



Predictors of work-related sensitisation, allergic rhinitis and asthma in early work life

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ABSTRACT Although work-related asthma and allergies are a huge burden for society, investigation of occupational exposures in early work life using an unexposed reference group is rare. Thus, the present analyses aimed to assess the potential impact of occupational exposure and other risk factors on the prevalence of work-related sensitisation and incidence of allergic rhinitis/asthma using a population-based approach and taking into account an unexposed reference group.

In SOLAR (Study on Occupational Allergy Risks) II, German participants of ISAAC (International Study of Asthma and Allergies in Childhood) phase II were followed from childhood (9–11 years) until early adulthood (19–24 years). Data on 1570 participants were available to fit predictive models.

Occupational exposure was not statistically significantly associated with disease prevalence/incidence. Sensitisation in childhood, parental asthma, environmental tobacco smoke exposure during puberty, sex and study location were statistically significant predictors of outcome.

Our results indicate that occupational exposure is of little relevance for work-related sensitisation prevalence and allergic rhinitis/asthma incidence in early work life, while other risk factors can be used to improve career guidance for adolescents. Further research on the role of a potential healthy hire effect and the impact of longer exposure duration is needed.



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Introduction

In many countries, occupational asthma is the most common work-related pulmonary disease [1]. It is a chronic disease that may have a differing impact on employees depending on their age or stage of work life [2]. In addition to potential socioeconomic concerns for the affected individual, occupational asthma is associated with a substantial economic burden at the population level [2, 3]. Depending on the country, the prevalence of asthma seems to vary between 1% and 18% [4]; ~16% of adult asthma is attributable to occupational exposure [5]. The prevalence of work-related rhinitis, which encompasses both occupational rhinitis and work-exacerbated rhinitis, is estimated to be 31–61%. Data on occupational rhinitis itself are scarce [6].

Besides occupational exposure, asthma and allergies are influenced by hereditary and environmental risk factors [7]. Many of these factors have already been reported in infancy, *e.g.* in birth cohort studies [8]. However, as described by TORÉN *et al.* [9], substantial investigation of risk factors later in life is rare. Most studies on the incidence of asthma and allergies during the first years of work life were performed in occupational cohorts, *e.g.* bakery apprentices [10, 11]. In one of the few population-based studies assessing risk of occupational exposure, the ECRHS (European Community Respiratory Health Survey) [12], an increased risk was seen for asthma [13], but not for allergic rhinitis [14]. For these analyses, only recent or current occupation was taken into account, and data assessment had not necessarily started before work life, thus the incidence of symptoms attributable to occupational exposure was difficult to assess.

Longitudinal analyses of the course of these diseases, especially in the crucial first years of work life, might help to predict new-onset of work-related asthma/allergies. To the best of our knowledge, only one population-based study on occupational asthma/allergies has followed participants from childhood until adulthood, using an unexposed reference group to assess the impact of occupational exposure [15]. However, that study assessed job history retrospectively later in life.

Therefore, the main aim of SOLAR (Study on Occupational Allergy Risks) was to follow participants from ISAAC (International Study of Asthma and Allergies in Childhood) phase II until adulthood in order to collect detailed information on first job experiences and its association with the course of symptoms/diseases. The objective of this analysis was to assess the potential impact of occupational exposure and other risk factors on participants' respiratory health during the first years of employment.

Methods

Study population

In 1995–1996, questionnaire and clinical data from 6399 primary school children aged 9–11 years were assessed in the German ISAAC phase II study [16, 17]. The participants were from Munich and Dresden (both Germany) and formed the baseline of this population-based cohort study. Questionnaire data of 3929 participants aged 16–18 years were obtained at first follow-up, SOLAR I, in 2002–2003 [18]. In the second follow-up, SOLAR II (2007–2009) [19], 2051 young adults (19–24 years old) completed a questionnaire and clinical data were assessed for 57% of them (fig. 1).

The study was approved by the Ethical Committee of the Medical Faculty of the University of Dresden (Dresden, Germany), the Ethical Committee of the Bavarian Chamber of Physicians (Munich) and by the Ethical Committee of the University of Ulm (Ulm, Germany).

Informed consent was obtained from all study participants, or their guardians if the participants were not yet of age (<18 years old).

Wherever possible, the questionnaires of the three time-points employed the same validated instruments from the ISAAC and the ECRHS [12, 16]. Items consisted of sociodemographic, environmental and health-related components.

Outcomes and potential predictors

Sensitisation to the ubiquitous allergens *Alternaria tenuis*, cat, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, mixed grass pollen and mixed tree pollen was tested for in both the ISAAC phase II and SOLAR II studies using skin prick tests (SPT). In addition to these allergens, rye, *Ambrosia artemisiifolia* and the following occupational allergens were also tested for in SOLAR II: α -amylase, *Aspergillus*, latex, *Lepidoglyphus destructor*-*Lep d 1*, mouse, rat and *Tyrophagus*. Rye flour was also tested in a subsample of the participants. Response to a single allergen was defined as positive when the corresponding wheal size was ≥ 3 mm larger than the negative control.

