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Poor agreement in questionnaire-based diagnostic criteria for adult atopic dermatitis is a challenge when examining cardiovascular comorbidity.

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Title Page

Title

Poor agreement in questionnaire-based diagnostic criteria for adult atopic dermatitis is a challenge when examining cardiovascular comorbidity

Running head

Atopic dermatitis and cardiovascular risk factors

Key words

Atopic dermatitis, diagnostic criteria, questionnaire, cardiovascular risk

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Drs. Andersen, Hamann, Linneberg, Skaaby and Egeberg had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Andersen, Egeberg, Skov, Linneberg and Thyssen. *Acquisition, analysis, and interpretation of data:* Andersen, Egeberg, Hamann, Skov and Thyssen. *Drafting of the manuscript:* Andersen and Thyssen. *Critical revision of the manuscript for important intellectual content:* All authors. *Statistical analysis:* Andersen and Hamann. *Administrative, technical, or material support:* All authors. *Study supervision:* Thyssen

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Declaration of interests

Dr. Thyssen has attended advisory boards for Roche and Sanofi-Genzyme and received speaker honorarium from LEO Pharma and Galderma. Dr. Skov has received consultancy and/or speaker honoraria from Abbvie, Pfizer, Janssen-Cilag, Merck Sharp & Dohme, and Leo Pharma and is a member of the advisory boards of Abbvie, Pfizer, Janssen-Cilag, Merck Sharp & Dohme, Eli Lilly, Celgene and Novartis. Dr. Egeberg has received research funding from Pfizer and Eli Lilly, and honoraria as consultant and/or speaker from Pfizer, Eli Lilly, Novartis, Galderma, and Janssen Pharmaceuticals. Drs. Andersen, Hamann, Gislason, Skaaby and Linneberg have no conflicts of interests to declare. This research was performed independently through the authors' academic university and hospital affiliations.

Abstract (247/250)

Background

The association between atopic dermatitis (AD) and cardio-metabolic risk factors is not yet established. Furthermore, no validated questionnaire-based method of identifying adults with AD is currently available.

Objectives

To assess the cardio-metabolic risk in adults with a history of AD by using three different questionnaire-based diagnostic criteria.

Methods

We utilized data from a general population study including questionnaire data and objective measurements of 9,656 Danish adults. To identify adults with a history of AD, we used a question regarding physician-diagnosed AD, and two versions of the UK Working Party Diagnostic Criteria. Associations between AD status and cardio-metabolic endpoints were estimated using survey weighted logistic and linear regression analysis.

Results

We identified 462 (4.8%) adults with self-reported physician-diagnosed AD, whereas 903 (9.4%) and 226 (2.3%) had AD according to the UK Working Party Criteria when at least two and three of four minor criteria were fulfilled. The populations were not comparable in terms of occurrence of cardio-metabolic risk factors. For example, the prevalence of obesity was lower in participants with physician-diagnosed AD but overall higher in UK 2/4 and UK 3/4.

Conclusion

Due to the heterogeneity in the captured study populations in terms of the studied outcomes and absence of a gold standard, no conclusions regarding the cardio-metabolic risk in adults with AD in a general population could be made. This study serves as an example of the challenges that are often encountered in questionnaire-based epidemiologic studies and highlights the need of better definitions for this patient group.

Introduction

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory, pruritic skin condition with a lifetime prevalence of 10-20%.[1] AD typically begins during infancy or early childhood and may, in some cases, persist into adulthood. Occasionally, individuals may also develop AD in adulthood.[1,2] While dermatitis is often located to the trunk and extensors in infancy, flexural involvement is common in childhood, adolescence and adulthood. Other typical involved areas include the head and neck, as well as the hands and feet.[2]

Patients with AD suffer from primary or secondary xerosis, in some cases driven by a loss-of-function mutation in the filaggrin gene (*FLG*),[3] and have increased risk of developing food allergies, allergic rhinitis and asthma.[4] Several sets of diagnostic qualitative criteria for AD have been developed based on the collection of clinical features in children, including the Hanifin and Rajka criteria, the UK Working Party Criteria and the ISAAC criteria.[5–8] While these criteria have been repeatedly validated in paediatric populations, this is not the case for adult populations.[9] It is thus uncertain whether these criteria are applicable to accurately identify adults with a history of (or active) AD. Moreover, translating a set of diagnostic criteria into questionnaires may carry additional challenges.

The recent surge in studies investigating the association between AD in adults and cardio-metabolic comorbidities has shown conflicting results.[10–16] The discrepancies are most likely explained by differences in cardiovascular risk profiles in patient populations, but methodological heterogeneity across the previous studies regarding study design, AD definition, statistical models and outcome measures may also have contributed to differing study conclusions. We investigated the prevalence of cardio-metabolic risk factors in a large adult Danish general population using questionnaire-based definitions of AD and objective outcome measures. Since there is currently little insight into which questionnaires are best at identifying adults with a history of AD, we applied three separate definitions to assess their agreement and homogeneity.

