Allergy98 and the Health2006, and the Inter99 studies, the analysis for specific IgE was positive if the measurement was $\geq$0.35 kU/l. Atopy was defined as a positive test for serum-specific IgE against at least one of the allergens tested.

In the Monica1 study and the 1936-cohort, aeroallergen sensitization measurements were performed by the ADVIA Centaur Allergy Screen assay (Bayer HealthCare Diagnostics division, Tarrytown, NY, USA) [20]. It is a multiallergen assay for the qualitative detection of specific serum IgE antibodies to a panel of 19 common inhalant allergens. Atopy was defined as a positive result of the dichotomous assay output as previously described [20].

Self-reported stroke, IHD, and diabetes

Self-reported ischemic heart disease/myocardial infarction was defined as an affirmative answer to the question: "Has a doctor ever/within the last 12 months told you that you had a heart attack?". Self-reported ischemic or haemorrhagic stroke was defined as an affirmative answer to either of the questions: "Has a doctor ever/within the last 12 months told you that you had a stroke?" or "Has a doctor ever/within the last 12 months told you that you had a brain haemorrhage?".

Self-reported diabetes was defined as an affirmative answer to the question: "Have you been diagnosed with diabetes?" or "Has a doctor ever/within the last 12 months told you that you have diabetes?".

Registry-based ischemic heart disease and stroke

All residents in Denmark have a permanent and unique civil registration number that allows individual level linkage of data from national registers. Information on diseases was obtained from the Danish National Patient Register [21] that holds information on all admissions to Danish hospitals since 1978. Each admission is registered by at least one diagnosis according to the International Classification of Diseases (ICD). Likewise, up to three diagnoses suspected to be the cause of death were obtained from the Danish Registry of Causes of Death [22]. The included diagnoses were the diagnoses involving IHD (ICD-10: I20–25 and ICD-8: 410–414) and stroke (ICD-10: I60–69 and ICD-8: 431, 433–434, and 436), since Denmark never used the ICD-9 but went directly from the ICD-8 to the ICD-10. We followed the participants until 31 December 2010.

Registry-based diabetes

The Danish National Diabetes Register provided information on registry-based diagnoses of diabetes [23]. The registry uses five diagnostic criteria for inclusion: hospitalization with a diagnosis of diabetes [ICD-8: 249, 250; ICD-10: DE10-14, DH 36.0, DO24 (excluding DO24.4)]; measurements of blood glucose either five times or more within 1 year, or two or more annual measurements of glucose during a 5-year period (registered in the National Health Insurance Service Registry); registration of chiropody (coded for diabetes) in the National Health Insurance Service Registry; or prescription of oral anti-diabetic medication or insulin at least twice (registered in the Register of Medicinal Product Statistics). A person is classified as having diabetes if one of these criteria is met.

For both the CVD and diabetes end points, information on emigrations and deaths was obtained from the Danish Civil Registration System. We defined three end points: a diagnosis of diabetes, a diagnosis of or death caused by IHD, a diagnosis of or death caused by stroke. A history of diabetes, IHD, or stroke, respectively, was defined as a registry-based or self-reported diagnosis prior to examination (baseline). Incident diabetes, IHD, or stroke were defined as a registry-based diagnosis of diabetes, IHD, or stroke during follow-up among persons without a history of diabetes, IHD, and stroke, respectively.

Covariates

The questionnaires provided information on the covariates education/vocational training [no education (only basic education), education including students]; physical activity during leisure time (sedentary, light, or moderate/vigorous); alcohol consumption (drinks per week); smoking habits (never smokers; former smokers; current smokers <15 g/day; current smokers 15 to <25 g/day; ≥ 25 g/day). Body mass index (BMI), serum triglycerides, total cholesterol, and systolic and diastolic blood pressures were used as continuous variables.

The number of missing values for the used variables was: sex ($N_{\text{missing}} = 0$); education ($N_{\text{missing}} = 277$); physical activity during leisure time ($N_{\text{missing}} = 188$); alcohol consumption ($N_{\text{missing}} = 580$); smoking habits ($N_{\text{missing}} = 42$); BMI ($N_{\text{missing}} = 7$), serum triglycerides ($N_{\text{missing}} = 4$), total cholesterol ($N_{\text{missing}} = 5$), and systolic ($N_{\text{missing}} = 38$) and diastolic blood pressures ($N_{\text{missing}} = 40$). In total, 921 persons (6.2 %) had a missing value in at least one of the covariates (Supplementary Figs. 1–5).

