Gut

Deciphering the complex interplay between pancreatic cancer, diabetes mellitus subtypes, and obesity/BMI through causal inference and mediation analyses

Journal:	*Gut*
Manuscript ID	Draft
Article Type:	Original Article
Date Submitted by the Author:	n/a
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Keywords:	PANCREATIC CANCER, DIABETES MELLITUS, OBESITY, CANCER EPIDEMIOLOGY

Title: Deciphering the complex interplay between pancreatic cancer, diabetes mellitus subtypes, and obesity/BMI through causal inference and mediation analyses

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Word count **-** Abstract: **248**
Word count - Text (excluding references): **4,005**
Number of References: **55**
Number of Tables: **4**
Number of Figures: **2**
Number of supplementary tables: **17**
Number of supplementary figures: **3**

Abstract

OBJECTIVES: To characterize the association between type 2 diabetes mellitus (T2DM) subtypes (new-onset-NODM or long-standing-LSDM) and pancreatic cancer (PC) risk, to explore the direction of causation through Mendelian randomization (MR) analysis, and to assess the mediation role of BMI.

DESIGN: Information about T2DM and related factors was collected from 2,018 PC cases and 1,540 controls from the PanGenEU study. A subset of PC cases and controls had glycated haemoglobin (Hb1Ac), C-Peptide, and genotype data. Multivariate logistic regression models were applied to derive odds ratios (ORs) and 95% confidence intervals (CIs). T2DM and PC-related SNPs were used as instrumental variables (IV) in bidirectional MR analysis to test for two-way causal associations between PC, NODM, and LSDM. Indirect and direct effects of the BMI-T2DM-PC association were further explored using multivariable and mediation analysis.

RESULTS: T2DM was associated with an increased PC risk when compared to non-T2DM (OR=2.50, 95%CI: 2.05-3.05), the risk being greater for NODM (OR=6.39, 95%CI: 4.18–9.78) and among insulin users (OR=3.69, 95%CI: 2.80-4.86). The causal association between T2DM (57-SNP IV) and PC was not statistically significant. On the contrary, there was a strong causal association between PC (40-SNP IV) and NODM (OR=2.85, 95%CI: 2.04-3.98), although genetic pleiotropy was present. Potential mediating effects of T2DM and obesity (125 SNPs as IV) on both associations were evidenced.

CONCLUSION: Findings of this study do not support a causal effect of LSDM on PC, but suggest that PC is the cause of NODM. The interplay between obesity and T2DM is complex.

Keywords: Pancreatic cancer risk; Diabetes mellitus type 2; Obesity; Case-control; Causal inference; Mendelian randomization analysis.

SUMMARY BOX

1. What is already known about this subject?

- The association between type 2 diabetes mellitus (T2DM) and risk of pancreatic cancer (PC) has been evidenced in numerous studies.
- Few studies have suggested the distinct role of T2DM subtypes, new-onset T2DM (NODM) and long-standing (LSDM), in PC aetiology; while both were associated with PC risk, they may exhibit a different causal relationship with PC.
- Uncertainties surrounding the association between T2DM and PC risk also concern confounding or mediation by obesity, T2DM medication effects, and the causal pathway linking both diseases.

2. What are the new findings?

- This study underlines the importance of a timely and accurate T2DM diagnosis in relation to PC cancer risk; it confirms the time-dependent association between T2DM and PC risk, and sheds new light on some of the existing knowledge gaps about the causal relationship between the two.
- Causal inference methods revealed different types of association: a non-existent causal link between LSDM and PC risk and an effect of PC on NODM, suggesting a reverse causal sequence, and possibly influenced by weight loss preceding PC.
- The interplay of obesity in the association between LSDM and PC risk is crucial according to causal pathways connecting the diseases, with LSDM likely being an intermediate step in the obesity and PC risk association.

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

- Differences in PC risk by T2DM subtypes and mediating effects by obesity point to a complex multi-pathway mechanism underlying pancreatic carcinogenesis. These mechanisms need to be fully explored to pursue PC prevention efforts in the population.

- Preventing obesity and related risk factors yield to valuable prevention interventions to reduce the burden of PC associated with LSDM.
- Recently diagnosed T2DM patients, i.e., NODM, can be a target group for routine PC screening and surveillance if early signs of PC disease (i.e., weight loss) is present.

Introduction

Pancreatic cancer (PC) has a high case-fatality rate in Western countries,[1] expected to rise in coming years if no immediate actions are taken.[2,3] Many unknowns in PC aetiology remain even regarding some of the well-established risk factors of this disease.[4] This also applies to type 2 diabetes mellitus (T2DM), despite representing an important hallmark for PC prevention given the relatively high PC incidence among T2DM patients.[5] One possible explanation is that observational epidemiological studies are prone to confounding and reverse causality bias, which makes inference about causal factors of PC impossible. Mendelian randomization (MR) overcomes this problem by using genetic variants as instrumental variable (IV) of the risk factor to estimate its causal effect on the outcome.[6,7]

Thus, while a large number of observational studies evidenced that T2DM increases PC risk,[8–10] the actual role of T2MD in pancreas carcinogenesis remains unsolved. These earlier studies have shown that the excess risk increases within the first years since the diagnosis of T2DM, decreasing thereafter and keeping the association with PC risk in the long-term.[9,11] Given this temporal relationship, it is believed that new-onset and long-standing T2DM (NODM and LSDM, respectively) could play a different role in PC aetiology.[8] In the former case, the tumour in the pancreas might induce T2DM development through tissue destruction or paracrine mechanisms. This form of diabetes has been described as pancreatogenic or type 3c.[12] The fact that up to 60-85% of newly diagnosed PC patients present T2DM or hyperglycemia,[12,13] and that T2DM frequently abates after tumour resection,[14] supports that this mechanism underpins PC-related T2DM. In the case of LSDM, however, chronic hyperinsulinemia could trigger PC development.[15] Experimental studies support this hypothesis.[16,17]

Common risk factors such as obesity could explain the association between LSDM and PC risk, but this has not yet been fully explored. Similarly, a common genetic susceptibility between both diseases also needs to be established.[18] Use of antidiabetic medication is another relevant aspect in the association between T2DM and PC risk. Insulin-users, relative to non-users, have a higher PC risk,[11] whereas PC risk lowers among metformin-users.[11,19] It remains to be determined whether this association differs between NODM and LSDM.

While a MR study on the association between T2DM and PC has been published, it only partially addressed the questions posed above.[20] Even though this study supported that T2DM and PC are not causally linked, it did not assess such a relation according to T2DM subgroups.[20] Interestingly, obesity was found to be a causal factor of PC in this study, but whether obesity interacts with T2DM or mediates the association between T2DM and PC risk was also not accounted for.[20] Therefore, whether NODM or LSDM, or both, promote the development of PC, with or without the interplay of obesity, continues to be uncertain. In fact, there have been few attempts to characterize both T2DM subtypes in PC pathogenesis given the likely under-ascertainment of NODM at PC diagnosis.[13] Studies reliably profiling characteristics of both T2DM subtypes are still missing.

The aim of this study was to explore the association between LSDM and NODM and PC risk, based on self-reported data and biomarker measures. To disentangle the causal link behind these associations, we explored through MR the unbiased effect of T2DM-related genetic variants as IV on PC risk and, *vice versa,* the effect of PC-related genetic variants as IV on T2DM risk. Potential mediating and modifying effects between T2DM and BMI on the associations were also explored.

Methods

Study Population: PanGenEU study information is provided in Supplementary Methods and in previous publications.[21] This study was conducted with ethical approvals of all the participating centres and the subject´s written consent to participate.

Data collection: Information about study protocols to collect data on PC risk factors is provided in Supplementary Methods. Nearly all PC cases and controls provided biological samples, among them blood, at enrolment.

Assessment of diabetes status: Participants who responded affirmatively to the question “has a doctor ever told you to have diabetes or elevated glucose levels” were regarded as having diabetes. They were asked further about the age at which they were first informed they had diabetes and about the use of antidiabetic medication: oral medication, insulin, or no-medication but diet. This information was used to derive variables

on diabetes status by time since diagnosis of T2DM (≤2 years, and >2 years since diagnosis to distinguish between NODM and LSDM, respectively), age at diagnosis (<55, 55-65, and ≥65 years) and by use of medication (use of oral medication, insulin, diet). T2DM biomarkers, glycated haemoglobin (Hb1Ac) and C-peptide, were determined in 509 PC cases and 413 controls with available non-fasting erythrocyte and serum samples as described in Supplementary Methods. These data allowed to refine the assessment of diabetes status.

SNP selection and genotyping: Details on the genotyping of the DNA samples in the PanGenEU study are provided in Supplementary Methods. A GWAS database review in the GWAS catalog [22] was performed to identify SNPs associated with T2DM in at least two independent GWAS studies and with a p-value of ≤5x10-5. SNPs with a minor allele frequency (MAF) ≥0.05 in our study population were selected. In addition, SNPs of previous T2DM-PC association studies were also included.[23–25] A total of 57 T2DM-related SNPs were considered. Using the same approach, we selected 40 PC-related SNPs and 125 obesity-related SNPs for the analyses (Supplementary Table 1).

Statistical analysis for the observational association study: There were 2,018 PC cases and 1,540 controls available for assessing the observational association between T2DM and PC risk (Supplementary Figure 1A). Missing data were imputed as described in Supplementary Methods, whereby a high imputation yield was reached (Supplementary Table 2). Multivariate unconditional logistic regression was applied to evaluate the association between T2DM and PC risk by Odds Ratios (ORs) and 95% Confidence Intervals (CI). Models were adjusted for age, sex and country (Model 1), and subsequently for smoking and body mass index (BMI) 2 years before recruitment (Model 2). Effect modification was evaluated by adding interaction terms in the models and comparing them with models lacking this interaction via the likelihood ratio test (LRT). Effect measure modification was further evaluated in stratified analyses by strata of these variables. Dose-response and trend analysis was conducted by fitting a T2DM ordinal score in the logistic models. The dose-response curve was evaluated by applying restricted cubic splines.[26] Interaction by centre but not by country was apparent; therefore, random centre effects in mixed models when appropriate were applied.[27] Further details are provided in Supplementary Methods.

Mediation analysis: As outlined in Supplementary Methods, the counterfactual mediation model for binary mediators and outcomes was used to explore mediation by estimating the natural indirect and direct effect of the associations (NIE and NDE, respectively).[28] We explored whether obesity leading to T2DM, and subsequently to PC, could explain the observational association between T2DM and PC. Similarly, potential mediating effects of body fat measures on the association between T2DM and PC risk were explored.

Mendelian Randomisation Analysis (MR): The causal effect of T2DM subtypes on PC (Supplementary Figure 1 B) was estimated using several MR tests (Wald ratio, 2-stage least squares -TSLS, inverse variance weighted method-IVW, and simple median),[29,30] adjusting estimates for potential confounders. Supplementary Methods detail how the genetic IV for T2DM was built. In addition, the weighted median estimation and the MR-Egger approach were applied to detect and correct bias due to pleiotropy.[29,31,32]

Bidirectional MR: The same procedure was used to explore the causal effect of PC on T2DM (Supplementary Figure 1 C). We kept 33 PC-related SNPs for the analyses after removing SNPs in LD and those associated with other traits (Supplementary Tables 1 and 3). The association of the IV with PC was estimated in non-T2DM individuals, followed by its association with T2DM in all subjects.

MR using pleiotropic genetic variants: Causal assessment of obesity (at two time points: age 50 and 2 years before the interview) and PC was explored considering an IV of 85 obesity-related SNPs (41 SNPs were removed due to LD and pleiotropy: Supplementary Tables 1 and 3). Multivariable MR was used to disentangle further the causal effect of T2DM and obesity on PC using T2DM-SNPs as IV, or PC-SNPs as IV in the opposite direction (Supplementary Figure 1 D and E). The IVW, TSLS, and Egger methods were applied in these analyses.[33,34] To extend the aforementioned mediation analyses, potential mediating effects of obesity or T2DM (mediators) were explored considering separate IVs for the exposure and mediator variables (Supplementary Figure 1 F and G).[35] NIE and NDE were likewise estimated using the counterfactual method.[28]

Sensitivity analyses regarding imputation and other issues are detailed in Supplementary Methods. For instance, we evaluated pleiotropy and unmeasured confounding using several approaches,[31,36,37,38] Results are presented as OR and 95% CI, considering p-values <0.05 as statistically significant. Statistical

analyses were conducted using software R-project (version 3.3.0).[39] Mediation models were fitted with the *paramed* module in Stata version 14.[40]

Results

Baseline characteristics of cases and controls are displayed in Supplementary Table 4. Cases and controls with genetic or biomarker data had similar baseline characteristics (data not shown). By T2DM subtypes, subjects with LSDM were diagnosed with T2DM at younger ages, and were more frequent users of antidiabetic oral medication than subjects with NODM (Supplementary Table 5).

Observational association study: The association between T2DM and PC risk is shown in Table 1. T2DM (*vs* non-T2DM) was associated with a 2.5-fold higher risk of PC (95%CI:2.05;3.05). PC risk was higher for NODM (OR=6.39; 95%CI:4.18;9.78) and notably lower for LSDM (OR=1.86; 95%CI:1.49;2.32). A significant positive trend of the association by time since diagnosis and age at T2DM diagnosis was observed (*p-trend*=6.3E-07). The PC risk nonlinear curve of time since T2DM showed a peak at two years following a gradual decrease of the risk (Supplementary Figure 2). Statistical significance persisted until nearly 30 years since T2DM diagnosis. Regarding T2DM control measure, the insulin use or non-use of oral medication, were both significantly associated with a higher PC risk among diabetic patients (OR=3.69 and 2.94, respectively) compared to non-T2DM. Adjustment for insulin use led to an attenuation of the risk estimates compared to that observed for age, sex and country-adjusted models (Supplementary Table 6). When adjusting for time since T2DM diagnosis, intriguingly, risk estimates turned non-significant, except for NODM (OR=2.64; 95%CI:1.40;4.97) and diabetic patients using insulin (OR=1.61; 95%CI:1.01;2.58). Family history (FH) of T2DM (*vs* no FH) was also associated with a significantly increased PC risk (OR=1.22; 95%CI:1.03;1.48).