Materials and Methods

Data sources

The Danish Study of Functional Disorders (DanFunD) is a large cross-sectional general population study that contains health care data derived from questionnaires and general health examination.[17] A total of 9,656 randomly sampled Danish adults aged 18 to 76 years participated in the DanFunD study in greater Copenhagen. The study was conducted at the Research Centre for Prevention and Health (RCPH) and data was collected in two phases. The data for part one was collected during 2011-2012 and was a follow-up study of a previous study cohort, the Health2006 cohort.[18] A total of 3,405 were invited, of which 2,308 (67.8%) individuals responded. Part two was conducted during 2012-2015, where a total of 25,368 adults were invited, of which 7,493 (29.5%) participated.[17]

Questionnaire data

Participants completed questionnaires about health related behaviour and symptoms as well as information on socio-economic factors. To identify individuals with AD, we utilized three sets of diagnostic criteria constructed from the questionnaire. Definition 1 was defined by a question regarding self-reported physician-diagnosed AD. Definitions 2 and 3 were based on modified versions of questions used in the UK Working Party Criteria for Atopic Dermatitis.[19,20]

The question that addressed the UK Working Party major criterion was ‘have you ever had an itchy skin condition?’ Questions that addressed the minor criteria were ‘did the skin condition begin before the age of 2?’, ‘has the skin condition involved the skin in front of the elbows, behind the knees, around the wrists, the neck or the eyes?’, ‘has a doctor ever told you that you have/ have had asthma or hay fever?’, and ‘have you ever had dry skin in general?’

- Definition 1 (physician-diagnosed): An affirmative answer to the question ‘has a doctor ever told you that you have/ have had AD’
- Definition 2 (UK 2/4): Fulfilled the major criterion and at least two of four minor criteria of the UK Working Party criteria.

- Definition 3 (UK 3/4): Fulfilled the major criterion and at least three of four minor criteria of the UK Working Party criteria.

UK 2/4 has been repeatedly used in Danish population-based studies, [21,22] since previous validation studies of different cut-off points showed slightly lower specificity, but a higher sensitivity when using two minor criteria instead of three.[23,24] To reduce possible diagnostic misclassification, participants were removed from the AD group and classified as controls if they also reported having physician-diagnosed psoriasis in the questionnaire. Questions regarding self-reported cardiovascular risk factors, including hypertension and hypercholesterolemia, were based on questions with the same wording, i.e., "has a doctor ever told you that you have/ have had…". Questions regarding smoking habits and alcohol consumption are described in detail elsewhere.[25]

Physical examination and biochemical measures

All participants underwent a physical health examination at the RCPH. Body mass index (BMI) was determined by measuring participants' weight and height in light clothing and without shoes (kg/m^2). Waist circumference was measured to nearest centimetre (cm) between the iliac crest and lowest rib. Body fat percentage (%) was measured using a foot-to-foot Tanita Body Composition Analyzer (TBF-300, TANITA Corporation of America, Inc., Illinois, USA.).[26] Systolic and diastolic blood pressures (mmHg) were measured at least twice per participant using a mercury sphygmomanometer (Mercuro 300, Speidel & Keller, GmbH & Co, Jungingen, Germany). A mean value of the last two blood pressure measurements was calculated for systolic and diastolic blood pressure, respectively. Hand grip strength in the dominant hand was measured using a Jamar dynamometer (Sammons Preston Rolyan, Chicago, Illinois, USA).[27] Cardio-respiratory fitness was measured as maximum oxygen intake (VO_2 max) using indirect maximal cycle ergometer test, or a step test.[28] Participants were asked to fast from the midnight prior to the day of examination to enable a fasting blood sample collection. Levels of total serum cholesterol (mmol/l) were determined enzymatically. Part one of the DanFunD cohort was genotyped for the three most common mutations in *FLG*, R501X, 2282del4, and R2447X, by methods described elsewhere.[29]

BMI was categorized according to the World Health Organization (WHO) classification (<18.5, 18.5-<25, 25-29, >30).[30] Waist circumference was divided into normal (<80cm for women, <94cm for men), overweight (80-88cm for women, 94-102 cm for men) and obese (>88cm for women, >102cm for men) according to the WHO classification.[31] High body fat percentage was defined by commonly used cut-off points (>30% in women and >25% in men).[32] Smoking (cigarettes, cheroots, or pipe tobacco) habits were classified as never, previous, current light smoker (less than 15 g tobacco per day) or current heavy smoker (15 g or more tobacco per day). Moderate to heavy consumption of alcohol was defined as consumption of more than 7 units and more than 14 units of alcohol per week for, respectively, women and men, according to recommendations by the Danish Health Authority.[33]

Statistical analysis

Descriptive statistics were used to present frequencies and percentages for categorical variables and mean and standard deviation (SD) for continuous variables. A binary value for AD was modelled as the dependent variable in multivariable logistic regression analyses to estimate adjusted odds ratios (aOR) with 95% confidence intervals (CI). Linear regression models were applied to continuous outcomes. All continuous variables were tested for normal distribution using histograms and regression diagnostics were used to assess linear model assumptions. Beta coefficients (β) for the slopes were estimated with 95% CI. Analyses regarding cardiovascular risk factors and physical fitness outcomes were adjusted for age and sex in multivariable models. Analyses of hypertension and hypercholesterolemia were further adjusted for BMI and smoking habits. Survey weights were calculated based on the fraction of responders among the invited individuals for each combination of sex and age group. Weighted analyses were applied in all adjusted models. P-values < 0.05 were considered statistically significant.

