Accepted Manuscript

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PII: S0022-202X(16)32791-9

DOI: 10.1016/j.jid.2016.11.031

Reference: JID 666

To appear in: *The Journal of Investigative Dermatology*

Received Date: 12 September 2016

Revised Date: 15 November 2016

Accepted Date: 30 November 2016

Please cite this article as: Standl M, Tesch F, Baurecht H, Rodríguez E, Müller-Nurasyid M, Gieger C, Peters A, Wang-Sattler R, Prehn C, Adamski J, Kronenberg F, Schulz H, Koletzko S, Schikowski T, von Berg A, Lehmann I, Berdel D, Heinrich J, Schmitt J, Weidinger S, Association of atopic dermatitis with cardiovascular risk factors and diseases, *The Journal of Investigative Dermatology* (2017), doi: 10.1016/j.jid.2016.11.031.

Association of atopic dermatitis with cardiovascular risk factors and diseases

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ABBREVIATIONS

AD	atopic dermatitis
AP	angina pectoris
aRR	adjusted risk ratio

BMI	body mass index
CAD	coronary artery disease
CARDIoGRAM	coronary artery disease genome-wide replication and meta analysis
CI	confidence interval
CVD	cardiovascular disease
CVRFs	cardiovascular risk factors
EAGLE	Early Genetics and Lifecourse Epidemiology
FDR	false discovery rate
GWAS	genome-wide association study
ICD	International Statistical Classification of Disease
KORA	Cooperative Health Research in the Region of Augsburg
MI	myocardial infarction
OR	odds ratio
PAD	peripheral arterial disease
RR	relative risk

ABSTRACT

Epidemiological studies suggested an association between atopic dermatitis (AD) and cardiovascular disease (CVD). Therefore, we investigate associations and potential underlying pathways of AD and CVD in large cohort studies: the AOK PLUS cohort (n=1.2Mio), the GINIplus/LISAplus birth cohorts (n=2286), and the KORA F4 cohort (n=2990). Additionally, metabolomics in KORA F4 and established cardiovascular risk loci in genome-wide data on 10,788 AD cases and 30,047 controls were analyzed. Longitudinal analysis of AD patients in AOK PLUS showed slightly increased risk for incident angina pectoris (AP) (adjusted risk ratio 1.17; 95%-confidence interval 1.12-1.23), hypertension (1.04 (1.02-1.06)) and peripheral arterial disease (PAD) (1.15 (1.11-1.19)) but not for myocardial infarction (MI) (1.05 (0.99-1.12) and stroke (1.02 (0.98-1.07)). In KORA F4 and GINIplus/LISAplus, AD was not associated with cardiovascular risk factors (CVRFs) and no differences in metabolite levels were detected. There was no robust evidence for shared genetic risk variants of AD and CVD. This study indicates only a marginally increased risk for AP, hypertension and PAD and no increased risk for MI or stroke in AD patients. Relevant associations of AD with CVRFs reported in US-populations could not be confirmed. Likewise, AD patients did not have increased genetic risk factors for CVD.

INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory disorder with a life time prevalence of 10-20% and represents a leading cause of illness and disability.(Weidinger and Novak, 2016) AD has a strong inherited background susceptibility and is pathophysiologically characterized by abnormalities of epidermal barrier function and T-cell driven cutaneous inflammation.(Weidinger and Novak, 2016) Genetic studies have revealed a complex polygenic architecture with striking overlaps to other

immune-mediated diseases,(Paternoster et al., 2015) and immunological research has indicated that AD involves more than just the skin and has systemic components.(Czarnowicki et al., 2015a, Czarnowicki et al., 2015b, Huang et al., 2014) This has fostered investigations on the risk for comorbidities to gain an improved understanding of the heterogeneity of the disease and help develop more effective management programs. Beyond the well-known association with atopic and mental health disorders (Schmitt et al., 2009a, Schmitt et al., 2009b, Yaghmaie et al., 2013) there is convincing data that AD also increases the risk for vitiligo and alopecia areata (Mohan and Silverberg, 2015) as well as rheumatoid arthritis and inflammatory bowel disease.(Schmitt et al., 2016) Preliminary studies also pointed to a link between AD and metabolic conditions and cardiovascular risk, but available data are less comprehensive and straightforward. Associations of AD with higher body mass index (BMI) and obesity have been demonstrated in North-American and Asian children and adults, but not European populations.(Silverberg, 2016, Zhang and Silverberg, 2015) Likewise, US and Asian studies reported an association with cardiovascular outcomes with, however, considerable variations in effect sizes within the same population background.(Lee et al., 2016, Silverberg, 2015, Silverberg and Greenland, 2015, Su et al., 2014) The presence and magnitude of such a risk in other populations and independence from an increased burden of CVRFs is yet unclear.(Andersen et al., 2016, Drucker et al., 2016, Zhang and Silverberg, 2015)

