**Title:** Pancreatic cancer and autoimmune diseases: An association suggested by bioinformatics and epidemiological approaches

**Authors:** Paulina Gomez-Rubio, PhD (1,2), Janet Piñero, PhD (3), Esther Molina-Montes, PhD (1,2), Alba Gutiérrez-Sacristán, PhD (3), Mirari Marquez, PhD (1,2), Marta Rava, PhD (1,2), Christoph W. Michalski, MD PhD (4,5), Antoni Farré, MD, PhD (6), Xavier Molero, MD, PhD (7,8), Matthias Löhr, MD, PhD (9), Lucas Ilzarbe, MD (10), José Perea, MD PhD (11), William Greenhalf, PhD (12), Michael O’Rorke, PhD (13), Adonina Tardón, MD, PhD (2,14), Thomas Gress, MD, PhD (15), Victor M. Barberà, PhD (16), Tatjana Crnogorac-Jurcevic, PhD (17), Luís Muñoz-Bellvís, MD (18), Enrique Domínguez-Muñoz, MD (19), Joaquim Balsells, MD (2,7,8), Eithne Costello, PhD (12), Jingru Yu (9), Mar Iglesias, MD (10), Jörg Kleeff, MD, PhD (3,12), Bo Kong, PhD (3), Josefina Mora, PhD (6), Liam Murray, PhD (13), Damian O’Driscoll, PhD (20), Pablo Peláez, MD (11), Ignasi Poves, MD (10), Rita T. Lawlor, PhD (21), Weimin Ye, MD, PhD (9), Manuel Hidalgo, MD, PhD (22), Aldo Scarpa, MD, PhD (21), Linda Sharp, PhD (20), Alfredo Carrato, MD, PhD (2,23), Francisco X. Real\* (2,24,25), Laura I. Furlong\* (3), Núria Malats (1,2) on behalf of the PanGenEU Study Investigators (26).

\* Equal contributions

**Authors’ affiliations**

1. Genetic and Molecular Epidemiology Group, Spanish National Cancer Research Center (CNIO), and CIBERONC, Madrid, Spain.
2. Centro de Investigación Biomédica en Red en Oncología (CIBERONC), , Enfermedades Hepáticas y Digestivas (CIBERHD), and Epidemiología y Salud Pública (CIBERESP), Madrid, Spain.
3. Research Program on Biomedical Informatics (GRIB), Hospital del Mar Research Institute (IMIM), Universidad Pompeu Fabra (UPF), Spain.
4. Technical University of Munich, Department of Surgery, Munich, Germany.
5. University of Heidelberg, Department of Surgery, Heidelberg, Germany.
6. Hospital de la Santa Creu i Sant Pau, Department of Gastroenterology, Barcelona, Spain.
7. Hospital Universitaru Vall d´Hebron, Exocrine Pancreas Research Unit and Vall d´Hebron Research Institute (VHIR), Barcelona, Spain.
8. Universitat Auntònoma de Barcelona, Campus de la UAB, Barcelona Spain.
9. Karolinska Institutet and University Hospital, Gastrocentrum Stockholm, Sweden.
10. Hospital del Mar-Parc De Salut Mar, Department of Gastroenterology, Barcelona, Spain.
11. University Hospital 12 de Octubre, Department of Surgery, Madrid, Spain.
12. The Royal Liverpool University Hospial, Department of Molecular and Clinical Cancer Medicine, Liverpool, UK.
13. Queen’s University Belfast, Centre for Public Health, Belfast, UK.
14. Instituto Universitario de Oncología del Principado de Asturias, Department of Medicine, Oviedo, Spain.
15. University Hospital of Giessen and Marburg, Department of Gastroenterology, Marburg, Germany.
16. Hospital General Universitario de Elche, Laboratorio de Genética Molecular, Elche, Spain.
17. Barts Cancer Institute, Queen Mary University of London, Centre for Molecular Oncology, John Vane Science Centre, London, UK.
18. Hospital Universitario de Salamanca, General and Digestive Surgery Department, Salamanca, Spain.
19. Hospital Clinico Universitario de Santiago de Compostela, Department of Gastroenterology, Santiago de Compostela, Spain.
20. National Cancer Registry Ireland, Cork, Ireland, and Institute of Health and Society, Newcastle University, UK.
21. University Hospital Trust of Verona, ARC-Net centre for Applied Research on Cancer and Department of Pathology and Diagnostics, Verona, Italy.
22. Hospital Madrid-Norte-Sanchinarro and Spanish National Cancer Research Centre (CNIO), Madrid, Spain.
23. Hospital Ramón y Cajal, Department of Oncology, Madrid, Spain.
24. Epithelial Carcinogenesis Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain.
25. Universitat Pompeu Fabra, Departament de Ciències Experimentals i de la Salut, Barcelona, Spain.
26. PanGenEU Study Investigators (Supplemental Annex S1)

**Short title:** Multiborbidity genetic network, autoimmune diseases and pancreatic cancer risk

**Key words:** Pancreatic cancer; Autoimmune diseases; Multimorbidity; Genetic network; Gene-disease associations; Case-control study

**Word count**

Abstract: 294

Main text: 3729

Number of figures: 1

Number of tables: 5

**Abstract**

Several morbidities have been associated with pancreatic cancer (PC) risk. Deciphering the underlying basis behind multimorbidities and PC could enhance our knowledge about this malignancy. In this study we aimed to study the common genetic background of PC and different morbidities through a bioinformatics approach and to further explore a hypothesis generated by this method in a large European case-control study (PanGenEU).

Gene-disease associations (GADs) of 26 morbidities and PC were obtained using the literature information available in the DisGeNET discovery platform. A case-control European population consisting of 1705 PC cases and 1084 controls were used to explore the association between autoimmune diseases (ADs) and PC risk through multivariate logistic regression models.

Fifteen morbidities shared at least one gene with PC in the literature. Based on common genes, the strongest associations with PC were for peptic ulcer, hypertension and ulcerative colitis. According to the enrichment analysis, PC shares biological processes and pathways with diseases like type 2 diabetes, peptic ulcer, and rheumatoid arthritis. Several ADs were found to be genetically associated with PC in DisGeNET. The epidemiologic analysis showed that having any one of the 9 studied ADs was significantly associated with a reduced risk of PC: Odds Ratio (OR)=0.74, 95% Confidence Interval (CI) 0.58-0.93) which further decreased in subjects having >2 or more ADs (OR=0.39, 95%CI: 0.21-0.73). Individually, only polymyalgia and rheumatoid arthritis were significantly associated with low PC risk (OR=0.4, 95%CI: 0.19-0.89 and OR=0.73, 95%CI: 0.53-1; respectively).