When T2DM status was established upon self-reported and Hb1Ac data (Table 2), the prevalence of T2DM increased by 15% among PC cases at the expenses of NODM (from 13% to 26%). Accordingly, the PC risk estimates when considering reclassified T2DM subtypes with biomarker data were OR=4.63 and 1.97 for NODM and LSDM, respectively (Supplementary Table 7). Assessment of T2DM status based on both data was associated with a 3-fold (95%CI:2.21;4.07) higher PC risk, with this risk being mainly driven by

uncontrolled and undiagnosed T2DM (OR=3.58; 95%CI:2.53;5.11). Increasing levels of Hb1Ac were also associated with increased PC risk (per 1-unit increase OR=1.49; 95%CI:1.30;1.70 and ≥6.5 *vs* <5.5 Hb1Ac levels OR=3.99; 95%CI:2.64;6.01, *p-trend*=2E-16), whereas C-Peptide levels were inversely associated with PC risk. Indeed, a remarkable PC risk (OR=8.38; 95%CI:4.71;16.11) was seen for Type 3c-like diabetes (*vs* non-T2DM) when both markers were considered.

Several factors appeared to modify the association between T2DM and PC risk (Table 3). PC risk was considerably higher in diabetic patients with a higher educational degree than in those with lower education attainment (*p-het* by education=0.004), for either T2DM subtype and irrespective of the type of control measure used. There was evidence for effect modification by smoking status, with former smokers with T2DM exhibiting the highest PC risk (*p-het* by smoking=0.03). By gender, there was a significantly increased PC risk in males with FH of T2DM, though not in females (*p-het* by gender=0.007). Estimates were similar across obese and non-obese subjects. Obesity was not associated with PC risk, except in subgroups of men (*p-het* by gender=0.03) (data not shown). There was no indication of effect modification by selected covariates on the association between Hb1Ac and C-Peptide levels and PC risk (data not shown).

By T2DM subtypes, there were differences in risk estimates across the strata of gender, smoking status, educational level and post-50s weight-loss compared to non-T2DM (Table 4). For NODM, PC risk appeared to be higher in men (OR=10.42) than in women (OR=3.73; *p-het* by gender=0.02); in former smokers (OR=11.51) than in never (OR=6.21), or current smokers (OR=3.09; *p-het* by smoking=0.04); and among those who lost weight (OR=13.06) compared to those who did not (OR=4.76, *p-het* by weight loss=0.04). By contrast, in LSDM, a slightly increased PC risk was seen with higher (OR=2.88) *vs* lower educational level (OR=1.49; *p-het* by educational level=0.006). While an interaction could not be established for other diabetes-related variables, risk of PC tended to be higher in NODM treated with insulin or if oral medication was not taken. This trend was less apparent for LSDM. Also, there was a borderline significant interaction effect with BMI in LSDM (Supplementary Table 8). The significance of some of these associations were lost (e.g., weight loss and gender) when the biomarker data were used to reclassify NODM (data not shown). A closer evaluation of the association between T2DM subtypes with PC risk revealed that certain subgroups with NODM (males, insulin users or non-users of oral medication) were more likely to develop PC, whereas

for LSDM this risk pattern differed (e.g., FH of PC, former alcohol drinkers, and insulin users were at higher PC risk) (Supplementary Table 9). There were no significant gender, smoking, body fat measures, or treatment differences between type-3 like NODM, NODM, and LSDM (data not shown).

Mendelian Randomization Analyses: Estimates for the causal association between T2DM and PC risk are shown in Figure 1 and Supplementary Table 10. The genetic score (IV) for T2DM was significantly associated with both NODM (p-value=1.7E-04) and LSDM (*p-value*=1.2E-05). However, the causal association between the IV and PC was not statistically significant for any T2DM subtypes and this finding was consistent when causal estimates were obtained with the MR-Egger regression. In the opposite direction, the PC genetic IV score was associated with PC (*p-value*=9.3E-09) as well as with NODM (p-value=2E-04), though not with LSDM (p-value=0.121). This resulted in a statistically significant causal association between PC and NODM (OR_{TSLS}=2.52; 95%CI:2.18;2.88). However, pleiotropy was present in MR-Egger (Intercept=0.09, *p-value*=0.03) and weighted median regression; these methods did not reach the level of statistical significance. Similar results were observed for the association between PC and Type 3c (OR_{TSLS}=2.29, p-value=0.02) (data not shown). In multivariable MR, using the T2DM-IV to assess causal effects on PC risk, comparable results were observed (Supplementary Table 11). Conversely, estimates were largely affected in the opposite direction, suggesting that PC has causal effects on T2DM risk independent of the potential pleiotropic effects of obesity (OR_{TSLS} =1.58; 95%CI:1.15;2.17), though still not supported by MR-Egger regression. Thus, obesity was likely to drive the observed pleiotropy, despite a causal association with PC risk not being observed (Supplementary Table 12).

Mediation analyses results are shown in Figure 2 and Supplementary Table 13. There was an indication for mediation by overweight/obesity 2 years before recruitment in the T2DM and PC risk association for both NODM and LSDM though in opposite directions. The association between NODM and PC risk was mediated by recent weight loss (NIE=0.55), whereas indirect effects by overweight/obesity were less noticeable in the LSDM-PC risk association. When exploring mediator effects of T2DM, a significant association between several obesity measures and either NODM or LSDM was seen, but the total effect did not reach the statistical significance except for overweight/obesity at age 50. Interestingly, NODM was not an intermediate step in the association between overweight/obesity at age 50 and PC risk, whereas LSDM seemed to be a

potential mediator in this association (NIE=1.04). These causal pathways were confirmed when implementing the use of IVs.

Sensitivity analyses: The overall results were not altered in sensitivity analyses (Supplementary Tables 14 and 15). Asymmetry in the funnel plots confirmed the presence of pleiotropy in the PC-NODM association (Supplementary Table 16; Figure 3), but unmeasured confounding was unlikely (Supplementary Table 17).

Discussion

In this large and standardized case-control study, T2DM was associated with an increased PC risk, with NODM being associated with a higher risk than LSDM. About 34% of PC patients presented with diabetogenic levels of Hb1Ac (>6.5%) at diagnosis, which entails a 3.3-fold increase in PC risk in comparison with normal blood levels. The proportion of undiagnosed T2DM in PC patients was notable (15%), showing the importance of assessing T2DM status with biomarkers at PC diagnosis. This study also showed that PC risk gradually increased from pre-diabetes range levels. A causal association between LSDM and PC risk was not observed in MR, whereas estimates derived from bidirectional analyses suggested a causal effect of PC on NODM risk, though affected by potential pleiotropy. A complex biological interplay between obesity and LSDM or NODM in PC aetiology was confirmed in mediation analyses.

Pre-existing studies based the assessment of T2DM on self-reports, which is prone to misclassification bias given that under-diagnosis of T2DM is likely. In case-control studies on PC, this bias is aggravated in view of the fact that around 30% of PC patients can present undiagnosed T2DM at diagnosis.[41] Moreover, pre-diabetes Hb1Ac levels can represent an important warning sign of subclinical PC, as evidenced in risk prediction models of PC for diabetic patients.[42] In our study, we used information on Hb1Ac and C-Peptide levels to reclassify T2DM status and to explore PC risk from pre-diabetes range levels. By doing so, we assessed more appropriately PC risk associated with T2DM status and Hb1Ac and C-Peptide levels. Only one previous study within the European Prospective Investigation into Cancer and Nutrition cohort (466 PC cases and matched controls) assessed PC risk by Hb1Ac levels.[43] Like us, this study also found that pre-diabetes was associated with an increased PC risk. Chari et al., also showed that elevated T2DM biomarker

levels (e.g., fasting glucose) 2-3 months prior to PC diagnosis were associated with a higher PC risk in a cohort of 848 PC patients.[44]

Our findings on the observational association between T2DM and PC risk are concordant with previous studies. Various meta-analyses have shown that T2DM is associated with an approximately two-fold increased risk of PC (summary RRs ranged from 1.82 to 1.94).[8,10] Also consistent with previous studies, e.g., the Pancreatic Cancer Case Control Consortium (PanC4) including 8,305 cases and 13,987 controls, PC risk differs upon timing of T2DM diagnosis, with T2DM lasting less than 2 years (NODM) posing a greater PC risk than LSDM.[45] Cohort studies using incident T2DM data also support that NODM and LSDM are two distinct entities in PC aetiology.[9,46,47] As reported within the PanC4 study, our study also evidenced differing PC risks in men and women with NODM, with men being at a greater PC risk.[45] However, in our study, this difference turned non-significant when considering reclassified NODM using biomarker data, probably because of lack of statistical power. By type of medication used to control T2DM, we also observed that among diabetic patients, non-use of oral antidiabetic agents or use of insulin conferred a higher PC risk.[45] Nonetheless, our study provides a more thorough assessment of PC risk by T2DM subtypes and reveals remarkable differences between them. For instance, NODM remained positively associated with PC risk irrespective of time since T2DM diagnosis (within a 2-year period) and was related to a more frequent use of insulin. This type of T2DM, if type 3c diabetes, has been previously associated with an earlier insulin treatment initiation due to a faster or more aggressive disease progression by inducing beta-cell dysfunction and insulin resistance, as well as by impairing proinsulin processing.[14,48]

A genetic link between T2DM and PC risk has been explored in three case-control studies, without finding any significantly associated T2DM-related variant with PC risk.[18,23,49] The causal link between both diseases has been previously investigated using MR.[20] Our findings on the absence of a causal association between T2DM and PC risk are in agreement with this study. In contrast, and as a new finding, in our study we performed a bidirectional MR in both T2DM subtypes and established their causal association with PC risk. This approach enabled a more appropriate dissection of the directional association between T2DM and PC. Thereby, we have elucidated that LSDM is not causally linked to PC, whereas PC may cause NODM, if the influencing effects of body weight are ruled out. However, our study does not

support the causal or observational association between BMI and PC risk, possibly due to reverse causation, a common bias in case-control studies, survival-selection bias, or misclassification of obesity.[50,51] Indeed, obesity measures were self-reported by the participants at recruitment. Adipose tissue loss in the early development of PC may explain this lack of association and support reverse causation.[52] In fact, the presence of coexisting PC and NODM has been related to weight loss prior to PC diagnosis.[53] This is also supported by a recent study in mouse models showing that adipose wasting is related to altered exocrine function in early PC.[54] In mediation analyses we could confirm that there is a 'cross-talk' between obesity and T2DM in relation to PC risk. Our findings suggest that weight loss related to NODM are related to the development of PC, whereas LSDM may mediate the association between obesity and PC risk.

Among the limitations of our study there is pleiotropic effects, i.e. genetic confounding, in the association study between PC and NODM, despite we accounted for potential pleiotropic associations in multivariable MR.[33] Thus, pleotropic effects may still have an influence effect on this association. Also, our study may be prone to confounding bias, although the likelihood of unmeasured confounder effects was low according to Evalue estimates. We used one-sample data rather than summarized data due to lack of information on summary statistics for NODM and LSDM in public GWAS databases. Therefore, when MR approaches for summarized data were applied, we accounted for the correlation between the variants associated with the exposure and the outcome. In addition, we provided causal estimates using the T2LS method, which is more convenient for one-sample MR.[32] We considered bidirectional MRA, but this approach also assumes that the causal association occurs in one direction, such that the impact of feedback loops between the exposure and outcome cannot be addressed.[29] Our study only included subjects with European ancestry, which may limit generalizability to other racial/ethnic groups.

The strengths of our study include a relatively large sample size, inclusion of a large number of standardized T2DM-related variables, accounting for biomarker data on Hb1Ac and C-Peptide levels to establish T2DM status, and the use of MR approaches to assess causal effects between T2DM and PC in both potential causal directions. We considered two T2DM subtypes and explored their role in PC aetiology, which was not done before. However, NODM definition was time-based (from self-reports) and misclassification is likely. Indeed, whether all NODM comprise type 3c diabetes cannot be established due to lack of dynamic

biomarkers.[40] However, using C-Peptide data we could better define this subtype and conduct a more proper assessment of PC risk. In addition, there might be other T2DM subtypes involved in this disease. Indeed, one study using medical claims data have identified relevant T2DM subtypes,[55] with possibly different effect measures in PC disease.

In conclusion, while this study confirms the association between T2DM and PC risk, it does not support a causal effect of T2DM on PC development. Our findings suggest that T2DM is likely to be either a consequence of an adverse milieu created during the progressive growth of pancreatic cancer cells in the case of NODM, or a mediator in the causal pathway between obesity and PC in the case of LSDM, rather than a cause of PC. This study also highlights the importance of diabetogenic levels of Hb1Ac not only for a proper classification of T2DM status in PC, but also as a predictor of PC risk. These findings, if confirmed in future studies, may have implications to achieve a breakthrough towards PC prevention.

Acknowledgements:

The authors are thankful to the coordinators, field and administrative workers, technicians and study participants of the European Study into Digestive Illnesses and Genetics (PanGenEU) study.

Funding:

The work was partially supported by Fondo de Investigaciones Sanitarias (FIS), Instituto de Salud Carlos III, Spain (#PI11/01542, #PI0902102, #PI12/01635, #PI12/00815, #PI15/01573); Red Temática de Investigación Cooperativa en Cáncer, Spain (#RD12/0036/0034, #RD12/0036/0050, #RD12/0036/0073); WCR (15-0391); European Cooperation in Science and Technology - COST Action #BM1204: EUPancreas. EU-6FP Integrated Project (#018771-MOLDIAG-PACA), EU-FP7-HEALTH (#259737-CANCERALIA, #256974-EPC-TM-Net); Associazione Italiana Ricerca sul Cancro (12182); Cancer Focus Northern Ireland and Department for Employment and Learning; and ALF (#SLL20130022), Sweden.

Competing interests: None

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Tables

Table 1: Association between diabetes-related variables and PC risk in the PanGenEU study (2,018 cases and 1,540 controls).

Table 2: Association between diabetes status based on biomarker levels and PC risk in the Spanish PanGenEU biomarker study (509 cases and 413 controls).

Table 3: Association between diabetes-related variables and PC risk by gender, educational level, obesity and smoking status in the PanGenEU study (2,018 cases and 1,540 controls).

Table 4: Association between diabetes and PC risk according to T2DM subtypes among different subgroups in the PanGenEU study (2,018 cases and 1,540 controls).

Figures

Figure 1: Forest plot of estimated results (OR and 95%CI) from the observational study and Mendelian randomisation (MR) analysis, conducted among 1,162 cases and 752 controls with epidemiological and genetic data.

The point estimates are represented by a bullet along with the 95% confidence intervals. LSDM and NODM were evaluated in comparison to T2DM-free individuals (1,489 subjects: 851 PC cases and 638 controls), with subjects classified as either NODM (N=136) or LSDM (N=289) being removed, respectively. All estimates were adjusted for age (<55, 55-65, 65-75, ≥75 years), gender, BMI (<25, 25-30, ≥30 kg/m2), smoking (never-smokers and tertiles of pack-years), country and the first five principal components for population ancestries. **A** and **B** refer to the directional association between T2DM and PC risk. The allele score (IV) included 35 T2DM-SNPs. Mr-Egger Intercept: 0.006 (p-value=0.964) and -0.022 (p-value=0.468), for NODM and LSDM, respectively. **C** and **D** refer to the directional association between PC and T2DM risk. The allele score (IV) included 33 PC-SNPs. Mr-Egger Intercept: 0.090 (p-value=0.027) and 0.07 (p-value=0.807), for NODM and LSDM, respectively.