We therefore set out to investigate the association of AD with CVDs and related risk factors using three different datasets: (1) the prospective AOK PLUS cohort of adult German National Health Insurance beneficiaries (n=1.2 Mio) with aggregated socioeconomic data and disease information from ICD-10 codes, (2) the adult KORA F4 population-based cohort (n=2990) comprehensively characterized for allergic, inflammatory and cardiometabolic phenotypes, and (3) the GINIplus and LISAplus birth cohorts (n=2286) with follow-up data into adolescence with a focus on environmental factors influencing allergic and metabolic phenotypes. Furthermore, in order to identify possible pathways, we investigated metabolomics profiles in KORA F4 for changes related to AD, and examined established risk loci for cardiovascular traits in 10,788 AD cases and 30,047 controls.

RESULTS

Complete information on AD, at least one exposure and all confounding variables was available for 1,180,678 and 1,214,133 subjects from the AOK PLUS cohort in the cross-sectional and prospective analyses, respectively, as well as from 2,990 participants of the KORA F4 study and 2,286 participants of GINIplus/LISAplus.

Basic characteristics of the study populations are presented in Tables S1-S4. Prevalences of AD were 3.1% during 2012-14 and 2.8% during 2005-07 in the AOK PLUS cohort (Table S1&S2), 7.0% in KORA F4 (Table S3) and 35.6% in GINIplus/LISAplus (Table S4).

Using an FDR corrected significance threshold of P<0.027, in the fully adjusted model of the cross-sectional analysis of the AOK PLUS cohort AD was associated with an increased risk for AP (aRR=1.32, 95%-CI=(1.26-1.38), p-value<$1x10^{-16}$), hypertension (1.07 (1.06-1.08), p<$1x10^{-16}$) and PAD (1.16 (1.13-1.20), p<$1x10^{-16}$), which accounted for 41.51, 147 and 48.52 excess cases of AP, hypertension and PAD, respectively, per 10,000 person-years (Table 1). AD severity was assessed by categorizing AD patients using treatment (no medication, exclusively topical medication or systemic medication) as proxy. For AP, hypertension and PAD, a clear dose-response relationship was observed, with strongest effects in the group of AD patients with systemic medication. Restriction to systemic therapy with corticosteroids only did not alter results.

In the prospective analysis (Table 2), prevalent AD during 2005-07 was regressed on comorbidities present during 2008-14. Using a FDR-corrected significance threshold of P<0.021, the findings of the cross-sectional analysis were confirmed, although magnitude and strength of the associations were weaker. In the fully adjusted model, AD significantly increased the risk for AP (1.17 (1.12-1.23), p=$3.14x10^{-11}$), hypertension (1.04 (1.02-1.06), p=$2.71x10^{-3}$) and PAD (1.15 (1.11-1.19), p=$3.18x10^{-13}$), accounting for 8.56, 15.34 and 9.15 excess cases of AP, hypertension and PAD, respectively, per

10,000 person-years. For AP and PAD, effects were increasing with AD severity. Restriction to systemic therapy with corticosteroids only did not alter results.

In the fully adjusted regression analyses of the KORA F4 cohort (Table 3) and the GINIplus/LISAplus studies (Table 4), AD was not significantly associated with any of the tested continuous CVRFs.

Genetic analysis

Of the 126 established CAD risk variants (Table S5) 118 were available in the AD-meta-analysis of the EAGLE consortium of 10,788 AD cases and 30,047 controls.(Paternoster et al., 2015) 13 of the variants showed nominal significance ($0.003<p<0.05$) but none of them was significant after Bonferroni correction (0.05/118=0.0004) (Table S6). The strongest nominal association with AD was observed for variants in *IL6R* (rs4845625) and *ADAMTS7* (rs4380028), but these associations pointed into the opposite direction, i.e. showed an inverse association with AD (rs4845625: OR=0.95, 95%-CI=(0.92-0.98), p-value=0.0026 and rs4380028: 0.96 (0.92-0.96), p=0.0078) as compared to the reported effects on CAD risk (rs4845625: 1.04 (1.02-1.07), $p=3.55x10^{-8}$ and rs4380028: 1.07 (1.05-1.10), $p=4.00x10^{-8}$). This indicates that there is no relevant genetic overlap between CVDs and AD.

Metabolomics analysis

No significant associations of AD with any metabolites or metabolite ratios were observed within the KORA F4 study (Table S7 and Figure S1).