In this study we show that several inflammatory-related morbidities share a common genetic component with PC. These molecular links could shed some light into the molecular mechanisms underlying PC development and simultaneously generate novel hypotheses. As a result, we report findings pointing to a negative association between ADs and a reduced risk of PC.

**Introduction**

Pancreatic cancer (PC) is a deadly disease with the lowest 5-year survival rate (7%) of all cancers 1 and the fourth leading cause of cancer-related death in Europe 2. Evidence indicates that morbidities such as chronic pancreatitis and type 2 diabetes (T2D) associate with an increased risk of PC 3,4 while others like nasal allergies and asthma associate with a reduced risk 5. Although seldom studied, the simultaneous presence of more than one morbidity, i.e. comorbidity, often sharing adverse lifestyle and/or genetic factors, could more than likely occur among PC patients since multimorbidiy is common in ageing, one of the main risk factors of PC. In this respect, a higher risk of PC has been reported among subjects having >3 metabolic syndrome-related disorders versus having none of them 6. Understanding the mechanisms shared between multimorbidities and PC could help improve prevention, early diagnosis, prognosis, and/or treatment of this cancer. For this purpose, bioinformatics tools become ideal to systematically explore the genetic complexity underlying the associations between different multimorbidities and PC.

 Autoimmune diseases (ADs) are characterized by an immune dysregulation in which immune cells react against self-antigens resulting in cell and tissue damage. ADs are classified into localized and systemic depending on whether the autoimmune response is directed against a particular tissue or against widespread antigens 7. Under the assumption that ADs and cancer share common genetic mechanisms, the association between these two disorders has been studied during the past couple of decades 8. Different studies have reported a positive association between certain ADs and some types of cancer like lupus erythematosus and leukemia, while a negative association has been suggested for others such as rheumatoid arthritis and colorectal cancer 9,10. However, to date, limited and conflicting information exists regarding the association between autoimmunity and the risk of PC.

In this study we seek to examine the genetic background between 26 morbidities and PC to identify their underlying common genes using DisGeNET, a publicly available bioinformatics tool that interrogates the literature and integrates information on gene-disease associations. Our aim was to gather a broader view of the multimorbidity patterns associated with PC on the basis of the genetic mechanisms underlying this malignancy and to confirm the novel hypothesis raised by the bioinformatics approach, i.e., the observed association between AD and PC risk, with individual data collected in the PanGenEU case-control study.

**Methods**

For the bioinformatics analysis we applied DisGeNET 11, a bioinformatics tool that uses information from public databases (UniProt, ClinVar, and CTD) and biomedical literature to obtain available information about gene-disease correlations on the basis of previously selected Concept Unique Identifiers (CUIs).

*Disease vocabulary*. The CUIs for PC and 26 morbidities potentially associated with PC risk were obtained using the Metathesaurus from the Unified Medical Language Systems (UMLS). After independent selection from three semantic types (disease or syndrome, sign or symptom, neoplastic process) by two members of the group (PG and NM), a mean of 4 (range 1 to 12) CUIs were used to define each disease (Supplementary Table 1).

*DisGeNET query*.For all but four conditions, DisGeNet was queried using manually curated data. Polymyalgia, mumps, pernicious anemia, and Addison’s disease were not found in the curated data sources and thus were queried using all data sources; the obtained genes were then manually curated by a member of the group (PG). The analysis was performed using DisGeNET version 3.0 and disgenet2r package in R version 3.1.2.

The number of common genes between disease pairs was used to determine disease “genetic” similarities. The Jaccard index (JI) was calculated to account for variation in gene findings due to differences between the differentially studied morbidities, i.e. diseases with more versus less total genes identified. The JI is defined as: |Genesdis1 **∩** Genesdis2| / |Genesdis1 **∪** Genesdis2|, where Genesdis1 and Genesdis2 are the genes associated with disease 1 and 2, respectively, **∩** is the intersection operator, and **∪** is the union operator between the two sets of genes. An empirical *P* value was calculated for each JI using 50,000 bootstrapped samples from a pool of the 7,878 genes available in DisGeNET. Additionally, disease specificity (DSI) and pleiotropy (DPI) indexes were calculated (www.disgenet.org/web/DisGeNET/menu/dbinfo#specificity). Both indexes range from 0 to 1, where DSI = 1 implies high disease specificity (genes associate only to one disease) and DPI = 1 implies high disease pleiotropy (the diseases associated to a gene that belongs to all disease classes).

*Gene Ontology analysis*. The ontology terms, restricted to the Biological Process (BP), shared between morbidities were identified through an enrichment analysis with GO.db and GOstats 12 packages in R. The JI for BPs was calculated for all disease pairs as: |BP Termscomorbidity1 BP **∩**Termscomorbidity2| / |BP Termscomorbidity1 **∪** BP Termscomorbidity2|, where comorbidity 1 and 2 represent pairs of morbidities. The JI was calculated only for statistically significant terms after multiple test correction as implemented by the package. In this study, the term comorbidity defines those disease pairs with common genes in the DisGeNET query.

*Pathway analysis*.An enrichment analysis was performed using the ReactomePA package in R to identify pathways shared between morbidities. The JI was calculated for all disease pairs as stated above except using pathways instead of BP terms. JI was calculated only for those pathways that remained statistically significant after multiple test correction as implemented by the package.

*The epidemiological analysis* was performed using the resources (population and data) from the PanGenEU case-control study.

*Study population*. This is a European population consisting in men and women >18 years of age from Spain, UK, Germany, Ireland, Sweden, and Italy, recruited from 2009 to 2014 (Supplemental Annex S1). Potentially eligible pancreatic ductal adenocarcinoma cases were approached for participation, and those for whom diagnosis was not confirmed by the physician were not included in the study. Eligible controls did not have previous history of PC nor diseases sharing known risk factors with PC, as primary diagnoses 5 when recruited in a hospital-based setting; controls from Ireland and Sweden were recruited from a population-based setting. Reasons for no participation where recorded for all subjects when applicable. IRB approval and written informed consent was obtained by all participating centers and study participants, respectively. Subjects without information in the entire medical section of the questionnaire were excluded from the analysis (N=268, 8.8%) leaving a total of 1705 PC cases and 1084 controls for analyses. Age, sex, and smoking distributions were similar between included and excluded subjects (*P* > 0.05).

*Study variables*. Information about demographics, lifestyle, and medical history were gathered through in-person interviews by trained monitors applying the same questionnaire. Subjects reported “yes/no” to “Has your doctor ever told you that you had any of the following illnesses, health problems or procedures?” for 25 morbidities including 9 autoimmune diseases. ADs were further categorized as systemic (rheumatoid arthritis, lupus erythematosus, scleroderma, and polymyalgia rheumatica), hematologic-localized (pernicious anemia), gastrointestinal-localized (Crohn’s disease, ulcerative colitis, and celiac disease), and endocrine-localized (Addison’s disease). Regular consumption of anti-inflammatory/pain killer medication (aspirin, paracetamol, NSAIDs and corticosteroids) was defined as subjects reporting ever taking one of these treatments at least once a week, on average, for 3 months or more.