Figure 2: Directed acyclic graphs showing results of causal mediation analyses evaluating mediator effects of obesity or T2DM on the PC risk associations by T2DM subtypes. Results are shown for overweight/obesity assessed 2 years before recruitment for NODM or at age 50 for LSDM. The natural indirect (NIE), direct (NDE) and total effect (TE) of the associations are shown with corresponding ORs [95% CIs]. Estimates are derived from counterfactual models (2,018 cases and 1,540 controls) and IV mediation analyses (1,162 cases and 752 controls with epidemiological and genetic data). **A** and **B** for LSDM or obesity (mediators) in association analyses between obesity or NODM and PC risk, respectively. **C** and **D** for LSDM or overweight/obesity (mediators) in association analyses between overweight/obesity or NODM and PC risk, respectively.

Table 1: Association between diabetes-related variables and PC risk in the PanGenEU study (2,018 cases and 1,540 controls).

	Cases N=2,018		Controls N=1,540			Model 1		Model 2	
	N	%	N	%	*p-value*[1]	OR	[95%CI]	OR	[95%CI]
Diabetes status:					<0.001				
no diabetes	1480	73.30	1342	87.10		Ref.		Ref.	
yes	538	26.70	198	12.90		2.56	[2.10;3.11]	2.50	[2.05;3.05]
Family history of diabetes[2]					<0.001				
no diabetes	1210	65.58	879	72.32		Ref.		Ref.	
yes	635	34.42	371	29.68		1.25	[1.05;1.49]	1.22	[1.03;1.48]
Diabetes by age at diagnosis (years)[3]					<0.001				
no diabetes	1480	73.30	1342	87.10		Ref.		Ref.	
≤ 55 y	162	8.03	82	5.32		1.56	[1.15;2.11]	1.5	[1.11;2.04]
55 to ≤ 65 y	173	8.57	57	3.70		2.68	[1.92;3.73]	2.59	[1.85;3.63]
> 65 y	203	10.10	59	3.83		4.06	[2.94;5.60]	4.06	[2.93;5.62]
					p-trend	2E-16		2E-16	
Diabetes by time since diagnosis (years)[3]					<0.001				
no diabetes	1480	73.30	1342	87.10		Ref.		Ref.	
≤1 y	159	7.88	12	0.78		11.14	[6.09;20.37]	11.28	[6.16;20.68]
1 to ≤2 y	41	2.03	15	0.97		2.64	[1.40;4.97]	2.47	[1.31;4.66]
2 to ≤5 y	72	3.57	32	2.08		2.40	[1.54;3.73]	2.35	[1.50;3.68]
5 to ≤10 y	125	6.19	41	2.66		2.67	[1.81;3.93]	2.60	[1.76;3.84]
10 to ≤20 y	89	4.41	53	3.44		1.59	[1.09;2.32]	1.57	[1.07;2.30]
>20 y	52	2.58	45	2.92		1.19	[0.76;1.85]	1.16	[0.74;1.81]
					p-trend	9.6E-08		6.3E-07	
Diabetes status by subtype					<0.001				
no diabetes	1480	73.30	1342	87.10		Ref.		Ref.	
yes, ≤ 2 years (NODM)	200	9.91	27	1.75		6.49	[4.25;9.90]	6.39	[4.18;9.78]
yes, > 2 years (LSDM)	338	16.70	171	11.10		1.90	[1.53;2.37]	1.86	[1.49;2.32]
Diabetes control measures									
Diet					<0.001				
no diabetes	1480	73.30	1342	87.10		Ref.		Ref.	
yes	420	20.80	149	9.68		2.60	[2.09;3.24]	2.53	[2.03;3.16]
no use	118	5.85	49	3.18		2.43	[1.69;3.49]	2.40	[1.67;3.46]
Use of oral medication					<0.001				
no diabetes	1480	73.30	1342	87.10		Ref.		Ref.	
yes	398	19.70	148	9.61		2.41	[1.93;3.00]	2.35	[1.88;2.95]
no use	140	6.94	50	3.25		3.01	[2.13;4.26]	2.94	[2.07;4.17]
Use of insulin					<0.001				
no diabetes	1480	73.30	1342	87.10		Ref.		Ref.	
yes	343	17.00	79	5.13		3.76	[2.85;4.95]	3.69	[2.80;4.86]
no use	195	9.66	119	7.73		1.77	[1.37;2.29]	1.72	[1.33;2.23]

[1] Differences between groups evaluated by the Chi-square test.
[2] Information on family history of diabetes was not collected in Ireland; results are based on data for 1,845 cases and 1,250 controls.
[3] Linear association for age since T2DM diagnosis and nonlinear association for time since T2DM (Supplementary Figure 1)
Model 1: adjusted for age (<55, 55-65, 65-75, ≥75 years), gender, country.
Model 2: Model 1 also adjusted for pack years (never-smokers and tertiles of pack-years) and BMI (<25, 25-30, ≥30 kg/m^2).

Table 2: Association between diabetes status based on biomarker levels and PC risk in the Spanish PanGenEU biomarker study (509 cases and 413 controls).

	Cases		Controls						
	N=509		N=413			Model 1		Model2	
	P50	IQR	P50	IQR	*p-value*[1]	OR	[95%CI]	OR	[95%CI]
HbA1c (%)[2] per 1 unit increase	6.1	5.6;6.9	5.6	5.4;6.0	<0.001	1.50	[1.31;1.71]	1.49	[1.30;1.70]
C-Peptide (µg/L)[2] per log2 increase	2.3	1.4;3.7	4.2	2.5;6.4	<0.001	0.46	[0.39;0.54]	0.46	[0.39;0.53]
	N	**%**	**N**	**%**					
Diabetogenic status by HbA1c levels					<0.001				
HbA1c <6.5%	336	66.00	354	85.70		Ref.		Ref.	
HbA1c ≥6.5%	173	34.00	59	14.30		3.29	[2.34;4.62]	3.27	[2.32;4.60]
Biomarker and self-reported diabetes status					<0.001				
no diabetes	286	56.20	322	78.00		Ref.		Ref.	
self-reported but normal Hb1Ac (<6.5%)	50	9.80	32	7.70		1.90	[1.18;3.10]	1.92	[1.19;3.13]
self-reported and HbA1c ≥6.5%	173	34.00	59	14.30		3.59	[2.55;5.11]	3.58	[2.53;5.11]
Reclassified diabetes status					<0.001				
no diabetes	286	56.20	322	78.00		Ref.		Ref.	
self-reported and/or HbA1c ≥6.5%	223	43.80	91	22.00		2.99	[2.21;4.06]	2.99	[2.21;4.07]
Reclassified diabetes status by subtype[3]									
no diabetes	286	56.20	322	78.00		Ref.		Ref.	
NODM	130	25.50	34	8.20		4.63	[3.08;7.12]	4.63	[3.07;7.15]
LSDM	93	18.30	57	13.80		1.98	[1.35;2.90]	1.97	[1.35;2.90]
Biomarker Hb1Ac levels					<0.001				
<5.5%	100	19.60	129	31.20		Ref.		Ref.	
5.5-5.8%	72	14.10	121	29.30		0.71	[0.47;1.06]	0.71	[0.47;1.06]
5.8-6.0%	50	9.90	51	12.50		1.26	[0.78;2.04]	1.23	[0.76;1.99]
6.0-6.5%	114	22.40	53	13.00		2.75	[1.80;4.24]	2.72	[1.77;4.17]
≥6.5%	173	34.00	59	14.00		4.03	[2.69;6.08]	3.99	[2.64;6.01]
					p-trend	2E-16		2E-16	
Reclassified NODM into type 3c-like diabetes[4]					<0.001				
no diabetes	286	56.20	322	77.97		Ref.		Ref.	
NODM and C-Peptide >4.2 µg/L	37	7.20	21	5.08		2.30	[1.31;4.13]	2.28	[1.30;4.10]
NODM and C-Peptide <4.2 µg/L (T3c)	93	18.30	13	3.15		8.31	[4.69;15.93]	8.38	[4.71;16.11]
LSDM	93	18.30	57	13.80		1.99	[1.36;2.92]	1.98	[1.35;2.92]

[1] Differences between groups evaluated by the Chi-square test (categorical variables) and Mann-Whitney test (continuous variables).
[2] Linear association for Hb1Ac and non-linear for C-Peptide levels (Supplementary Figure 1).
[3] NODM and LSDM was classified with questionnaire and Hb1Ac biomarker data in the biomarker study population. NODM and LSDM assessment based on questionnaire data only or with
[4] NODM based on self-reported and Hb1Ac biomarker data was additionally reclassified into NODM and type 3c-like diabetes (T3C) with C-peptide biomarker data.
Hb1Ac data in PanGenEU-Spain and PanGenEU is shown in Supplementary Table 6.
Model 1: adjusted for age (<55, 55-65, 65-75, ≥75 years), sex and center (Spain) or country.
Model 2: Model 1 also adjusted for pack years (never-smokers and tertiles of pack-years) and BMI (<25, 25-30, ≥30 kg/m2).

Table 3: Association between diabetes-related variables and PC risk by gender, educational level, obesity and smoking status in the PanGenEU study (2,018 cases and 1,540 controls).

	Gender[1]				Educational level				Obese[1,2]				Smoking status[1]					
	Females (N=1,578)		Males (N=1,980)		<5-9 years (N=1,405)		≥10 years (N=2,153)		No (N=2,872)		Yes (N=686)		Never (N=1,451)		Former (N=1,246)		Current (N=861)	
	OR	**[95%CI]**	**OR**	**[95%CI]**	**OR**	**[95%CI]**	**OR**	**[95%CI]**	**OR**	**[95%CI]**	**OR**	**[95%CI]**	**OR**	**[95%CI]**	**OR**	**[95%CI]**	**OR**	**[95%CI]**
Diabetes status by subtype																		
no diabetes	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
yes, ≤ 2 years (NODM)	3.67	[2.05;6.58]	10.35	[5.44;19.67]	4.22	[2.38;7.49]	9.54	[5.01;18.16]	6.84	[4.14;11.3]	5.12	[2.28;11.49]	6.07	[3.17;11.89]	11.66	[5.21;26.08]	3.08	[1.44;6.61]
yes, > 2 years (LSDM)	1.71	[1.19;2.46]	2.03	[1.54;2.67]	1.39	[1.02;1.89]	2.64	[1.92;3.62]	1.66	[1.29;2.15]	2.36	[1.52;3.67]	1.58	[1.12;2.21]	2.58	[1.80;3.70]	1.49	[0.90;2.45]
p-value for interaction				*0.078*				*0.004*				*0.310*				*0.028*		
FH of diabetes[3]																		
no	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
yes	0.93	[0.72;1.21]	1.50	[1.19;1.89]	1.22	[0.95;1.58]	1.23	[0.97;1.56]	1.31	[1.08;1.59]	0.95	[0.64;1.39]	1.03	[0.78;1.34]	1.59	[1.19;2.15]	1.19	[0.83;1.70]
p-value for interaction				*0.007*				*0.971*				*0.263*				*0.070*		
Diabetes by age at diagnosis																		
no diabetes	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
≤ 55 y	1.53	[0.88;2.62]	1.53	[1.06;2.21]	1.03	[0.65;1.63]	2.06	[1.37;3.11]	1.35	[0.95;1.92]	1.97	[1.05;3.65]	1.29	[0.75;2.20]	2.23	[1.35;3.67]	1.22	[0.88;1.68]
55 to ≤ 65 y	2.14	[1.24;3.83]	2.99	[1.98;4.50]	1.42	[0.88;2.28]	4.55	[2.80;7.39]	2.47	[1.66;3.69]	2.72	[1.44;5.12]	1.69	[1.00;2.87]	4.01	[2.30;7.01]	2.78	[1.32;5.85]
> 65 y	2.62	[1.69;4.06]	6.57	[4.00;10.81]	3.05	[2.02;4.60]	6.27	[3.62;10.86]	3.93	[2.71;5.71]	4.25	[2.17;8.32]	3.43	[2.20;5.36]	5.11	[3.00;8.70]	4.92	[1.59;15.23]
p-value for interaction				*0.073*				*4.7E-4*				*0.682*				*0.115*		
Diabetes controlled with diet																		
no diabetes	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
yes	2.13	[1.51;2.92]	2.91	[2.18;3.89]	1.86	[1.38;2.55]	3.48	[2.55;4.76]	2.38	[1.85;3.07]	2.87	[1.81;4.52]	2.05	[1.46;2.82]	3.76	[2.62;5.39]	2.00	[1.21;3.3]
no	2.37	[1.24;4.39]	2.52	[1.61;3.94]	1.61	[1.01;2.59]	4.08	[2.27;7.35]	2.27	[1.47;3.49]	2.7	[1.35;5.38]	2.52	[1.43;4.44]	2.85	[1.51;5.39]	1.62	[0.8;3.28]
p-value for interaction				*0.419*				*0.002*				*0.669*				*0.054*		
Diabetes and oral medication																		
no diabetes	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
yes	2.14	[1.5;3.01]	2.54	[1.96;3.40]	1.64	[1.23;2.23]	3.51	[2.52;4.88]	2.27	[1.75;2.96]	2.47	[1.6;3.81]	1.72	[1.23;2.42]	3.69	[2.52;5.42]	2.06	[1.25;3.42]
no	2.25	[1.25;3.87]	3.60	[2.31;5.63]	2.31	[1.40;3.80]	3.82	[2.34;6.23]	2.56	[1.74;3.77]	4.7	[2.04;10.82]	4.36	[2.33;8.16]	3.27	[1.93;5.55]	1.51	[0.75;3.05]
p-value for interaction				*0.496*				*0.003*				*0.354*				*0.005*		
Diabetes and insulin																		
no diabetes	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
yes	3.24	[2.05;5.14]	3.95	[2.79;5.60]	2.92	[1.97;4.34]	4.56	[3.1;6.71]	3.42	[2.5;4.67]	4.62	[2.51;8.49]	3.42	[2.24;5.33]	4.66	[3;7.25]	2.64	[1.45;4.81]
no	1.51	[1.01;2.25]	1.99	[1.42;2.78]	1.17	[0.82;1.67]	2.78	[1.89;4.08]	1.58	[1.16;2.15]	1.98	[1.21;3.23]	1.45	[0.98;2.14]	2.64	[1.7;4.09]	1.34	[0.77;2.35]
p-value for interaction				*0.723*				*0.003*				*0.498*				*0.094*		

[1] Odds ratios (ORs) adjusted for age (<55, 55-65, 65-75, ≥75 years), gender, country, pack years (never-smokers and tertiles of pack-years) and BMI (<25, 25-30, ≥30 kg/m^2) (Model 2), except: sex in analyses stratified by sex, BMI in analyses stratified by obesity and pack-years in analyses stratified by smoking status.
[2] Obesity status defined based on BMI 2 years before recruitment.
[3] Information on family history (FH) of diabetes was not collected in Ireland; results based on data for 1,845 cases and 1,250 controls.