DISCUSSION

AD is one of the most common chronic diseases both among children and adults. An important implication of chronic diseases are comorbidities and sequelae, which are often key drivers of morbidity and mortality,(Global Burden of Disease Study, 2015, Prados-Torres et al., 2014) may

influence individual treatment decisions, and have considerable consequences for health care and related costs. The study of co-morbidity patterns can also provide pointers to causes and pathophysiological mechanisms of index diseases. For AD, comorbidities other than atopic diseases have only recently received attention. There is robust evidence that AD is associated with mental health disorders,(Yaghmaie et al., 2013) and a number of (auto-)immune diseases such as vitiligo and alopecia areata, (Mohan and Silverberg, 2015) rheumatoid arthritis and inflammatory bowel disease.(Schmitt et al., 2016) More recently, associations with metabolic syndrome and CVD have been reported by studies from North-America and Asia.(Andersen et al., 2016, Lee et al., 2016, Silverberg, 2015, Su et al., 2014) In the questionnaire based US NHIS 2010 and 2012 surveys, associations of AD with coronary artery disease (CAD), AP, heart attack, stroke, peripheral vascular disease(Silverberg, 2015) and hypertension(Silverberg and Greenland, 2015) have been reported. In addition, cardiovascular risk factors (CVRFs) such as smoking, alcohol consumption, physical activity and BMI, were more prevalent in AD patients in one of these surveys (NHIS 2012). Also several other studies from the US and Asia reported direct associations of AD and AD severity with BMI, overweight and obesity (Mitchell et al., 2013, Murray et al., 2011, Silverberg, 2016, Silverberg et al., 2015, Silverberg et al., 2011, Silverberg and Simpson, 2014, Weinmayr et al., 2014, Zhang and Silverberg, 2015). Thus, it has been hypothesized that negative lifestyle factors increase the risk for cardiometabolic diseases in AD patients.(Silverberg and Greenland, 2015) In line with this, after adjustment of CVRFs such as BMI, smoking and alcohol consumption only in one of the above mentioned US surveys (NIHS 2010) showed an association between AD and MI nominally significant with attenuated effect size (Silverberg, 2015) and the association is mainly driven by CVRF, which appear to be more prevalent in US patients than in Europeans. Likewise, in the Nurses' Health Study II, AD was not independently associated with stroke and MI after adjustment for CVD-related comorbidities, such as hypertension, hypercholesterolemia and diabetes. (Drucker et al., 2016)

Like other European studies before (Kreissl et al., 2014, Radtke et al., 2016, Saadeh et al., 2014, Van Gysel et al., 2009, Zhang and Silverberg, 2015) neither in the KORA F4 adult cohort nor in the GINIplus/LISAplus birth cohort we observed an association of AD with CVRFs, despite a post hoc

power of more than 90% to detect differences of ≥10%. Likewise, metabolite profiling of participants form the KORA F4 study did not show significant differences between AD cases and controls. In the large prospective AOK PLUS cohort the risk for AP, hypertension and PAD, was only slightly increased for individuals affected by AD, which translated in an estimated absolute excess risk increment of 9, 15 and 9 per 10,000 person-years, respectively. Stated another way, among 10.000 AD patients 9, 15 and 9 additional cases of AP, hypertension and PAD, respectively, would be expected per year. In a sensitivity analysis, these risk increments were largest in AD patients receiving systemic treatment, which is often used as a proxy for high disease severity. No associations were observed for MI and stroke.

The analysis of large genome-wide datasets did not reveal robust overlaps between AD and CVD risk loci.

In conclusion, AD patients in Germany do not seem to be more likely to have unhealthy lifestyles and CVRFs which together with methodological differences might partly explain the weaker associations with cardiovascular endpoints as compared to US and Asian studies. Further, the "dose–response" relationship suggests that the increased inflammatory status of (severe) AD patients with high circulating levels of inflammatory molecules such as interleukins and extracellular matrix proteins (Kou et al., 2014, Tamagawa-Mineoka et al., 2014, Yamanaka et al., 2014) and/or immunosuppressive treatments may also influence the risk.

Strength and limitations

To study patterns of comorbidity it is important to use (sufficiently large) general population samples, since significant biases may be present in hospital-based observational studies. Limitations of datasets used such as incomplete information on potential confounders need to adequately considered when interpreting findings. Findings also need to be interpreted with caution with respect to causality, clinical impact and relevance.(Nijsten and Wakkee, 2009, Schmitt and Weidinger, 2014)

The major strength of this study is the combination of epidemiological data from three different cohort studies, each with own strengths and limitations, along with molecular analyses. The AOK PLUS cohort allowed the prospective and cross-sectional analysis of cardiovascular outcomes in relation to AD status in a very large, unselected population. The risk of misclassification is expected to be lower than in previous questionnaire-based surveys.[13,] (Silverberg and Greenland, 2015) However, adjustment for individual factors, such as smoking, alcohol consumption or BMI, which might modify disease associations, was not possible, and the observation period was relatively short. Potential confounders and CVRFs were comprehensively assessed in the KORA F4 study, but the number of AD patients and cardiovascular events was low, and no stratification by AD severity was possible. The GINIplus and LISAplus birth cohort studies provided detailed information on AD from birth to adolescence, but due to the young age there were no incident CVDs throughout the follow-up period, and thus analysis was limited to CVRFs, such as blood pressure, blood lipid concentrations and BMI in subjects with and without AD. Together, we feel that despite the limitations mentioned the different analyses complement each other to cover various aspects.

