Reduced risk of pancreatic cancer associated with asthma and nasal allergies

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ABSTRACT

Objective Studies indicate an inverse association between ductal adenocarcinoma of the pancreas (PDAC) and nasal allergies. However, controversial findings are reported for the association with asthma. Understanding PDAC risk factors will help us to implement appropriate strategies to prevent, treat and diagnose this cancer. This study assessed and characterised the association between PDAC and asthma and corroborated existing reports regarding the association between allergies and PDAC risk.

Design Information about asthma and allergies was collated from 1297 PDAC cases and 1024 controls included in the PanGenEU case–control study. Associations between PDAC and atopic diseases were studied using multilevel logistic regression analysis. Meta-analyses of association studies on these diseases and PDAC risk were performed applying random-effects model.

Results Asthma was associated with lower risk of PDAC (OR 0.64, 95% CI 0.47 to 0.88), particularly long-standing asthma (>=17 years, OR 0.39, 95% CI 0.24 to 0.65). Meta-analysis of 10 case–control studies sustained our results (metaOR 0.73, 95% CI 0.59 to 0.89). Nasal allergies and related symptoms were associated with lower risk of PDAC (OR 0.66, 95% CI 0.52 to 0.83 and OR 0.59, 95% CI 0.46 to 0.77, respectively). These results were supported by a meta-analysis of nasal allergy studies (metaOR 0.6, 95% CI 0.5 to 0.72). Skin allergies were not associated with PDAC risk.

Conclusions This study shows a consistent inverse association between PDAC and asthma and nasal allergies, supporting the notion that atopic diseases are associated with reduced cancer risk. These results point to the involvement of immune and/or inflammatory factors that may either foster or restrain pancreas carcinogenesis warranting further research to understand the molecular mechanisms driving this association.

SIGNIFICANCE OF THIS STUDY

What is already known on this subject?

There is an important lack of knowledge on pancreatic cancer aetiology and its associated factors, both environmental and genetic.

Present knowledge points to a role of chronic inflammation in pancreas carcinogenesis.

Nasal allergies are associated with decreased risk of pancreatic cancer.

Studies on the association between asthma and pancreatic cancer are inconclusive.

There is a need of studies that accurately characterise asthma, allowing for a more reliable assessment of the association between this exposure and pancreatic cancer risk.

What are the new findings?

Asthma, asthma severity and duration are significantly associated with a lower risk of pancreatic cancer.

Meta-analysis of 10 case–control studies further support the inverse association of asthma with pancreatic cancer risk.

Nasal allergies and its symptoms are also consistently associated with reduced pancreatic cancer risk.

How might it impact on clinical practice in the foreseeable future?

Combining precise data on pancreatic ductal adenocarcinoma risk and protective factors, including atopic diseases, would allow building accurate risk prediction models to potentially discriminate high-risk individuals from the general population, those deserving to be entered in primary prevention interventions and screening programmes.

Understanding the mechanism through which atopic diseases associate with pancreatic cancer will shed light into the inflammatory aetiology of this cancer and might support primary prevention interventions and treatments by modulating such mechanisms in high-risk populations and patients, respectively.

INTRODUCTION

In the USA, it is projected that pancreatic cancer mortality will become the second leading cause of cancer-related deaths before 2030.1 In Europe, this is the only cancer for which death rates increased in both genders in 2014.2 Pancreatic ductal adenocarcinoma (PDAC), representing 95% of pancreatic cancers, is a rare disease with a 5-year relative survival rate of <4%.3 To date, our understanding of PDAC aetiology is still limited. Among the risk factors of PDAC, several medical conditions have been extensively studied, including chronic pancreatitis, obesity and type II diabetes (T2D), which have been consistently associated with an increased risk of PDAC4 ,5 pointing to a chronic inflammatory hypothesis. In addition, under the assumption of a participation of the immune system in the disease development, epidemiological studies have explored the association between allergic disorders and PDAC risk.6 ,7 A meta-analysis published in 2005 included 14 case–control and cohort studies summarising initial reports on the subject.6 ,8–20 In this meta-analysis, pooled estimates showed a significantly reduced risk of PDAC in subjects reporting having any allergy, nasal allergies or skin allergies, but there was no association with a history of asthma. Other reports have largely replicated the inverse association between PDAC and nasal allergies with only one study reporting a non-significant reduced estimate.21–25 Regarding skin allergies, two additional articles reported reduced estimates but only one showed statistical significance.24 ,25Conversely, the association between asthma and PDAC risk has remained inconclusive. From the 12 studies that have evaluated this association, 3 resulted in a significant association between asthma and PDAC risk; however, 2 of them reported a negative association while the other reported a positive association.9 ,11–13 ,15 ,16 ,18 ,19 ,21 ,24–26 These inconsistencies can be explained, in part, by the difficulties in the correct assessment of the asthma