Statistical analyses

We pooled data from the five cohorts. All analyses were performed with SAS, version 9.4 (SAS Institute Inc. Cary, NC, USA). All P values were two-sided, and P values <0.05 were considered statistically significant. Baseline characteristics according to study population and atopic status are presented as % (n) or mean (standard deviation, SD) and compared with the χ^2 test or Kruskal–Wallis test, respectively (Table 1). Table 2 shows the % (number) of persons with a history of or incident diabetes and fatal and

Table 1 Baseline characteristics according to study population and atopic status

	% (*n*)* or mean (SD)**									
	Monica1		Allergy98		Inter99		Health2006		1936-cohort	
	Non-atopic	Atopic	Non-atopic	Atopic	Non-atopic	Atopic	Non-atopic	Atopic	Non-atopic	Atopic
Participants	82.9 (2,887)	17.1 (594)	62.7 (735)	37.3 (437)	65.6 (3,903)	34.5 (2,058)	76.7 (2,488)	23.3 (758)	85.1 (842)	14.9 (147)
Age, years	45.7 (11.2)	41.8 (10.4)	41.5 (15.7)	37.6 (13.6)	46.6 (7.9)	45.1 (7.9)	50.0 (13.0)	45.8 (13.0)	40.4 (0.4)	40.4 (0.4)
		P < 0.0001		*P < 0.0001*		*P < 0.0001*		*P < 0.0001*		*P = 0.703*
Gender										
Male	80.9 (1,425)	19.1 (336)	54.2 (290)	45.8 (245)	62.8 (1,840)	37.2 (1,090)	72.6 (1,065)	27.4 (402)	83.6 (386)	16.4 (76)
Female	85.0 (1,462)	15.0 (258)	69.9 (445)	30.1 (192)	68.1 (2,063)	31.9 (968)	80.0 (1,423)	20.0 (356)	86.5 (456)	13.5 (71)
		P = 0.002		P < 0.0001		P < 0.0001		P < 0.0001		P = 0.184
Alcohol, drinks/week	8.7 (11.3)	10.2 (12.0)	6.7 (8.1)	6.8 (7.8)	10.2 (13.7)	10.7 (13.0)	9.7 (10.4)	9.4 (9.9)	8.0 (10.5)	11.7 (14.2)
		P = 0.0004		*P = 0.678*		*P = 0.161*		*P = 0.400*		*P = 0.002*
Education										
No	86.2 (897)	13.8 (144)	62.2 (209)	37.8 (127)	68.9 (663)	31.1 (299)	81.8 (360)	18.2 (80)	89.0 (251)	11.0 (31)
Yes	81.6 (1,990)	18.4 (450)	62.9 (523)	37.1 (309)	64.5 (3,081)	35.5 (1,696)	75.9 (2,092)	24.1 (664)	83.6 (590)	16.4 (116)
		P = 0.0007		P = 0.904		P = 0.010		P = 0.059		P = 0.030
BMI, kg/m^2	24.6 (3.9)	24.6 (3.8)	25.7 (4.5)	25.7 (4.7)	26.3 (4.6)	26.3 (4.4)	25.9 (4.7)	25.8 (4.8)	23.9 (3.5)	24.1 (4.2)
		P = 0.689		*P = 0.973*		*P = 0.288*		*P = 0.230*		*P = 0.563*
Physical activity										
Sedentary	84.5 (832)	15.5 (153)	62.0 (188)	38.0 (115)	64.4 (809)	35.6 (448)	77.8 (463)	22.2 (132)	85.4 (293)	14.6 (50)
Light	83.0 (1,484)	17.0 (303)	64.2 (377)	35.8 (210)	66.5 (2,382)	33.5 (1,199)	77.7 (1,506)	22.3 (432)	85.2 (430)	14.8 (75)
Moderate/vigorous	80.9 (570)	19.1 (135)	60.3 (167)	39.7 (110)	62.8 (616)	37.2 (365)	72.6 (491)	27.4 (185)	84.4 (119)	15.6 (22)
		P = 0.150		P = 0.506		P = 0.070		P = 0.102		P = 0.959
Smoking habits										
Never smokers	81.7 (731)	18.3 (164)	55.7 (274)	44.3 (218)	60.9 (1,271)	39.1 (816)	73.2 (985)	26.8 (360)	87.7 (284)	12.3 (40)
Former smokers	81.4 (524)	18.6 (120)	68.1 (141)	31.9 (66)	67.6 (1,017)	32.4 (488)	79.7 (825)	20.3 (210)	87.0 (114)	13.0 (17)
Smokers, <15 g/day	84.6 (746)	15.4 (136)	66.2 (145)	33.8 (74)	68.4 (623)	31.6 (288)	73.0 (286)	27.0 (106)	85.6 (184)	14.4 (31)
Smokers, 15–25 g/day	84.2 (727)	15.8 (136)	70.9 (124)	29.1 (51)	67.6 (716)	32.4 (344)	82.3 (274)	17.7 (59)	81.1 (215)	18.9 (50)
Smokers, ≥25 g/day	80.7 (159)	19.3 (38)	69.6 (48)	30.4 (21)	69.4 (276)	30.6 (122)	87.2 (95)	12.8 (14)	83.3 (45)	16.7 (9)
		P = 0.210		P = 0.0002		P < 0.0001		P < 0.0001		P = 0.243
Systolic BP, mmHg	124 (17)	123 (16)	129 (19)	128 (16)	130 (18)	130 (17)	131 (19)	128 (17)	124 (17)	123 (16)
		P = 0.638		*P = 0.613*		*P = 0.790*		*P < 0.0001*		*P = 0.259*
Diastolic BP, mmHg	77 (11)	78 (11)	79 (12)	80 (11)	82 (11)	82 (11)	82 (11)	81 (11)	74 (11)	75 (10)
		P = 0.034		*P = 0.762*		*P = 0.503*		*P = 0.087*		*P = 0.186*
Triglycerides, mmol/l	1.3 (1.1)	1.4 (1.1)	1.6 (1.0)	1.7 (1.4)	1.4 (1.5)	1.3 (1.0)	1.3 (1.1)	1.3 (0.7)	1.1 (0.9)	1.1 (0.7)
		P = 0.573		*P = 0.872*		*P = 0.762*		*P = 0.723*		*P = 0.386*