Conclusions

The present study shows modest associations of severe AD with AP, hypertension and PAD, but fails to confirm increased CVRFs in AD patients. Likewise, no apparent genetic overlap between AD and cardiovascular outcomes was detected. Even for severe AD the excess risks for CVDs reported and observed here are very modest in absolute terms, and call into question their clinical relevance.

MATERIAL AND METHODS

Study approval

This study was approved by the local ethical committee, and participants gave written informed consent in accordance with the Declaration of Helsinki.

Study population

All investigated cohorts are briefly described below and more details can be found in the Supplementary Material.

AOK PLUS

This cohort is a sample from the anonymized population-based AOK Saxony healthcare database,(Schmitt et al., 2009a, Schmitt et al., 2009b, Schmitt et al., 2016) with complete information on outpatient health care (diagnoses according to the International Statistical Classification of Diseases, Tenth Revision [ICD-10]), treatments according to Anatomical Therapeutic Chemical (ATC) Classification code and Inpatient care.

These routine data on outpatient diagnoses, medication and sociodemographic characteristics (age, sex, area ZIP code) in the timespan from 2005 until 2014 are accessible for research. Inpatient care is covered from 2008 to 2014. The sample for this study consists of all individuals aged 40 years or older in 2005 who were consistently insured from 2005 to 2014 or to their death.

KORA F4

The KORA F4 study is the seven years follow-up of the population-based survey KORA S4 from southern Germany and recruited 3080 individuals aged 32 to 81 between 1999 and 2001.

GINIplus and LISAplus

The GINIplus(von Berg et al., 2010) and LISAplus(Heinrich et al., 2002) studies are two German, prospective birth cohort studies. In both studies frequent follow-ups were conducted between birth and 15 years.

Definition of AD

AOK PLUS

Primary exposure was defined as prevalent AD during two different time periods: in 2005-2007 (longitudinal analysis) as well as in 2012-2014 (cross-sectional analysis). To minimize misclassification, we defined a priori that the ICD-10 code for AD (L20) had to be documented at least twice in outpatient care to classify patients having AD.(Schmitt et al., 2009b, Schmitt et al., 2016) We attempted to deal with unmeasured disease severity by stratification by AD-specific medication to differentiate participants with AD into those with no anti-inflammatory treatment prescribed, those with topical anti-inflammatory therapy (ATC codes D07 [topical corticosteroids], D11AX14 [topical tacrolimus], and D11AX15 [topical pimecrolimus]), and those with both topical and systemic anti-inflammatory therapy (L04AA01/L04AD01 [ciclosporin] and H02AB [systemic corticosteroids]) prescribed in the years 2005-07 and 2012-14, respectively.

KORA F4

AD was defined as reported physician diagnosis ever. For the definition of current AD, participants who reported that AD healed completely were excluded from analysis.

GINIplus and LISAplus

Information on a doctor diagnosis of AD was collected using questionnaires administered to the parents at each follow-up, asking for AD separately for each year of life since the previous follow-up. Cases were defined as ever reporting a doctor diagnosis. Control subject were those answering every question regarding a doctor diagnosis of AD with “no” from birth to 15 years of age without any missing values.

Definition of cardiovascular diseases and risk factors

AOK PLUS

For defining CVRFs and other potentially confounding comorbidities, we used relevant ICD10-codes (Table S8). For the longitudinal analyses, incident cardio-metabolic events were identified through health insurance records. Health Insurance beneficiaries entered the study in 2005 and were followed up from 2008 (start of person time) until the end of the follow-up period in 2014 (end of person time). Outcomes of interest were incident MI (ICD–10 code I21– I23), incident AP (ICD: I20), incident stroke (ICD: I63 and I64), incident hypertension (ICD: I10) and incident PAD (ICD: I70-73) in 2008 through 2014. Incident cases were defined as patients having no respective diagnosis documented in 2005 thru 2007, and documentation of the respective ICD–10 code was at least twice in 2008 until 2014 for outpatient data or once for inpatient data. Patients with prevalent CVDs in 2005 thru 2007 were excluded.

KORA F4

All participants underwent a medical examination by trained medical staff, which comprised anthropometrical (weight, height), and blood pressure measurements according to standardized protocols previously published.(Rathmann et al., 2003) BMI (in kg/m^2) was calculated as weight divided by height squared. Venous blood samples were drawn from all subjects. Lipids were measured using the Dimension RxL (Dade Behring).(van Vliet-Ostaptchouk et al., 2014) Continuous variables were visually inspected for outliers. BMI above 50kg/m^2, systolic blood pressure above 206mmHg, total cholesterol above 9.11mmol/l and triglycerides above 10.2mmol/l were removed from the analysis and treated as missing values. HDL and triglycerides were log-transformed for regression analysis due to their non-normal distribution.