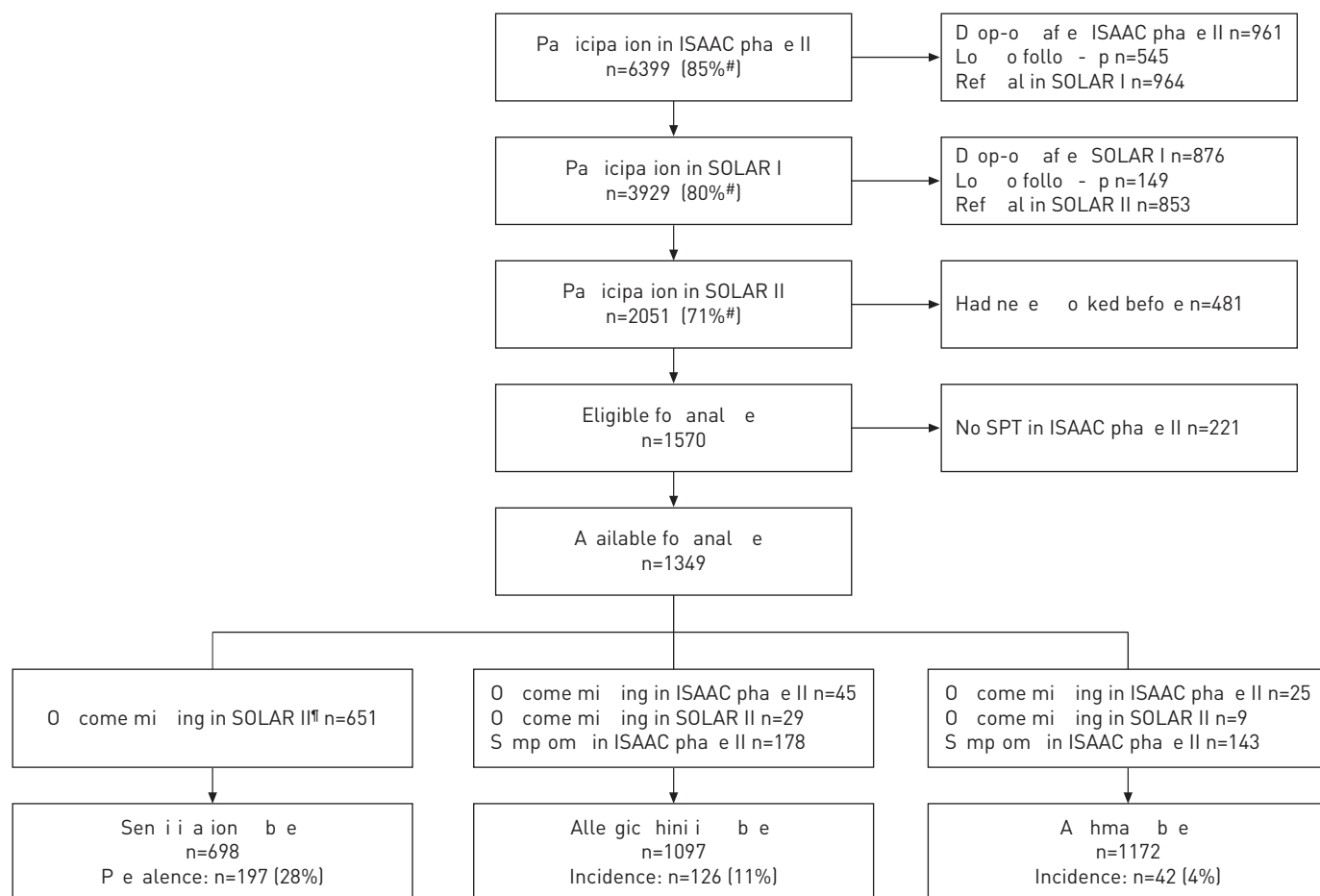


FIGURE 1 Flow chart showing the study participation and formation of the final data analysis subsets. ISAAC: International Study of Asthma and Allergies in Childhood; SOLAR: Study on Occupational Allergy Risks; SPT: skin prick test; drop-out: persons that refused to be contacted again after participation in ISAAC phase II; lost to follow-up: persons that could not be traced or contacted, e.g. due to unknown address, health reasons or death; refusal: persons that could be traced and contacted but refused to participate in the first or second follow-up. #: response refers to the net sample after exclusion of drop-outs and those lost to follow-up; *: SPT missing (n=584) or incomplete (n=48) or use of antihistamine prior to testing (n=19).

Outcomes

Prevalence of work-related sensitisation in SOLAR II was defined as a positive SPT response to at least one of the occupational allergens described above, except rye flour. Additional analyses for the subset of participants with rye flour SPT are presented in the supplementary material.

Allergic rhinitis was defined as a combination of a physician's diagnosis of allergic rhinitis and a 12-month prevalence of rhinoconjunctivitis symptoms, based on the questionnaire data.

A physician's diagnosis of asthma and either a 12-month prevalence of asthma symptoms or current use of asthma medication, as indicated in the questionnaire, was used to define asthma.

Incidence of allergic rhinitis and asthma was defined as the absence of outcome at baseline but presence of outcome at second follow-up, regardless of the condition at first follow-up. Incident cases were compared to those who did not report outcome at baseline and second follow-up. Hence, for each outcome, only participants who did not report that outcome at baseline were analysed for subsequent incidence. Participants with prevalent symptoms at baseline were excluded from the respective analyses.

Potential predictors

Participants' complete job histories were assessed by means of the questionnaires in SOLAR I and SOLAR II. These included holiday, part time and permanent jobs as well as internships, apprenticeships and civilian service. Occupational exposure was considered as a potential predictor for incidence of the outcomes described. Thus, only participants who had reported at least one job considered relevant for exposure assessment and data analysis (any job that had been held for ≥ 4 weeks with ≥ 8 working hours per week) were included in the analyses. All the jobs deemed relevant regarding potential exposure were classified

according to an asthma-specific job exposure matrix [20], and categorised exposure was summarised per participant. Participants' lifetime exposure was defined as presenting either no risk (reference), or low risk or high risk of asthma. If a participant had ever held a relevant job with high risk exposure, their lifetime exposure was set at high risk. If they had not held any high risk job, but at least one with low risk exposure, their lifetime exposure was set at low risk. Only if all the jobs ever held were not associated with any exposure of relevance, was the lifetime exposure set at no risk. Further details are provided in the supplementary material.

Items listed in table 1 were considered as additional potential predictors. Socioeconomic status and sex were considered as confounders and thus adjusted for in all models. SPT response in ISAAC phase II was defined as positive when there was at least one positive response to any of the ubiquitous allergens described above. With the exception of the SPT response, all the information is from the self-reported questionnaire data.

Statistical methods

Missing information on potential risk factors was assumed to be missing at random. The potential predictors marked in table 1 were multiply imputed, using R software (version 2.10.1; www.R-project.org).

Multiple logistic regression models were fitted for each of the three outcomes, taking all the potential predictors into consideration. The confounders socioeconomic status and sex, as well as occupational exposure, were included in all models. Inclusion of additional predictors was determined in a model selection process based on the Akaike information criterion for each outcome.

Probabilities and odds ratios for prevalence/incidence of the outcomes were calculated for presence of single risk factors and for the full models, including all non-occupational risk factors in combination with either having had: 1) no occupational exposure ever (no risk); or 2) occupational low risk (but no high risk) exposure ever; or 3) occupational high risk exposure ever.

TABLE 1 Potential risk factors considered for fitting the predictive models

Risk factors	Total participants [#]	Missing data [¶]	Imputed
Subjects n	1570		
Subjects in SOLAR II aged ≤21 years⁺	552 (35.2)	0	No
Female	918 (58.5)	0	No
Study location Munich	758 (48.3)	0	No
Nationality German	1518 (96.7)	5 (0.3)	Yes
High socioeconomic status[§]	921 (58.7)	21 (1.3)	Yes
Exposure to environmental tobacco smoke		25 (1.6)	Yes
ISAAC phase II: current exposure	439 (28.0)		
ISAAC phase II: former exposure	135 (8.6)		
SOLAR I	960 (61.2)	6 (0.4)	Yes
Ever smokers^f as indicated in SOLAR I	480 (30.6)	12 (0.8)	Yes
Having been breastfed	1348 (85.9)	12 (0.8)	Yes
Kindergarten attendance	1550 (98.7)	10 (0.6)	Yes
Presence of siblings	1273 (81.1)	13 (0.8)	Yes
Parental history of			
Allergic rhinitis	595 (37.9)	138 (8.8)	Yes
Asthma	166 (10.6)	127 (8.1)	Yes
Atopic dermatitis	304 (19.4)	157 (10.0)	Yes
Positive skin prick test response in ISAAC phase II	320 (23.7)	221 (14.1)	No
Occupational exposure		166 (10.6)	Yes ^{##}
No risk	624 (39.7)		
Low risk	383 (24.4)		
High risk	563 (35.9)		

Data are presented as n (%), unless otherwise stated. SOLAR: Study on Occupational Allergy Risks; ISAAC: International Study of Asthma and Allergies in Childhood. [#]: frequencies displayed for one random imputed data set; [¶]: frequencies of missing values before imputation; ⁺: age was dichotomised in two groups of comparable range (19–21 years and 22–24 years); [§]: mother or father qualified for university entrance or university diploma; ^f: ≥1 pack-year, never-smoker defined as <1 pack-year until SOLAR I; ^{##}: only missing time values were imputed to assess relevance of job regarding duration and intensity of potential occupational exposure; jobs lasting ≥4 weeks with ≥8 working hours per week were deemed relevant.

All analyses were performed with SAS software (version 9.4; SAS Institute, Inc., Cary, NC). Further details are provided in the supplementary material.