Table 1 continued

	% (*n*)* or mean (SD)**									
	Monica1		Allergy98		Inter99		Health2006		1936-cohort	
	Non-atopic	Atopic	Non-atopic	Atopic	Non-atopic	Atopic	Non-atopic	Atopic	Non-atopic	Atopic
Cholesterol, mmol/l	6.1 (1.2)	6.0 (1.3) *P = 0.069*	5.8 (1.3)	5.7 (1.2) *P = 0.029*	5.5 (1.1)	5.5 (1.1) *P = 0.644*	5.4 (1.1)	5.3 (1.0) *P = 0.073*	6.3 (1.1)	6.4 (1.3) *P = 0.651*

BMI body mass index, *SD* standard deviation, *BP* blood pressure. * *P* values according to the χ^2 test. ** *P values according to Kruskal–Wallis test*

non-fatal ischemic heart disease and stroke according to study population.

Multivariate Cox regression analyses were used to determine the association of atopy and the incidence of ischemic heart disease, stroke, and diabetes. Age was used as underlying time axis which means that age is automatically accounted for. Also, we used delayed entry. If participants were lost to follow-up (unknown cause of death, emigrated, or disappeared), they contributed risk time until the date of their last registered activity. Estimates are presented as hazard ratios, HR (95 % confidence intervals, CI). We used complete case analysis, where only participants with complete information on all considered variables were included. In model 1, we adjusted for study population and gender. In model 2, we further adjusted for education, smoking habits, and alcohol intake. In model 3, we further adjusted for physical activity during leisure time, BMI, triglycerides, total cholesterol, and systolic and diastolic blood pressures. The results are presented as HR and 95 % CI (Table 3). There were no statistically significant interactions between atopic state and study population or between atopic state and sex.