Missing data

For all covariates and endpoints the number of missing observations was less than 5% except for the question regarding alcohol consumption (9.3%) and the cardio-respiratory fitness test (14.4%).

Complete case analyses were applied where participants with missing data were excluded from each analysis. Frequencies of missing observations are presented in supplementary table 1.

Results

Population characteristics

A total of 9,656 individuals participated in the study, of which 462 (4.8%), 903 (9.4%) and 226 (2.3%) were classified as having a history of AD according to definition 1 (physician-diagnosed), 2 (UK 2/4), and 3 (UK 3/4), respectively (Table 1). The sizes and overlaps of the three AD populations are illustrated in Figure 1. A total of 1,076 individuals were identified as having AD by at least one of the definitions, however only 136 (12.6%) of these fulfilled all three definitions. A total of 289 (32.0%) of 903 participants who fulfilled UK 2/4 also reported physician-diagnosed AD. Participants who reported physician-diagnosed AD were slightly younger (mean age [SD] 45.1 [13.8]) compared with UK 2/4 (mean age [SD] 49.3 [13.9]) and UK 3/4 (mean age [SD] 49.3 [13.9]). The proportion of female participants was higher in the AD group compared with the control group across all three definitions (67.8%, 66.0%, and 68.6%). Participants who reported physician-diagnosed AD had slightly higher education levels compared to controls and AD individuals by UK criteria 2/4 and 3/4. The prevalence of loss-of-function mutations in *FLG* was 25.3%, 19.8%, and 27.9% in participants with physician diagnosed AD, UK 2/4 and UK 3/4, respectively.

Cardio-metabolic risk factors

The prevalence of adiposity varied across the three AD groups, with lower prevalence in participants with physician-diagnosed AD and overall higher prevalence in UK 2/4 and UK 3/4. (Table 2) In age- and sex-adjusted analyses, physician-diagnosed AD was not associated with measures of BMI, waist circumference or body fat percentage (Table 3). Obesity measured as BMI and waist circumference, respectively, was significantly associated with UK 2/4 (aOR 1.47; 95% CI 1.21-1.78 and aOR 1.23; 95% CI 1.04-1.44) and for BMI in UK 3/4 (aOR 1.47; 95% CI 1.03-2.11); however analyses for

overweight were statistically non-significant. High body fat percentage was not significantly associated with AD across all three definitions in multivariate analyses. The prevalence of self-reported history of smoking was similar in adults with AD and controls across the three definition groups. Physician-diagnosed AD was negatively associated with current heavy smoking (aOR 0.48; 95% CI 0.29-0.80), while the other endpoints remained non-significant. Alcohol overuse was not associated with AD in any of the definitions. Self-reported hypertension and hypercholesterolemia were not associated with AD in any of the groups after adjusting for age, sex, BMI and smoking status (Table 5). Similarly, none of the measured parameters for high blood pressure or moderate to high serum cholesterol levels showed any significant associations with AD in fully adjusted models.

Physical fitness

Participants with physician-diagnosed AD reported to have a better physical fitness compared with participants in UK 2/4 and UK 3/4. In analyses where the three AD groups were compared with controls adjusted for age and sex, individuals with physician-diagnosed AD and UK 3/4 had comparable fitness to controls. UK 2/4 was negatively associated with 'self-perceived good physical fitness' (aOR 0.77; 95% CI 0.65-0.91) and positively associated with 'less good' (aOR 1.40; 95% CI 1.16-1.70) and 'poor' (aOR 1.55; 95% CI 1.14-2.12) physical fitness. Furthermore, participants with AD according to UK 2/4 reported significantly higher rates of sedentary lifestyles compared with controls (aOR 1.34; 95% CI 1.09-1.65). Participants with physician-diagnosed AD performed better in the cardio-respiratory fitness test (β 2.40; 95% CI 1.49, 3.31), however in age and sex adjusted analysis no significant association was found (Table 4). Adults with AD had slightly poorer performance in the hand-grip test in UK 2/4 (β -4.74; 95% CI -6.46, -3.01) and UK 3/4 (β -4.89; 95% CI -8.21, -1.57), respectively. In age and sex adjusted models, participants with AD by UK 2/4 performed slightly poorer in the cardio-respiratory fitness test (β -0.98; 95% CI -1.61, -0.35) and in the hand-grip test (β -1.12; 95% CI -2.15, -0,09).