Results

Participants were followed, on average, for 12.2 years between ISAAC phase II and SOLAR II (median (range) 12.2 (10.8–13.8) years). At least one relevant job was indicated by 1570 participants. Of these, 221 with missing baseline SPT values were excluded from the evaluation. Depending on previous symptoms and missing outcome information, data of 698 participants were available for analysis of sensitisation prevalence, 1097 for incidence of allergic rhinitis and 1172 for incidence of asthma (fig. 1).

Unfortunately, it was not possible to include information on kindergarten attendance in the analyses since 99% of participants had been to kindergarten.

Participants indicated, on average, 2.5 relevant jobs (median (range) 2.0 (1–10)), which they kept for a mean duration of 13 weeks (median (range) 7 (1–91) weeks) per single job. Cumulatively, participants had worked for an average duration of 31 weeks (median (range) 24 (1–242) weeks). 40% had never had a job with asthma-relevant exposure, while 36% had worked in at least one job considered to be of high risk.

The four most frequently indicated jobs, as classified by the International Standard Classification of Occupations-88, were office clerks, waiters/waitresses/bartenders, shop sales persons and demonstrators, and institution-based personal care workers.

Prevalence of work-related sensitisation in SOLAR II was 28% (n=197). The allergens that predominated among the positive SPT results were mouse (19%), *Lep d 1* (18%) and *Tyrophagus* (17%). For allergic rhinitis, 11% (n=126) of the participants without symptoms or doctor's diagnosis at baseline indicated incident diagnoses with current symptoms, corresponding to an incidence density of nine new cases per 1000 person-years. Reported cumulative incidence for asthma was 4% (n=42), while the incidence density was three incident cases per 1000 person-years.

Prediction of work-related sensitisation

Statistically significant predictors for prevalence of work-related sensitisation in SOLAR II were SPT response at baseline, parental history of allergic rhinitis, study location and sex. The overall probability of incidence of work-related sensitisation without occupational exposure was 92% (95% CI 77–97%). The prediction changed only marginally when occupational exposure was included (table 2).

Prediction of allergic rhinitis

Sex and a positive SPT response in ISAAC phase II were statistically significantly associated with incidence of allergic rhinitis. Moreover, parental history of allergic rhinitis and asthma, and environmental tobacco smoke exposure in SOLAR I improved the model. Occupational exposure did not enhance the prediction quality of the model. The overall probability for incidence of allergic rhinitis without occupational exposure was 63% (95% CI 46–78%). It decreased to 53% (95% CI 34–72%) for the presence of occupational low-risk exposure (table 3).

Prediction of asthma

In the final model for incident asthma, parental history of asthma, environmental tobacco smoke exposure in SOLAR I and a positive SPT response at baseline showed statistically significant associations. Again, occupational exposure was not statistically significantly associated with the outcome. Altogether, the probability for new-onset of asthma without occupational exposure was 60% (95% CI 30–84%). Including occupational low-risk exposure decreased the probability to 48% (95% CI 19–79%) (table 4).

Discussion

Due to the early inclusion of participants and the long follow-up time of the study, SOLAR II offers the unique possibility for long-term prediction and exploration of specific predictors for work-related respiratory diseases and allergies in early work life. For the first time, extensive job history and course of health in this age period (*i.e.* adolescence and early adulthood) could be assessed and analysed in a population-based cohort, including an unexposed reference group.

Among the SOLAR II study participants, 77% had already had at least one job considered relevant for potential occupational exposure. None of the predictive models showed any statistically significant influence of occupational exposure on the outcomes being investigated. This finding is in accordance with previous studies that did not reveal such an association [21, 22]. However, the results also indicate a “healthy hire effect”, with participants not having been exposed to low- or high-risk occupational exposure exhibiting higher risks of presenting with the outcomes than those who were exposed (albeit not statistically

TABLE 2 Prevalence of work-related sensitisation in SOLAR II from the final multiple regression model

	Probability % (95% CI)	Adjusted OR (95% CI) [#]
Intercept (β_0)	7.8	
G: general risk factors		
Male <i>versus</i> female [¶]	10.8 (6.5–17.5)	1.4 (1.0–2.1)
Low <i>versus</i> high socioeconomic status [¶]	8.6 (5.3–13.9)	1.1 (0.7–1.7)
Study location, Munich <i>versus</i> Dresden	12.7 (7.6–20.3)	1.7 (1.1–2.6)
Nationality, other <i>versus</i> German	16.4 (5.8–38.5)	2.3 (0.8–6.6)
ETS exposure in SOLAR I, no <i>versus</i> yes	9.7 (5.8–15.8)	1.3 (0.9–1.9)
Parental history of allergic rhinitis, yes <i>versus</i> no	11.1 (6.8–17.7)	1.5 (1.0–2.2)
Positive <i>versus</i> negative SPT response in ISAAC phase II	46.9 (33.3–61.0)	10.4 (6.9–15.7)
Occupational exposure		
L: ever <i>versus</i> never having had occupational low-risk exposure [¶]	8.0 (3.9–15.5)	1.0 (0.6–1.7)
H: never <i>versus</i> ever having had occupational high risk exposure [¶]	8.4 (5.1–13.5)	1.1 (0.7–1.7)
Full model, including		
Never had occupational exposure (G+H)	91.8 (77.3–97.3)	11.2 (3.4–36.6)
Occupational low-risk exposure ever (G+L+H)	91.9 (77.2–97.5)	11.4 (3.4–38.2)
Occupational high-risk exposure ever (G)	91.2 (75.7–97.2)	10.3 (3.1–34.3)

exp(β_0)=0.085. G: general (non-occupational) risk factors; L: occupational low-risk exposure; H: occupational high-risk exposure; ETS: environmental tobacco smoke; SOLAR: Study on Occupational Allergy Risks; SPT: skin prick test; ISAAC: International Study of Asthma and Allergies in Childhood. [#]: based on the full model (G+L+H); [¶]: forced in.

significant). It is possible that participants who developed symptoms after ISAAC phase II (but before SOLAR II) intuitively avoided jobs or tasks that would have been associated with certain exposures. Thus, their increased risk for the outcome could have influenced their exposure status, rather than the other way round.

Overall prediction probabilities for prevalent work-related sensitisation were substantially higher than the positive predictive value (PPV) of SPT for new-onset occupational hypersensitivity, which had previously been found in apprentice bakers (33%) [23]. As seen in previous studies, SPT at baseline was strongly predictive of this outcome [24–26].

Prediction of incidence of allergic rhinitis was moderate, with a maximum overall probability of 63%. The combination of non-occupational predictors included in the model accounts for more than half of the new cases and, thus, is better than SPT alone (PPV 14–49%) [27, 28]. Intrinsic factors such as parental disease

TABLE 3 Incidence of physician-diagnosed allergic rhinitis up to SOLAR II from the final multiple regression model

	Probability % (95% CI)	Adjusted OR (95% CI) [#]
Intercept (β_0)	2.7	
G: general risk factors		
Female <i>versus</i> male [¶]	4.2 (2.0–8.5)	1.6 (1.0–2.4)
High <i>versus</i> low socioeconomic status [¶]	3.3 (1.6–6.8)	1.2 (0.8–1.9)
Parental history of allergic rhinitis, yes <i>versus</i> no	3.6 (1.6–7.7)	1.3 (0.9–2.1)
Parental history of asthma, yes <i>versus</i> no	4.5 (1.8–11.0)	1.7 (0.9–3.2)
ETS exposure in SOLAR I, no <i>versus</i> yes	3.4 (1.6–7.4)	1.3 (0.9–1.9)
Positive <i>versus</i> negative SPT response in ISAAC phase II	16.8 (8.6–30.0)	7.2 (4.8–11.0)
Occupational exposure		
L: never <i>versus</i> ever having had occupational low-risk exposure [¶]	4.0 (2.3–6.9)	1.5 (0.9–2.6)
H: never <i>versus</i> ever having had occupational high risk exposure [¶]	2.7 (1.5–5.1)	1.0 (0.6–1.6)
Full model, including		
Never had occupational exposure (G+L+H)	63.4 (45.5–78.2)	1.7 (0.8–3.6)
Occupational low-risk exposure ever (G+H)	53.5 (33.5–72.4)	1.1 (0.5–2.6)
Occupational high-risk exposure ever (G+L)	63.2 (44.5–78.6)	1.7 (0.8–3.7)

exp(β_0)=0.028. G: general (non-occupational) risk factors; L: occupational low-risk exposure; H: occupational high-risk exposure; ETS: environmental tobacco smoke; SOLAR: Study on Occupational Allergy Risks; SPT: skin prick test; ISAAC: International Study of Asthma and Allergies in Childhood. [#]: based on the full model (G+L+H); [¶]: forced in.