*Statistical analysis*. Imputation of missing values was performed using the missForest package 13. Missing values, 3.7% in cases and 2.9% in controls, were assumed to be missing at random. Variables used for imputation (% missings) included case-control status, country, age (2.3%), sex (0.2%), smoking (pack/years, 9.4%), alcohol status (1.5%), medication treatments (6.1- 7.9%), and morbidities and time since diagnosis (0.8%-21.7%). An imputation test introducing the same proportions of missing values to a complete-case dataset resulted in a concordance mean between imputed and real data >90% and out of bag errors < 0.35 (0= good imputation performance, 1= bad imputation performance).

Multivariate logistic regression models were used to test the association between ADs and PC risk. Adjustment variables were selected based on the 10% change in estimate as well as the likelihood ratio tests and the Akaike Information Criterion (AIC). Variables considered as potential confounders were smoking, alcohol, type 2 diabetes, obesity, family history of pancreas cancer, years of education, and medication. Final models were adjusted for age, country, sex, smoking and alcohol status, as well as medical treatment in separate models. Interactions with age, sex, smoking, alcohol and corticoids were explored by including the interaction terms in the models.

**Results**

DisGeNET analysis showed that 26 out of the 27 morbidities are connected through common genes to at least one other morbidity; hypothyroidism was the only disease for which no shared genes were observed (Supplementary Figure 1). PC was associated with 73 genes according to the DisGeNET curated literature; half of these showed disease specificity above 0.75 and disease pleiotropy below 0.30 (Supplementary Table 2). The total number of genes associated with the remaining 26 medical conditions averaged 41.3 and ranged from 1 in heartburn to 185 in hypertension; the number of common genes between PC and specific morbidities ranged from 0 to 10 (Table 1). Twenty-two out of the 73 genes associated with PC were associated with other morbidities (Table 2). From these, the genes shared with more morbidities were *TNF*, *MMP9*, *PTGS2*, and *SOD2* (DSI < 0.58). Conversely, *ABO*, *SPINK1*, *PDX1*, *TFPI2*, and *STK11* had the highest disease specificity and lowest disease pleiotropy (DSI > 0.73 and DPI < 0.41). Fifteen morbidities were associated trough at least one gene with PC, specifically peptic ulcer (JI=0.055), hypertension (JI=0.04), and ulcerative colitis (JI=0.04) showed the most robust genetic relation with PC (Table 1 and Figure 1). In general, the strongest genetic associations were found between mumps and polymyalgia, Crohn’s disease and ulcerative colitis, asthma and nasal allergies, and diabetes and hypertension (average JI= 0.124, range, 0.10 – 0.14) (Supplementary Table 3). The average number of shared BPs between morbidities was 147.2 (range 9 - 386). PC and hypertension had the highest number of shared BPs (N=69), followed by peptic ulcer (N=31) and obesity (N=31); 125 unique BPs were shared between PC and seven morbidities (Table 3). The BP that was shared between PC and more morbidities was ‘negative regulation of fat cell differentiation’ (Supplementary Table 4). Moreover, the average number of shared pathways between morbidities was 29.7 (range 4-96). Twenty-one unique pathways were shared between PC and at least one morbidity with peptic ulcer sharing the highest number of pathways (N=16), followed by T2D (N=10), and rheumatoid arthritis (N=7); no other diseases shared pathways with PC based on the Reactome-DisGeNET analysis (Table 3). ‘TNF signaling’ and ‘TNFR1-mediated proapoptotic signaling’ pathways were shared between PC, T2D, peptic ulcer and rheumatoid arthritis (Supplementary Table 5).

Five ADs were found among the 15 morbidities genetically associated with PC. Consequently, we sought to explore the association between ADs and PC risk in a European case-control study population (Table 4). Multivariate logistic regression models showed that having >1 ADs was associated with a significant reduced risk of PC (OR=0.74, 95%CI 0.58-0.93). Furthermore, the number of ADs was significantly associated with a reduced PC risk trend (*P* trend = 0.002). Having >1 systemic or localized ADs was significantly associated with lower PC risk (OR=0.74, 95%CI: 0.55-0.99; OR=0.71, 05%CI 0.52-0.97, respectively). Among localized diseases, having any one or more gastrointestinal AD was borderline associated with a low risk of PC (OR= 0.51, 95%CI 0.26-1). Analysis of individual ADs showed significant and borderline significant associations between polymyalgia and rheumatoid arthritis, respectively (OR=0.4, 95%CI: 0.18-0.89; OR=0.73, 95%CI: 0.53-1, respectively). While further adjustment of the models by medication treatment resulted in the loss of significance of some of these associations, the association with >1 ADs and number of ADs was maintained even after treatment adjustment (Table 5). No significant interactions were observed.

**Discussion**

Using a bioinformatics approach we showed that 15 out of the 26 morbidities of interest share a genetic background with PC. Moreover, we confirmed the AD-PC correlation hypothesis generated by the genetic network analysis with results from a large European case-control study population suggesting a negative association between autoimmune diseases and PC risk.

Growing evidence suggests that integrative approaches will help to better grasp disease complexity. Disentangling the underlying mechanisms behind multimorbidities could improve prevention and handling of illnesses. To this end, molecular studies, while ideal, are often expensive and hampered by statistical power when considering low prevalent diseases. Alternatively, exploration of potential multimorbidity links through literature search is accessible to most researchers and provides a hypothesis-generation approach for multiple assessments. Moreover, the limitation by time and effort spent in manually mining databases has been overcome by new bioinformatics tools such as DisGeNET that generate multimorbidity networks based on gene-disease associations available from public datasets in a more efficient way.

Our results show that many of the morbidities previously associated with PC risk in epidemiological studies 14 are also related to this malignancy at a genetic level with a total of 22 genes shared between 15 morbidities and PC in DisGeNET. Many of these genes are known to be relevant for pancreatic carcinogenesis, while others are important players in the inflammatory process 15,16. Likewise, many of the BPs and pathways shared with PC are essential in inflammation and carcinogenic processes. Importantly, some of these genes show high disease specificity and low disease pleiotropy, meaning that they are associated only to a small set of diseases and that they belong to a few disease classes (< than 10 diseases and < 6 classes). Others genes like *TNF*, *PTGS2* and *MMP9* are associated with a much larger set of diseases making them less informative.