Discussion

Main findings

In the current study different questionnaire-based criteria for a history of AD resulted in striking heterogeneity regarding demographics and cardio-metabolic risk factors in a large adult general population cohort despite all being convincingly associated with *FLG* mutations. Participants with self-reported physician-diagnosed AD had a similar cardio-metabolic risk profile as controls, while adults with a history of AD according to UK Working Party Criteria for AD were more obese and had poorer physical activity levels than controls. The risk of hypertension and hypercholesterolemia were similar to controls across all three definitions.

Interpretation

The three questionnaire-based definitions of a history of AD in adults yielded alarmingly different prevalence estimates and with relatively small areas of overlap, indicating that different phrasing of questions may significantly influence the participants that are captured. The absence of a gold standard reference in this study hindered us from assessing the most accurate criteria for AD. Several factors may explain why identifying individuals with AD through questionnaires is challenging. Firstly, although AD is a chronic condition, it is characterized by periods of flare and remission, which can cause difficulties for patients to report certain symptoms at a given time. Furthermore, the presentation of AD is heterogeneous with slightly different phenotypes depending on ethnicity and age.[34,35] Notably, xerosis may be of particular importance in populations where *FLG* mutations are prevalent, e.g. in Northern Europe.[36] Additionally, while differential diagnoses of AD are relatively limited in children, adults may have experienced a range of skin conditions that resemble symptoms of AD during their lifetime.[37]

Self-reported physician-diagnosed AD is commonly used in questionnaire settings. We found a relatively low life-time prevalence of AD (4.8%), perhaps due to a low sensitivity as mild cases of AD may not ever present to a physician. A validation study conducted in the US examined the diagnostic

accuracy of the question: 'have you ever been told by a doctor or other health professional that you had eczema or any kind of skin allergy?' in adults, and found a low sensitivity (0.43; 95% CI 0.37-0.51) but a high positive predictive value (0.91; 95% CI 0.85-0.97) when using clinical examination of the Hanifin and Rajka Criteria as reference.[38] A Swedish study used the question 'have you had childhood eczema?' in adults with health records of AD during childhood compared with adults without childhood records of AD. 29% of participants with a history of AD during childhood did not report AD in the questionnaire. The participants' ability to remember their childhood condition was influenced by disease severity, disease activity at the time of survey and who noticed the symptoms during childhood.[39]

The UK Working Party Criteria for Atopic Dermatitis definitions of AD were introduced in 1994 to create a simpler and more suitable tool for epidemiologic research compared with the Hanifin and Rajka Criteria.[6] Originally designed for paediatric populations, validation studies of the UK Working Party Criteria in adults in hospital settings have shown relatively high sensitivity and positive predictive values.[9] Nevertheless, these criteria may be problematic when applied in a questionnaire setting in adult populations. Adults who have been in remission since childhood or adolescence may not be able to recall their past symptoms accurately, introducing a significant risk of recall bias. Moreover, pruritus (major criterion) and flexural involvement (one of the minor criteria) in adults can be unspecific and represent different conditions such as irritant or allergic contact dermatitis, scabies, lichen planus or intertrigo.[37] These possible misclassifications could have polluted the UK 2/4 and UK 3/4 groups in our study, thereby complicating the interpretation of results. For example, that AD according to the UK 2/4 or UK 3/4 criteria was significantly associated with obesity, but not with being overweight might be explained by such misclassification.

Due to the heterogeneity in AD study populations and results in the current study, as well as the absence of a gold standard of questionnaire-based AD diagnosis, we cannot draw firm conclusions regarding the cardio-metabolic risk in adults with a history of AD. The majority of previous questionnaire-based studies that investigated the relationship between AD in adults and adiposity have found positive results regardless of the applied definitions.[10,40–42] Levels of physical activity were

investigated in two US cohorts using the questions 'during the past 12 months, have you had dermatitis, eczema, or any other red, inflamed skin rash?' and 'during the past 12 months, have you been told by a doctor or other health professional that you had eczema or any kind of skin allergy?' where adults with AD had more sedentary lifestyle compared with controls.[10] Previous questionnaire studies on the association between AD and hypertension or hypercholesterolemia have applied different inclusion criteria with inconsistent results.[10,15,41,43] For example, a large Canadian study used the wording 'has a doctor ever told you that you had eczema?' and concluded that an inverse association existed between AD and cardiovascular risk factors.[15] It is therefore possible that previous questionnaire-based studies also have been challenged by the putative imprecision of AD diagnosis.

Strengths and limitations

We utilized a large set of general population data, which makes the results more generalizable as opposed to studies based on selected patient cohorts. Furthermore, objective anthropometric measurements in adults with AD are not commonly reported. Study limitations include a relatively low response rate and a skewed age and gender distribution. Additionally, no information regarding disease activity or severity of AD was available.