TABLE 4 Incidence of physician-diagnosed asthma up to SOLAR II from the final multiple regression model

	Probability % (95% CI)	Adjusted OR (95% CI) [#]
Intercept (β_0)	0.3	
G: general risk factors		
Female <i>versus</i> male [†]	0.4 (0.1–1.7)	1.4 (0.7–2.8)
Low <i>versus</i> high socioeconomic status [†]	0.4 (0.1–1.6)	1.2 (0.6–2.4)
Parental history of asthma, yes <i>versus</i> no	1.0 (0.2–4.6)	3.4 (1.5–7.4)
Parental history of atopic dermatitis, yes <i>versus</i> no	0.4 (0.1–2.1)	1.5 (0.7–3.2)
ETS exposure in SOLAR I, yes <i>versus</i> no	0.7 (0.2–2.5)	2.4 (1.0–5.5)
Ever <i>versus</i> never smoking status in SOLAR I	0.5 (0.1–2.1)	1.5 (0.8–3.0)
Having been breastfed, no <i>versus</i> yes	0.6 (0.1–2.6)	1.9 (0.8–4.2)
Positive <i>versus</i> negative SPT response in ISAAC phase II	1.3 (0.3–4.9)	4.3 (2.2–8.3)
Occupational exposure		
L: never <i>versus</i> ever having had occupational low-risk exposure [†]	0.5 (0.2–1.5)	1.6 (0.7–3.8)
H: never <i>versus</i> ever having had occupational high risk exposure [†]	0.4 (0.1–1.3)	1.2 (0.6–2.6)
Full model, including		
Never had occupational exposure (G+L+H)	60.0 (30.0–84.0)	1.5 (0.4–5.3)
Occupational low-risk exposure ever (G+H)	48.4 (18.5–79.4)	0.9 (0.2–3.9)
Occupational high-risk exposure ever (G+L)	54.8 (24.8–81.7)	1.2 (0.3–4.5)

$\exp(\beta_0)=0.003$. G: general (non-occupational) risk factors; L: occupational low-risk exposure; H: occupational high-risk exposure; ETS: environmental tobacco smoke; SOLAR: Study on Occupational Allergy Risks; SPT: skin prick test; ISAAC: International Study of Asthma and Allergies in Childhood. [#]: based on the full model (G+L+H); [†]: forced in.

history or SPT seem to be at least as important for allergic rhinitis as modifiable ones. This finding supports European Academy of Allergy and Clinical Immunology recommendations for occupational rhinitis, which stated that no single factors were known that would predict incidence with sufficient certainty (as in high PPV) to exclude persons from jobs associated with probable exposure [29].

The logistic regression model for incidence of asthma had the lowest overall prediction probabilities of all full models with broad confidence intervals, and the single factor probabilities were rather small due to the very low base risk of developing asthma. Including all potential risk factors in the model yielded a high probability of 60%, especially compared to the low PPV of SPT for current asthma (5%) [28]. The included factors are in accordance with known risk factors for the development of asthma in adulthood [30]. The only modifiable factors were being breastfed and avoidance of environmental tobacco smoke exposure and smoking during puberty.

We could not confirm some of the predictors found in other longitudinal studies on occupational exposure, *e.g.* parental asthma was not associated with work-related sensitisation in our analyses, and even though sex, socioeconomic status and smoking were included in our asthma prediction model, they were not statistically significant [26, 31–33]. However, those studies were based on occupational cohorts and did not include never-exposed reference groups, so the results are not necessarily comparable.

Strengths and limitations

Previous studies on the impact of occupational exposure on sensitisation, allergic rhinitis or asthma were mostly based on occupational cohorts only (*e.g.* apprentice pastry makers, bakery workers and workers exposed to laboratory animals) and, thus, in contrast to our study, did not include an unexposed reference group [10, 11, 34]. However, having such a group is crucial in estimating the excess risk that is attributable to a certain exposure compared to the background risk in the population without that exposure. GHOSH *et al.* [15] also followed a population-based approach and, thus, were able to include an unexposed reference group. However, complete job history in this study was assessed retrospectively at age 33 years and 42 years. Hence, information, especially from early work life, could be prone to poor recall and, therefore, be less exhaustive and reliable than in the present analyses.

Our results indicate that relevance of occupational exposure in early work life is low compared to other factors that can be easily assessed in childhood. This may initially seem counterintuitive, and may even appear contradictory to the results of some previous studies. However, on closer inspection this is not the case. Some other prospective studies including unexposed reference groups have also indicated that the incidence of asthma and allergies in young adults who had just started their careers was often independent of occupational exposure [21, 22, 25].

A limitation of our study might be that even though participants were followed for ~12 years, they were still very young in SOLAR II and just at the beginning of their working lives. Many studies have shown that incidence of asthma and allergies may be highest in the first 6–12 months of a job [18, 32, 35], whereas our participants had indicated average job durations of 3 months, with a maximum of 21 months. Therefore, exposure times might have been too short to detect potential adverse health effects.

The study population was sampled from the general population; hence it can be assumed that the presented results are essentially representative for the population in Germany. Some response bias was seen in the study, and a few differences were observed comparing those included in the analyses subsets with those excluded because of previous disease or missing values [19] (supplementary material). However, this may bias the results towards the null rather than away from the null. It is unclear whether the associations found in this study also hold true for other populations; further research is needed to assess the generalisability.

Unfortunately, it was not possible to use a time-dependent approach for the analysis of this study, since the exact timing of symptom or disease onset was not known. Information on absence or presence of symptoms was only available for the 12 months prior to each study time point; sensitisation was only assessed at baseline and the second follow-up.

A pre-determined panel of work-related allergens was tested for by SPT regardless of reported jobs and suspected exposures. It is possible that some participants were sensitised to other occupational substances that had not been included in this panel. However, the most relevant work-related allergens for asthma and allergies in Germany were selected for the panel, and it would hardly be possible to test for all existing substances or test specific allergens on an individual basis.

Instead of complete case analysis or single imputation, we used multiple imputation to account for missing values and the uncertainty associated with these. This approach generally assumes that data are missing at random, which unfortunately cannot be tested. However, this procedure has become common practice in epidemiological studies and was shown to perform better than other methods [36].

Conclusion

In conclusion, we could not show overall a statistically significant contribution of occupational exposures to disease prevalence/incidence; thus, our results might challenge received knowledge. The difference might be explained by a lack of unexposed reference groups in previous studies. More research is needed to assess the role of a potential healthy hire effect and to evaluate longer exposure duration.