A main limitation of the bioinformatics approach is that we can only consider gene-disease associations that have been published in the literature and curated and registered in databases, and hence are available in DisGeNET. The fact that some morbidities showed a few or no genetic associations with other morbidities may result from either a real absence of a genetic association between certain morbidities or a lack of published and/or registered gene-disease association studies. Therefore, we cannot rule out that some associations could have been missed due to the limited spectrum of the information available. Exemplary of this is the fact that we only detect one overlapping gene between chronic pancreatitis and PC, SPINK1, while there are, in fact, other genes such as PRSS1 that have been associated with both morbidities 15. Furthermore, we relied on the JI to overcome problems due to differences between diseases with more or less associated genes which could be a reflection of how well or poorly studied some diseases are over others. Finally, DisGeNET do not differentiate between somatic and germline genetic alterations nor between type of alteration. However, in spite of these limitations, the main objective of this study was to gather a broader view of the mechanisms underlying PC risk relying on the publicly available information. In addition, a great advantage of applying a systems approach to explore PC multimorbidities is that it also has the potential to generate new hypotheses. For example, among the 15 morbidities genetically associated with PC (Figure 1), those not previously reported as risk factors of PC were mostly ADs, namely rheumatoid arthritis, lupus erythematosus, ulcerative colitis, Crohn’s disease, and scleroderma; five out of the eight autoimmune morbidities included in the analysis. Interestingly, it has been suggested that ADs could predispose individuals to cancer or, alternatively, that some tumors could trigger ADs. Mechanisms such as hypoxia and angiogenesis have been reported to overlap between both conditions 17. Overall, current studies point to an association between certain ADs and increased risk of different types of cancers such as small intestine and esophageal cancers with celiac disease, or hematological neoplasms with rheumatoid arthritis, systemic lupus erythematous, and scleroderma 9,10,18,19. Yet, some of these ADs have been associated with a decreased risk of other cancers such as breast and colorectal 10,20,21, suggesting that the association may not be the same for all cancer types. For pancreas cancer, however, the information is limited and conflicting, possibly in part due to the low incidence of this malignancy.

To our knowledge, no study has explored the association between PC and scleroderma. On the other hand, the association with pernicious anemia seems to be the only one that has been purposely analyzed in the context of PC in a retrospective cohort study, but no significant association was reported 22. Other studies in the subject have explored the association between specific ADs and the development of cancer, some of which report on PC, yet results appear inconclusive 23–26. Most of such studies, however, are cohort designs reporting standardized incidence ratios, limiting the adjustment of studies for potential confounders. The design of the PanGenEU case-control study allowed us to explore these associations accounting for confounding and interaction of a broad set of factors.

In this study, we report a significant negative association between suffering one or more of the 9 ADs under study and PC risk. Moreover, we observed that the estimate further decreased when subjects reported having >2 ADs, with a significant negative trend between number of reported ADs and PC risk. The significant negative association holds when considering systemic and localized AD separately. At the individual AD level, we did not find a significant association between lupus or Addison’s disease and PC, supporting existing reports 9,20,26–30. Contradictory results have been published in association with pernicious anemia, Crohn’s disease, and ulcerative colitis with some studies reporting no significant association 22,23,25,26,31 while others showing a significant increased risk of PC with these diseases 24,32,33. Regarding celiac disease, studies have reported both significantly reduced and increased risk of PC 21,26, but a recent meta-analysis showed no significant association 18. Furthermore, most studies have described a lack of association between rheumatoid arthritis and PC risk 26,34–36. However, a study performed with the Scottish Cancer Registry reported a significant negative association between rheumatoid arthritis and PC among women but not among men 37 while in our study sex stratification showed a significant negative association only among males (OR=0.6, 95%CI 0.35-0.97 for males and OR=0.8, 95%CI 0.52-1.26 for females, *P-value* for interaction= 0.23). Other studies evaluating cancer risk among patients with ulcerative colitis, Crohn’s disease, rheumatoid arthritis, polymyalgia and giant cell arthritis, and pernicious anemia have reported significant increased risk of PC mostly restricted to subjects that reported less than one year difference between diagnoses of both diseases; after the first year however, loss of significance is commonly reported as well as a reduction in the risk estimate 24,32,33,38,39. In this regard, due to limited sample size, we were unable to stratify the analyses by time since ADs diagnosis. However, in our population, most of the ADs (82%) were diagnosed more than 2 years before PC diagnosis, which could potentially explain, at least in part, the results observed in this study. Information of hypothyroidism and hyperthyroidism was available in the PanGenEU study; however, while autoimmune disorders are the most common cause of these diseases 40,41, the questionnaire did not discriminate between autoimmune and non-autoimmune related forms of these thyroid conditions. Therefore, including these diseases in the analysis would knowingly introduce a fraction of misclassified non-AD disorders. As expected, a sensitivity analysis including these thyroid conditions showed similar but attenuated estimates for all composite variables (OR=0.79, 95%CI 0.65-0.97 for any ADs and OR=0.61, 95%CI 0.39-0.94 for two or more ADs).

Overall, our results are suggestive of a negative association between PC risk and ADs. Comparison of these results with the existing literature is challenging since this is the first study that we are aware of that incorporates different confounders into the models and that combines different ADs into single variables. Although the epidemiological literature is inconclusive regarding their link, atopy and autoimmunity are known hypersensitive reactions of the immune system and they share immunologic mechanisms 42. Consistently, we have, along with others, reported a similar negative association between atopic conditions and PC 5. Conversely, while autoimmune pancreatitis is an AD that has been suggested to potentially develop into chronic pancreatitis, its link with increased PC risk has not been established 43,44. Moreover, it is reasonable to expect a different association from an AD localized in the pancreas that an AD that occurs in other organs or that act systematically. In addition, one could hypothesize that the decreased risk of certain cancers and ADs could be the consequence of treatment confounding. However, we did not collected this information and are unable to check confounding from medications normally used to treat ADs such as TNF inhibitors. *In vivo* studies suggest that anti-TNF therapy could inhibit pancreatic tumor growth and metastasis 45,46, though its link with carcinogenesis is still not completely elucidated 47–49. Moreover, combination of gemcitabine with TNF inhibitors at doses approved for AD treatment don’t seem to significantly improve gemcitabine treatment in pancreatic cancer patients 50. Notwithstanding, we show that further adjusting the models for anti-inflammatory/pain reliever treatment results in the loss of significance of some the associations. While these results could suggest a potential confounding effect, additionally supporting common pathways between PC and ADs, we cannot completely rule out the possibility of chance findings giving the small effect of the treatment adjustment on the estimates and the sustained significance of the variables considered.