In additional analyses, individual results from the five studies were pooled by the inverse variance method in fixed and random effects meta-analyses. The I^2 test was used to examine the heterogeneity between studies. The meta-analyses of the fully adjusted individual estimates are shown in Figs. 1, 2 and 3.

Results

In total, 26.9 % ($n = 3{,}994$) were classified as atopics at baseline. This ranged from below 20 % in the Monica1 study and the 1936-cohort to above 30 % in the Inter99 and Allergy98 study, the Health2006 study in between. In crude baseline analyses, atopy was significantly associated with younger age and male gender except in the 1936-cohort (Table 1).

There were a total of 345 (2.3 %), 236 (1.6 %), and 110 (0.7 %) persons with a history of diabetes, IHD, and stroke at baseline, respectively (Table 2). The incidence of diabetes, IHD, or stroke was 7.3 % ($n = 1{,}063$), 8.0 ($n = 1{,}170$), and 5.5 % ($n = 817$), respectively (Table 2).

In the Cox regression analyses, the median (min, max) follow-up was 11.3 (0.0, 34.7) years (Monica1: 27.3–27.4 years; Inter99: 11.0 years; Allergy98: 12.6–12.7 years; 1936-cohort: 33.8 years; Health2006: 3.5 years) for all three outcomes. We found no statistically significant associations between atopy and diabetes, IHD, or stroke in either the partly or the fully adjusted models (Table 3). However, there was a borderline-significant higher risk of incident stroke among atopics with a HR 1.18 (95 % CI 0.99, 1.41).

Table 2 History and incidence of diabetes, fatal and non-fatal ischemic heart disease, and stroke according to study population

	Monica1 % (number)	Allergy98 % (number)	Inter99 % (number)	Health2006 % (number)	1936-cohort % (number)
History of[a]					
Ischemic heart disease	1.5 (51)	2.0 (23)	1.4 (81)	2.5 (80)	0.1 (1)
Stroke	0.4 (15)	1.1 (13)	0.6 (38)	1.4 (44)	0 (0)
Diabetes	1.5 (52)	2.2 (26)	2.2 (133)	4.1 (132)	0.2 (2)
Incidence of[b]					
Ischemic heart disease	15.5 (533)	5.6 (64)	5.3 (310)	1.9 (61)	20.5 (202)
Stroke	11.7 (405)	4.4 (51)	3.0 (178)	1.3 (41)	14.4 (142)
Diabetes	13.2 (452)	5.4 (62)	6.1 (358)	1.5 (47)	14.6 (144)

[a] A history of diabetes, IHD, or stroke, respectively, was defined as a registry-based or self-reported diagnosis prior to examination (baseline)

[b] Among persons without a history of diabetes, ischemic heart disease, and stroke, respectively

Table 3 Hazard ratios and 95 % confidence intervals for the associations between atopic status and incident ischemic heart disease, stroke and diabetes

	Events/persons included (person-years)	Model 1[a] HR (95 % CI)	Model 2[b] HR (95 % CI)	Model 3[c] HR (95 % CI)
Ischemic heart disease				
Non-atopic	887/10,015 (142,712)	1 (reference)	1 (reference)	1 (reference)
Atopic	226/3,699 (45,560)	0.98 (0.84, 1.14)	1.01 (0.87, 1.18)	1.00 (0.86, 1.16)
P value		$P = 0.759$	$P = 0.870$	$P = 0.998$
Stroke				
Non-atopic	621/10,097 (145,644)	1 (reference)	1 (reference)	1 (reference)
Atopic	163/3,734 (46,488)	1.14 (0.96, 1.36)	1.17 (0.98, 1.39)	1.18 (0.99, 1.41)
P value		$P = 0.146$	$P = 0.087$	$P = 0.073$
Diabetes				
Non-atopic	773/9,972 (142,124)	1 (reference)	1 (reference)	1 (reference)
Atopic	235/3,667 (45,433)	1.07 (0.92, 1.24)	1.08 (0.93, 1.26)	1.06 (0.91, 1.23)
P value		$P = 0.391$	$P = 0.292$	$P = 0.450$