Table 4: Association between diabetes and PC risk according to T2DM subtypes among different subgroups in the PanGenEU study (2,018 cases and 1,540 controls).

	No diabetes (Ref.)	NODM		LSDM	
	Cases;Controls	Cases;Controls	OR[1] [95%CI]	Cases;Controls	OR[1] [95%CI]
Gender					
females	691;624	67;16	3.73 [2.13;6.86]	115;65	1.75 [1.22;2.51]
males	789;718	133;11	10.42 [5.74;20.89]	223;106	2.03 [1.54;2.68]
p-value for interaction		0.0213		0.5704	
Obese[2]					
<30 kg/m^2	1228;1094	154;19	6.91 [4.29;11.74]	244;129	1.76 [1.36;2.27]
≥30 kg/m^2	252;248	46;8	5.01 [2.34;12.04]	94;42	2.37 [1.53;3.71]
p-value for interaction		0.5862		0.2048	
Smoking status					
never	573;601	67;11	6.21 [3.3;12.79]	120;79	1.58 [1.13;2.23]
former	457;494	87;7	11.51 [5.5;28.17]	139;62	2.55 [1.79;3.67]
current	450;247	46;9	3.09 [1.49;7.04]	79;30	1.52 [0.93;2.53]
p-value for interaction		0.0418		0.0699	
Family history diabetes[3]					
no	1063;1009	105;12	6.66 [3.68;13.10]	162;90	1.61 [1.19;2.19]
yes	417;333	95;15	6.07 [3.49;11.26]	176;81	2.12 [1.52;2.96]
p-value for interaction		0.8253		0.1825	
Diabetes controlled with diet					
yes	0	156;18	7.31 [4.51;12.55]	264;131	1.89 [1.49;2.42]
no	0	44;9	4.61 [2.28;10.32]	74;40	1.89 [1.25;2.88]
p-value for interaction		NA		NA	
Diabetes with oral medication					
yes	0	120;19	4.63 [2.83;7.94]	278;129	2.03 [1.59;2.59]
no	0	80;8	10.71 [5.42;24.37]	60;42	1.48 [0.97;2.27]
p-value for interaction		NA		NA	
Diabetes with insulin					
yes	0	123;6	16.97 [7.98;43.91]	220;73	2.60 [1.93;3.52]
no	0	77;21	3.45 [2.12;5.85]	118;98	1.36 [1.01;1.83]
p-value for interaction		NA		NA	
Diabetes by age at diagnosis					
≤ 55 y	0	32;5	4.47 [1.78;13.65]	128;75	1.39 [1.01;1.91]
55 to ≤ 65 y	0	56;7	6.47 [3.03;16.01]	121;52	2.13 [1.47;3.11]
> 65 y	0	112;15	7.02 [4.11;12.82]	89;44	2.60 [1.76;3.80]
p-value for interaction		NA		NA	
Educational level					
<5 y	230;132	39;5	5.54 [2.21;16.87]	74;40	1.49 [0.92;2.44]
6 to 9 y	353;328	55;11	3.82 [1.94;8.11]	78;60	1.35 [0.89;2.04]
10 to 13 y	517;456	61;8	6.9 [3.35;16.14]	120;44	2.56 [1.70;3.90]
≥14 y	380;426	45;3	16.34 [5.75;68.71]	66;27	2.88 [1.76;4.79]
p-value for interaction		0.1533		0.0059	
Weight loss since age 50					
yes	486;390	65;6	13.06 [6.05;34.11]	121;55	2.23 [1.61;3.11]
no	994;952	135;21	4.76 [2.59;9.37]	217;116	1.67 [1.15;2.45]
p-value for interaction		0.0441		0.2868	

[1] Odds ratios (ORs) adjusted for age (<55, 55-65, 65-75, ≥75 years), gender, country, pack years (never-smokers and tertiles of pack-years) and BMI (<25, 25-30, ≥30 kg/m^2), except: sex in analyses stratified by sex, BMI in analyses stratified by obesity and pack-years in analyses stratified by smoking status.

[2] Obesity status defined based on BMI 2 years before recruitment.

[3] Information on family history (FH) of diabetes was not collected in Ireland; results based on data for 1,845 cases and 1,250 controls.

Figure 1

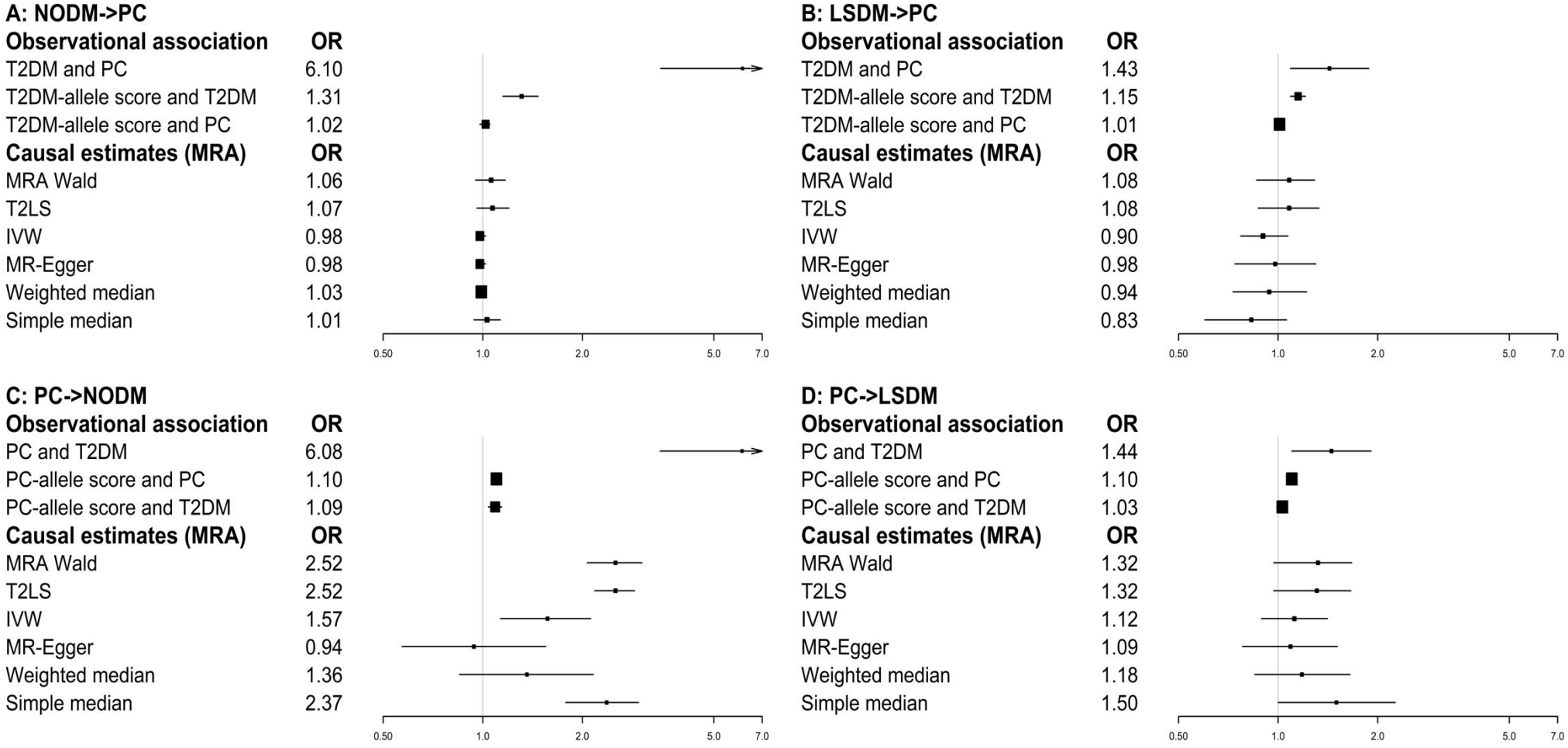
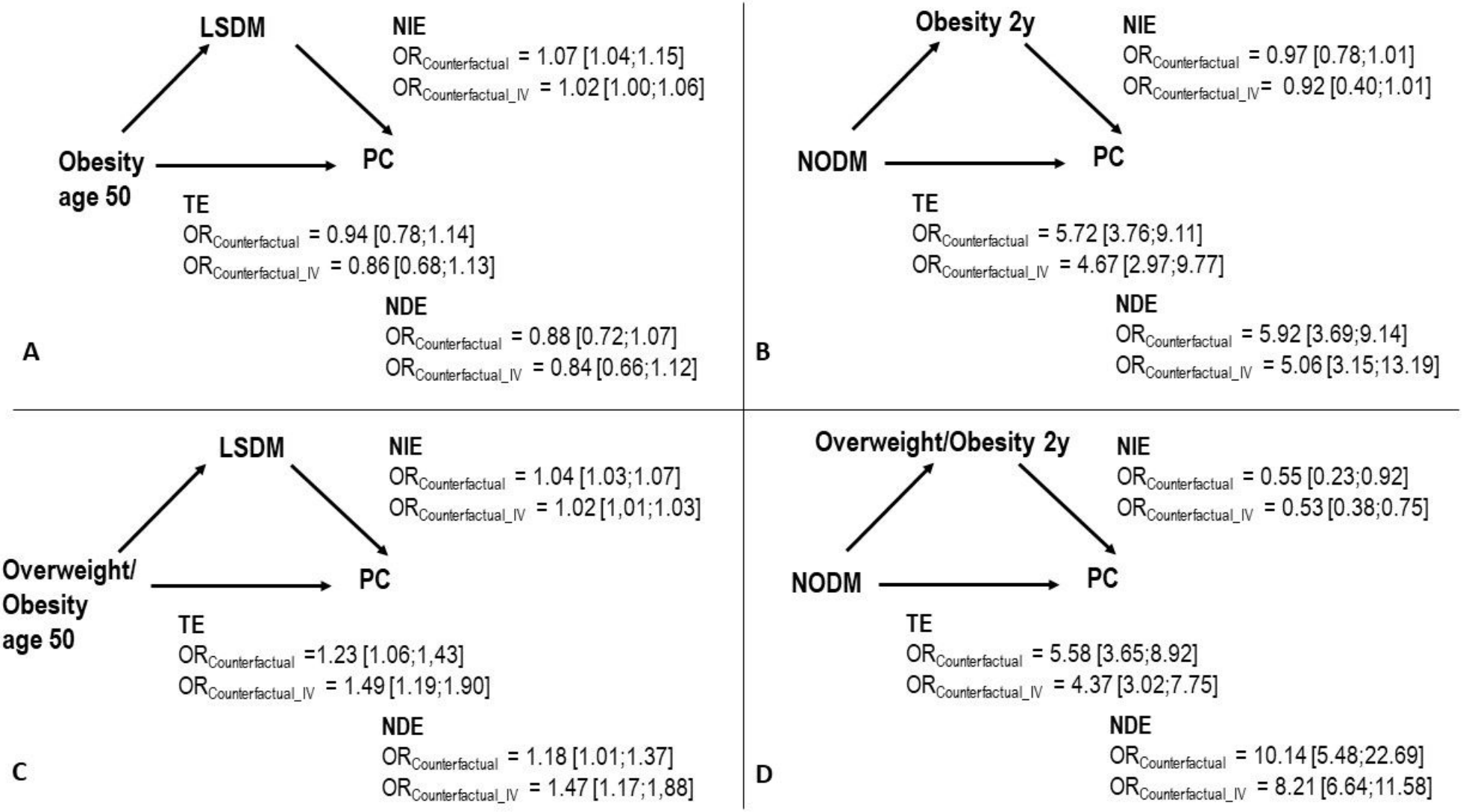

A: NODM->PC
Observational association OR
T2DM and PC 6.10
T2DM-allele score and T2DM 1.31
T2DM-allele score and PC 1.02
Causal estimates (MRA) OR
MRA Wald 1.06
T2LS 1.07
IVW 0.98
MR-Egger 0.98
Weighted median 1.03
Simple median 1.01
0.50 1.0 2.0 5.0 7.0
B: LSDM->PC
Observational association OR
T2DM and PC 1.43
T2DM-allele score and T2DM 1.15
T2DM-allele score and PC 1.01
Causal estimates (MRA) OR
MRA Wald 1.08
T2LS 1.08
IVW 0.90
MR-Egger 0.98
Weighted median 0.94
Simple median 0.83
0.50 1.0 2.0 5.0 7.0
C: PC->NODM
Observational association OR
PC and T2DM 6.08
PC-allele score and PC 1.10
PC-allele score and T2DM 1.09
Causal estimates (MRA) OR
MRA Wald 2.52
T2LS 2.52
IVW 1.57
MR-Egger 0.94
Weighted median 1.36
Simple median 2.37
0.50 1.0 2.0 5.0 7.0
D: PC->LSDM
Observational association OR
PC and T2DM 1.44
PC-allele score and PC 1.10
PC-allele score and T2DM 1.03
Causal estimates (MRA) OR
MRA Wald 1.32
T2LS 1.32
IVW 1.12
MR-Egger 1.09
Weighted median 1.18
Simple median 1.50
0.50 1.0 2.0 5.0 7.0

Figure 2


LSDM
Obesity age 50
PC
NIE
OR Counterfactual = 1.07 [1.04;1.15]
OR Counterfactual_IV = 1.02 [1.00;1.06]
TE
OR Counterfactual = 0.94 [0.78;1.14]
OR Counterfactual_IV = 0.86 [0.68;1.13]
NDE
OR Counterfactual = 0.88 [0.72;1.07]
OR Counterfactual_IV = 0.84 [0.66;1.12]
A
Obesity 2y
NODM
PC
NIE
OR Counterfactual = 0.97 [0.78;1.01]
OR Counterfactual_IV = 0.92 [0.40;1.01]
TE
OR Counterfactual = 5.72 [3.76;9.11]
OR Counterfactual_IV = 4.67 [2.97;9.77]
NDE
OR Counterfactual = 5.92 [3.69;9.14]
OR Counterfactual_IV = 5.06 [3.15;13.19]
B
LSDM
Overweight/ Obesity age 50
PC
NIE
OR Counterfactual = 1.04 [1.03;1.07]
OR Counterfactual_IV = 1.02 [1,01;1.03]
TE
OR Counterfactual =1.23 [1.06;1,43]
OR Counterfactual_IV = 1.49 [1.19;1.90]
NDE
OR Counterfactual = 1.18 [1.01;1.37]
OR Counterfactual_IV = 1.47 [1.17;1,88]
C
Overweight/Obesity 2y
NODM
PC
NIE
OR Counterfactual = 0.55 [0.23;0.92]
OR Counterfactual_IV = 0.53 [0.38;0.75]
TE
OR Counterfactual = 5.58 [3.65;8.92]
OR Counterfactual_IV = 4.37 [3.02;7.75]
NDE
OR Counterfactual = 10.14 [5.48;22.69]
OR Counterfactual_IV = 8.21 [6.64;11.58]
D

Deciphering the complex interplay between pancreatic cancer, diabetes mellitus subtypes, and obesity/BMI through causal inference and mediation analyses. Molina-Montes E et al.