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**Predictors of work-related sensitization, allergic rhinitis and asthma in
early work-life**

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Supplementary Material

Methods

Occupational exposure assessment

The following steps were only taken for relevant jobs that had been held for ≥ 4 weeks with ≥ 8 working hours per week.

First, jobs were independently coded according to the International Standard Classification of Occupations (ISCO-88 (1)) by two trained persons. Codings for each job were compared and revised by an expert if differing. If a task description was too unspecific for classification by ISCO-88, the according job was labeled as “unclear”.

Subsequently, jobs were matched by their ISCO-88 codes with the asthma-specific Job Exposure Matrix (JEM) by Susan Kennedy (2) and all expert steps necessary were conducted. This JEM assigns each ISCO-88 coded job the asthma - relevant occupational exposure that it is commonly associated with. Exposures are classified as being of high risk for asthma if they belong to one of the following categories:

- High molecular weight (HMW) agents
- Low molecular weight (LMW) agents
- Mixed environments of high risk
- High probability of peak exposure to irritants.

The exposure group with low asthma risk includes exposures such as exhaust, low antigens, environmental tobacco smoke and irritant gases or fumes. Jobs without occurrence of any asthma-relevant exposure are classified as being of no risk and may be used as non-exposed reference group for jobs with relevant exposure. Application of this JEM involves several expert steps, as described in (2), to reassure the most precise exposure assessment for every single job examined.

Jobs labeled “unclear” as described above could not be matched with the JEM for exposure assessment. For these jobs, it was assumed that no relevant exposure was involved and the according job was classified as being of no risk. This conservative approach leads to a possible underestimation of the exposure, which increases specificity compared to sensitivity.

After the described procedures had been performed for all jobs mentioned by the participants, summarized lifetime exposure per person was assessed. High risk exposure was considered dominant over low risk exposure over no risk exposure.

Statistical methods

Missing data

Missing information on potential risk factors was assumed to be missing at random. All potential predictors listed in Table 1 that had been assessed by questionnaire were multiply imputed, except for age, sex, and study location, which were complete. Two different methods were applied for imputation of 5 data sets each, using R software (version 2.10.1, <http://www.R-project.org> (3)):

- sampling without replacement from the empirical distribution of each variable
- application of the Amelia II package (R package version 1.2-14, <http://CRAN.R-project.org/package=Amelia> (4)).

In a second step, any missing date and/or time information of participants' jobs was multiply imputed as well. These jobs were checked for relevance afterwards and if applicable, ISCO-88 coded and matched with the JEM as described above. Lifetime exposure evaluation as explained above was carried out for each participant after completion of imputation process.

Analyses

Bivariate associations between potential risk factors and incidence of the outcomes were tested using chi-square tests for each of the 10 imputed data sets.

Factors showing ≥ 1 significant association ($p_{\chi^2} < 0.1$) with the outcome were then included as predictors in multiple logistic regression models. The Akaike information criterion was used to distinguish the model that best predicted incidence of the outcome. Socioeconomic status, sex and occupational exposure were included in all models. The predictors in the final models were all coded in the same direction (odds ratio (OR) > 1), so that they presented a risk for new-onset of the outcome. Reference category was always the one with the lowest odds.

Probabilities and odds ratios for incidence of the outcomes were calculated for presence of single risk factors (assuming absence of all other factors from the model) and for the full models. The full models for each outcome consisted of a combination of all non-occupational risk factors with either (a) never having had occupational exposure, (b) ever having had occupational low risk exposure but never having had occupational high risk exposure, or (c) ever having had occupational high risk exposure.

The according probabilities for any combination of risk factors $x_1 \dots x_k$ may be calculated pursuant to the following formula (cf. (5) for further details):

Formula 1:

$$\begin{aligned} P(\text{incidence of outcome} | x_1 \dots x_k) &= \frac{\exp(\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_k x_k)}{1 + [\exp(\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_k x_k)]} \\ &= \frac{\exp(\beta_0) \times (OR_1 \times OR_2 \times \dots \times OR_k)}{1 + [\exp(\beta_0) \times (OR_1 \times OR_2 \times \dots \times OR_k)]} \end{aligned}$$

$x_1 \dots x_k$ represent the single risk factors from the model with the coefficients $\beta_1 \dots \beta_k$, $OR_1 \dots OR_k$ are their corresponding OR and β_0 is the model's intercept.

Results

Subset comparison of included/excluded participants

A comparison of the participants included in and excluded from the analysis subsets for work-related sensitization, allergic rhinitis and asthma is displayed in Table E1. For the sensitization subset, two groups of excluded participants are presented: those excluded due to missing baseline skin prick test (SPT) and those with missing outcome (either due to missing values or refusal of SPT at SOLAR II). For allergic rhinitis and asthma, it was taken into account whether exclusion of participants was due to symptoms or doctor's diagnosis of disease at baseline or due to missing SPT or outcome information.

For the work-related sensitization subset, the fraction of participants with high socioeconomic status (SES) was lowest in the participants excluded due to missing outcome and highest in those with missing baseline SPT. The proportion of current environmental tobacco smoke (ETS) exposure both at baseline and first follow-up was statistically significantly higher in the participants excluded due to missing outcome information, while it was comparable between the other two groups. On the other hand, previous ETS exposure as indicated in ISAAC Phase II was higher in subjects who were included in the analysis. Moreover, smoking prevalence was higher in the participants excluded because of missing outcome information than in the other two groups. Overall, these observations are in line with the evaluation previously described by Heinrich et al. (6), that participants with lower SES, who smoked or were exposed to ETS exposure were less likely to participate in the clinical examinations in SOLAR II. Despite this slight selection bias of the analysis sample, results of the present analyses should not be biased in terms of the study

questions, since inclusion or exclusion of the participants in the analyses seems to have been non-differential regarding their occupational exposure status.

For allergic rhinitis, the proportion of subjects with parental atopic diseases and positive SPT response at baseline differed between the included and two excluded subsets. It was highest in persons excluded due to reported disease at baseline, and similarly lower in participants included in the analyses and excluded due to missing values. This might raise concerns of potential bias at first, however, at closer inspection this is rather unlikely. In line with previous findings it is plausible that children who are atopic or have parents with atopic diseases are at higher risk of developing such diseases themselves. In our study, it seems that participants with atopy or parental atopic disease were more likely to develop the symptoms before baseline, and thus were excluded from the analyses of disease incidence. Therefore, the prediction of disease incidence between baseline and second follow-up is unlikely to be biased by the exclusion of these subjects.