phenotype and the relative small sample size of the studies, mainly in the case groups.
Because of the importance of understanding factors associated with PDAC development, we looked to corroborate existing reports regarding allergies and PDAC risk and aimed at evaluating the association between PDAC and asthma by using a targeted set of questions that provided a more reliable assessment of atopic diseases. This assessment was performed within the PanGenEU, a European case–control study, with the largest set of cases examined for this association so far.

METHODS

Study population

Participants were recruited in the PanGenEU case–control study between 2009 and 2014. The PanGenEU is an ongoing study that was designed to recruit 2000 cases and 2000 controls from centres in England, Germany, Ireland, Italy, Spain and Sweden (see online supplementary annex). Men and women above 18 years of age were eligible. To reduce ascertainment and information biases resulting from the very poor prognosis of this disease, all identified suspected PDAC cases were approached for participation in the study. After physician's confirmation of the diagnosis, subjects not diagnosed with PDAC were excluded.
Controls were recruited from a hospital-based setting in all countries with the exception of Ireland, where controls were population based. Eligible controls did not have history of PDAC and hospital-based controls were eligible if their principal diagnosis was not related to any risk factor of PDAC (see online supplementary table 1).
This study reports the findings on 1297 cases and 1024 controls included in the English, German, Irish and Spanish centres.

Information

Information was collected through direct in-person interviews performed by trained health monitors applying the same protocol and structured questionnaire that includes detailed information about lifestyle, environmental exposures and medical history. The questionnaire included 18 questions about atopic diseases and their symptoms. These questions are a subset of the standardised questionnaire developed by the European Community Respiratory Health Survey for the study of asthma and allergies that have been validated in the participating countries.27 ,28 Detailed description of all atopic diseases variables is shown in table 1.

[TABLE 1]

Other information considered for model adjustment were age and years of education (continuous), body mass index calculated using weight 2 years before recruitment and usual adult height (kg/m2, underweight and normal weight/overweight/obese), smoking status (never/former/current), smoking pack/years (tertiles based on population distribution), alcohol consumption (never/ever), periodontitis (no/yes), T2D (never/diagnosed 2 years within recruitment/diagnosed >2 years before recruitment) and chronic pancreatitis (no/yes).

Statistical analysis

To avoid potential bias resulting from complete-case analysis, imputation was performed using missForest package.29 Based on the distribution of missing counts (4.3% in cases and 3% in controls), data were assumed to be missing at random. Imputation was performed using case–control status, centre, country, age, sex, smoking status, pack/years, T2D, chronic pancreatitis, nasal allergies, nasal allergies' detailed phenotype, skin allergies, skin allergies' detailed phenotype, asthma, asthma medication, asthma age of onset, asthma score and asthma duration (description of atopic variables in table 1). Imputation was performed with no maximum number of iterations and with 100 trees. Performance was evaluated using out of bag (OOB) error rates: normalised squared error for continuous variables and proportion of falsely classified entries for categorical variables (values close to zero indicated good performance and values close to one indicated bad performance). Data imputation OOB estimates were <0.34 (mean: 0.14, 95% CI 0.07 to 0.2). Prevalences of atopic diseases were calculated adjusting for sex and age category (<54, 55–64, 65–74, >75; online supplementary table S2). Prevalences before and after imputation were compared using the test of equality of proportions.

OR estimates and 95% CIs were estimated with multilevel logistic regression using lme4 package to evaluate subject-level factors while accounting for clustering within country. Stepwise regression was used for confounder selection considering the aforementioned variables. Median OR was calculated to measure between country variability.30 Potential effect modifications by sex and smoking were tested by including sex and pack/years as interaction terms in the regression models. All statistical analyses were performed as two-sided test using R V.3.1.2.31

Meta-analysis

Studies on the association between atopic diseases and PDAC risk were searched in PubMed and Web of Science using the following terms: 'asthma' or 'allergy' or 'medical history' and 'pancreas cancer' or 'pancreatic cancer'. All epidemiological studies reporting separately on these diseases and using similar phenotype definitions were selected regardless of the year of publication. Dai et al16 was found through the reference list of other publications. Pooled estimates and heterogeneity among studies were calculated using the metafor package by random-effects meta-analysis and Cochran's Q-test, respectively.