Supplementary material

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Supplementary Methods

Study population: PanGenEU (the European Study into Digestive Illnesses and Genetics) is a mostly hospital-based case-control study of PC conducted in six European countries (Spain, Germany, Ireland, United Kingdom, Italy and Sweden) and 28 centers, designed to evaluate environmental and genetic factors associated with PC. Recruitment of PC cases and corresponding controls matched by region, sex and age (± 10 years) took place from 2007 to 2014 in all participating centers, except in those from Italy were only cases were ascertained. Inclusion criteria were cases diagnosed or suspected of having PC, who had lived in one of the study areas and aged older than 18 years. All medical records were reviewed to ensure the PC diagnosis for study entry. Participants incapable of participating in the study due to impairment of physical ability were excluded. Response rates varied by center and were on average 76% among cases and 85% among controls.

Data collection: A standardized epidemiological questionnaire including self-reported socio-demographic and anthropometric data (location of body fat, height and weight at different ages: age 20 and 50 years, 2 years before recruitment and at PC diagnosis), the likely fat accumulation zone (abdominal, hips, all equally, no extra weight gain), family history of cancer including PC, medical history (e.g., chronic pancreatitis, diabetes and others) including regular use of specific medication, and lifestyle behaviors (e.g., smoking and alcohol habits) was administered by trained personnel in a face-to-face interview. This information was used as input to generate other variables such as body mass index (BMI: weight in kg / height in m^2: <25, 25-30, ≥30 kg/m^2) at different ages (20, 50 and two years before recruitment). Weight gain (> 5 or 10 kg) between young and old adulthood (20 and 50 years, respectively), and weight loss since age 50 until two years before recruitment, was also derived (younger than 50 years, yes weight gain/loss, no weight gain/loss).

T2DM biomarker assays: Non-fasting erythrocyte and serum samples collected at subject recruitment and stored at -80ºC from 509 PC cases and 413 controls of the Spanish PanGenEU study were analysed blinded to the disease status. All individuals had epidemiological information; 356 cases and 298 controls also participated in the genetic study. Glycated haemoglobin or Hb1Ac (as percentage of haemoglobin and mmol/mol) was measured with an automated HPLC analyzer (Menarini Diagnostics, Spain) at the Hospital 12 de Octubre, Madrid (Spain). Mean intra-batch and inter-batch coefficients of variations were 0.42% and 8.46%, respectively. Diabetes status based on Hb1Ac data was established for values above 6.5%. Undiagnosed T2DM, most likely NODM, was identified on this basis. Other predefined levels of Hb1Ac were considered to distinguish between prediabetes (≥6% and <6.5%) and non-diabetes (<6%). Furthermore, undiagnosed or uncontrolled T2DM (Hb1Ac≥6.5%), or HbA1c levels <6.5% but self-reported T2DM diagnosis, i.e., controlled T2DM patients, were considered in separate categories. C-peptide was measured at University Hospital Giessen and Marburg using a Cobas e411 (Roche Diagnostics, Mannheim, Germany) by means of Electro-chemiluminescence immune assay. Coefficients of variations were <5%. Type 3c-like diabetes was defined as NODM with C-peptide levels below the median (4.2 µg/L in controls).

SNP selection and genotyping: Consistent quality SNP data was available for 1,162 cases and 540 controls who provided blood samples. DNA samples were genotyped on the Infinium OncoArray-500K at the CEGEN (Spanish National Cancer Research Centre, CNIO). The genotype data was filtered for call rate, relatedness, European ancestry <80% and sex chromosome abnormalities. Overall, 451,883 SNPs passed these quality filters and underwent imputation of missing genotypes using IMPUTE v2. The control group was enlarged with 212 controls participating in two Spanish bladder cancer case-control studies (EPICURO and ISBlaC), with analogous characteristics to the source population (Spanish PC cases; 44% females and mean age=64.7 years) and with genotype and epidemiological data available. Similar protocols for data collection and genotyping were used in all studies. Genotype distributions of each SNP and deviation from Hardy-Weinberg equilibrium were assessed separately in each of the geographical areas. Principal components to control for population stratification were calculated with the *prcomp* function in *R*.

Imputation: Missing data (9.8% in the dataset containing 63 variables with predictors to improve the imputation performance), assumed to be at random, was substituted by the *random forest* (RF) imputation algorithm. RF tress (n=100) trained on the observed values of the data set predicted the missing values of the data. The out-of-bag error (OOB) was considered as a measure of the imputation error. A further test of imputation performance consisted of comparing observed imputed values *versus* the expected values (% of concordance) in a test set resembling the pattern of missingness of the original data. Mean OOB error (0.05) and concordance estimates (92.5%) demonstrated good imputation performance (Supplementary Table 2).

Statistical analysis for the observational association study: There were 2,018 PC cases and 1,540 controls available for assessing the observational association between T2DM and PC risk (Supplementary Figure 1A). Descriptive statistics by case-control status were performed, evaluating differences between the groups via Pearson chi-square and Student's t-test or Mann-Whitney test, where appropriate. Multivariate unconditional logistic regression was applied to evaluate the association between T2DM and PC risk by Odds Ratios (ORs) and 95% Confidence Intervals (CIs). The influence of smoking, obesity (BMI variables), alcohol status, asthma and/or allergies, educational level, and family history of PC, was evaluated in age, sex and country-adjusted models (Model 1), whereby only smoking (non-smokers and smokers in tertiles of pack-years) proved to be a confounder (>10% change of the risk estimators). The lowest Akaike´s Information Criterion value was reached by further including BMI 2 years before recruitment (normal weight/overweight/obese) (Model 2).
Effect modification by country, center, age, gender, smoking and alcohol status, and BMI variables was evaluated by adding interaction terms in the models, and comparing them with models lacking this interaction (likelihood ratio test, LHR). Effect measure modification was further evaluated in stratified analyses by subgroups of these variables.
Dose-response and trend analysis was conducted by fitting the categorized variables (time since T2DM, age at T2DM diagnosis and Hb1Ac levels) as an ordinal score in the logistic models. The dose-response curve was evaluated by applying restricted cubic splines (3 knots at the 10%, 50% and 90% percentile).[24] Linearity tests were performed by comparing via the LHR test the continuous variable models as nonlinear or as linear. Interaction by centre but not by country was apparent; therefore, random centre effects in mixed models when appropriate were applied.[25]

Mediation analysis: The counterfactual mediation model for binary mediators and outcomes was used to explore mediation effects on the associations.[26] We explored whether obesity leading to T2DM, and subsequently to PC, could explain the observational association between T2DM and PC. With this method, we estimated the total effect (TE) of obesity on PC by determining a natural direct effect (NDE) of obesity on PC and a natural indirect effect (NIE) of obesity on T2DM accounting by the influence of confounders. Standard errors were generated using Monte Carlo bootstrapping with 1,000 replications. Similarly, potential mediating effects of obesity on the association between T2DM and PC risk were explored.

Mendelian Randomization Analysis (MRA): The causal effect of T2DM subtypes on PC (Supplementary Figure 1 B) was estimated using several MRA approaches (Wald ratio, 2-stage least squares -TSLS, inverse variance weighted method-IVW, and simple median),[27] adjusting estimates for the aforementioned potential confounders. Some of these methods were applied via the *MendelianRandomization* R package.[28] A total of 16 variants in high LD (R^2>0.8) were removed for these analyses (Supplementary Table 1). Since genetic variants for T2DM can be confounded by BMI effects due to sharing of variants (i.e., pleiotropy), we tested for the association between the variants and BMI, as well as other confounders, and removed those variants showing an association with other traits (Supplementary Table 3). After removing them, 35 T2DM-SNPs remained to build the IV. The genetic association of this IV with T2DM was estimated in controls only, and subsequently with PC in the case-control setting. Logistic regression models adjusted for age, sex and five principal components to control for population stratification were used to assess the per allele effect of each SNP and of the genetic score. In addition, the weighted median estimation and the MR-Egger approach were applied to detect and correct bias due to pleiotropy.[27,29,30] The weighted median estimator reflects the median of the distribution of weighted Wald ratio estimates. This test is less sensitive to the influence of pleiotropic variants since less weight is given to outlying estimates.[29,30] The MR-Egger approach performs a weighted linear regression of the genetic associations with the outcome on the genetic associations with the exposure, while keeping the intercept unconstrained. This test provides evidence for directional pleiotropy when the intercept differs from zero.[29]

Bidirectional MRA: The same procedure was used to explore the causal effect of PC on T2DM (Supplementary Figure 1 C). We kept 33 PC-related SNPs for the analyses after removing SNPs in LD and those associated with other traits (Supplementary Tables 1 and 3). The association of the IV with PC was estimated in non-T2DM, followed by its association with T2DM in all subjects.

MRA using pleiotropic genetic variants: Causal assessment of obesity (at age 50 and 2 years before the interview) and PC was explored considering 85 obesity-related SNPs (41 SNPs were removed due to LD and associations with other traits: Supplementary Tables 1 and 3). Multivariable MRA was used to disentangle further the causal effect of T2DM and obesity on PC using T2DM-SNPs as IV (Supplementary Figure 1 D), or PC-SNPs as IV in the opposite direction (Supplementary Figure 1 E). The IVW, TSLS and Egger methods were applied in these analyses.[31,32] In line with the aforementioned mediation analyses, we explored potential mediating effects of obesity or T2DM (mediators) using separate IVs (Supplementary Figure 1 F and G).[33] Direct and indirect effects were estimated using the counterfactual method.[26]

Sensitivity analyses: We compared estimates from the unimputed and imputed data to assess the robustness of the results. Although heterogeneity by country was absent, we evaluated the consistency of the results across countries by removing each country at a time from the analyses. This was particularly relevant for PC cases from Italy due to the lack of matched controls. Sensitivity analyses also comprised the assessment of T2DM status based on questionnaire, i.e. self-reported (SR) data, or biomarker data in different study settings. In MRA, to further detect potential pleiotropic variants, we also removed SNPs that were outliers based on Cook´s distances and removed additional variants potentially associated with other phenotypes.[29] The latter were identified in publicly available data from GWAS studies (PhenoScanner database).[34] The MR-base platform was also used to inspect the presence of pleiotropy. For instance, scatter plots of the gene-outcome and gene-exposure associations and for the SNP risk increase against the strength of instrumental SNPs were constructed, along with leave-one out analyses funnel plots for visual assessment of pleitropy.[35] In addition, since unmeasured confounding is a major concern of causal inference in observational studies, we tested by estimating the E-Value how strong such confounders would have to be related to the exposure and the outcome to explain away the observed association.[36] High E-Values reflect less impact of these confounders on the observed associations.

Results were comparable to those seen in analyses of the original data, regarding the use of unimputed missing data (Supplementary Tables 14), country-specific data (data not shown), reclassified T2DM status with biomarker data (e.g., Supplementary Table 15), and in analyses of the influence of pleiotropic effects in MRA (Supplementary Table 16 and Supplementary Figure 3). The E-value for the causal effect between NODM or LSDM with PC risk (E-value = 12.29 and 3.12, respectively) suggested that unmeasured confounders are unlikely to explain away the effect of the observed association, especially with regard to NODM (Supplementary Table 17).

Supplemental Table 1: Selected genetic variants of T2DM, PC, and obesity.

	T2DM			PC			Obesity		
ID	SNP	Chr	Position	SNP	Chr	Position	SNP	Chr	Position
1	rs2641348	1	120437884	rs13303010	1	894573	rs11208659	1	65979280
2	rs340874	1	214159256	rs1747924	1	64538961	rs3101336	1	72751185
3	rs13414140	2	43671176	rs351365	1	113046395	rs2568958	1	72765116
4	rs243021	2	60584819	rs10919791	1	199965168	rs7531118	1	72837239
5	rs2943641	2	227093745	rs2816938	1	199985368	rs1993709	1	72838529
6	rs780094	2	27741237	rs3790844	1	200007432	rs1514177	1	74991402
7	rs1801282	3	12393125	rs962856	2	67593803	rs1514174	1	74993063
8	rs1470579	3	185529080	rs1486134	2	67639769	rs17381664	1	78048331
9	rs4402960	3	185511687	rs12478462	2	153654720	rs12408810	1	106640943
10	rs11708067	3	123065778	rs9854771	3	189508471	rs17024258	1	110147321
11	rs2877716	3	123094451	rs6537481	4	148396094	rs633715	1	177852580
12	rs4411878	3	64703665	rs2736098	5	1294086	rs12130212	1	209727257
13	rs6802898	3	12391207	rs35226131	5	1295373	rs2605100	1	219644224
14	rs10012946	4	6293350	rs401681	5	1322087	rs6429082	1	235600129
15	rs7708285	5	76425867	rs31490	5	1344458	rs12145833	1	243483754
16	rs9472138	6	43811762	rs17688601	7	40866663	rs6711012	2	624034
17	rs1535500	6	39284050	rs73328514	7	47488569	rs12463617	2	629244
18	rs4712523	6	20657564	rs6971499	7	130680521	rs11127485	2	632028
19	rs10946398	6	20661034	rs2941471	8	76470404	rs10189761	2	646364
20	rs7754840	6	20661250	rs10094872	8	128719884	rs10182181	2	25150296
21	rs7766070	6	20686573	rs1561927	8	129568078	rs17025867	2	40578559
22	rs7756992	6	20679709	rs10991043	9	106797388	rs6726292	2	55156630
23	rs13234407	7	130438214	rs2417487	9	106887581	rs6731302	2	58833493
24	rs1635852	7	28189411	rs687289	9	136137106	rs887912	2	59302877
25	rs2191348	7	15064255	chr9_136149229	9	136149229	rs7581710	2	121195181
26	rs4607517	7	44235668	rs7310409	12	121424861	rs16867321	2	181362379
27	rs13266634	8	118184783	chr12_121454622	12	121454622	rs7603514	2	206836612
28	rs3802177	8	118185025	rs9554197	13	28476978	rs2943650	2	227105921
29	rs896854	8	95960511	rs9581943	13	28493997	rs11680012	2	238672425
30	rs2383208	9	22132076	rs9543325	13	73916628	rs12635698	3	16408489
31	rs10811661	9	22134094	chr16_75263661	16	75263661	rs1435703	3	25560231
32	rs10512085	9	81924713	rs7200646	16	86335351	rs13078807	3	85884150
33	rs7903146	10	114758349	rs4795218	17	36078510	rs7638110	3	138903985
34	rs5015480	10	94465559	rs77038344	17	38644214	rs1516725	3	185824004
35	rs1111875	10	94462882	chr17_70400166	17	70400166	rs9816226	3	185834499
36	rs7901695	10	114754088	rs7214041	17	70401476	rs13130484	4	45175691
37	rs11257655	10	12307894	rs1517037	18	56878274	rs10938397	4	45182527
38	rs11603334	11	72432985	rs6073450	20	43086648	rs4833407	4	113311790
39	rs1552224	11	72433098	rs450960	22	18316304	rs10433903	4	118093137
40	rs5215	11	17408630	rs16986825	22	29300306	rs4864201	4	130731284
41	rs5219	11	17409572				rs925642	4	187678866
42	rs10830963	11	92708710				rs2307111	5	75003678
43	rs2237892	11	2839751				rs2112347	5	75015242