GINIplus and LISAplus

During the physical examination at age 15 years, height, weight, systolic and diastolic blood pressure was measured and blood samples were collected. BMI was calculated from height and weight measurements and transferred to WHO z-scores.(de Onis et al., 2007) Lipids were measured in serum using homogenous enzymatic colorimetric methods on a Modular Analytics System from Roche Diagnostics GmbH Mannheim according to the manufactures instructions. External controls were used in accordance with the guidelines of the German Society of Clinical Chemistry and Laboratory Medicine. LDL, total cholesterol and tryglycerides were log-transformed for regression analysis due to their non-normal distribution.

Definition of confounding variables

AOK PLUS

As confounders we considered age and sex as well as socioeconomic status, which was indirectly inferred by socioeconomic characteristics of the living environment and access to health care using external databases. Detailed description can be found in the Supplementary Methods.

KORA F4

Statistical models were adjusted for sex, age, smoking habit, educational attainment, alcohol intake, physical activity and medication for antihypertensive, antidiabetic or lipid reducing treatment. More details on categorization can be found in the Supplementary Methods.

GINIplus and LISAplus

As confounders, age, sex parental education and passive smoking exposure were considered. Detailed description of categorization can be found in the Supplementary Methods.

Metabolomics analysis

In KORA F4, metabolite concentrations were measured in fasting serum samples using electrospray ionisation tandem mass spectrometry (ESI-MS/MS) with the Absolute*IDQ*^{TM} p150 kit (BIOCRATES Life Sciences AG, Innsbruck, Austria). A list of metabolites is provided in Table S9. Details on the metabolomics analysis are provided in the Supplementary Methods. After quality control, 151 metabolites and 2878 participants with complete information on current AD and confounding variables remained for analysis.

Genetic analysis

In an additional analysis, the overlap of genetic risk variants between CAD and AD was evaluated using published datasets from GWAS meta-analysis. All variants associated with CAD on a genome-wide significance level ($p<5x10^{-8}$) were extracted from the CARDIoGRAM GWAS (22,233 CAD cases vs. 64,762 controls) (Schunkert et al., 2011) and the GWAS catalogue.(Burdett et al., Accessed July 2016, Welter et al., 2014) These variants were looked up for association with AD using the GWAS summary results of the EAGLE eczema consortium (10,788 AD cases vs. 30,047 controls), the latest and most comprehensive GWAS meta-analysis for AD.(Paternoster et al., 2015) In total, 126 variants associated with CAD were identified (Table S5), of which 118 variants were also available in the AD GWAS (Table S6). KORA F4 is part of both the CARDIoGRAM and EAGLE while GINIplus/LISAplus is only involved in EAGLE.

Statistical analysis

Descriptive analysis

Counts and percentage were calculated for each categorical confounding, exposure or outcome variable and for each severity group. For normal distributed variables the arithmetic mean, and for log-normal distributed variables the geometric mean were reported with their corresponding 95%-CI.

All variables were tabulated for AD cases and controls as well as for the different AD severity categories in the AOK PLUS data. In KORA F4, GINIplus/LISAplus formal tests were applied using t-test for continuous variables, Fisher's exact test for binary variables and Chi-squared tests for categorical variables with more than two categories.

AOK PLUS

Risk ratios (RRs) were calculated with the help of generalized linear models using a Poisson link function with robust error variance as suggested by Zou.(Zou, 2004) In the cross-sectional analysis, prevalent AD during 2012-14 was regressed on comorbidities prevalent during the same time period. In the prospective analysis, AD prevalent during 2005-07 was regressed on comorbidities incident during 2008-14. Model I was adjusted for sex and cubic age. Model II was additionally adjusted for socioeconomic characteristics and access to health care of their region. Data were analyzed using Stata version 13.1 (Stata Corp, College Station, Tex). To correct for multiple testing of these correlated outcomes we used the false discovery rate in order to avoid over adjustment. We present the p-value corresponding to the highest FDR<0.05 as the corrected significance threshold.

KORA F4 and GINIplus/ LISAplus

Associations of AD with each continuous cardiovascular risk factor as outcome were modeled using linear regression models. All models were adjusted for sex and age. Additional adjustment variables were BMI (if not the outcome), alcohol consumption, physical activity, smoking, medication and education level in KORA F4 and parental education, study center, study (GINI observational arm, GINI interventional arm, LISA), second hand smoke exposure, exact age at the 15-year examination and BMI z-scores (if not the outcome) for GINIplus/LISAplus. Results are presented as beta estimates or, for log-transformed variables, means ratios (MR) with corresponding 95%-CI.