RESULTS

Characteristics of the subjects are listed in table 2. Study subjects with written consent and available questionnaire data consisted in 1297 cases and 1024 controls of the initial eligible 1975 cases and 1554 controls. Reasons for no participation in the study were recorded for all subjects not included in the study. Proportion of males was slightly higher than females in both cases and controls. Average age was 65.3 years old (SD 12.4). Most of the study population was recruited in Spain (62.8%), followed by Ireland (19.9%), Germany (10.9%) and England (6.4%).

[TABLE 2]

Prevalences of atopic diseases for each country are summarised in online supplementary table S2. No significant differences were observed between imputed and non-imputed data (p>0.75). Since prevalence of nasal and skin allergies differed between cases and controls in England, we performed a sensitivity analysis removing England from the study. Only slight changes were observed and the direction and significance of the associations were not altered; therefore, we report on the analysis of the whole population.

Table 3 shows the distribution of allergy and asthma phenotypes in cases and controls and their estimates for PDAC risk. Since similar estimates were obtained from univariate and multivariate multilevel models, we only report multivariate results. Nasal allergies were associated with reduced risk of PDAC (OR 0.66, 95% CI 0.52 to 0.83). Specific nasal allergy symptoms including the year before recruitment (table 1) were associated with decreased risk of PDAC (OR 0.59, 95% CI 0.46 to 0.77), while symptoms occurring more than a year before recruitment were not associated with risk (OR 1.09, 95% CI 0.76 to 1.59). Ever having had skin allergies was not associated with PDAC risk (OR 0.95, 95% CI 0.78 to 1.17). Having had skin allergy symptoms including the year before recruitment was associated with high risk of PDAC; a significant association was observed when those symptoms were reported in atopic-related body parts (OR 2.47, 95% CI 1.60 to 3.81).

[TABLE 3]

Among self-reported asthmatics, 91% reported confirmation by their doctor. Ever having had asthma was associated with significantly reduced risk of PDAC (OR 0.64, 95% CI 0.47 to 0.88), as well as asthma duration (p trend= 0.0002). Having asthma for >=17 years showed the lowest risk of PDAC (OR 0.39, 95% CI 0.24 to 0.65). Current asthma medication use was associated with decreased risk of PDAC (OR 0.47, 95% CI 0.31 to 0.69), while not currently taking asthma medication was not. Reduced estimates were observed regardless of asthma age of onset; however, this was significant only for onset >=16 years (OR 0.65, 95% CI 0.47 to 0.91). Subjects with asthma score >=2 showed a significantly reduced risk of PDAC (OR 0.49, 95% CI 0.34 to 0.71). A significant risk reduction trend was also observed when analysing the score as a continuum (p=0.0002).

Subjects reporting having only asthma or only nasal allergies were significantly associated with lower risk of PDAC (OR 0.55, 95% CI 0.38 to 0.81 and OR 0.62, 95% CI 0.48 to 0.79, respectively). Having both diseases resulted in a reduced, though non-significant, estimate (OR 0.69, 95% CI 0.42 to 1.13). All associations were assessed for interaction with sex and smoking, but no significant effect modification was observed (data not shown).

Due to the small number of prospective cohort studies reporting on atopic diseases and PDAC, the differences between populations and variable definitions, we did not consider it appropriate to perform meta-analysis using these studies. Therefore, we report only on case–control studies. Details of the publications are provided in online supplementary tables S3–S5. Meta-analysis estimate including our results showed a significant reduced PDAC risk among asthmatics (metaOR 0.73, 95% CI 0.59 to 0.89, figure 1). Similarly, pooled estimates for nasal and skin allergies showed a

significant reduced risk of PDAC: metaOR 0.6, 95%CI 0.5 – 0.72, and metaOR 0.77, 95% CI 0.64 to –0.93, respectively (figures 2 and 3).