The interpretation and generalization of these results must be carefully performed, and some points must be considered. While the combination of ADs into categories helped us overcome the problem of statistical power, our study size is limited for the inquiry of specific disorders and for some stratified analysis. Additionally, considering that our information is self-reported, it is possible that some degree of disease misclassification might have occurred with a lower rate of false positive than negative reports, probably those with less severe conditions, which would attenuate the risk estimates. Despite these limitations, as far as we know, this is the first study to explore in depth the association between several autoimmune diseases and PC risk. While it is necessary to replicate and further characterize these associations in order to establish and extrapolate these results to the general population, we are not aware of large case-control nor cohort studies with similar information that could support, or discard, our epidemiological findings. Nevertheless, our results are sustained by sound bioinformatics-based observations.

This report highlights the importance of multimorbidities in pancreatic cancer risk from a systemic genetic point of view. Many of these results are confirmatory of the mechanistic notions about pancreatic carcinogenesis. Importantly, a novel genetic association between PC and ADs was identified, which was further indicated in an epidemiological setting as a negative association between certain ADs and PC risk. Defining a set of morbidities setting up a risk pattern for PC could potentially help in better defining prevention strategies and high-risk population groups for screening and timely diagnosis of this deadly cancer.

**References**

1. Angelis R De, Sant M, Coleman MP, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE-5-a population-based study. Lancet Oncol. 2013;2045:1–12.

2. Malvezzi M, Bertuccio P, Rosso T, et al. European cancer mortality predictions for the year 2015: does lung cancer have the highest death rate in EU women? Ann. Oncol. 2015.

3. Raimondi S, Lowenfels AB, Morselli-Labate AM, et al. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best Pract. Res. Clin. Gastroenterol. 2010;24:349–358.

4. Bosetti C, Rosato V, Li D, et al. Diabetes, antidiabetic medications, and pancreatic cancer risk: an analysis from the International Pancreatic Cancer Case-Control Consortium. Ann. Oncol. 2014;25:2065–2072.

5. Gomez-Rubio P, Zock J-P, Rava M, et al. Reduced risk of pancreatic cancer associated with asthma and nasal allergies. Gut 2015:gutjnl–2015–310442.

6. Rosato V, Tavani A, Bosetti C, et al. Metabolic syndrome and pancreatic cancer risk: A case-control study in Italy and meta-analysis. Metabolism. 2011;60:1372–1378.

7. Fairweather D. Autoimmune Disease: Mechanisms. Encycl. Life Sci. 2007:1–6.

8. Sara Achenza MI, Selmi C. Autoimmunity and Cancer. Asian Pacific J. Cancer Prev. 2012;13:29–40.

9. Cao L, Tong H, Xu G, et al. Systemic lupus erythematous and malignancy risk: A meta-analysis. PLoS One 2015;10:1–21.

10. Simon T, Thompson A, Gandhi K, et al. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Res. Ther. 2015;17:212.

11. Piñero J, Queralt-Rosinach N, Bravo Á, et al. DisGeNET: A discovery platform for the dynamical exploration of human diseases and their genes. Database 2015;2015:1–17.

12. Beißbarth T, Speed TP. GOstat: Find statistically overrepresented Gene Ontologies with a group of genes. Bioinformatics 2004;20:1464–1465.

13. Stekhoven DJ, Bühlmann P. MissForest - nonparametric missing value imputation for mixed-type data. Bioinformatics 2012;28:112–8.

14. Maisonneuve P, Lowenfels a. B. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. Int. J. Epidemiol. 2014:1–13.

15. Amundadottir LT. Pancreatic cancer genetics. Int. J. Biol. Sci. 2016;12:314–325.

16. Hausmann S, Kong B, Michalski C, et al. The Role of Inflammation in Pancreatic Cancer. Adv. Exp. Med. Biol. 2014;816:129–51.

17. Rahat MA, Shakya J. Parallel Aspects of the Microenvironment in Cancer and Autoimmune Disease. Mediators Inflamm. 2016;2016:4375120.

18. Han Y, Chen W, Li P, et al. Association Between Coeliac Disease and Risk of Any Malignancy and Gastrointestinal Malignancy: A Meta-Analysis. Medicine (Baltimore). 2015;94:e1612.

19. Bonifazi M, Tramacere I, Pomponio G, et al. Systemic sclerosis (scleroderma) and cancer risk: systematic review and meta-analysis of observational studies. Rheumatology (Oxford). 2013;52:143–154.

20. Bernatsky S, Ramsey-Goldman R, Labrecque J, et al. Cancer risk in systemic lupus: An updated international multi-centre cohort study. J. Autoimmun. 2013;42:130–135.

21. Ilus T, Kaukinen K, Virta LJ, et al. Incidence of malignancies in diagnosed celiac patients: a population-based estimate. Am. J. Gastroenterol. 2014;109:1471–7.

22. Shah P, Rhim A, Haynes K, et al. Diagnosis of pernicious anemia and the risk of pancreatic cancer. Pancreas 2014;19:161–169.

23. Brinton LA, Gridley G, Hrubec Z, et al. Cancer risk following pernicious anaemia. Br. J. Cancer 1989;59:810–3.

24. Hsing AW, Hansson L-E, McLaughlin JK, et al. Pernicious anemia and subsequent cancer. A population-based cohort study. Cancer 1993;71:745–750.

25. Mellemkjaerl L, Gridley G, Moller H, et al. Pernicious anaemia and cancer risk in Denmark. Br. J. Cancer 1996;73:998–1000.

26. Landgren AM, Landgren O, Gridley G, et al. Autoimmune disease and subsequent risk of developing alimentary tract cancers among 4.5 million U.S. male Veterans. 2011;117:1163–1171.

27. Abu-Shakra M, Gladman DD, Urowitz MB. Malignancy in systemic lupus erythematosus. Arthritis Rheum 1996;39:1050–1054.

28. Mellemkjér L, Andersen V, Linet MS, et al. Non‐Hodgkin’s lymphoma and other cancers among a cohort of patients with systemic lupus erythematosus. Arthritis Rheum. 1997;40:761–768.

29. Parikh-Patel A, Allen M, Cress R, et al. Cancer risk in a cohort of patients with systemic lupus erythematosus (SLE) in California. Cancer Causes Control 2008;19:887–894.

30. Dreyer L, Faurschou M, Mogensen M, et al. High incidence of potentially virus-induced malignancies in systemic lupus erythematosus: A long-term followup study in a Danish cohort. Arthritis Rheum. 2011;63:3032–3037.

31. Pedersen N, Duricova D, Elkjaer M, et al. Risk of extra-intestinal cancer in inflammatory bowel disease: meta-analysis of population-based cohort studies. Am. J. Gastroenterol. 2010;105:1480–1487.

32. Hemminki K, Li X, Sundquist J, et al. Cancer risks in ulcerative colitis patients. Int. J. Cancer 2008;123:1417–1421.