In KORA F4, the associations of AD with log2-transformed metabolite concentrations per interquartile range increase were analyzed using generalized linear models with logit link, adjusting for the same confounder variables and further for batch. In addition to the metabolite concentrations, the ratios of all metabolites with each other were calculated. Bonferroni correction

was applied for multiple testing. The corrected significance level was determined by dividing 0.05 by the number of tests, yielding a corrected alpha level of 0.0003 (0.05/151) for the analysis of the 151 metabolites and a corrected alpha level of $4.4x10^{-6}$ when analyzing the 151 metabolites including the ratios between all metabolites (151 metabolites + 11325 metabolite ratios). Metabolite concentrations were log-transformed with base 2 and results are presented per interquartile range increase in metabolite level.

All analyses were conducted using R, version 3.3.1 (www.R-project.org). (R Core Team, 2016) and detailed power analyses are outlined in the Supplementary Material and Supplementary Table S10.

CONFLICT OF INTEREST

J. Schmitt reports financial support for IITs from Sanofi, Novartis, ALK and Pfizer. All other authors declare that they have no relevant conflicts of interest.

ACKNOWLEDGEMENT

GINIplus / LISAplus

The authors thank all the families for their participation in the GINIplus and LISAplus studies. Furthermore, we thank all members of the GINIplus and LISAplus Study Groups for their excellent work. The GINIplus Study group consists of the following: Institute of Epidemiology I, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg (Heinrich J, Brüske I, Schulz H, Flexeder C, Zeller C, Standl M, Schnappinger M, Sußmann M, Thiering E, Tiesler C); Department of Pediatrics, Marien-Hospital, Wesel (Berdel D, von Berg A); Ludwig-Maximilians-University of Munich, Dr von Hauner Children's Hospital (Koletzko S); Child and Adolescent Medicine, University Hospital rechts der Isar of the Technical University Munich (Bauer CP, Hoffmann U); IUF-Environmentafl Health Research Institute, Düsseldorf (Schikowski T, Link E, Klümper C). The LISAplus Study group consists of the following: Helmholtz Zentrum München, German Research Center for

Environmental Health, Institute of Epidemiology I, Munich (Heinrich J, Schnappinger M, Brüske I, Sußmann M, Lohr W, Schulz H, Zeller C, Standl M); Department of Pediatrics, Municipal Hospital "St. Georg", Leipzig (Borte M, Gnodtke E); Marien Hospital Wesel, Department of Pediatrics, Wesel (von Berg A, Berdel D, Stiers G, Maas B); Pediatric Practice, Bad Honnef (Schaaf B); Helmholtz Centre of Environmental Research – UFZ, Department of Environmental Immunology/Core Facility Studies, Leipzig (Lehmann I, Bauer M, Röder S, Schilde M, Nowak M, Herberth G , Müller J, Hain A); Technical University Munich, Department of Pediatrics, Munich (Hoffmann U, Paschke M, Marra S); Clinical Research Group Molecular Dermatology, Department of Dermatology and Allergy, Technische Universität München (TUM), Munich (Ollert M).

KORA F4

We thank all the individuals and clinicians for their participation in the KORA F4 study. The KORA study was initiated and financed by the Helmholtz Zentrum München—German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria. Furthermore, KORA research was supported within the Munich Center of Health Sciences (MC-Health), Ludwig-Maximilians-Universität, as part of LMUinnovativ.

AOK PLUS

We thank the Saxony Compulsory Health Insurance AOK PLUS for cooperation in data utilization and for providing technical support.

The project received infrastructure support through the DFG Clusters of Excellence ''Inflammation at Interfaces'' (grants EXC306 and EXC306/2), and was supported by the German Federal Ministry of Education and Research (BMBF) within the framework of the e:Med research and funding concept (sysINFLAME, grant 01ZX1306A). This study makes use of data generated by the CARDIoGRAM Consortium and the EAGLE Eczema Consortium. Members of the consortia are listed in the Supplementary Material.

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TABLES

Table 1 Cross-sectional generalized linear regression analysis in the AOK PLUS cohort