Table E1: Description of analysis subsets and persons excluded from these subsets

potential risk factor	Sensitization subset				Allergic rhinitis subset				Asthma subset			
	included	excluded due to missing		p	included	excluded due to		p	included	excluded due to		p
		baseline SPT	outcome SPT			baseline AR	missing values			baseline asthma	missing values	
	N=698	N=221	N=651		N=1097	N=120	N=353		N=1172	N=96	N=302	
	n (%) *	n (%) *	n (%) *		n (%) *	n (%) *	n (%) *		n (%) *	n (%) *	n (%) *	
Age at SOLAR II(≤21 years) [#]	250 (35.8)	82 (37.1)	220 (33.8)	0.60	388 (35.4)	43 (35.8)	121 (34.3)	0.92	416 (35.5)	28 (29.2)	194 (64.2)	0.45
Sex (female)	404 (57.9)	132 (59.7)	382 (58.7)	0.88	654 (59.6)	60 (50.0)	204 (57.8)	0.12	706 (60.2)	31 (32.3)	181 (59.9)	<0.0001
Study location (Munich)	321 (46.0)	119 (53.9)	318 (48.9)	0.12	510 (46.5)	59 (49.2)	189 (53.5)	0.07	556 (47.4)	54 (56.3)	148 (49.0)	0.24
Nationality (German)	679 (97.3)	215 (97.3)	624 (95.9)	0.30	1060 (96.6)	118 (98.3)	340 (96.3)	0.55	1131 (96.5)	93 (96.9)	294 (97.4)	0.76
Socioeconomic status (high) [†]	424 (60.7)	146 (66.1)	351 (53.9)	<0.01	626 (57.1)	73 (60.8)	222 (62.9)	0.14	694 (59.2)	47 (49.0)	180 (59.6)	0.14
ETS exposure in ISAAC Phase Two				<0.0001				0.87				0.78
current	156 (22.4)	51 (23.1)	232 (35.6)		315 (28.7)	32 (26.7)	92 (26.1)		327 (27.9)	26 (27.1)	86 (28.5)	
former	72 (10.3)	13 (5.9)	50 (7.7)		95 (8.7)	11 (9.2)	29 (8.2)		107 (9.1)	7 (7.3)	21 (7.0)	
ETS exposure in SOLAR I (yes)	406 (58.2)	126 (57.0)	428 (65.8)	<0.01	687 (62.6)	71 (59.2)	202 (57.2)	0.17	730 (62.3)	55 (57.3)	175 (58.0)	0.28
Smoking status in SOLAR I (ever) [‡]	186 (26.7)	57 (25.8)	237 (36.4)	<0.001	345 (31.5)	36 (30.0)	99 (28.1)	0.48	368 (31.4)	35 (36.5)	77 (25.5)	0.06
Having been breastfed	599 (85.8)	193 (87.3)	556 (85.4)	0.78	944 (86.1)	103 (85.8)	301 (85.3)	0.93	1017 (86.8)	81 (84.4)	250 (82.8)	0.19
Kindergarten attendance	693 (99.3)	216 (97.7)	641 (98.5)	0.15	1085 (98.9)	120 (100)	345 (97.7)	0.10 [§]	1157 (98.7)	96 (100)	297 (98.3)	0.45 [§]
Presence of siblings	570 (81.7)	181 (81.9)	522 (80.2)	0.74	898 (81.9)	95 (79.2)	280 (79.3)	0.49	952 (81.2)	79 (82.3)	242 (80.1)	0.87
Parental history of:												
allergic rhinitis	273 (39.1)	85 (38.5)	237 (36.4)	0.58	371 (33.8)	79 (65.8)	145 (41.1)	<0.0001	426 (36.4)	51 (53.1)	118 (39.1)	<0.01
asthma	68 (9.7)	22 (10.0)	76 (11.7)	0.49	96 (8.8)	26 (21.7)	44 (12.5)	<0.0001	112 (9.6)	17 (17.7)	37 (12.3)	0.03
atopic dermatitis	132 (18.9)	34 (15.4)	138 (21.2)	0.15	192 (17.5)	38 (31.7)	74 (21.0)	<0.001	215 (18.3)	26 (27.1)	63 (20.9)	0.09
SPT response in ISAAC Phase Two (positive)	169 (24.2)	Ø	151 (23.2)	0.66	176 (16.0)	81 (86.2)	63 (39.9)	<0.001	242 (20.7)	44 (58.7)	34 (33.33)	<0.0001
Occupational exposure:												
no risk	276 (39.5)	92 (41.6)	256 (39.3)	0.82	439 (40.0)	40 (33.3)	145 (41.1)	0.31	471 (40.2)	31 (32.3)	122 (40.4)	0.30
low risk	160 (22.9)	45 (20.4)	178 (27.3)	0.05	268 (24.4)	34 (28.3)	81 (23.0)	0.49	294 (25.1)	28 (29.2)	61 (20.2)	0.11
high risk	262 (37.5)	84 (38.0)	217 (33.3)	0.21	390 (35.6)	46 (38.3)	127 (36.0)	0.83	407 (34.7)	37 (38.5)	119 (39.4)	0.27

* frequencies displayed for 1 random imputed data set

[#] age was dichotomized in two groups of comparable range (19-21 years, 22-24 years)

[†] high: mother or father had qualified for university entrance or university diploma; low: else

[‡] ever: ≥ 1 pack-year; never: <1 pack-year until SOLAR I

p – chi-square test p-values comparing included and excluded participants per analysis subset

[§] Fisher's exact test p-value

AR – allergic rhinitis, ETS – environmental tobacco smoke, ISAAC – International Study on Asthma and Allergies in Childhood, SOLAR – Study on Occupational Allergy Risks, SPT – skin prick test

The fraction of females differed between the persons included in and excluded from the asthma analyses; it was lower in the participants excluded due to previous disease than in the other two groups. This is not surprising, as boys are more likely to develop asthma before puberty than girls and were thus more likely to be excluded from the analyses due to disease at baseline. Similar to allergic rhinitis, the proportion of positive SPT responses in ISAAC Phase II and parental atopic diseases was highest in the participants excluded from the asthma analyses with symptoms or doctor's diagnosis at baseline and lowest in the subjects included in the analyses. As explained above, both of these differences should not bias the results of the presented analyses.

Moreover, Figure E1 gives an overview of overlap between presence of the three outcomes across the three analysis subsets for those participants without missing outcome values (n=169).

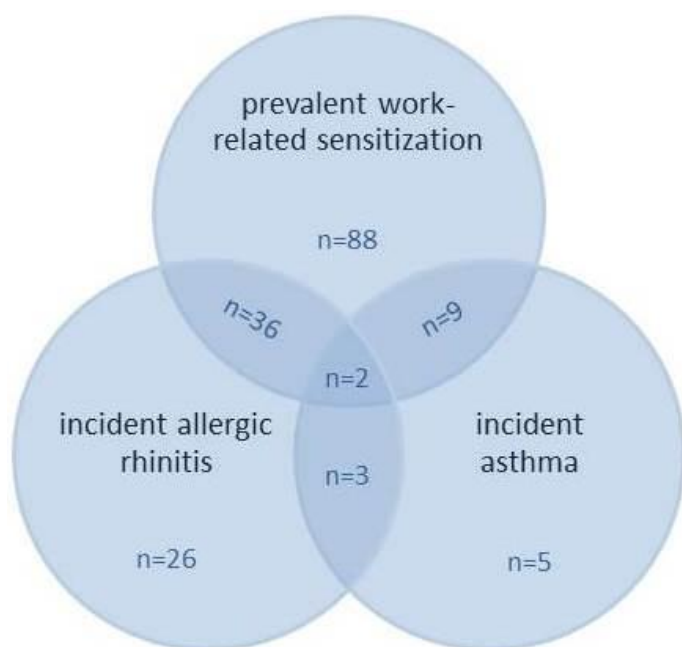


Figure E1: Overlap of outcome presence between the three analysis subsets in participants with at least one outcome present and no missing outcome information (n=169)

Occupational history and exposure

Among the 1570 participants who had indicated at least one job deemed relevant for exposure assessment, 40 % had never held a job with asthma-relevant exposure, while 36 % had worked at least in one job considered to be of high risk. Among the persons with high risk jobs, 63 % were exposed to HMW agents, 80 % to LMW agents, 18 % to mixed environments and 5 % to potential irritant peaks.

Unadjusted effect estimates and 95% confidence intervals

Unadjusted odds ratios for the prevalence of work-related sensitization (without consideration of rye flour) and the incidence of allergic rhinitis and asthma are presented in Table E2 (n=698).