Complete case analysis. Persons suffering from ischemic heart disease, stroke, or diabetes at baseline, respectively, were excluded

CI confidence interval, *HR* hazard ratio

[a] Adjusted for study and gender (age is underlying time axis)

[b] Further adjusted for education, smoking habits, and alcohol intake

[c] Further adjusted for physical activity, body mass index, systolic and diastolic blood pressure, serum triglycerides, and total cholesterol

In comparison, the combined estimates (Table 3) and the meta-estimates (Figs. 1, 2, 3) were very similar. Also, we found no sign of heterogeneity between the studies in the meta-analyses of stroke and diabetes which suggests that differences between the studies did not seriously bias our results (Figs. 1 and 3). In the meta-analysis of ischemic heart disease there was moderate heterogeneity but it had only minor effect on the HR (Fig. 2).

Discussion

We found no statistically significant associations between atopy and incident ischemic heart disease, stroke or diabetes. However, there was a borderline-significant higher risk of stroke among atopics compared to non-atopics. The pooled analyses and the meta-estimates were very similar.

Previous studies on atopy and CVD show inconsistent results: Hospers et al. [8] found skin prick test positivity to inhalant allergens to be associated with a reduced cardiovascular mortality in non-smokers with normal weight and lung function but a higher cardiovascular mortality among persons with above-normal BMI, reduced lung function, or smokers; a study by Langer et al. [10] found that IgE predicted incident non-fatal myocardial infarction in men but not in women; a study by Jaramillo et al. [9] found that atopy as assessed by both the number of positive specific IgE tests and as the sum of specific IgE values was

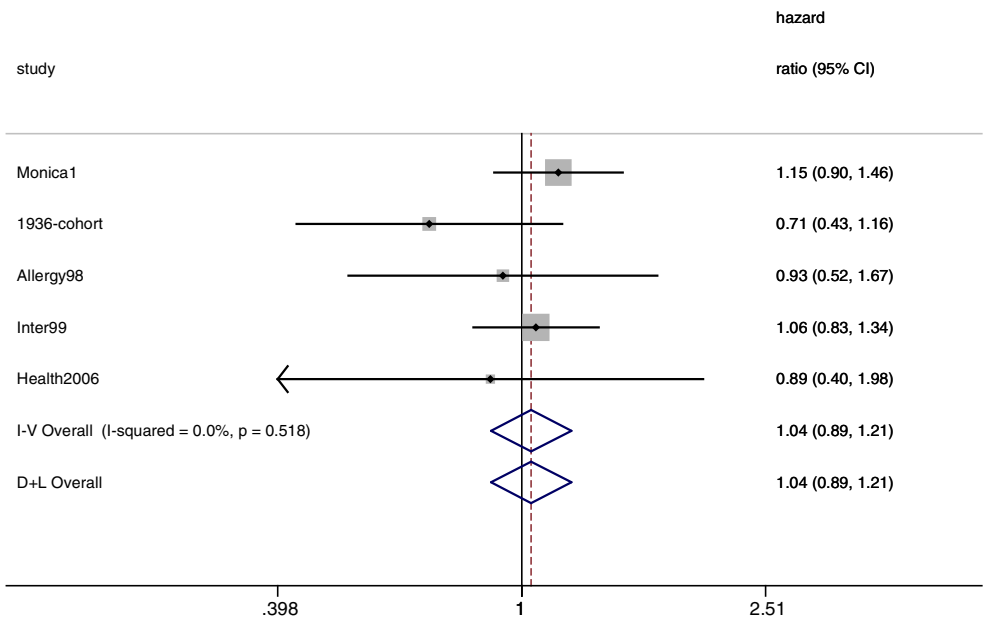

Fig. 1 Meta-analysis of the study-specific estimates of the association between atopy and incident diabetes. *A98* Allergy98, *C36* 1936-cohort, *H06* Health2006, *I99* Inter99, *M1* Monica1, and *CI* confidence interval