[FIGURE 1]

[FIGURE 2]

[FIGURE 3]

DISCUSSION

This is the largest and more exhaustive analysis of the association between PDAC and atopic disease-related factors reported until now. We confirm the reduced risk of PDAC associated with nasal allergies and provide strong support for an inverse association between PDAC risk and asthma, including its severity and duration.
The reduction of PDAC risk was stronger among asthmatics who reported currently taking asthma medication. While we cannot rule out the possibility that asthma medication could contribute to risk reduction, reporting current consumption of asthma medication not only provides confirmatory evidence of the accuracy of diagnosis but it also suggests stronger effects associated with increased disease severity. Reduced estimates were observed for both childhood and adult asthma onset, but the association was only significant for the latter group, possibly due to sample size. While most of childhood onset asthma has an atopic component, biological testing is the best way to discriminate atopic from non-atopic asthma. Given the potential biological differences underlying these two phenotypes, this area needs additional investigation.
To provide further strength to our findings, we analysed the association between asthma score and PDAC risk. Asthma score is based on asthma symptoms, allowing a more objective assessment of asthma severity. The reduction of PDAC risk was significantly associated with an increase in asthma severity. The consistency of our results is probably due to the more careful assessment of clinical phenotypes. Until now, studies evaluating the association between asthma and PDAC risk have largely yielded reduced, non-significant, estimates. One study, in the context of clinical trial of antioxidants, has reported a significant association between asthma and increased risk of PDAC.19 However, this study was small (172 PDAC cases) and recruited only male smokers aged 50–69. Similarly, another prospective study looking at the association between atopic diseases and pancreatic cancer death rate showed a non-significant association between self-reported asthma-only phenotype and death.26 Sample size, the questionnaire applied and the definition of the asthma phenotype may account for the discordant findings. A meta-analysis using the existing published case–control studies in combination with our results showed a significantly reduced risk of PDAC among asthmatics. Moreover, both nasal allergies and asthma were independently associated with reduced PDAC risk. Having both diseases also showed a reduced estimate, which was not significant probably due to the small sample size. Altogether, these results support the notion that asthma is inversely associated with PDAC risk.

Consistent with the current literature, nasal allergies were associated with a significant reduced risk of PDAC.18 ,21 ,22 ,25 Meta-analysis of independent studies corroborated this pattern of risk. When we detailed the nasal allergies phenotype using specific symptoms, the reduced risk of PDAC was stronger. Subjects with nasal allergy symptoms showed a reduced risk of PDAC, and considering 'itchy and watery eyes'—a typical nasal allergy symptom—in the phenotype, was associated with a further decrease in risk. We cannot rule out the possibility of reverse causation, that is, PDAC reducing nasal allergies, because the study lacks information on the age of onset of the condition. However, a previous prospective nested case–control study reported that IgE levels were not lower in pancreatic cancer cases when compared with controls.32 Moreover, another study with smaller sample size reported high IgE serum levels in patients with PDAC,33 altogether arguing against this issue. A possible explanation for not observing a significant association among subjects reporting symptoms more than a year before recruitment is low statistical power since fewer people were assigned into this category. It is also likely that subjects report recent symptoms more accurately independently of the case–control status of the subject. This is supported by the fact that including itchy and watery eyes was associated with further risk reduction.

Concordant with other reports, we observed a non-significantly reduced PDAC risk for skin allergies.13 ,14 ,16 ,25 However, a meta-analysis of this association showed a significantly reduced risk. Subjects reporting skin allergy symptoms anytime showed a higher risk of PDAC than those who not presented symptoms during the year before recruitment. Up to 20–40% of patients with PDAC34 report severe itching due to hyperbilirubenemia,35 thus making reverse causality a possibility. However, localised itching is rarely caused by a systemic process and the observed association was only significant when subjects reported having rash in specific body parts commonly affected by atopic dermatitis. This is the first time skin allergies have been characterised in such a detail in the study of pancreatic cancer risk. While we cannot discard this result may be due to chance, future studies should be encouraged to replicate this finding.

The mechanisms underlying the association between atopic diseases and PDAC risk are largely unknown. This remains an important area of study because it may provide opportunities for disease prevention. The contribution of a hyperactive immune system in individuals with atopic conditions, characterised by sustained elevated IgE levels,36 has been proposed. Furthermore, susceptibility and severity of asthma and allergies are known to be affected by genetic factors and gene–environment interactions.37 ,38 A recent study exploring single-nucleotide polymorphism in 56 allergy-related candidate genes suggested that certain genetic variants may be associated with a reduction of pancreatic cancer risk.39 More studies will help us to understand the role of genetics in these associations. Additionally, it has been reported that the anti-allergic drug cromolyn can inhibit proliferation and invasion of human pancreatic cancer cells in vitro and tumour growth in mice.40 The potential confounding of treatment for allergy or asthma was previously assessed and only minimal negative confounding effect for some medications was reported.25 Future studies are needed to corroborate and extend these findings. Unknown exposures could also be relevant since individuals suffering from atopic diseases may avoid

specific exposures or lifestyles that could be associated with PDAC development. Moreover, a reduced incidence of asthma and nasal allergies has been associated with Porphyromonas gingivalis,41 a bacteria involved in the causation of caries,42that has been associated with high PDAC risk,43 suggesting potential confounding effect. Importantly, we considered self-reported periodontitis in our initial analysis and did not observe any confounding effect. The analysis of the specific oral microbiota using state-of-the-art metagenetic studies should contribute to unravel the relationship between these factors.