Table E2: Crude odds ratios and 95% confidence intervals for prevalence of work-related sensitization, incidence of allergic rhinitis and incidence of asthma, based on the respective final analysis subsets

Analysis subset →	sensitization N=698	allergic rhinitis N=1097	asthma N=1172
Potential risk factor ↓	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
Age at SOLAR II(≤21 years) [#]	0.8 (0.6; 1.1)	1.2 (0.8; 1.7)	1,1 (0,6; 2,1)
Sex (female)	0.6 (0.4; 0.8)	1.2 (0.8; 1.7)	1,3 (0,7; 2,6)
Study location (Munich)	1.5 (1.1; 2.0)	1.0 (0.7; 1.4)	1,2 (0,7; 2,3)
Nationality (German)	0.5 (0.2; 1.3)	2.4 (0.6; 9.9)	1,3 (0,2; 9,9)
Socioeconomic status (high) [†]	1.0 (0.7; 1.4)	1.4 (0.9; 2.0)	0,8 (0,4; 1,5)
Exposure to environmental tobacco smoke in ISAAC Phase Two:			
current	0.9 (0.6; 1.4)	0.6 (0.4; 1.0)	1,0 (0,5; 2,1)
former	0.9 (0.5; 1.5)	1.0 (0.5; 2.0)	1,4 (0,5; 3,7)
Exposure to environmental tobacco smoke in SOLAR I (yes)	0.7 (0.5; 1.0)	0.8 (0.5; 1.1)	2,5 (1,2; 5,6)
Smoking status as indicated in SOLAR I (ever) [‡]	0.8 (0.5; 1.2)	1.1 (0.8; 1.7)	2,0 (1,1; 3,8)
Having been breastfed	1.0 (0.6; 1.6)	0.7 (0.4; 1.1)	0,5 (0,3; 1,2)
Kindergarten attendance	1.0 (0.1; 9.9)	0.6 (0.1; 2.8)	0,2 (0,0; 1,0)
Presence of siblings	1.0 (0.6; 1.5)	0.7 (0.5; 1.1)	0,8 (0,4; 1,7)
Parental history of:			
allergic rhinitis	1.8 (1.3; 2.5)	1.7 (1.2; 2.5)	1,2 (0,6; 2,3)
asthma	1.4 (0.8; 2.4)	2.0 (1.2; 3.5)	4,1 (2,0; 8,5)

atopic dermatitis	1.2 (0.8; 1.8)	1.3 (0.8; 2.1)	1,9 (0,9; 3,9)
Skin prick test response in ISAAC Phase Two (positive)	10.3 (6.9; 15.2)	6.7 (4.5; 10.0)	4,1 (2,2; 7,7)
Occupational exposure:			
low risk	1.2 (0.8; 1.8)	0.7 (0.4; 1.1)	0,7 (0,3; 1,5)
high risk	0.9 (0.6; 1.3)	1.1 (0.7; 1.6)	0,9 (0,5; 1,8)

age was dichotomized in two groups of comparable range (19-21 years, 22-24 years)

† high: mother or father had qualified for university entrance or university diploma; low: else

‡ ever: ≥1 pack-year; never: <1 pack-year until SOLAR I

Prediction of work-related sensitization including rye flour data

For purposes of a sensitivity analysis, the analyses as described in the main text were repeated for the subset of participants who had a skin prick test (SPT) for rye flour. The results of these analyses are presented in Table E3 (n=277). Since the sample size for this model was less than one half of that in the model presented in Table 2 in the main article, it is not very surprising that fewer variables were included during the model selection procedure. In addition to this difference, it can be noted that the reference categories for SES and occupational high risk exposure changed in the reduced model. Moreover, except for the SPT response in ISAAC Phase Two, the single probabilities for the smaller model are slightly higher, while the overall probabilities are a bit smaller than in the main model. In both models, study location and SPT response at baseline are the only statistically significant predictors of prevalence of work-related sensitization in SOLAR II.

Table E3: Probabilities, unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI) for prevalence of **work-related sensitization** in SOLAR II for the subset of participants who were also tested for **rye flour** (n=277). These are presented for presence of single risk factors and for combinations of all non-occupational risk factors (part G) with never having been occupationally exposed, having had occupational low risk exposure (L) and having had occupational high risk exposure (H)

	probability	unadjusted OR	adjusted OR**
	(%) (95 % CI)	OR (95 % CI)	OR (95 % CI)
Intercept (β_0)	11.4		0.1

	Sex (male vs. female) *	12.1 (5.5; 24.6)	1.2 (0.7; 2.0)	1.1 (0.6; 1.9)
	Socioeconomic status (high vs. low) *	13.3 (7.0; 23.9)	1.2 (0.7; 2.1)	1.2 (0.7; 2.1)
G	Study location (Munich vs. Dresden)	23.2 (12.9; 38.1)	1.6 (1.0; 2.7)	2.4 (1.2; 4.4)
	Nationality (other vs. German)	25.6 (7.5; 59.3)	3.2 (1.0; 10.9)	2.7 (0.7; 10.1)
	Skin prick test response in ISAAC Phase Two (positive vs. negative)	45.8 (28.2; 64.5)	4.8 (2.6; 8.9)	6.6 (3.3; 13.0)
L	Occupational low risk exposure (ever vs. never) *	13.6 (6.5; 26.3)	1.3 (0.7; 2.3)	1.2 (0.6; 2.5)
H	Occupational high risk exposure (ever vs. never) *	12.4 (6.5; 22.5)	0.8 (0.5; 1.4)	1.1 (0.6; 2.2)
Full model, including:				
	never occupational exposure (G)	87.2 (61.0; 96.7)	Ø	6.8 (1.6; 29.6)
	occupational low risk exposure ever (G+L)	89.3 (64.1; 97.5)	Ø	8.3 (1.8; 38.8)
	occupational high risk exposure ever (G+H)	88.2 (61.2; 97.3)	Ø	7.5 (1.6; 35.6)

* forced in

** based on full model (G+L+H)

G – general (non-occupational) risk factors, L – occupational low risk exposure, H – occupational high risk exposure
 $\exp(\beta_0)=0.128$

Comparison of results obtained from the multiple imputations and complete case analysis

For purposes of a sensitivity analysis, the models described above were also fitted for the complete case data, i.e., data sets including all participants who did not have missing values in any of the potential risk factors or outcome variables (n=508 for work-related sensitization, n=808 for allergic rhinitis, n=856 for asthma). The models that were fitted on the unimputed data set are described in **Error! Reference source**

not found. Tables E4-E6. Overall, the complete case models did not differ substantially from the models obtained from the imputed data sets.

Work-related sensitization

Magnitude and direction of the effect estimates for prevalence of work-related sensitization were more or less comparable between the complete case and the multiply imputed analysis. Probabilities and OR for the full model were somewhat larger in the non-imputed model.

Allergic rhinitis

For allergic rhinitis, magnitude and direction of the effect estimates were very similar between the two versions of the model, both for single variables and for the full models.

Asthma

For the prediction of asthma incidence, the reference category for sex differed between the complete case and the imputed final models, while this was not the case for the other factors included in the models. Again, magnitude of effect estimates did not differ considerably between the two model versions, but probabilities were generally lower for the imputed model, while some OR were higher and some lower. Full model probabilities and OR were a bit higher for the imputed model than for the model based on complete cases.