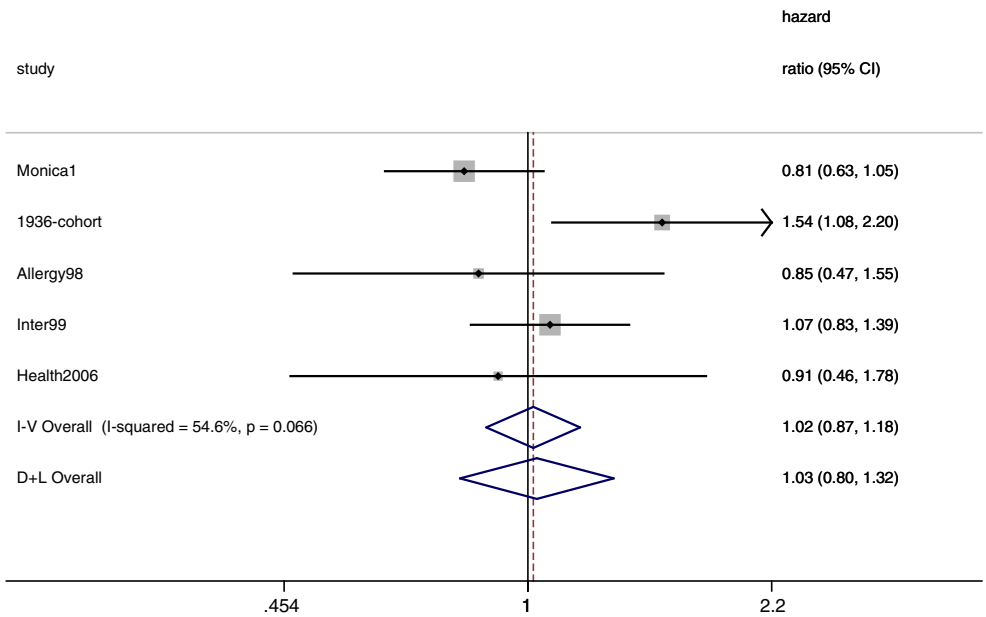

Fig. 2 Meta-analysis of the study-specific estimates of the association between atopy and incident ischemic heart disease. *A98* Allergy98, *C36* 1936-cohort, *H06* Health2006, *I99* Inter99, *M1* Monica1, and *CI* confidence interval

inversely related to past myocardial infarction; and a study by Criqui et al. [7] of 262 men and 315 women reported a cross-sectional association between serum total IgE and coronary heart disease and stroke in men but not in women. However, serum total IgE is not a specific biomarker of atopy and is known to increase with smoking and intake of alcohol [24, 25]. The observed lack of associations between atopy and incident ischemic heart disease and stroke in the present study are somewhat inconsistent with the above mentioned studies. Regarding the observed lack of association between atopy and diabetes development, our results are inconsistent with two relatively small studies studies by Wang et al. [11, 12] of 340 and 260 persons, respectively, where serum total IgE and chymase positively associated with diabetes status and the risk of pre-diabetes.