rs1387153	11	92673828	
rs2334499	11	1696849	
rs231362	11	2691471	
rs1353362	12	71613276	
rs2612067	12	66170163	
rs7965349	12	121471931	
rs1359790	13	80717156	
rs2028299	15	90374257	
rs7172432	15	62396389	
rs4778582	15	80420966	
rs8042680	15	91521337	
rs8050136	16	53816275	
rs9939609	16	53820527	
rs4430796	17	36098040	
rs374748	5	127699375	
rs9328321	6	5600438	
rs4712652	6	22078615	
rs999943	6	33624733	
rs2274459	6	33762242	
rs2206277	6	50798526	
rs987237	6	50803050	
rs734597	6	50836279	
rs2207139	6	50845490	
rs2807278	6	131809920	
rs10953454	7	104503813	
rs545854	8	10002570	
rs17150703	8	9745798	
rs17126232	8	17977650	
rs4735692	8	76615663	
rs10968576	9	28414339	
rs1412239	9	28425515	
rs16933812	9	36969205	
rs2275848	9	95887320	
rs10508503	10	16299951	
rs16923476	10	23858211	
rs7474896	10	37982097	
rs10999409	10	72332440	
rs2116830	10	78646536	
rs11042023	11	8662516	
rs297325	11	16389594	
rs4756846	11	16403511	
rs12295638	11	26605331	
rs988712	11	27563382	
rs2030323	11	27728539	
rs564343	11	65895166	
rs1048466	12	551550	
rs3782724	12	6466081	
rs10875976	12	50226467	
rs7138803	12	50247468	
rs11109072	12	97901270	
rs9568856	13	54064981	
rs9568867	13	54107352	
rs17081231	13	66967622	
rs534870	13	80959207	
rs7989336	13	97017548	
rs1957894	14	61908111	
rs699363	14	72692493	
rs11624704	14	78786077	
rs7141420	14	79899454	
rs2370983	14	79903376	

90	rs8028313	15	68043057
91	rs970843	15	98876029
92	rs2531995	16	4013467
93	rs12446554	16	19935073
94	rs12446632	16	19935389
95	rs11639988	16	19944363
96	rs7498665	16	28883241
97	rs7184597	16	28921809
98	rs1421085	16	53800954
99	rs1558902	16	53803574
100	rs1121980	16	53809247
101	rs17817449	16	53813367
102	rs8043757	16	53813450
103	rs8050136	16	53816275
104	rs7185735	16	53822651
105	rs9941349	16	53825488
106	rs9923451	16	78952439
107	rs1424233	16	79682751
108	rs7187365	16	86511915
109	rs9299	17	46669430
110	rs7503807	17	78591111
111	rs1805081	18	21140432
112	rs17697518	18	38765659
113	rs1631486	18	53026357
114	rs17700144	18	57811982
115	rs538656	18	57850422
116	rs17782313	18	57851097
117	rs10871777	18	57851763
118	rs476828	18	57852587
119	rs11152213	18	57852948
120	rs17773430	18	57963117
121	rs1800437	19	46181392
122	rs10423928	19	46182304
123	rs6110577	20	15335754
124	rs13041126	20	51092996
125	rs11088859	21	22689344
126	rs5762430	22	28378472

SNPs in LD (>0.8) for T2DM-related variants: rs4712523, rs10946398, rs7754840, rs7756992, rs9939609, rs8050136, rs5215, rs1552224, rs11603334, rs5015480, rs7903146, rs10811661, rs3802177, rs1801282, rs2877716, rs1470579

SNPs in LD (>0.8) for PC-related variants: rs31490, rs9554197

SNPs in LD (>0.8) for Obesity-related variants: rs2568958, rs7531118, rs1514174, rs12463617, rs11127485, rs10189761, rs10938397, rs2112347, rs987237, rs734597, rs2207139, rs1412239, rs7184597, rs1558902, rs1121980, rs17817449, rs8043757, rs8050136, rs7185735, rs9941349, rs9923451, rs12446554, rs12446632, rs11639988, rs538656, rs17782313, rs10871777, rs476828, rs11152213, rs10423928

Supplemental Table 2: Evaluation of the performance of the missing data imputation.

Variable	Proportion of missings (%)	OOB Error Test[1] in test set	Imputed values	Proportion of concordance ()	OOB Error Test[1] in full set
status	0.00	0.0000	0	**NA**	0.0000
country	0.00	0.0000	0	**NA**	0.0000
gender	0.11	0.1315	2	**50**	0.1320
smoking status	3.29	0.0103	30	**96.67**	0.0015
alcohol status	1.83	0.4893	21	**57.14**	0.4117
chronic pancreatitis status	3.71	0.0052	37	**100**	0.0053
diabetes by type	2.67	0.0031	26	**100**	0.0003
educational level	2.22	0.6254	21	**47.62**	0.5677
FH of pancreatic cancer	3.57	0.0576	26	**100**	0.0498
FH of diabetes[2]	20.15	0.4210	226	**100**	0.3537
periodontitis	26.39	0.1903	257	**81.71**	0.1745
recession	37.16	0.4041	362	**67.96**	0.2862
diabetes diet control	3.99	0.0031	41	**100**	0.0000
diabetes oral medication	3.23	0.0021	42	**97.62**	0.0000
diabetes insulin control	3.65	0.0021	29	**100**	0.0000
Pancreatitis type	3.71	0.0294	46	**93.48**	0.0330
asthma status	9.33	0.0215	113	**100**	0.0015
nasal allergies	8.63	0.0088	94	**98.94**	0.0018
cancer	8.12	0.1393	86	**90.70**	0.1367
diabetes status	1.60	0.0000	15	**100.00**	0.0000
metabolic syndrome	18.27	0.0061	182	**97.25**	0.0007
center	0.00	0.0000	0	**NA**	0.0000
weighton body site	8.68	0.0621	96	**91.67**	0.0160
BMI 2 years before	4.86	0.0000	42	**100**	0.0000
BMI at age 20	19.93	0.0447	192	**95.31**	0.0074
BMI at age 50	27.18	0.0351	257	**94.55**	0.0108
pack-years in tertiles	10.20	0.0055	90	**96.67**	0.0006
age in categories	0.37	0.0643	2	**100**	0.0220
place fat deposition	8.68	0.0132	92	**97.83**	0.0031
weight gain 5 kg	32.66	0.0029	309	**95.15**	0.0008
weight gain 10 kg	32.66	0.0000	324	**94.75**	0.0004
weight at age 20 in tertiles	18.94	0.0109	173	**98.27**	0.0010
weight at age 50 in tertiles	25.74	0.0202	257	**94.55**	0.0019
Weight since age 50	26.45	0.0000	250	**98.00**	0.0000
hypertension	9.19	0.0044	96	**94.79**	0.0009
cholesterol	10.85	0.0000	116	**98.28**	0.0022
height in tertiles	2.22	0.0206	27	**100**	0.0040
smoking duration in tertiles	9.47	0.0143	90	**97.78**	0.0053
smoking intensity in tertiles	3.20	0.0145	31	**100**	0.0044

NA=not applicable

FH=family history

Covariates used to improve imputation were case-control status, country, center, medical history (cancer, asthma, allergies, chronic pancreatitis), smoking variables (intensity and duration) and weight and height.

[1] Out of bag (OOB) error rates: normalized squared error for continuous variables (e.g. age) and proportion of falsely classified entries for categorical variables. Values close to zero indicated good performance and values close to one indicated bad performance.

[2] Concordance test applied to the study population without Ireland since this country did not collect information on family history of the disease.

Supplemental Table 3: Genetic variants associated individually at p-value level <0.05 with T2DM and PC, as well as with selected covariates in the study population (752 controls).

T2DM-SNPs				
NODM	**LSDM**	**PC**	**smoking**	**obesity**
any	rs2943641 (p=0.018) rs1801282 (p=0.051) rs7901695 (p=0.045) rs7903146 (p=0.016)	rs2191348 (p=0.015) rs13266634 (p=0.006) rs3802177 (p=0.005) rs7965349 (p=0.011)	rs2641348 (p=0.006) rs13234407 (p=0.011) rs1111875 (p=0.018) rs5015480 (p=0.020) rs2334499 (p=0.043)	rs10830963 (p=0.044) rs4430796 (p=0.031)
PC-SNPs				
NODM	**LSDM**	**PC**	**smoking**	**obesity**
rs2816938.199985368.T.A (p=0.006) rs7310409 (p=0.016) chr12_121454622_C_T (p=0.005)	any	rs351365.113046395 (p=0.002) rs2816938.199985368 (p=0.001) rs1486134.67639769 (p=0.049) rs31490 (p=0.029) rs73328514.47488569 (p=0.024) rs6971499 (p=0.007) rs2941471.76470404 (p=0.031) rs9543325 (p=0.003) chr16_75263661 (p=0.001) chr17_70400166 (p=0.005) rs7214041.70401476 (p=0.005)	rs6537481.148396094 (p=0.001)	rs1747924.64538961 (p=0.011) rs2816938.199985368 (p=0.012) rs2736098.1294086 (p=0.005) rs17688601.40866663 (p=0.026)

NA: not applicable

Supplemental Table 4: General characteristics of the study population. PanGenEU study (2,018 cases and 1,540 controls). Imputed data.

		Cases N=2018		Controls N=1540				
		N	%	N	%	p-value	OR	[95%CI]
Country						<0.001		
	Spain	884	43.80	770	50.00			
	England	126	6.24	22	1.43			
	Germany	131	6.49	111	7.21			
	Ireland	173	8.57	290	18.80			
	Italy	533	26.40	0	0.00			
	Sweden	171	8.47	347	22.50			
Gender						0.143		
	females	873	43.30	705	45.80		Ref.	
	males	1145	56.70	835	54.20		1.11	[0.97;1.27]
Age (years)		64.3	12.10	66.8	12.50	<0.001	0.98	[0.98;0.99]
Age in categories						<0.001		
	<55 y	409	20.30	261	16.90		Ref.	
	55-65 y	500	24.80	323	21.00		0.99	[0.80;1.22]
	65-75 y	708	35.10	500	32.50		0.90	[0.74;1.10]
	≥75 y	401	19.90	456	29.60		0.56	[0.46;0.69]
BMI 2 years before						0.971		
	<25	761	37.70	575	37.30		Ref.	
	25-29.99	868	43.00	668	43.40		0.98	[0.85;1.14]
	≥30	389	19.30	297	19.30		0.99	[0.82;1.19]
BMI at age 20						0.263		
	<25	1750	86.70	1330	86.40		Ref.	
	25-29.99	228	11.30	189	12.30		0.92	[0.75;1.13]
	≥30	40	1.98	21	1.36		1.44	[0.85;2.51]
BMI at age 50						<0.001		
	<25	620	30.70	612	39.70		Ref.	
	25-29.99	929	46.10	604	39.20		1.52	[1.30;1.77]
	≥30	468	23.20	324	21.00		1.43	[1.19;1.71]
Weight gain >5kg (age 20-50)						0.343		
	no	391	19.40	319	20.70		Ref.	
	yes	1627	80.60	1221	79.30		1.09	[0.92;1.28]
Weight gain >10kg (age 20-50)						<0.001		
	no	742	36.80	676	43.90		Ref.	
	yes	1276	63.20	864	56.10		1.35	[1.18;1.54]
Weight loss since age 50						0.012		
	no	1346	66.70	1089	70.70		Ref.	
	yes	672	33.30	451	29.30		1.21	[1.04;1.39]
Smoking status						<0.001		
	never	760	37.70	691	44.90		Ref.	
	former	683	33.80	563	36.60		1.10	[0.95;1.28]
	current	575	28.50	286	18.60		1.83	[1.53;2.18]
Pack-years in tertiles						<0.001		
	never smokers	760	37.70	691	44.90		Ref.	
	[0.05,12.95]	259	12.80	269	17.50		0.88	[0.72;1.07]
	[13,36]	583	28.90	327	21.20		1.62	[1.37;1.92]
	[36.3,240]	416	20.60	253	16.40		1.49	[1.24;1.80]
Alcohol status						<0.001		

	never	599	29.70	390	25.30		Ref.	
	former	508	25.20	234	15.20		1.41	[1.16;1.73]
	current	911	45.10	916	59.50		0.65	[0.55;0.76]
Pancreatitis type						<0.001		
	no	1918	95.00	1523	98.90		Ref.	
	acute	81	4.01	15	0.97		4.25	[2.51;7.71]
	chronic	19	0.94	2	0.13		7.06	[2.03;48.0]
Educational level (years of education)						<0.001		
	<5 y	343	17.00	177	11.50		Ref.	
	6 to 9 y	486	24.10	399	25.90		0.63	[0.50;0.79]
	10 to 13 y	698	34.60	508	33.00		0.71	[0.57;0.88]
	≥14 y	491	24.30	456	29.60		0.56	[0.44;0.69]
Family history of PC						<0.001		
	no	1889	93.60	1499	97.30		Ref.	
	yes	129	6.39	41	2.66		2.49	[1.76;3.60]
Periodontitis						0.643		
	no	1744	86.40	1340	87.00		Ref.	
	yes	274	13.60	200	13.00		1.05	[0.87;1.28]
Recession						0.003		
	no	1481	73.40	1197	77.70		Ref.	
	yes	537	26.60	343	22.30		1.27	[1.08;1.48]
Asthma						<0.001		
	no	1887	93.50	1381	89.70		Ref.	
	yes	131	6.49	159	10.30		0.60	[0.47;0.77]
Nasal allergies						<0.001		
	no	1771	87.80	1236	80.30		Ref.	
	yes	247	12.20	304	19.70		0.57	[0.47;0.68]
Hypertension						<0.001		
	no	1324	65.60	913	59.30		Ref.	
	yes	694	34.40	627	40.70		0.76	[0.67;0.88]
Cholesterol						<0.001		
	no	1459	72.30	1000	64.90		Ref.	
	yes	559	27.70	540	35.10		0.71	[0.61;0.82]

Differences between cases and controls evaluated via Chi-squared test (categprocal variables) and Student´s t-test or Mann-Whitney (continuous variables).
Odds Ratios (OR) derived from unadjusted unconditional logistic resgression models.
Data of all variables was self-reported.