Table E4: Probabilities, unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI) for prevalence of **work-related sensitization** until SOLAR II based on **complete case analysis** (n=508). These are presented for presence of single risk factors and for combinations of all non-occupational risk factors (part G) with never having been occupationally exposed, having had occupational low risk exposure (L) and having had occupational high risk exposure (H)

	probability	unadjusted OR	adjusted OR**
	(%) (95 % CI)	OR (95 % CI)	OR (95 % CI)
Intercept (β_0)	5.8		
Sex (male vs. female) *	10.1 (5.4; 18.2)	2.0 (1.4; 3.0)	1.8 (1.1; 2.9)
Socioeconomic status (low vs. high) *	6.6 (3.5; 12.1)	1.0 (0.7; 1.5)	1.1 (0.7; 1.8)
Study location (Munich vs. Dresden)	11.6 (6.8; 19.1)	1.6 (1.1; 2.3)	2.1 (1.3; 3.5)
Nationality (other vs. German)	14.4 (3.0; 47.7)	3.3 (0.9; 12.5)	2.7 (0.6; 12.8)
G Environmental tobacco smoke exposure in SOLAR I (no vs. yes)	7.1 (3.8; 13.0)	1.3 (0.9; 2.0)	1.2 (0.8; 2.0)
Parental history of allergic rhinitis (yes vs. no)	8.0 (4.0; 15.1)	1.9 (1.3; 2.8)	1.4 (0.9; 2.2)
Skin prick test response in ISAAC Phase Two (positive vs. negative)	43.4 (28.4; 59.8)	11.8 (7.4; 18.9)	12.4 (7.5; 20.4)
L Occupational low risk exposure (ever vs. never) *	6.8 (3.4; 13.1)	1.2 (0.8; 1.9)	1.2 (0.6; 2.2)
H Occupational high risk exposure (ever vs. never) *	6.6 (3.5; 12.1)	1.0 (0.7; 1.5)	1.1 (0.7; 2.0)
Full model, including:			
never occupational exposure (G)	94.0 (74.3; 98.8)	Ø	15.8 (2.9; 85.8)
occupational low risk exposure ever (G+L)	94.9 (76.9; 99.0)	Ø	18.5 (3.3; 103.1)
occupational high risk exposure ever (G+H)	94.7 (77.0; 99.0)	Ø	18.0 (3.4; 97.0)

* forced in

** based on full model (G+L+H)

G – general (non-occupational) risk factors, L – occupational low risk exposure, H – occupational high risk exposure

$$\exp(\beta_0)=0.062$$

Table E5: Probabilities, unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI) for incidence of physician-diagnosed **allergic rhinitis** in SOLAR II based on **complete case analysis** (n=808). These are presented for presence of single risk factors and for combinations of all non-occupational risk factors (part G) with never having been occupationally exposed, having had occupational low risk exposure (L) and having had occupational high risk exposure (H)

	probability (%) (95 % CI)	unadjusted OR OR (95 % CI)	adjusted OR** OR (95 % CI)
Intercept (β_0)	2.7 (1.1; 6.4)		
Sex (female vs. male) *	4.5 (2.0; 10.2)	1.2 (0.8; 1.9)	1.7 (1.0; 2.8)
Socioeconomic status (high vs. low) *	2.9 (1.2; 6.8)	1.1 (0.7; 1.8)	1.1 (0.7; 1.7)
Parental history of allergic rhinitis (yes vs. no)	3.5 (1.4; 8.7)	1.8 (1.1; 2.8)	1.3 (0.8; 2.2)
G Parental history of asthma (yes vs. no)	4.7 (1.6; 13.3)	2.1 (1.1; 3.9)	1.8 (0.9; 3.7)
Environmental tobacco smoke exposure in SOLAR I (no vs. yes)	3.1 (1.2; 7.6)	1.1 (0.7; 1.7)	1.2 (0.7; 1.8)
Skin prick test response in ISAAC Phase Two (positive vs. negative)	17.5 (8.1; 33.8)	6.9 (4.4; 11)	7.6 (4.7; 12.4)
L Occupational low risk exposure (never vs. ever) *	4.2 (2.2; 7.9)	1.4 (0.8; 2.5)	1.6 (0.8; 2.9)
H Occupational high risk exposure (never vs. ever) *	2.9 (1.4; 5.9)	1.0 (0.6; 1.5)	1.1 (0.6; 1.8)
Full model, including:			
never occupational exposure (G+L+H)	63.8 (42.8; 80.7)	Ø	1.8 (0.7; 4.2)
occupational low risk exposure ever (G+H)	52.9 (30.0; 74.6)	Ø	1.1 (0.4; 2.9)
occupational high risk exposure ever (G+L)	62.4 (40.0; 80.5)	Ø	1.7 (0.7; 4.1)

* forced in

** based on full model (G+L+H)

G – general (non-occupational) risk factors, L – occupational low risk exposure, H – occupational high risk exposure

$\exp(\beta_0)=0.028$

Table E6: Probabilities, unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI) for incidence of physician-diagnosed **asthma** in SOLAR II based on **complete case analysis** (n=856). These are presented for presence of single risk factors and for combinations of all non-occupational risk factors (part G) with never having been occupationally exposed, having had occupational low risk exposure (L) and having had occupational high risk exposure (H)

	probability (%)(95 % CI)	unadjusted OR OR (95 % CI)	adjusted OR** OR (95 % CI)
Intercept (β_0)	0.1		
Sex (male vs. female) *	0.1 (0; 0.9)	1.0 (0.5; 2.2)	1.1 (0.5; 2.5)
Socioeconomic status (low vs. high) *	0.2 (0.0; 1)	1.2 (0.6; 2.6)	1.1 (0.5; 2.6)
Parental history of asthma (yes vs. no)	0.5 (0.1; 3.7)	5.2 (2.2; 11.9)	3.9 (1.6; 9.8)
Parental history of atopic dermatitis (yes vs. no)	0.1 (0.0; 1.2)	1.7 (0.7; 4.0)	1.1 (0.4; 2.9)
G Environmental tobacco smoke exposure in SOLAR I (yes vs. no)	0.4 (0.1; 2.2)	3.2 (1.2; 8.6)	3.1 (1.1; 8.9)
Smoking status in SOLAR I (ever vs. never)	0.2 (0.0; 1.3)	2.0 (0.9; 4.3)	1.4 (0.6; 3.3)
Having been breastfed (no vs. yes)	0.3 (0.0; 2.0)	2.2 (0.9; 5.7)	2.0 (0.7; 5.4)
Skin prick test response in ISAAC Phase Two (positive vs. negative)	0.5 (0.1; 3.1)	4.2 (1.9; 9.0)	3.6 (1.6; 8.4)
L Occupational low risk exposure (never vs. ever) *	0.4 (0.1; 1.4)	1.9 (0.7; 5.6)	2.7 (0.9; 8.4)
H Occupational high risk exposure (never vs. ever) *	0.3 (0.1; 1.3)	1.7 (0.7; 4.4)	2.1 (0.8; 5.6)
Full model, including:			
never occupational exposure (G+L+H)	56.1 (22.1; 85.2)	Ø	1.3 (0.3; 5.8)
occupational low risk exposure ever (G+H)	32.3 (7.5; 73.6)	Ø	0.5 (0.1; 2.8)

occupational high risk exposure ever (G+L)	37.7 (10.4; 75.9)	Ø	0.6 (0.1; 3.2)
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* forced in

** based on full model (G+L+H)

G – general (non-occupational) risk factors, L – occupational low risk exposure, H – occupational high risk exposure

$\exp(\beta_0)=0.001$

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