One of the major strengths of this study is the largest sample size of cases ever used to test the association between atopic diseases and PDAC risk. Nevertheless, some stratified analyses may be impaired because of lack of power, warranting further consideration. The fact that the association of PDAC with smoking status in our study (OR 1.67, 95% CI 1.32 to 2.11) resulted in expected estimates44 supports the internal validity of the PanGenEU study. Atopic diseases constitute a syndromic constellation and are a heterogeneous group of diseases. In this study, we aimed to thoroughly characterise three major atopic conditions using data obtained through personal interviews conducted by trained monitors that applied the same structured questionnaire. A major concern with self-reported medical conditions is potential misclassification and bias. The inverse associations observed make the latter issue less likely. In addition, the questionnaire used here has been previously validated and includes a wide set of questions on specific symptoms for a more accurate assessment of these phenotypes. This detailed information allowed us to perform the most exhaustive analysis of the association between PDAC and atopic disease-related factors reported until now. The study population has been homogeneously recruited in centres from four European countries. While the focus of this study was subject-level factors, we also accounted for country-level differences since prevalence of PDAC varies between countries and both country-level and individual-level factors may contribute to this heterogeneity. Multilevel model showed a country-level median OR of 2.08 (variance $\sigma 2 = 0.59$), interpreted as the median OR of developing PDAC if two persons with similar covariates were chosen randomly from two different countries. This suggests that between-country effect may be an important factor to understand differences of PDAC risk.

Altogether, our study provides consistent evidence on the significant inverse association between PDAC and nasal allergies and asthma. These results point to the involvement of immune/inflammatory exposures in pancreas carcinogenesis and further support the notion that atopic diseases are associated with a reduced risk for cancer. Future studies should focus on potential key confounders of these associations, including country-level specific variables, and on exploring the underlying biological mechanism for the reduced risk of PDAC among subjects with nasal allergies and asthma.

Pancreas cancer is a complex disease. By disentangling its aetiological landscape and combining precise information on PDAC risk factors, including atopic diseases, we could build and validate risk prediction models that help discriminate those individuals from the population with a high risk of PDAC. Those subjects will deserve to be included in primary prevention interventions and in screening programmes. Furthermore, understanding the genetic mechanisms subjacent to the

inverse association between atopic diseases and asthma might allow the development and implementation of primary prevention interventions by modifying the immunological status of the high-risk population as well as by identifying effective treatments for patients with pancreatic cancer.

FOOTNOTES

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Contributors
NM; PG-R, J-PZ, FXR, MR: design of the study; analysis and interpretation of the data; preparation of the manuscript; and review and approval of the manuscript. MM: design, organisation and coordination of the study; management of the data and databases. LS, MH, AC, LI, CM, XM, AF, JP, WG, MOR, AT, TG, VB, TC-J, ED-M, LM-B, CA-U, JB, LB, EC, CG-P, JK, BK, RL, ML, JM, LM, DOD, PP, IP, AS: design of the study; recruitment of subjects; collection of biological samples; and review and approval of the manuscript.