Conclusion

In this large population-based study, we used three sets of definitions for AD in adults to investigate the prevalence of cardio-metabolic risk factors. The study populations and results varied substantially according to the applied criteria and we could therefore not draw any conclusion on the association between cardio-metabolic risk factors and AD. Our study indicates that a clinical diagnosis is necessary for a reliable diagnosis of AD in adults and that questionnaire studies should be carefully interpreted. Register based or clinical cohort studies with AD diagnoses given by dermatologist are likely to provide more accurate estimates and are preferable. Studies are needed to evaluate the exact performance of the UK criteria when used in questionnaires to adults.

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Table 1. Baseline characteristics of study populations

	Physician-diagnosed AD	Controls	AD, UK 2/4	Controls	AD, UK 3/4	Controls
	n= 462 (4.8)	n=9194 (95.2)	n= 903 (9.4)	n=8753 (90.7)	n=226 (2.3)	n=9430 (97.7)
Mean age (SD)	45.1 (13.8)	52.9 (13.1)	49.3 (13.9)	52.9 (13.1)	48.6 (14.1)	52.6 (13.2)
Age category						
18-30	80 (17.3)	701 (7.6)	110 (12.2)	671 (7.7)	29 (12.8)	752 (8.0)
31-45	149 (32.3)	1709 (18.6)	216 (23.9)	1642 (18.8)	55 (24.3)	1803 (19.1)
46-60	159 (34.4)	3664 (39.9)	342 (37.9)	3481 (39.8)	91 (40.3)	3732 (39.6)
≥61	74 (16.0)	3120 (33.9)	235 (26.0)	2959 (33.8)	51 (22.6)	3143 (33.3)
Sex						
Women (%)	313 (67.8)	4890 (53.2)	596 (66.0)	4607 (52.6)	155 (68.6)	5048 (53.5)
Men (%)	149 (32.3)	4304 (46.8)	307 (34.0)	4146 (47.4)	71 (31.4)	4382 (46.5)
Educational level						
No education beyond high school	60 (13.1)	928 (10.2)	105 (11.7)	883 (10.2)	26 (11.5)	962 (10.3)
Technical school or job training	165 (35.9)	4457 (49.0)	412 (46.1)	4210 (48.6)	98 (43.4)	4524 (48.5)
University education	171 (37.3)	2746 (30.2)	286 (32.0)	2631 (30.4)	75 (33.2)	2842 (30.4)
Master's degree or higher	63 (13.7)	973 (10.7)	91 (10.2)	945 (10.9)	27 (12.0)	1009 (10.8)
Subgroup analysis of DanFund part 1	n= 87	n= 2076	n= 192	n= 1971	n= 61	n= 2101
***FLG* mutation**	22 (25.3)	220 (10.6)	38 (19.8)	204 (10.4)	17 (27.9)	225 (10.7)

AD, atopic dermatitis; *FLG*, filaggrin gene; SD, standard deviation

Physician diagnosed AD: An affirmative answer to the question 'has a doctor ever told you that you have/ have had atopic eczema?' UK 2/4: Fulfilled the major criterion and at least two of four

minor criteria of the modified version of UK Working Party Criteria for Atopic Dermatitis, UK 3/4: Fulfilled the major criterion and at least three of four minor criteria of the modified version of UK Working Party Criteria for Atopic Dermatitis.

Table 2. Prevalence of cardiovascular risk factors in adults with a history of atopic dermatitis, n (%)

	Physician-diagnosed AD	Controls	AD, UK 2/4	Controls	AD, UK 3/4	Controls
	n=462	n=9194	n=903	n=8753	n=226	n=9430
BMI						
Underweight, BMI ≤18.5	10 (2.2)	164 (1.8)	13 (1.44)	161 (1.84)	3 (1.3)	171 (1.8)
Normal weight	227 (49.1)	4031 (43.8)	394 (43.6)	3864 (44.1)	104 (46.0)	4154 (44.1)
Overweight, BMI ≥25	156 (33.8)	3424 (37.2)	313 (34.7)	3267 (37.3)	71 (31.4)	3509 (37.2)
Obese, BMI ≥30	69 (14.9)	1575 (17.1)	183 (20.3)	1461 (16.7)	48 (21.2)	1596 (16.9)
Waist circumference						
Normal, women <80cm / men <94cm	244 (52.8)	4332 (47.2)	409 (45.3)	4177 (47.7)	100 (44.3)	4476 (47.5)
Overweight, women 80-88cm / men 94-102cm	108 (23.4)	2215 (24.1)	207 (22.9)	2116 (24.2)	54 (23.9)	2269 (24.1)
Obese, women >88cm / men >102cm	110 (23.8)	2637 (28.7)	287 (31.8)	2460 (28.1)	72 (31.9)	2675 (28.4)
Body fat percentage						
Normal	205 (44.6)	3889 (42.8)	352 (39.0)	3800 (43.4)	90 (39.8)	4004 (42.7)
High, women ≥ 30%/ men ≥ 25%	255 (55.4)	5249 (57.8)	551 (61.0)	4953 (56.6)	136 (60.2)	5368 (57.3)
Self-reported fitness level						
Very good	14 (3.0)	336 (3.7)	26 (2.9)	324 (3.7)	7 (3.1)	343 (3.7)
Good	148 (32.1)	3325 (36.4)	255 (28.4)	3218 (37.0)	66 (29.6)	3407 (36.3)
Fair	202 (43.8)	3760 (41.2)	373 (41.5)	3589 (41.3)	92 (41.3)	3870 (41.3)
Less good	79 (17.1)	1328 (14.5)	187 (20.8)	1220 (14.0)	45 (20.2)	1362 (14.5)
Poor	18 (3.9)	386 (4.3)	57 (6.4)	347 (4.0)	13 (5.8)	391 (4.2)
Leisure time activity level						
Athletic	7 (1.5)	137 (1.5)	11 (1.2)	133 (1.5)	4 (1.8)	140 (1.5)
Vigorous	156 (33.8)	2699 (29.6)	251 (28.0)	2604 (30.0)	73 (32.4)	2782 (29.8)
Moderate	233 (50.5)	5054 (55.4)	473 (52.7)	4814 (55.5)	111 (49.3)	5176 (55.4)