Supplemental Table 5: Baseline characteristics of NODM and LSDM in the PanGenEU study (538 cases and 198 controls). Imputed data.

	LSD M N=509 N	%	NODM N=227 N	%	*p-value*	OR NODM *vs* LSDM	95%CI NODM *vs* LSDM
Age (years)					<0.001		
<55	37	7.27	28	12.30		Ref.	
55-65	92	18.10	67	29.50		1.04	[0.58;1.86]
65-75	213	41.80	83	36.60		1.94	[1.11;3.37]
≥75	167	32.80	49	21.60		2.57	[1.42;4.63]
Gender					0.818		
females	180	35.40	83	36.60		Ref.	
males	329	64.60	144	63.40		1.05	[0.76;1.46]
Smoking status					0.441		
never	199	39.10	78	34.40		Ref.	
former	201	39.50	94	41.40		0.84	[0.58;1.20]
current	109	21.40	55	24.20		0.78	[0.51;1.18]
Alcohol status					0.127		
never	155	30.50	57	25.10		Ref.	
former	140	27.50	78	34.40		0.66	[0.44;1.00]
current	214	42.00	92	40.50		0.86	[0.58;1.26]
Chronic pancreatitis					0.298		
no	504	99.00	222	97.80		Ref.	
yes	5	0.98	5	2.20		0.44	[0.12;1.65]
Educational level (years)					0.632		
<5 y	114	22.40	44	19.40		Ref.	
6 to 9 y	138	27.10	66	29.10		0.81	[0.51;1.27]
10 to 13 y	164	32.20	69	30.40		0.92	[0.58;1.43]
≥14 y	93	18.30	48	21.10		0.75	[0.46;1.23]
Family history PC					0.318		
no	478	93.90	218	96.00		Ref.	
yes	31	6.09	9	3.96		1.55	[0.75;3.54]
Family history Diabetes					0.667		
no	252	49.50	117	51.50		Ref.	
yes	257	50.50	110	48.50		1.08	[0.79;1.48]
Periodontitis					0.221		
no	421	82.70	197	86.80		Ref.	
yes	88	17.30	30	13.20		1.37	[0.88;2.17]
Recession					0.667		
no	381	74.90	174	76.70		Ref.	
yes	128	25.10	53	23.30		1.1	[0.77;1.60]
Diabetes age diagnosis					<0.001		
≤ 55y	207	40.70	37	16.30		Ref.	
55 to ≤ 65y	167	32.80	63	27.80		0.48	[0.30;0.75]
> 65y	135	26.50	127	55.90		0.19	[0.12;0.29]
Diabetes with diet					0.770		
yes	395	77.60	174	76.70		Ref.	
no	114	22.40	53	23.30		0.95	[0.65;1.38]
Diabetes with oral medication					<0.001		
yes	407	80.00	139	61.20		Ref.	
no	102	20.00	88	38.80		0.4	[0.28;0.56]
					0.916		

Diabetes with insulin								
	yes	293	57.60	129	56.80		Ref.	
	no	216	42.40	98	43.20		0.97	[0.71;1.33]
Asthma						0.135		
	no	467	91.70	216	95.20		Ref.	
	yes	42	8.25	11	4.85		1.75	[0.91;3.65]
Nasal allergies						0.46		
	no	453	89.00	197	86.80		Ref.	
	yes	56	11.00	30	13.20		0.81	[0.51;1.32]
Metabolic syndrome						0.116		
	Any one	146	28.70	58	25.60		Ref.	
	Any two	170	33.40	96	42.30		0.7	[0.47;1.04]
	Any three	151	29.70	60	26.40		1	[0.65;1.53]
	All four	42	8.25	13	5.73		1.27	[0.65;2.64]
BMI 2 years before						0.172		
	<25	128	25.10	47	20.70		Ref.	
	25-29.99	245	48.10	126	55.50		0.72	[0.48;1.06]
	≥30	136	26.70	54	23.80		0.93	[0.58;1.47]
BMI at age 20						0.713		
	<25	421	82.70	184	81.10		Ref.	
	25-29.99	72	14.10	37	16.30		0.85	[0.55;1.32]
	≥30	16	3.14	6	2.64		1.15	[0.46;3.29]
BMI at age 50						0.99		
	<25	110	21.60	48	21.10		Ref.	
	25-29.99	241	47.30	108	47.60		0.97	[0.64;1.46]
	≥30	158	31.00	71	31.30		0.97	[0.62;1.51]
Pack-years in tertiles						0.585		
	never smokers	199	39.10	78	34.40		Ref.	
	[0.05,12.95]	51	10.00	27	11.90		0.74	[0.43;1.28]
	[13,36]	129	25.30	64	28.20		0.79	[0.53;1.18]
	[36.3,240]	130	25.50	58	25.60		0.88	[0.59;1.32]
Weightgain >5kg (age 20-50)						0.943		
	no	58	11.40	27	11.90		Ref.	
	yes	451	88.60	200	88.10		1.05	[0.64;1.70]
Weightgain >10kg (age 20-50)						0.797		
	no	155	30.50	72	31.70		Ref.	
	yes	354	69.50	155	68.30		1.06	[0.75;1.48]
Hypertension						0.596		
	no	241	47.30	113	49.80		Ref.	
	yes	268	52.70	114	50.20		1.1	[0.81;1.51]
Cholesterol						0.981		
	no	316	62.10	140	61.70		Ref.	
	yes	193	37.90	87	38.30		0.98	[0.71;1.36]
Weight loss since age 50						0.429		
	no	333	65.4	156	68.7		Ref.	
	yes	176	34.6	71	31.3		1.16	[0.83;1.63]

Differences between cases and controls evaluated via Chi-squared test (categprocal variables) and Student´s t-test (continuous variables). Odds Ratios (OR) derived from unadjusted unconditional logistic resgression models.

Supplemental Table 6: Association between diabetes-related variables and PC risk in the PanGenEU study (2,018 cases and 1,540 controls) when adjusting for T2DM treatment and duration of the disease.

	Age, sex, country-adjusted (Model 1)		Model 1 + use of oral medication		Model 1 + use of insulin		Model 1 + duration of diabetes	
	OR	[95%CI]	OR	[95%CI]	OR	[95%CI]	OR	[95%CI]
Diabetes status:								
no diabetes	Ref.		Ref.		Ref.		Ref.	
yes	2.56	[2.10;3.11]	3.01	[2.13;4.26]	1.77	[1.37;2.29]	1.19	[0.76;1.85]
Diabetes status by subtype								
no diabetes	Ref.		Ref.		Ref.		Ref.	
yes, ≤ 2 years (NODM)	6.49	[4.25;9.90]	6.36	[3.95;10.26]	4.51	[2.88;7.06]	2.64	[1.4;4.97]
yes, > 2years (LSDM)	1.90	[1.53;2.37]	1.85	[1.25;2.73]	1.27	[0.96;1.69]	1.19	[0.76;1.85]
Family history of diabetes[1]								
no diabetes	Ref.		Ref.		Ref.		Ref.	
yes	1.25	[1.05;1.49]	1.07	[0.89;1.28]	1.07	[0.89;1.28]	1.07	[0.89;1.28]
Diabetes by age at diagnosis (years)[2]								
no diabetes	Ref.		Ref.		Ref.		Ref.	
≤ 55 y	1.56	[1.15;2.11]	1.83	[1.21;2.76]	0.91	[0.62;1.32]	1.17	[0.75;1.83]
55 to ≤ 65 y	2.68	[1.92;3.73]	3.23	[2.02;5.15]	1.81	[1.25;2.61]	1.50	[0.79;2.86]
> 65 y	4.06	[2.94;5.60]	4.75	[3.13;7.28]	2.79	[1.96;3.97]		
	p-trend	2E-16	*p-trend*	1.2E-05	*p-trend*	6.6E-07	*p-trend*	0.122
Diabetes by time since diagnosis (years)[2]								
no diabetes	Ref.		Ref.		Ref.		Ref.	
≤1 y	11.14	[6.09;20.37]	11.04	[5.83;20.93]	7.24	[3.89;13.5]	NA	NA
1 to ≤2 y	2.64	[1.40;4.97]	2.61	[1.3;5.22]	1.72	[0.89;3.35]	NA	NA
2 to ≤5 y	2.40	[1.54;3.73]	2.36	[1.35;4.14]	1.73	[1.09;2.76]	NA	NA
5 to ≤10 y	2.67	[1.81;3.93]	2.63	[1.57;4.47]	1.73	[1.14;2.66]	NA	NA
10 to ≤20 y	1.59	[1.09;2.32]	1.56	[0.94;2.62]	0.91	[0.58;1.42]	NA	NA
>20 y	1.19	[0.76;1.85]	1.17	[0.69;1.98]	0.61	[0.36;1.04]	NA	NA
	p-trend	9.6E-08	*p-trend*	5.5E-10	*p-trend*	1.4E-11	*p-trend*	NA
Diabetes controlled with diet								
no diabetes	Ref.		Ref.		Ref.		Ref.	
yes	2.60	[2.09;3.24]	3.08	[2.14;4.43]	1.75	[1.32;2.32]	1.22	[0.78;1.92]
no use	2.43	[1.69;3.49]	2.84	[1.81;4.47]	1.82	[1.24;2.69]	1.04	[0.6;1.82]
Use of oral medication								
no diabetes	Ref.		Ref.		Ref.		Ref.	
yes	2.41	[1.93;3.00]	NA	NA	1.74	[1.33;2.28]	1.19	[0.75;1.9]
no use	3.01	[2.13;4.26]	NA	NA	1.89	[1.25;2.85]	1.17	[0.69;1.98]
Use of insulin								
no diabetes	Ref.		Ref.		Ref.		Ref.	
yes	3.76	[2.85;4.95]	3.96	[2.71;5.79]	NA	NA	1.61	[1.01;2.58]
no use	1.77	[1.37;2.29]	1.89	[1.25;2.85]	NA	NA	0.61	[0.36;1.04]

[1] Information on family history of diabetes was not collected in Ireland; results are based on data for 1,845 cases and 1,250 controls

[2] Linear associations for age since T2DM diagnosis and nonlinear association for time since T2DM (Supplemental Figure 1)

Model 1: adjusted for age (<55, 55-65, 65-75, ≥75 years), gender, country.

Model 2: Model 1 also adjusted for use of oral medication.

Model 3: Model 1 also adjusted for use of insulin.

Model 4: Model 1 also adjusted for duration of T2DM.

NA=not applicable

Supplemental Table 7: Association between T2DM status based on Hb1Ac levels and questionnaire data and PC risk in the PanGenEU study.

	Cases		Controls			Crude Model		Model1		Model2	
	P50	IQR	P50	IQR	p-value[1]	OR	[95%CI]	OR	[95%CI]	OR	[95%CI]
HbA1c (%)[2,3] per 1 unit increase	6.1	5.6;6.9	5.6	5.4;6.0	<0.001	1.48	[1.30;1.69]	1.50	[1.31;1.71]	1.49	[1.30;1.70]
C-Peptide[2,3] per log2 increase	2.3	1.4;3.7	4.2	2.5;6.4	<0.001	0.45	[0.38;0.56]	0.46	[0.39;0.54]	0.46	[0.39;0.53]
	N	**%**	**N**	**%**							
Diabetogenic status by HbA1c levels[3]					<0.001						
HbA1c <6.5%	336	66	354	85.7		Ref.		Ref.		Ref.	
HbA1c ≥6.5%	173	34	59	14.3		3.08	[2.22;4.32]	3.29	[2.34;4.62]	3.27	[2.32;4.60]
Biomarker and self-reported diabetes status					<0.001						
no diabetes	286	56.2	322	78		Ref.		Ref.		Ref.	
self-reported but normal Hb1Ac levels	50	9.8	32	7.7		1.76	[1.10;2.84]	1.9	[1.18;3.10]	1.92	[1.19;3.13]
self-reported and HbA1c ≥6.5%	173	34	59	14.3		3.3	[2.37;4.65]	3.59	[2.55;5.11]	3.58	[2.53;5.11]
Diabetes status[3]					<0.001						
no diabetes	350	68.7	341	82.6		Ref.		Ref.		Ref.	
yes	159	31.3	72	17.40		2.15	[1.57;2.96]	2.26	[1.64;3.15]	2.26	[1.64;3.15]
Reclassified diabetes status[3]					<0.001						
no diabetes	286	56.2	322	78		Ref.		Ref.		Ref.	
self-reported and/or HbA1c ≥6.5%	223	43.8	91	22		2.76	[2.07;3.70]	2.99	[2.21;4.06]	2.99	[2.21;4.07]
Diabetes status by subtype[3]					<0.001						
no diabetes	350	68.7	341	82.6		Ref.		Ref.		Ref.	
NODM	66	13	15	3.6		4.29	[2.47;7.93]	4.53	[2.59;8.42]	4.58	[2.61;8.55]
LSDM	93	18.3	57	13.8		1.59	[1.11;2.29]	1.65	[1.14;2.41]	1.64	[1.13;2.40]
Reclassified diabetes status by subtypes[3]					<0.001						
no diabetes	286	56.2	322	78		Ref.		Ref.		Ref.	
NODM	130	25.5	34	8.2		4.3	[2.89;6.57]	4.63	[3.08;7.12]	4.63	[3.07;7.15]
LSDM	93	18.3	57	13.8		1.84	[1.28;2.66]	1.98	[1.35;2.90]	1.97	[1.35;2.90]
Biomarker Hb1Ac levels[3]					<0.001						
<5.5	100	19.6	129	31.2		Ref.		Ref.		Ref.	
5.5-5.8	72	14.1	121	29.3		0.77	[0.52;1.14]	0.71	[0.47;1.06]	0.71	[0.47;1.06]
5.8-6.0	50	9.9	51	12.5		1.26	[0.79;2.03]	1.26	[0.78;2.04]	1.23	[0.76;1.99]
6.0-6.5	114	22.4	53	13		2.76	[1.83;4.22]	2.75	[1.80;4.24]	2.72	[1.77;4.17]