33. Hemminki K, Li X, Sundquist J, et al. Cancer risks in Crohn disease patients. Ann. Oncol. 2009;20:574–580.

34. Gridley G, McLaughlin JK, Ekbom A, et al. Incidence of cancer among patients with rheumatoid arthritis. J. Natl. Cancer Inst. 1993;85:307–11.

35. Askling J, Fored CM, Brandt L, et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Ann. Rheum. Dis. 2005;64:1421–6.

36. Yu K-H, Kuo C-F, Huang LH, et al. Cancer Risk in Patients With Inflammatory Systemic Autoimmune Rheumatic Diseases: A Nationwide Population-Based Dynamic Cohort Study in Taiwan. Medicine (Baltimore). 2016;95:e3540.

37. Thomas E, Brewster DH, Black RJ, et al. Risk of malignancy among patients with rheumatic conditions. Int.J.Cancer 2000;88:497–502.

38. Hemminki K, Li X, Sundquist K, et al. Cancer risk in hospitalized rheumatoid arthritis patients. Rheumatology 2008;47:698–701.

39. Ji J, Liu X, Sundquist K, et al. Cancer risk in patients hospitalized with polymyalgia rheumatica and giant cell arteritis: A follow-up study in Sweden. Rheumatology 2010;49:1158–1163.

40. Leo S De, Lee SY, Braverman LE. Hyperthyroidism. Lancet 2016;6736:1–13.

41. Gaitonde DY, Rowley KD, Sweeney LB, et al. Hypothyroidism: An Update. Am. Fam. Physician 2012;86.

42. Rabin RL, Levinson AI. The nexus between atopic disease and autoimmunity: A review of the epidemiological and mechanistic literature. Clin. Exp. Immunol. 2008;153:19–30.

43. Maruyama M, Watanabe T, Kanai K, et al. Autoimmune pancreatitis can develop into chronic pancreatitis. Orphanet J. Rare Dis. 2014;9:77.

44. Hart PA, Law RJ, Dierkhising RA, et al. Risk of cancer in autoimmune pancreatitis: A case-control study and review of the literature. Pancreas 2014;43.

45. Egberts JH, Cloosters V, Noack A, et al. Anti-tumor necrosis factor therapy inhibits pancreatic tumor growth and metastasis. Cancer Res. 2008;68:1443–1450.

46. Tiwari S, Egberts JH, Korniienko O, et al. Assessment of anti-inflammatory tumor treatment efficacy by longitudinal monitoring employing sonographic micro morphology in a preclinical mouse model. BMC Med. Imaging 2011;11:15.

47. Askling J, Fahrbach K, Nordstrom B, et al. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: Meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. Pharmacoepidemiol. Drug Saf. 2011;20:119–130.

48. Nyboe Andersen N, Pasternak B, Basit S, et al. Association between tumor necrosis factor-alpha antagonists and risk of cancer in patients with inflammatory bowel disease. JAMA 2014;311:2406–2413.

49. Shelton E, Laharie D, Scott FI, et al. Cancer Recurrence Following Immune-Suppressive Therapies. Gastroenterology 2016;151:97–109.e4.

50. Wu C, Fernandez S, Criswell T, et al. Disrupting cytokine signaling in pancreatic cancer: a phase I/II study of etanercept in combination with gemtacibine in patients with advanced disease. Pancreas 2013;42:813–818.

|  |
| --- |
| **Table 1. Number of concept unique identifiers, total genes, common genes with pancreatic cancer and respective Jaccard indexes for diseases under study** |
| **Disease1** | **Number of CUIs** | **Genesdis1** | **Common Genes** | **JI** | ***P* val\*** |
| Peptic ulcer | 3 | 23 | 5 | 0.0549 | 0 |
| Hypertension | 9 | 185 | 10 | 0.0403 | 0 |
| Ulcerative colitis | 1 | 57 | 5 | 0.0400 | 0 |
| Asthma | 6 | 83 | 5 | 0.0331 | 0.0001 |
| Obesity | 10 | 156 | 7 | 0.0315 | 0.0001 |
| Type 2 diabetes | 3 | 124 | 6 | 0.0314 | 0.0002 |
| Acid regurgitation | 2 | 5 | 2 | 0.0263 | 0 |
| Rheumatoid arthritis | 1 | 123 | 5 | 0.0262 | 0.0010 |
| Crohn’s disease | 3 | 41 | 2 | 0.0179 | 0.0065 |
| Lupus erythematosus | 6 | 68 | 2 | 0.0144 | 0.025 |
| *H.pylori* | 2 | 5 | 1 | 0.0130 | 0.0009 |
| Chronic pancreatitis | 1 | 6 | 1 | 0.0128 | 0.0013 |
| Periodontitis | 4 | 9 | 1 | 0.0123 | 0.0032 |
| Hyperthyroidism | 4 | 10 | 1 | 0.0122 | 0.0037 |
| Scleroderma | 12 | 11 | 1 | 0.0120 | 0.0048 |
| Nasal allergies | 3 | 17 | 0 | 0 | - |
| Skin allergies | 9 | 43 | 0 | 0 | - |
| Hypercholesterolemia | 12 | 40 | 0 | 0 | - |
| Heartburn | 1 | 1 | 0 | 0 | - |
| Hypothyroidism | 2 | 3 | 0 | 0 | - |
| Mumps | 1 | 9 | 0 | 0 | - |
| Pernicious anemia | 1 | 2 | 0 | 0 | - |
| Gallstones | 3 | 6 | 0 | 0 | - |
| Celiac disease | 1 | 28 | 0 | 0 | - |
| Polymyalgia | 3 | 7 | 0 | 0 | - |
| Addison disease | 1 | 11 | 0 | 0 | - |
| \* Empirical p value calculated after performing 50,000 bootstraps  |
| CUI: Concept unique identifier, JI= Jaccard index  |  |  |  |
| Note: pancreatic cancer CUIs = 3, Genes = 73. |  |  |

|  |
| --- |
| **Table 2. Common genes between pancreatic cancer and other diseases in DisGeNET** |
| **Gene**  | **Ndis** | **Diseases** |
| TNF | 9 | Asthma, obesity, type 2 diabetes, hypertension, peptic ulcer, rheumatoid arthritis, scleroderma, crohn’s disease, ulcerative colitis |
| MMP9 | 6 | Asthma, obesity, peptic ulcer, periodontitis, lupus erythematosus, ulcerative colitis |
| PTGS2 | 6 | Obesity, hypertension, peptic ulcer, acid regurgitation, rheumatoid arthritis, lupus erythematosus |
| SOD2 | 5 | Obesity, type 2 diabetes, hypertension, hyperthyroidism, rheumatoid arthritis,  |
| PPARG | 4 | Obesity, type 2 diabetes, hypertension, crohn’s disease |
| TGFB1 | 4 | Asthma, type 2 diabetes, hypertension, peptic ulcer |
| AHR | 2 | Hypertension, rehumatoid arthritis |
| CDH1 | 2 | Ulcerative colitis, *H. pylori* infection |
| CXCL8 | 2 | Acid regurgitation, Ulcerative colitis |
| PTEN | 2 | Asthma, hypertension |
| ABO | 1 | Peptic ulcer |
| BCL2L1 | 1 | Type 2 diabetes |
| CNR1 | 1 | Obesity |
| DPYD | 1 | Obesity |
| HIF1A | 1 | Hypertension |
| PDX1 | 1 | Type 2 diabetes |
| PLAU | 1 | Asthma |
| SPINK1 | 1 | Chronic pancreatitis |
| STAT3 | 1 | Ulcerative colitis |
| STK11 | 1 | Hypertension |
| TFPI2 | 1 | Rheumatoid arthritis |
| TP53 | 1 | Hypertension |