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TABLES AND FIGURES

Table 1 Description of atopic diseases variables

Variable name	Full variable description	Categories
Nasal allergies	Subjects were classified as having nasal allergies when answering yes to the question, "Do you have any nasal allergies, including hay fever?"	No Yes
Nasal allergy symptoms anytime	Subjects answered to the question, "Have you ever had a problem with sneezing, or a runny or a blocked nose when you did not have a cold or the flu?"	Never Ever (sneezing w/o cold/flu)
Nasal allergies' detailed phenotype	Subjects answered the following questions: (1) "Have you ever had a problem with sneezing, or a runny or a blocked nose when you did not have a cold or the flu?" (2) "Have you ever had (the latter) nasal allergy symptoms in the past 12 months?" and (3) "Has this nasal problem been accompanied by itchy or watery eyes?" Answering affirmatively to all three of these questions was considered as the best characterised nasal allergy phenotype (symptoms anytime+e)	Never Symptoms but not in the last year Symptoms anytime Symptoms anytime+e
Sink allergies	Subjects were classified as having skin allergies when answering yes to the question, "Have you ever had eczema or any kind of skin allergy?"	No Yes
Skin allergy symptoms anytime	Subjects answered to the question, "Have you ever had an itchy rash that came and went for at least six months?"	Never Ever
Skin allergies' detailed phenotype	Subjects answered the following questions: (1) "Have you ever had an itchy rash that came and went for at least six months?" (2) "Have you had this itchy rash in the last 12 months?" and (3) "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?" This resulted in four categories since question three is not dependent on answer to question two. The best characterised skin allergy phenotype was considered having the itchy rash for at least six months including the last 12 months and in the specific body parts mentioned (symptoms anytime+p)	Never Symptoms but not in the last year Symptoms but not in the last year+p Symptoms anytime Symptoms anytime +p
Asthma	Subjects were categorised as asthmatics if answering positively to the question, "Have you ever had asthma?"	No Yes
Asthma medication	Subjects answered to the question, "Are you currently taking any medicines including inhalers, aerosols or tablets for asthma?"	No medication Medication
Asthma duration	Asthma duration was calculated by subtracting age of first asthma attack to age of the most recent attack and divided into tertiles based on the population's distribution	<=4 years 5–16 years >=17 years
Age of asthma onset	Subjects answered to the question, "How old were you when you had your first attack of asthma?"	<16 years >=16 years
Asthma score	Asthma score was determined based on the definition of the European Community Respiratory Health Survey and the available questions in the questionnaire. Asthma score was categorised from 0 to 4 according to the number of positive answers to these questions: (1) "Have you had wheezing or whistling in your chest in the past 12 months and have you been breathless when wheezing noise was present?" (2) "Have you been woken by an attack of shortness of breath at any time in the last 12 months?" (3) "Have you had an attack of asthma in the last 12 months?" and (4) "Are you currently taking any medicines for asthma?"	0 1 >=2
Disease combination	Subjects answered the following questions: (1) "Do you have any nasal allergies, including hay fever?" and (2) "Have you ever had asthma?" and were classified according to the combination of their answers	None Asthma only Nasal allergies only Asthma and nasal allergies

+e: symptoms accompanied by itchy or watery eyes.
+p: symptoms affected the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes.

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Table 2 Characteristics of the study

	Cases		Controls	
	N= 1297	%	N= 1024	%
Country				
England	126	9.7	22	2.1
Germany	142	10.9	110	10.7
Ireland	173	13.3	290	28.3
Spain	856	66.0	602	58.8
Sex*				
Female	565	43.6	487	47.6
Male	732	56.4	537	52.4
Age*				
Mean (SD)	65.2 (12)		65.2 (13.3)	
<=54	237	18.3	220	21.5
55–64	322	24.8	215	21.0
65–74	446	34.4	313	30.6
>=75	292	22.5	276	27.0
Years of education				
Mean (SD)	11.2 (6.21)		11 (5.57)	
<=9	380	29.3	329	32.1
9.1–13	402	31.0	324	31.6
>=13.1	382	29.5	308	30.1
NA	133	10.3	63	6.2
BMI				
Mean (SD)	27 (4.73)		27 (5)	
<=24.9	454	35.0	360	35.2
25–29.9	493	38.0	390	38.1
>=30	268	20.7	210	20.5
NA	82	6.3	64	6.3
Cigarette smoking*				
Never	561	43.3	524	51.2
Former	391	30.1	303	29.6
Current	345	26.6	197	19.2
Tertiles of pack/years*				
<=20.9	219	16.9	186	18.2
21–44.9	273	21.0	156	15.2
>=45	244	18.8	158	15.4
Alcohol consumption				
No	363	28.0	315	30.8
Yes	918	70.8	686	67.0
NA	16	1.2	23	2.2
Periodontitis				
No	991	76.4	808	78.9
Yes	210	16.2	149	14.6
NA	96	7.4	67	6.5
Diabetes*				
No	929	71.6	891	87.0
<=2 years	156	12.0	22	2.1
>2 years	212	16.3	111	10.8
Chronic pancreatitis*				
No	1289	99.4	1023	99.9
Yes	8	0.6	1	0.1

*Missing data were imputed for these variables. Number of cases/controls with missing data: sex 4/4, age 40/27, smoking 55/28, pack/years 102/75, diabetes 40/19, chronic pancreatitis 58/20.
BMI, body mass index; NA, data not available.