Sedentary	65 (14.1)	1225 (13.4)	163 (18.2)	1127 (13.0)	37 (16.4)	1253 (13.4)
Smoking status						
Current heavy smoking ≥ 15 g daily	17 (3.7)	664 (7.3)	60 (6.6)	621 (7.1)	10 (4.4)	671 (7.1)
Current light smoking <15 g daily	47 (10.2)	854 (9.3)	88 (9.8)	813 (9.3)	19 (8.4)	882 (9.4)
Former smoking	157 (34.0)	3489 (38.1)	337 (37.3)	3309 (38.0)	83 (36.7)	3563 (38.0)
Never smoked	241 (52.2)	4143 (45.3)	418 (46.3)	3966 (45.5)	114 (50.4)	4270 (45.5)
Alcohol consumption						
Heavy use, women > 7 units, men > 14 units	79 (18.5)	2143 (25.7)	182 (22.2)	2040 (25.7)	42 (21.1)	2180 (25.5)
Normal use, women ≤ 7 units, men ≤ 14 units	348 (81.5)	6189 (74.3)	637 (77.8)	5900 (74.3)	157 (78.9)	6380 (74.5)

AD, atopic dermatitis; BMI, body mass index

Physician diagnosed AD: An affirmative answer to the question 'has a doctor ever told you that you have/ have had atopic eczema?' UK 2/4: Fulfilled the major criterion and at least two of four minor criteria of the modified version of UK Working Party Criteria for Atopic Dermatitis, UK 3/4: Fulfilled the major criterion and at least three of four minor criteria of the modified version of UK Working Party Criteria for Atopic Dermatitis.

Table 3. Association between self-reported atopic dermatitis and cardio-metabolic risk factors

Outcomes	**Physician diagnosed AD**			**AD by UK 2/4**			**AD by UK 3/4**		
	OR*	**95% CI**	**p-value**	**OR***	**95% CI**	**p-value**	**OR***	**95% CI**	**p-value**
BMI									
Underweight, BMI ≤18.5	0.84	0.41-1.71	0.586	0.71	0.39-1.30	0.099	0.60	0.18-2.00	0.297
Normal weight	-	-	-	-	-	-	-	-	-
Overweight, BMI ≥25	1.08	0.87-1.35	0.368	1.11	0.94-1.31	0.469	1.00	0.73-1.39	0.857
Obese, BMI ≥30	0.99	0.74-1.32	0.908	**1.47**	**1.21-1.78**	**<0.001**	**1.47**	**1.03-2.11**	**0.032**
Waist circumference									
Overweight, women 80-88cm / men 94-102cm	0.90	0.71-1.14	0.815	0.99	0.83-1-18	0.179	1.02	0.73-1.44	0.606
Obese, women >88cm / men >102cm	0.76	0.60-0.97	0.046	**1.23**	**1.04-1.44**	**0.006**	1.23	0.90-1.69	0.180

Body fat percentage									
High, women ≥ 30%/ men ≥ 25%	0.98	0.79-1.22	0.839	1.16	0.98-1.36	0.086	1.07	0.79-1.45	0.649
Self-reported fitness level									
Very good	0.81	0.46-1.44	0.653	0.84	0.55-1.28	0.160	0.85	0.39-1.86	0.584
Good	0.89	0.71-1.11	0.861	**0.77**	**0.65-0.91**	**<0.001**	0.78	0.56-1.09	0.153
Fair	-	-	-	-	-	-	-	-	-
Less good	1.05	0.80-1.39	0.215	**1.40**	**1.16-1.70**	**<0.001**	1.28	0.88-1.86	0.153
Poor	0.79	0.47-1.32	0.521	**1.55**	**1.14-2.12**	**0.003**	1.25	0.69-1.86	0.384
Leisure time activity level									
Athletic	0.94	0.41-2.13	0.797	0.88	0.44-1.75	0.525	1.11	0.39-3.21	0.950
Vigorous	1.20	0.96-1.51	0.192	0.99	0.84-1.18	0.669	1.26	0.92-1.74	0.562
Moderate	-	-	-	-	-	-	-	-	-
Sedentary	0.95	0.70-1.29	0.638	**1.34**	**1.09-1.65**	**0.028**	1.21	0.81-1.82	0.753
Smoking status									
Current heavy smoking ≥ 15 g daily	**0.48**	**0.29-0.80**	**0.015**	0.96	0.72-1.29	0.784	0.92	0.68-1.23	0.148
Current light smoking <15 g daily	0.80	0.57-1.12	0.807	0.96	0.75-1.24	0.768	0.77	0.46-1.28	0.916
Former smoking	0.93	0.75-1.16	0.061	1.04	0.89-1.21	0.470	0.92	0.68-1.23	0.255
Alcohol consumption									
Heavy use, women > 7 units, men > 14 units	0.88	0.67-1.14	0.325	0.94	0.78-1.12	0.468	0.92	0.65-1.31	0.644