|  |
| --- |
| **Table 3. Number of unique biological processes and pathways shared between each diseases and any other diseases and number of processes shared between the diseases and pancreatic cancer** |
| **Disease** | **N unique processes shared** | **N processes shared with PC** | **N unique pathways shared** | **N pathways shared with PC** |
| Hypertension | 386 | 69 | 96 | 0 |
| Type 2 diabetes | 340 | 18 | 54 | 10 |
| Asthma | 278 | 14 | 46 | 0 |
| Rheumatoid arthritis | 277 | 13 | 36 | 7 |
| Crohn’s disease | 266 | 0 | 36 | 0 |
| Obesity | 251 | 31 | 37 | 0 |
| Ulcerative colitis | 195 | 18 | 30 | 0 |
| Peptic ulcer | 177 | 31 | 37 | 16 |
| Lupus erythematosus | 169 | 0 | 32 | 0 |
| Skin allergies | 139 | 0 | 26 | 0 |
| Pancreatic cancer | 125 | - | 21 | - |
| Hyperthyroidism | 50 | 0 | 12 | 0 |
| Hypercholesterolemia | 36 | 0 | 16 | 0 |
| Celiac disease | 30 | 0 | 12 | 0 |
| Mumps | 24 | 0 | 4 | 0 |
| Addison disease | 17 | 0 | 14 | 0 |
| Polymyalgia | 17 | 0 | 16 | 0 |
| Scleroderma | 10 | 0 | 6 | 0 |
| Nasal allergies | 9 | 0 | 0 | 0 |
| PC: pancreatic cancer |
| Note: Only diseases for which biological processes and/or pathways were found through enrichment analyses are presented. |

|  |
| --- |
| **Table 4. Characteristics of the PanGen study population** |
|   | **Cases** |  | **Controls** |  |  |
|   | **N=1705** | **%** | **N=1084** | % |   |
| **Country** |  |  |  |  |  |
| Spain | 842 | 49.38 | 595 | 54.89 |  |
| England | 121 | 7.10 | 22 | 2.03 |  |
| Germany | 140 | 8.21 | 110 | 10.15 |  |
| Ireland | 173 | 10.15 | 290 | 26.75 |  |
| Italy | 292 | 17.13 | 0 | 0.00 |  |
| Sweden | 137 | 8.04 | 67 | 6.18 |  |
| **Sex** |  |  |  |  |  |
| Female | 741 | 43.46 | 518 | 47.79 |  |
| Male | 964 | 56.54 | 566 | 52.21 |  |
| **Age** |  |  |  |  |  |
| <=54 | 363 | 21.29 | 221 | 20.39 |  |
| 55-64 | 413 | 24.22 | 230 | 21.22 |  |
| 65-74 | 592 | 34.72 | 333 | 30.72 |  |
| >=75 | 337 | 19.77 | 300 | 27.68 |  |
| **Smoking pack/years** |  |  |  |  |  |
| Never | 673 | 39.47 | 540 | 49.82 |  |
| <18.5 | 315 | 18.48 | 233 | 21.49 |  |
| 18.6-40.9 | 365 | 21.41 | 145 | 13.38 |  |
| >41 | 352 | 20.65 | 166 | 15.31 |  |
| **Alcohol status** |  |  |  |  |  |
| Never | 468 | 27.45 | 323 | 29.80 |  |
| Former | 421 | 24.69 | 158 | 14.58 |  |
| Current | 816 | 47.86 | 603 | 55.63 |   |