	RR (95% CI)				Excess risk per 10,000 person-years	
Exposure Variable	Model I	P value	Model II	P value	Model I	Model II
Angina Pectoris (i20) in 2012-14						
AD (primary exposure)	1.34 (1.28-1.41)	$<1.00x10^{-16}$	1.32 (1.26-1.38)	$<1.00x10^{-16}$	44.00	41.51
Treatment of AD						
AD, no medication	1.20 (1.10-1.31)	$3.73x10^{-5}$	1.18 (1.08-1.29)	$1.79x10^{-4}$	25.94	23.35
AD, exclusively topical medication	1.33 (1.25-1.42)	$<1.00x10^{-16}$	1.31 (1.23-1.39)	$2.22x10^{-16}$	42.80	40.21
AD, systemic medication	1.60 (1.45-1.77)	$<1.00x10^{-16}$	1.57 (1.43-1.74)	$<1.00x10^{-16}$	77.83	73.94
Myocardial infarction (i21-23) in 2012-14						
AD (primary exposure)	0.98 (0.90-1.05)	0.542	0.98 (0.91-1.06)	0.657	-1.35	-1.35
Treatment of AD						
AD, no medication	0.94 (0.82-1.08)	0.361	0.95 (0.82-1.09)	0.424	-4.06	-3.38
AD, exclusively topical medication	0.95 (0.85-1.05)	0.327	0.95 (0.86-1.06)	0.384	-3.38	-3.38
AD, systemic medication	1.12 (0.94-1.32)	0.213	1.12 (0.94-1.33)	0.192	8.11	8.11
Stroke (i60-64) in 2012-14						
AD (primary exposure)	1.06 (1.01-1.11)	0.027	1.05 (1.00-1.11)	0.032	9.02	7.52
Treatment of AD						
AD, no medication	1.03 (0.94-1.12)	0.550	1.03 (0.94-1.12)	0.526	4.51	4.51
AD, exclusively topical medication	1.06 (0.99-1.13)	0.095	1.05 (0.99-1.13)	0.118	9.02	7.52
AD, systemic medication	1.08 (0.96-1.21)	0.194	1.08 (0.96-1.21)	0.209	12.03	12.03
Hypertension (i10) in 2012-14						
AD (primary exposure)	1.07 (1.06-1.07)	$<1.00x10^{-16}$	1.07 (1.06-1.08)	$<1.00x10^{-16}$	147.00	147.00
Treatment of AD						
AD, no medication	1.04 (1.02-1.05)	$1.47x10^{-7}$	1.04 (1.02-1.05)	$3.87x10^{-8}$	84.00	84.00
AD, exclusively topical medication	1.08 (1.07-1.09)	$<1.00x10^{-16}$	1.08 (1.07-1.09)	$<1.00x10^{-16}$	168.00	168.00
AD, systemic medication	1.09 (1.08-1.11)	$<1.00x10^{-16}$	1.10 (1.08-1.12)	$<1.00x10^{-16}$	189.00	210.00
Peripheral arterial disease (i70-73) in 2012-14						
AD (primary exposure)	1.16 (1.12-1.19)	$<1.00x10^{-16}$	1.16 (1.13-1.20)	$<1.00x10^{-16}$	48.52	48.52
Treatment of AD						
AD, no medication	1.14 (1.08-1.21)	$2.13x10^{-6}$	1.15 (1.09-1.22)	$6.74x10^{-7}$	42.45	45.49
AD, exclusively topical medication	1.14 (1.08-1.18)	$1.27x10^{-8}$	1.14 (1.09-1.19)	$5.18x10^{-9}$	42.45	42.45
AD, systemic medication	1.24 (1.16-1.34)	$1.18x10^{-9}$	1.26 (1.17-1.35)	$2.63x10^{-10}$	72.78	78.84

Results of generalized linear regression analysis in the AOK PLUS cohort (AOK PLUS Database Saxonia 2012-14, INKAR Database): Multivariable-adjusted relative risk (RR; 95% confidence interval in parentheses) and excess risk per 10,000 person-years in period 2012 to 2014 for patients 40+ years in 2012 with AD versus patients without AD (n=1.180 Mio.); Model I was adjusted for sex and cubic age. Model II was adjusted for sex, cubic age and socioeconomic status of region and access to health care. Excess risks calculated on the basis of adjusted risk ratios.

Table 2: Longitudinal generalized linear regression analysis in the AOK PLUS cohort