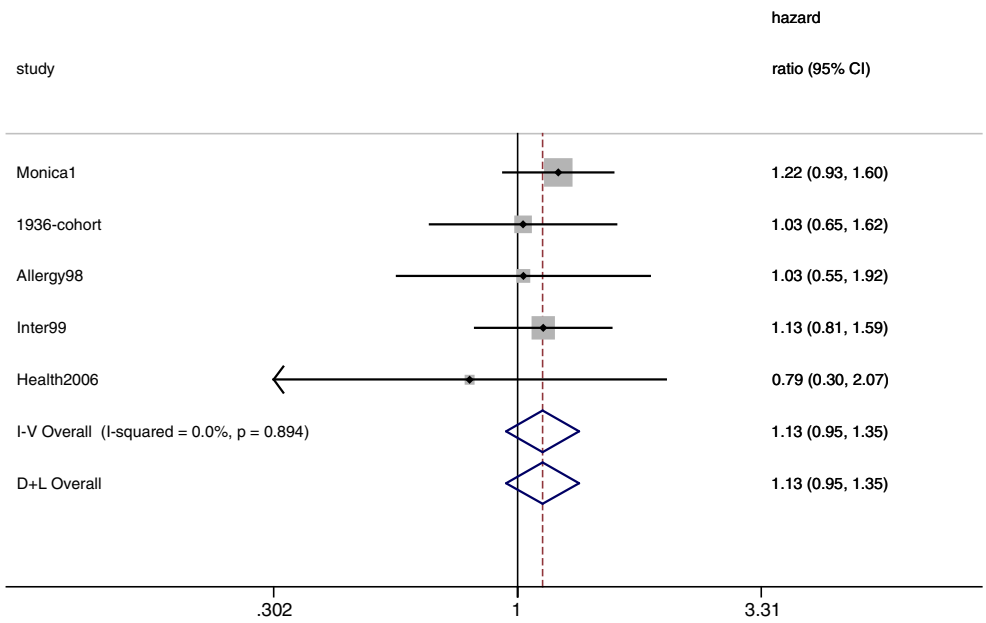

Fig. 3 Meta-analysis of the study-specific estimates of the association between atopy and incident stroke. *A98* Allergy98, *C36* 1936-cohort, *H06* Health2006, *I99* Inter99, *M1* Monica1, and *CI* confidence interval

Several possible mechanisms may link atopy with the pathogenesis of CVD and diabetes. First, atopy-related disease and atherosclerosis may share central effector pathways such as mast cells or leukotrienes that are hallmarks of allergy but are also becoming recognized as key factors of atherosclerosis [26]. Mast cells are known to be important in IgE-mediated allergic immune responses. They are at the center of anaphylaxis and allergic inflammation, where IgE provides the link between antigen (allergen) and the IgE-receptor [27]. Mast cell products have a variety of biological functions [27]. IgE-mediated release of histamine or other mast cell products may produce spasm in the coronary arteries [28], and mast cell tryptase is suggested as a new biomarker of coronary heart disease [29]. Regarding glucose homeostasis and diabetes, Liu et al. [5, 6] have shown that genetically induced mast cell deficiency or pharmacological mast cell stabilization reduced weight gain and improved glucose homeostasis in mice [5]. Many mast cell mediators associate with diabetes mellitus. Also, the levels of the mast cell mediator, serum tryptase, seem to be higher in individuals with the metabolic syndrome [30]. Second, inflammation is involved in the pathogenesis of both atherosclerosis and asthma, and the localized allergic disease causes a systemic inflammatory response that potentially promotes atherosclerosis [26]. Third, IgE-mediated antigenic response can cause platelet activation and aggregation [7]. Nastalek et al. [31] found altered plasma fibrin clot properties associated with reduced efficiency of fibrinolysis in patients with atopic dermatitis. Of note, however, atopy could also be protective of cardiovascular mortality since they have a mild haemostatic imbalance [32].

The strengths of our study include its prospective study design and the long follow-up period that allowed assessment of temporal relationships; an objective marker of atopy; the detailed information on possible confounders; the large population-based samples; and the use of standardized registry-based diagnoses with almost no loss to follow-up. Data from the Danish National Diabetes Register ensured an objective standardized definition of diabetes and almost complete follow-up. Serum-specific IgE positivity to inhalant allergens is considered a valid marker of atopy in epidemiological studies. We used commercial immunoassays for determination of serum-specific IgE, and we have previously found that results obtained with these assays are in agreement with skin prick test reactivity and a diagnosis of allergic respiratory disease [33, 34].

The limitations of the study include the possible shortage of power to detect small to moderate effect sizes, and the fact that the Danish National Diabetes Register does not distinguish between different types of diabetes. However, by far, the majority of incident cases of type 1 diabetes is among children and adolescents making the contribution of type 1 diabetes cases among adults negligible. The difference in prevalence of atopy in the 5 study populations is probably due to the different time periods and mean ages, i.e., atopy is more common at younger ages and has shown a general increase in the last decades [35]. Thus, the prevalence of atopy is smallest in the earliest studies.

In conclusion, atopy as assessed by specific IgE positivity appeared to have no role in subsequent risk of developing ischemic heart disease, stroke, or diabetes in the present study. The implications of our results are that the trend of increasing atopy is not likely to contribute to the worldwide burden of CVD or diabetes. However, there was a borderline-significant higher risk of stroke among atopics compared to non-atopics, and we cannot exclude smaller effects of atopy in the development of ischemic heart disease, stroke, or diabetes.

Conflict of interest The authors have no conflicts of interest.

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