|  |
| --- |
| **Table 5. Odds ratios for the association between autoimmune diseases and pancreatic ductal adenocarcinoma.** |
|   | **Cases** |  | **Controls** |  |  |   |   |   |   |   |   |   |   |
|   | **N=1705** | **%** | **N=1084** | % |   | **OR1** | **95%CI** |  | **OR2** | **95%CI** |  | **OR3** | **95%CI** |
| **Lupus** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 1696 | 99.47 | 1081 | 99.72 |  | Ref. | Ref. |  | Ref. | Ref. |  | Ref. | Ref. |
| Yes | 9 | 0.53 | 3 | 0.28 |  | 1.91 | [0.48;7.53] |  | 2.08 | [0.51;8.44] |  | 2.04 | [0.49;8.39] |
| **Scleroderma** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 1697 | 99.53 | 1080 | 99.63 |  | Ref. | Ref. |  | Ref. | Ref. |  | Ref. | Ref. |
| Yes | 8 | 0.47 | 4 | 0.37 |  | 0.91 | [0.23;3.54] |  | 0.81 | [0.20;3.20] |  | 0.83 | [0.21;3.25] |
| **Polymyalgia** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 1692 | 99.24 | 1065 | 98.25 |  | Ref. | Ref. |  | Ref. | Ref. |  | Ref. | Ref. |
| Yes | 13 | 0.76 | 19 | 1.75 |  | **0.42** | **[0.20;0.92]** |  | **0.4** | **[0.18;0.89]** |  | 0.46 | [0.21;1.04] |
| **Pernicious anemia** |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 1630 | 95.6 | 1014 | 93.54 |  | Ref. | Ref. |  | Ref. | Ref. |  | Ref. | Ref. |
| Yes | 75 | 4.4 | 70 | 6.46 |  | 0.75 | [0.53;1.06] |  | 0.72 | [0.51;1.02] |  | 0.75 | [0.53;1.07] |
| **Crohn's disease** |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 1701 | 99.77 | 1079 | 99.54 |  | Ref. | Ref. |  | Ref. | Ref. |  | Ref. | Ref. |
| Yes | 4 | 0.23 | 5 | 0.46 |  | 0.26 | [0.05;1.46] |  | 0.32 | [0.05;1.94] |  | 0.36 | [0.58;2.24] |
| **Celiac disease** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 1698 | 99.59 | 1078 | 99.45 |  | Ref. | Ref. |  | Ref. | Ref. |  | Ref. | Ref. |
| Yes | 7 | 0.41 | 6 | 0.55 |  | 0.54 | [0.15;1.95] |  | 0.63 | [0.18;2.17] |  | 0.62 | [0.18;2.19] |
| **Addison's disease** |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 1698 | 99.59 | 1078 | 99.45 |  | Ref. | Ref. |  | Ref. | Ref. |  | Ref. | Ref. |
| Yes | 7 | 0.41 | 6 | 0.55 |  | 0.89 | [0.30;2.68] |  | 0.91 | [0.29;2.81] |  | 0.96 | [0.31;2.99] |
| **Rheumatoid arthritis** |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 1597 | 93.67 | 1000 | 92.25 |  | Ref. | Ref. |  | Ref. | Ref. |  | Ref. | Ref. |
| Yes | 108 | 6.33 | 84 | 7.75 |  | 0.81 | [0.59;1.11] |  | 0.73 | [0.53;1.00] |  | 0.78 | [0.56;1.08] |
| **Ulcerative colitis** |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 1690 | 99.12 | 1068 | 98.52 |  | Ref. | Ref. |  | Ref. | Ref. |  | Ref. | Ref. |
| Yes | 15 | 0.88 | 16 | 1.48 |  | 0.55 | [0.24;1.30] |  | 0.49 | [0.21;1.16] |  | 0.54 | [0.23;1.30] |
| **Autoimmune diseases** |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 1483 | 86.92 | 908 | 83.76 |  | Ref. | Ref. |  | Ref. | Ref. |  | Ref. | Ref. |
| Any | 222 | 13.02 | 176 | 16.24 |  | **0.78** | **[0.62;0.98]** |  | **0.74** | **[0.58;0.93]** |  | **0.78** | **[0.61;0.99]** |
| **Number of AD** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 1483 | 86.92 | 908 | 83.76 |  | Ref. | Ref. |  | Ref. | Ref. |  | Ref. | Ref. |
| 1 | 201 | 11.79 | 146 | 13.47 |  | 0.85 | [0.66;1.08] |  | 0.81 | [0.63;1.04] |  | 0.85 | [0.66;1.09] |
| >2 | 21 | 1.23 | 30 | 2.77 |  | **0.45** | **[0.25;0.83]** |  | **0.39** | **[0.21;0.73]** |  | **0.44** | **[0.24;0.81]** |
| *P* trend\* |  |  |  |  |  |  | 0.009 |  |  | 0.002 |  |  | 0.01 |
| **Type of AD** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| None | 1483 | 86.92 | 908 | 83.76 |  | Ref. | Ref. |  |  |  |  |  |  |
| Systemic only | 120 | 7.04 | 86 | 7.93 |  | 0.85 | [0.62;1.16] |  | 0.78 | [0.58;1.08] |  | 0.83 | [0.60;1.15] |
| Localized only | 88 | 5.16 | 73 | 6.73 |  | 0.77 | [0.55;1.08] |  | 0.76 | [0.54;1.07] |  | 0.78 | [0.55;1.11] |
| Both systemic and localized | 14 | 0.82 | 17 | 1.57 |  | 0.5 | [0.24;1.07] |  | **0.42** | **[0.19;0.90]** |  | 0.48 | [0.22;1.05] |
| **Systemic AD** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 1571 | 92.14 | 981 | 90.50 |  | Ref. | Ref. |  | Ref. | Ref. |  | Ref. | Ref. |
| Any | 134 | 7.86 | 103 | 9.50 |  | 0.81 | [0.60;1.08] |  | **0.74** | **[0.55;0.99]** |  | 0.79 | [0.59;1.07] |
| **Localized AD** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 1603 | 93.96 | 994 | 91.70 |  | Ref. | Ref. |  | Ref. | Ref. |  | Ref. | Ref. |
| Any | 102 | 5.98 | 90 | 8.30 |  | 0.73 | [0.53;0.99] |  | **0.71** | **[0.52;0.97]** |  | 0.74 | [0.54;1.02] |
| **Gastrointestinal AD** |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 1679 | 98.48 | 1059 | 97.69 |  | Ref. | Ref. |  | Ref. | Ref. |  | Ref. | Ref. |
| Any | 26 | 1.52 | 25 | 2.31 |  | 0.54 | [0.27;1.06] |  | 0.51 | [0.26;1.00] |  | 0.55 | [0.28;1.09] |
| **Specific types of AD** |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 1483  | 86.92  | 908  | 83.76  |  | Ref. | Ref. |  | Ref.  | Ref.  |  | Ref. | Ref. |
| Systemic | 120  | 7.04  | 86  | 7.93  |  | 0.85 | [0.62;1.16] |  | 0.78  | [0.57;1.08]  |  | 0.83 | [0.60;1.15] |
| Localized hematologic | 65  | 3.81  | 53  | 4.89  |  | 0.82 | [0.56;1.21] |  | 0.80  | [0.54;1.18]  |  | 0.82 | [0.55;1.21] |
| Localized gastrointestinal | 20  | 1.17  | 15  | 1.38  |  | 0.58 | [0.25;1.32] |  | 0.60  | [0.26;1.37]  |  | 0.64 | [0.28;1.46] |
| Localized endocrine | 2  | 0.12  | 1  | 0.09  |  | 1.84 | [0.16;2.11] |  | 2.65  | [0.23;3.07]  |  | 2.91 | [0.25;3.34] |
| Mixed localized | 1  | 0.06  | 4  | 0.37  |  | 0.28 | [0.03;2.64] |  | 0.29  | [0.03;2.74]  |  | 0.29 | [0.03;2.85] |
| Systemic and localized | 14  | 0.82  | 17  | 1.57  |   | 0.5 | [0.24;1.07] |   | **0.42**  | **[0.19;0.90]**  |   | 0.48 | [0.22;1.05] |
| 1 Adjusted for age (continuous), sex and country |  |  |  |  |  |  |  |  |  |  |  |
| 2 Model adjusted for age (continuous), sex, country, smoking (pack/years, tertiles based on the population distribution and alcohol status (never, former, current) |
| 3 Model adjusted for age (continuous), sex, country, smoking (pack/years, tertiles based on the population distribution, alcohol status (never, former, current), and treatment (no treatment, aspirin only, NSAIDs only, paracetamol only, more than one treatment type) |
| \*Trend was calculated using number of ADs as a continuous variable (range from 0 to 4). |

****

**Figure 1. Gene network of medical conditions associated with PC through common genes.** A) Network of diseases that share genes with pancreatic cancer and all corresponding connections; B) Network of diseases that share genes with pancreatic cancer, only connections with pancreatic cancer shown. Edge width represents the Jaccard index for each disease pair; Jaccard indexes were multiplied by 100 in order to allow better visualization. Node size represents the number of genes obtained through DisGeNET for each medical condition.