	RR (95% CI)				Excess risk per 10,000 person-years	
Exposure Variable	Model I	P value	Model II	P value	Model I	Model II
Angina Pectoris (i20) 2008-14						
AD (primary exposure)	1.18 (1.13-1.23)	$4.31x10^{-12}$	1.17 (1.12-1.23)	$3.14x10^{-11}$	9.06	8.56
Treatment of AD						
AD, no medication	0.94 (0.85-1.04)	0.216	0.93 (0.84-1.03)	0.190	-3.02	-3.52
AD, exclusively topical medication	1.21 (1.13-1.29)	$1.03x10^{-8}$	1.20 (1.12-1.28)	$4.52x10^{-8}$	10.57	10.07
AD, systemic medication	1.38 (1.26-1.50)	$3.72x10^{-13}$	1.37 (1.25-1.49)	$1.05x10^{-12}$	19.13	18.63
Myocardial infarction (i21-23) 2008-14						
AD (primary exposure)	1.05 (0.98-1.12)	0.156	1.05 (0.99-1.12)	0.127	1.53	1.53
Treatment of AD						
AD, no medication	0.91 (0.79-1.04)	0.171	0.92 (0.80-1.05)	0.194	-2.75	-2.44
AD, exclusively topical medication	1.10 (1.01-1.20)	0.024	1.11 (1.02-1.21)	0.021	3.05	3.36
AD, systemic medication	1.07 (0.94-1.22)	0.282	1.08 (0.95-1.22)	0.255	2.14	2.44
Stroke (i60-64) 2008-14						
AD (primary exposure)	1.03 (0.98-1.07)	0.238	1.02 (0.98-1.07)	0.346	2.48	1.66
Treatment of AD						
AD, no medication	0.92 (0.84-1.01)	0.078	0.92 (0.84-1.01)	0.070	-6.63	-6.63
AD, exclusively topical medication	1.06 (1.00-1.13)	0.055	1.05 (0.99-1.12)	0.094	4.97	4.14
AD, systemic medication	1.07 (0.98-1.17)	0.136	1.06 (0.98-1.16)	0.160	5.80	4.97
Hypertension (i10) 2008-14						
AD (primary exposure)	1.04 (1.01-1.06)	$1.84x10^{-3}$	1.04 (1.02-1.06)	$2.71x10^{-3}$	15.34	15.34
Treatment of AD						
AD, no medication	1.01 (0.97-1.06)	0.594	1.02 (0.97-1.06)	0.462	3.83	7.67
AD, exclusively topical medication	1.05 (1.02-1.08)	$1.69x10^{-3}$	1.06 (1.03-1.09)	$3.65x10^{-3}$	19.17	23.01
AD, systemic medication	1.03 (0.99-1.08)	0.175	1.04 (0.99-1.08)	0.104	11.50	15.34
Peripheral arterial disease (i70-73) 2008-14						
AD (primary exposure)	1.13 (1.09-1.17)	$4.38x10^{-11}$	1.15 (1.11-1.19)	$3.18x10^{-13}$	7.93	9.15
Treatment of AD						
AD, no medication	0.98 (0.90-1.06)	0.567	0.99 (0.92-1.07)	0.818	-1.22	-0.61
AD, exclusively topical medication	1.14 (1.08-1.20)	$1.03x10^{-6}$	1.15 (1.09-1.21)	$8.01x10^{-8}$	8.54	9.15
AD, systemic medication	1.29 (1.20-1.38)	$7.82x10^{-13}$	1.30 (1.22-1.40)	$4.26x10^{-14}$	17.70	18.31

Results of generalized linear regression analysis in the AOK PLUS cohort (AOK PLUS Database Saxonia 2005-14, INKAR Database): Multivariable-adjusted relative risk (RR; 95% confidence interval in parentheses) and excess risk per 10,000 person-years in period 2008 to 2014 for patients 40+ years in 2005 with AD versus patients without AD in 2005-07 (n=1.214 Mio.); Model I was adjusted for sex and cubic age. Model II was adjusted for sex, cubic age and socioeconomic status of region and access to health care. Excess risks calculated on the basis of adjusted risk ratios.

Table 3: Linear regression models of reported physicians diagnosis ever having AD on cardiovascular risk factors in KORA F4

	N	beta / MR[1]	95%-CI	P value
BMI	2990	-0.169	(-0.79, 0.45)	0.5902
Waist-Hip Ratio	2990	0.002	(-0.01, 0.01)	0.5711
Systolic blood pressure [mmHg]	2985	0.529	(-1.77, 2.82)	0.6513
Diastolic blood pressure [mmHg]	2986	-0.175	(-1.51, 1.16)	0.7972
Total cholesterol [mmol/l]	2989	-0.010	(-0.15, 0.13)	0.8811
HDL [mmol/l][1]	2989	0.986	(0.96, 1.02)	0.3495
Triglycerides [mmol/l][1]	2987	1.006	(0.94, 1.08)	0.8724
LDL [mmol/l]	2989	0.010	(-0.11, 0.13)	0.8759

Beta estimates or, for log-transformed variables means ratios (MR) with corresponding 95%-confidence interval (95%-CI) are presented. [1] HDL and triglycerides were log-transformed for analysis to obtain normal distribution. Means ratios (MR) with corresponding 95%-CI are presented.

Table 4: Linear regression models of ever having doctor diagnosed AD up to the age of 15 years on cardiovascular risk factors in GINIplus/LISAplus

	N	beta / MR[1]	95%-CI	P value
BMI z-scores	2286	0.032	(-0.05, 0.12)	0.4573
Total cholesterol[1]	2136	0.991	(0.98, 1.01)	0.3022
HDL	2136	0	(-0.03, 0.03)	0.9846
Triglycerides[1]	2136	0.992	(0.95, 1.03)	0.6942
LDL[1]	2136	0.987	(0.96, 1.01)	0.3007
Systolic blood pressure	2239	0.211	(-0.72, 1.14)	0.6570
Diastolic blood pressure	2239	0.221	(-0.53, 0.97)	0.5640

Beta estimates or, for log-transformed variables means ratios (MR) with corresponding 95%-confidence interval (95%-CI). [1] Total cholesterol, LDL and triglycerides were log-transformed for analysis to obtain normal distribution. Means ratios (MR) with corresponding 95%-CI are presented.