* OR estimates were adjusted for age, sex and survey weights in multivariable logistic regression analyses. AD, atopic dermatitis; BMI, body mass index; CI, confidence interval; OR, odds ratio Physician diagnosed AD: An affirmative answer to the question 'has a doctor ever told you that you have/ have had atopic eczema?' UK 2/4: Fulfilled the major criterion and at least two of four minor criteria of modified version of UK Working Party Criteria for Atopic Dermatitis, UK 3/4: Fulfilled the major criterion and at least three of four minor criteria of modified version of UK Working Party Criteria for Atopic Dermatitis.

Table 4. Linear associations between self-reported atopic dermatitis and physical fitness tests performance

			Crude			Adjusted for age, sex and survey weights		
Fitness test	**Physician diagnosed AD**	**Controls**	beta	95% CI	p value	beta	95% CI	p value
VO_2 max (ml/kg/min), mean (SD)	35.57 (9.95)	33.17 (9.52)	**2.40**	**1.49, 3.31**	**<0.001**	0.54	-0.34, 1.41	0.228
Hand grip test (kg), mean (SD)	76.53 (24.57)	77.87 (25.15)	-1.79	-4.01, 0.43	0.1144	1.32	-0.04, 2.69	0.058
	AD by UK 2/4	**Controls**	beta	95% CI	p value	beta	95% CI	p value
VO_2 max (ml/kg/min), mean (SD)	33.44 (9.85)	33.29 (9.53)	0.15	-0.57, 0.87	0.682	**-0.98**	**-1.61, -0.35**	**0.002**
Hand grip test (kg), mean (SD)	73.51 (25.06)	78.25 (25.08)	**-4.74**	**-6.46, -3.01**	**<0.001**	**-- 1.12**	**-2.15, -0.09**	**0.033**
	AD by UK 3/4	**Controls**	beta	95% CI	p value	beta	95% CI	p value
VO_2 max (ml/kg/min), mean (SD)	33.87 (9.77)	33.29 (9.55)	0.58	-0.81, 1.97	0.410	-0.55	-1.78, 0.67	0.372
Hand grip test (kg), mean (SD)	73.03 (24.18)	77.92 (25.13)	**-4.89**	**-8.21, -1.57**	**0.004**	-0.88	-2.66, 0.90	0.333

AD, atopic dermatitis; CI, confidence interval; OR, odds ratio; SD, standard deviation

Physician diagnosed AD: An affirmative answer to the question 'has a doctor ever told you that you have/ have had atopic eczema?' UK 2/4: Fulfilled the major criterion and at least two of four minor criteria of the modified version of UK Working Party Criteria for Atopic Dermatitis, UK 3/4: Fulfilled the major criterion and at least three of four minor criteria of the modified version of UK Working Party Criteria for Atopic Dermatitis

Table 5. Association between self-reported atopic dermatitis and hypertension and hypercholesterolemia