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Table 3 Multilevel logistic regression models for nasal allergies, skin allergies, and asthma and pancreatic cancer

	Multivariate*					
	Cases		Controls			
	N=1297	%	N=1024	%	OR (95% CI)	p Trend
Do you have any nasal allergies, including hay fever?†						
No	1111	85.7	812	79.3	1	
Yes	186	14.3	212	20.7	0.66 (0.52 to 0.83)	
Nasal allergy symptoms anytime†						
Never	922	71.1	645	63.0	1	
Ever (sneezing w/o cold/flu)†	375	28.9	379	37.0	0.73 (0.6 to 0.87)	
Nasal allergies' detailed phenotype						
Symptoms but not in the last year	82	6.3	59	5.8	1.09 (0.76 to 1.59)	
Symptoms anytime	148	11.4	151	14.7	0.74 (0.57 to 0.96)	
Symptoms anytime+e‡	145	11.2	169	16.5	0.59 (0.46 to 0.77)	
						0.00003
Have you ever had eczema or any kind of skin allergy?†						
No	997	76.9	769	75.1	1	
Yes	300	23.1	255	24.9	0.95 (0.78 to 1.17)	
Skin allergy symptoms anytime†						
Never	1091	84.1	890	86.9	1	
Ever (rash during 6 months)†	206	15.9	134	13.1	1.33 (1.04 to 1.69)	
Skin allergies' detailed phenotype						
Symptoms but not in the last year	38	2.9	41	4.0	0.84 (0.52 to 1.34)	
Symptoms but not in the last year+p§	26	2.0	22	2.1	0.86 (0.47 to 1.58)	
Symptoms anytime	52	4.0	40	3.9	1.2 (0.77 to 1.87)	
Symptoms anytime+p¶	90	6.9	31	3.0	2.47 (1.6 to 3.81)	
						0.0005
Have you ever had asthma?†						
No	1209	93.2	914	89.3	1	
Yes	88	6.8	110	10.7	0.64 (0.47 to 0.88)	
No medication†	42	3.2	31	3.0	1.09 (0.67 to 1.79)	
Medication†	46	3.5	79	7.7	0.47 (0.31 to 0.69)	
Asthma duration (years)†						
<=4	36	2.8	27	2.6	1.22 (0.72 to 2.07)	
5–16	26	2.0	35	3.4	0.59 (0.35 to 1.04)	
>=17	26	2.0	48	4.7	0.39 (0.24 to 0.65)	
						0.0002
Age of asthma onset (years)†						
<16	14	1.1	19	1.9	0.61 (0.29 to 1.27)	
>=16	74	5.7	91	8.9	0.65 (0.47 to 0.91)	
Asthma score**†						
0	1063	82.0	794	77.5	1	
1	173	13.3	141	13.8	0.96 (0.75 to 1.24)	
<=2	61	4.7	89	8.7	0.49 (0.34 to 0.71)	
						0.0002
Disease combination†						
None	1055	81.3	741	72.4	1	
Asthma only	56	4.3	71	6.9	0.55 (0.38 to 0.81)	
Nasal allergies only	154	11.9	173	16.9	0.62 (0.48 to 0.79)	
Asthma and nasal allergies	32	2.5	39	3.8	0.69 (0.42 to 1.13)	

Models were built with imputed data using country variable as random effect.
*Multivariate multilevel models adjusted for age, sex, pack/years of smoking, type II diabetes and chronic pancreatitis.
†Number of cases/controls with missing (imputed) data: nasal allergies 35/14, nasal allergy symptoms anytime 50/14 nasal allergies' detailed phenotype 69/21, skin allergies 36/9, skin allergy symptoms anytime 50/33, skin allergies' detailed phenotype 61/40, asthma 45/27, asthma medication 50/32, asthma duration 74/57, age of asthma onset 62/45, asthma score 79/54 and disease combination 60/34.
‡Nasal allergy symptoms and itchy and watery eyes anytime (+e).
§Skin allergy symptoms and itch in specific body parts but not in the last year (+p).
¶Skin allergy symptoms and itch in specific body parts anytime (+p).
**Combination of asthma symptoms; see table 1 for full definition.