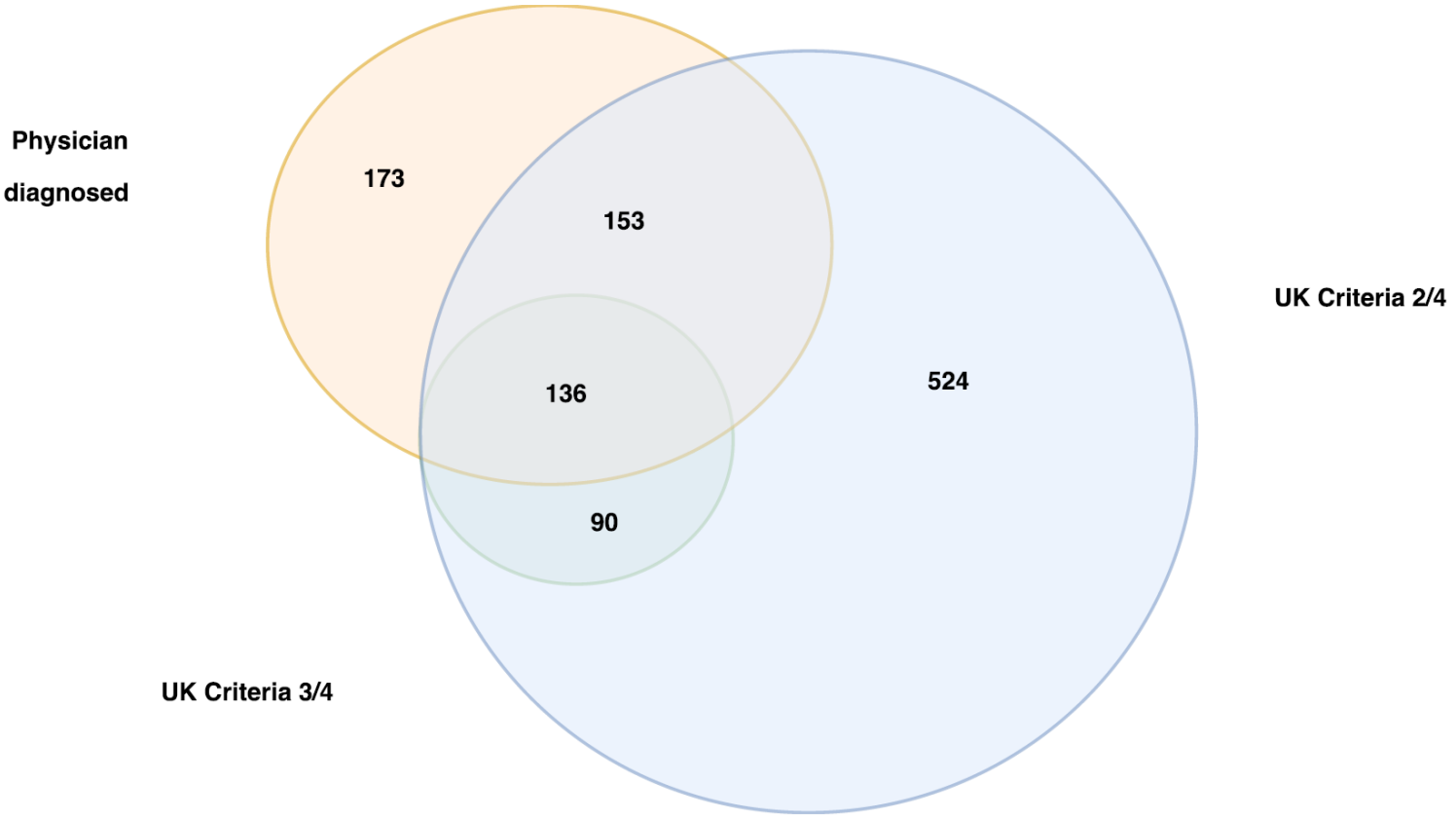
	Physician diagnosed AD			AD by UK 2/4			AD by UK 3/4		
	OR*	95% CI	p-value	OR*	95% CI	p-value	OR*	95% CI	p-value
Self-reported hypertension	1.00	0.77-1.30	0.984	1.07	0.90-1.27	0.418	0.92	0.65-1.29	0.611
Clinically measured high SBP ≥ 140 mmHg	1.01	0.76-1.44	0.971	0.96	0.80-1.15	0.647	1.05	0.73-1.44	0.794
Clinically measured high DBP ≥ 90 mmHg	1.07	0.78-1.48	0.670	1.00	0.81-1.24	0.989	1.01	0.66-1.53	0.980
Self-reported hypercholesterolemia	1.18	0.90-1.53	0.228	1.14	0.96-1.36	0.135	1.28	0.92-1.78	0.140
Screen-detected moderate to high cholesterol >6.5 mmol/l	0.73	0.52-1.02	0.064	0.91	0.73-1.12	0.367	0.79	0.51-1.22	0.283

* OR estimates were adjusted for age, sex, BMI, smoking status, and survey weights in multivariable logistic regression analyses.

AD, atopic dermatitis; CI, confidence interval; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure

Physician diagnosed AD: An affirmative answer to the question 'has a doctor ever told you that you have/ have had atopic eczema?' UK 2/4: Fulfilled the major criterion and at least two of four minor criteria of the modified version of UK Working Party Criteria for Atopic Dermatitis, UK 3/4: Fulfilled the major criterion and at least three of four minor criteria of the modified version of UK Working Party Criteria for Atopic Dermatiti

Figure 1. Venn diagram of the applied inclusion criteria



The circles represent the three diagnostic criteria applied in this study. The numbers indicate the number of participants who fulfilled each definition of atopic dermatitis. Physician diagnosed: An affirmative answer to the question 'has a doctor ever told you that you have/ have had atopic eczema?' UK Criteria 2/4: Fulfilled the major criterion and at least two of four minor criteria of the modified version of UK Working Party Criteria for Atopic Dermatitis. UK Criteria 3/4: Fulfilled the major criterion and at least three of four minor criteria of the modified version of UK Working Party Criteria for Atopic Dermatitis.