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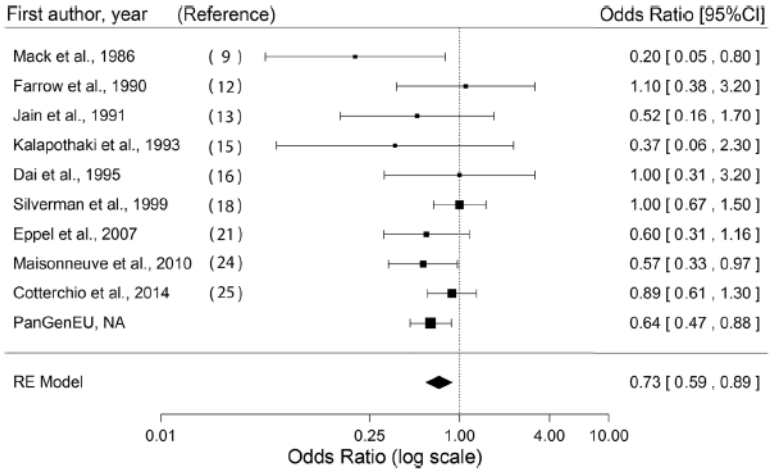

Figure 1 Meta-analysis of case–control studies of the association between asthma and pancreatic cancer risk. The pooled estimate and 95% CI for a random-effects (RE) model is shown in the bottom of the figure. Non-significant heterogeneity was observed between studies (I^2=13.5%, p=0.36). NA, not available.

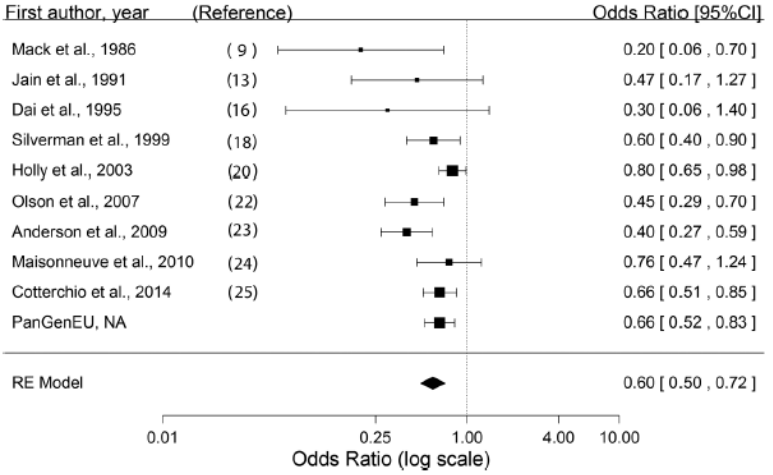

Figure 2 Meta-analysis of case–control studies of the association between nasal allergies and pancreatic cancer risk. The pooled estimate and 95% CI for a random-effects (RE) model is shown in the bottom of the figure. Significant heterogeneity was observed between studies (I^2=50.99%, p=0.035). NA, not available.

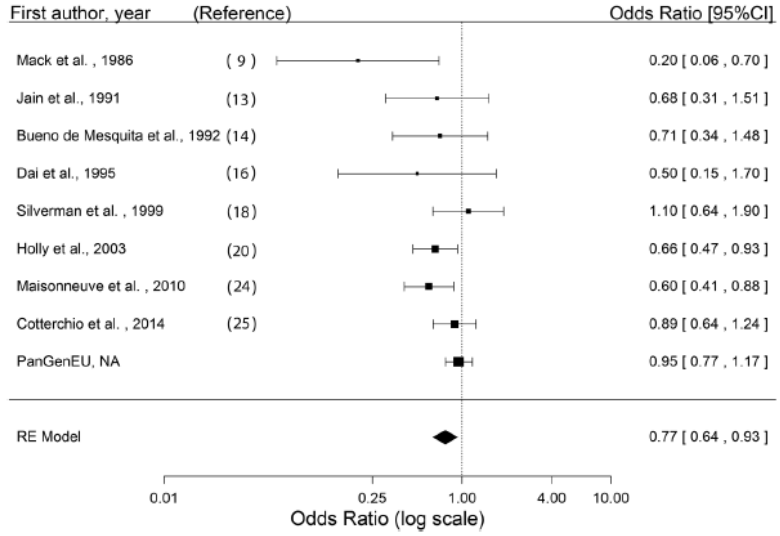

Figure 3 Meta-analysis of case–control studies of the association between skin allergies and pancreatic cancer risk. The pooled estimate and 95% CI for a random-effects (RE) model is shown in the bottom of the figure. Non-significant heterogeneity was observed between studies (I^2=30%, p=0.13). NA, not available.