≥6.5	173	34	59	14		3.77	[2.55;5.62]		4.03	[2.69;6.08]		3.99	[2.64;6.01]
					p-trend	2.70E-10		*p-trend*	2.00E-16		*p-trend*	2.00E-16	
Reclassified NODM into type 3c-like diabetes[3]													
no diabetes	286	56.20	322	77.97		Ref.			Ref.			Ref.	
NODM and C-Peptide >4.2 µg/L	37	7.20	21	5.08		1.98	]1.15;3.52]		2.30	[1.31;4.13]		2.28	[1.30;4.10]
NODM and C-Peptide <4.2 µg/L (T3c)	93	18.30	13	3.15		8.05	[4.57;15.37]		8.31	[4.69;15.93]		8.38	[4.71;16.11]
LSDM	93	18.30	57	13.80		1.84	[1.28;2.66]		1.99	[1.36;2.92]		1.98	[1.35;2.92]
Diabetes status[4]					<0.001								
no diabetes	1480	73.3	1342	87.1		Ref.			Ref.			Ref.	
yes	538	26.7	198	12.9		2.46	[2.06;2.95]		2.56	[2.10;3.11]		2.5	[2.05;3.05]
Reclassified diabetes status[4]					<0.001								
no diabetes	1416	70.2	1323	85.9		Ref.			Ref.			Ref.	
self-reported and/or HbA1c ≥6.5%	602	29.8	217	14.1		2.59	[2.18;3.08]		2.85	[2.36;3.45]		2.79	[2.31;3.39]
Diabetes status by subtype PanGenEU[4]					<0.001								
no diabetes	1480	73.3	1342	87.1		Ref.			Ref.			Ref.	
NODM	200	9.91	27	1.75		6.68	[4.52;10.3]		6.49	[4.25;9.90]		6.39	[4.18;9.78]
LSDM	338	16.7	171	11.1		1.79	[1.47;2.19]		1.9	[1.53;2.37]		1.86	[1.49;2.32]
Reclassified diabetes status by subtypes[4]					<0.001								
no diabetes	1416	70.2	1323	85.9		Ref.			Ref.			Ref.	
NODM	264	13.1	46	3		5.36	[3.93;7.49]		5.74	[4.14;8.11]		5.67	[4.09;8.03]
LSDM	338	16.7	171	11.1		1.85	[1.52;2.26]		2.03	[1.62;2.53]		1.98	[1.59;2.48]
Reclassified NODM into type 3c-like diabetes[4]					<0.001								
no diabetes	1416	70.2	1323	85.9		Ref.			Ref.			Ref.	
NODM and C-Peptide >4.2 µg/L	171	8.5	33	2.2		4.84	[3.36;7.20]		4.65	[3.16;7.02]		4.51	[3.06;6.83]
NODM and C-Peptide <4.2 µg/L (T3c)	93	4.6	13	0.8		6.68	[3.86;12.58]		8.83	[5.06;1.67]		8.86	[5.07;1.68]
LSDM	338	16.7	171	11.1		1.85	[1.52;2.26]		2.06	[1.65;2.56]		2.00	[1.61;2.51]
diabetes status[5]					<0.001								
no diabetes	596	67.4	628	81.6		Ref.			Ref.			Ref.	
yes	288	32.6	142	18.4		2.14	[1.70;2.70]		2.09	[1.64;2.66]		2.07	[1.62;2.64]
Reclassified diabetes status[5]					<0.001								
no diabetes	532	60.2	609	19.1		Ref.			Ref.			Ref.	
self-reported and/or HbA1c ≥6.5%	352	39.8	161	80.9		2.5	[2.01;3.12]		2.57	[2.04;3.24]		2.54	[2.01;3.22]
Diabetes status by subtype[5]					<0.001								

no diabetes	596	67.4	628	81.6		Ref.		Ref.		Ref.	
NODM	109	12.2	20	2.6		5.74	[3.60;9.63]	5.7	[3.54;9.62]	5.67	[3.52;9.60]
LSDM	179	20.3	122	15.8		1.55	[1.20;2.00]	1.47	[1.12;1.93]	1.45	[1.11;1.91]
Reclassified diabetes status by subtypes[5]					<0.001						
no diabetes	532	60.2	609	79.1		Ref.		Ref.		Ref.	
NODM	173	19.6	39	5.1		5.08	[3.56;7.42]	5.4	[3.75;7.94]	5.35	[3.71;7.88]
LSDM	179	20.2	122	15.8		1.68	[1.30;2.18]	1.63	[1.24;2.15]	1.62	[1.23;2.14]
Reclassified NODM into type 3c-like diabetes[5]											
no diabetes	532	60.2	609	79.1		Ref.		Ref.		Ref.	
NODM and C-Peptide >4.2 µg/L	80	9.1	26	3.4		3.52	[2.26;5.66]	3.49	[2.21;5.68]	3.41	[2.15;5.57]
NODM and C-Peptide <4.2 µg/L (T3c)	93	10.5	13	1.7		8.19	[4.70;15.50]	9.46	[5.40;17.96]	9.47	[5.40;18.02]
LSDM	179	20.2	122	15.8		1.68	[1.30;2.18]	1.65	[1.26;2.18]	1.63	[1.24;2.16]

[1] Differences between groups evaluated by the Chi-square test (categorical variables) and Mann-Whitney test (continuous variables).
[2] Linear association for Hb1Ac levels and non-linear for C-Peptide (Supplemental Figure 1).
[3] NODM and LSDM was classified with questionnaire and biomarker data in the biomarker study population (509 cases and 413 controls).
[4] NODM and LSDM was classified with questionnaire and biomarker data in the entire study population (2,018 cases and 1,540 controls).
[5] NODM and LSDM was classified with questionnaire and biomarker data in the PanGenEU-Spain study population (884 cases and 770 controls).
Crude Model: unadjusted.
Model 1: adjusted for age (<55, 55-65, 65-75, ≥75 years), sex and center (Spain) or country.
Model 2: Model 1 also adjusted for pack years (never-smokers and tertiles of pack-years) and BMI (<25, 25-30, ≥30 kg/m2).

Supplemental Table 8: Association between T2DM and PC risk by T2MD subtypes and other covariates in the PanGenEU study (2,018 cases and 1,540 controls).

	No diabetes (Ref.)	NODM		LSDM	
	Cases;Controls	Cases;Controls	OR[1] [95%CI]	Cases;Controls	OR[1] [95%CI]
Alcohol status					
never	451;326	47;10	3.62 [1.81;7.90]	101;54	1.43 [0.95;2.16]
former	329;195	71;7	6.59 [3.09;16.33]	108;32	2.61 [1.66;4.20]
current	700;821	82;10	8.21 [4.30;17.34]	129;85	1.71 [1.24;2.37]
	p-value for interaction	0.3530		0.3914	
Chronic pancreatitis					
no	1469;1342	195;27	6.31 [4.2;9.83]	335;169	1.92 [1.55;2.40]
yes	11;0	5;0	NA	3;2	NA
	p-value for interaction	NA		NA	
Family history PC					
no	1378;1305	191;27	6.26 [4.16;9.77]	311;167	1.88 [1.50;2.35]
yes	93;37	9;0	NA	27;4	2.79 [0.90;10.72]
	p-value for interaction	0.2209		0.4220	
Asthma					
no	1378;1207	192;24	6.83 [4.46;10.9]	317;150	2 [1.59; 2.52]
yes	102;135	8;3	2.56 [0.6;13.26]	21;21	1.34 [0.61; 2.9]
	p-value for interaction	0.1853		0.1832	
Nasal allergies					
no	1292;1065	172;25	5.5 [3.59; 8.75]	307;146	1.84 [1.46; 2.34]
yes	188;277	28;2	17.39 [4.92; 110.72]	31;25	2.1 [1.14; 3.88]
	p-value for interaction	0.1131		0.8289	
BMI 2 years before					
<25	635;524	45;2	20.35 [6.11;126.34]	79;49	1.22 [0.79;1.87]
25-29.99	593;570	109;17	5.41 [3.2;9.65]	165;80	2.16 [1.57;2.99]
≥30	252;248	46;8	5.01 [2.34;12.04]	94;42	2.37 [1.53;3.71]
	p-value for interaction	0.1222		0.0496	
BMI at age 20					
<25	1311;1162	163;21	6.72 [4.26;11.12]	271;147	1.78 [1.40;2.26]
25-29.99	143;161	31;6	5.06 [2.08;14.28]	53;19	3.11 [1.69;5.93]
≥30	26;19	6;0	NA	11;5	2.69 [0.63;13.71]
	p-value for interaction	0.5767		0.3708	
BMI at age 50					
<25	516;562	39;9	4.21 [2.04;9.57]	66;44	1.58 [1.02;2.44]
25-29.99	665;517	100;8	11.03 [5.55;25.21]	164;77	1.93 [1.39;2.70]
≥30	299;263	61;10	4.98 [2.48;10.92]	108;50	2.14 [1.40;3.28]
	p-value for interaction	0.1333		0.635	
Age categorized:					
<55	356;249	24;4	4.73 [1.69;16.79]	29;8	3.17 [1.42;7.78]
55-65	369;295	61;6	7.94 [3.56;21.15]	70;22	2.20 [1.28;3.86]
65-75	482;430	75;8	7.54 [3.72;17.45]	151;62	2.18 [1.54;3.11]
≥75	273;368	40;9	4.74 [2.27;10.89]	88;79	1.34 [0.93;1.94]
	p-value for interaction	0.7985		0.2534	

Place fat deposition					
Never carried any extra weight	90;72	4;1	4.95 [0.59;111.11]	10;4	2.71 [0.77;11.19]
Abdominal	966;927	140;20	6.24 [3.87;10.53]	239;134	1.78 [1.38;2.30]
Hips	127;120	10;2	7.52 [1.66;53.69]	12;5	4.94 [1.55;18.11]
All over equally	297;223	46;4	8.9 [3.43;30.4]	77;28	2.05 [1.24;3.47]
p-value for interaction		0.8896		0.5682	
Weight gain >5kg between age 20-50					
no	326;299	26;1	19.9 [4.08;359.30]	39;19	1.64 [0.89;3.10]
yes	1154;1043	174;26	6.12 [4.02;9.67]	299;152	2.04 [1.61;2.59]
p-value for interaction		0.1841		0.4969	
Weight gain >10kg between age 20-50					
no	578;613	62;10	6.08 [3.17;12.90]	102;53	2.06 [1.42;3.01]
yes	902;729	138;17	6.62 [3.98;11.66]	236;118	1.87 [1.42;2.46]
p-value for interaction		0.8334		0.7456	

[1] Odds ratios (ORs) adjusted for age (<55, 55-65, 65-75, ≥75 years), gender, country, pack years (never-smokers and tertiles of pack-years) and BMI (<25, 25-30, ≥30 kg/m^2), except: sex in analyses stratified by sex, BMI in analyses stratified by obesity and pack-years in analyses stratified by smoking status.
[2] Obesity status defined based on BMI 2 years before recruitment.

Supplemental Table 9: Factors associated with PC risk among patients with NODM and LSDM in the PanGenEU study (2,018 cases and 1,540 controls).

		NODM (N=227)				LSDM (N=509)				NODM SR + BIOM (N=310)			
		Cases; Controls	OR[1]	[95%CI]	*p-value*	Cases; Controls	OR[1]	[95%CI]	*p-value*	Cases; Controls	OR[1]	[95%CI]	*p-value*
Gender	females	67;16	Ref.			115;65	Ref.			103;22	Ref.		
	males	133;11	2.59	[1.07;6.32]	0.04	223;106	1.07	[0.7;1.63]	0.75	161;24	1.2	[0.62;2.35]	0.59
Age groups	<65y	85;10	Ref.			99;30	Ref.			106;17	Ref.		
	≥65y	115;17	3.94	[0.8;19.44]	0.09	239;141	1.33	[0.67;2.67]	0.42	158;29	1.73	[0.54;5.60]	0.36
Pbese[2]	no	154;19	Ref.			244;129	Ref.			207;32	Ref.		
	yes	46;8	0.6	[0.22;1.61]	0.31	94;42	1.22	[0.78;1.93]	0.39	57;14	0.56	[0.27;1.19]	0.13
Smoking status	never	67;11	Ref.			120;79	Ref.			96;18	Ref.		
	former	87;7	1.03	[0.32;3.32]	0.96	139;62	1.46	[0.88;2.40]	0.14	108;15	0.87	[0.36;2.1]	0.76
	current	46;9	0.52	[0.15;1.74]	0.29	79;30	1.25	[0.69;2.28]	0.46	60;14	0.56	[0.22;1.46]	0.24
Alcohol status	never	47;10	Ref.			101;54	Ref.			69;16	Ref.		
	former	71;7	1.97	[0.59;6.60]	0.27	108;32	1.91	[1.06;3.43]	0.03	91;13	1.64	[0.66;4.06]	0.29
	current	82;10	1	[0.29;3.45]	1	129;85	0.76	[0.45;1.3]	0.32	104;17	1.27	[0.51;3.14]	0.61
Family history PC	no	191;27	Ref.			311;167	Ref.			252;44	Ref.		
	yes	9;0	NA		NA	1	27;4	3.98	[1.33;11.93]	0.01	12;2	1.34	[0.27;6.61]	0.72
Family history diabetes	no	105;12	Ref.			161;90	Ref.			154;26	Ref.		
	yes	95;15	1.02	[0.42;2.47]	0.97	176;81	1.34	[0.89;2.02]	0.16	110;20	1.07	[0.54;2.10]	0.84
Periodontitis	no	175;22	Ref.			280;141	Ref.			234;37	Ref.		
	yes	25;5	0.48	[0.15;1.57]	0.22	58;30	1.01	[0.60;1.70]	0.98	30;9	0.5	[0.2;1.22]	0.13
Diabetes with diet[3]	yes	156;18	Ref.			264;131	Ref.			156;18	Ref.		
	no	44;9	0.8	[0.3;2.12]	0.66	74;40	1.04	[0.65;1.67]	0.86	44;9	NA		
Diabetes with oral medication[3]	yes	120;19	Ref.			278;129	Ref.			120;19	Ref.		
	no	80;8	2.75	[1.04;7.26]	0.04	60;42	0.73	[0.46;1.18]	0.2	80;8	NA		
Diabetes with insulin[3]	yes	123;6	Ref.			220;73	Ref.			123;6	Ref.		
	no	77;21	0.2	[0.07;0.55]	0	118;98	0.52	[0.35;0.78]	0	77;21	NA		
Diabetes age at diagnosis[3]	<55	32;5	Ref.			130;77	Ref.			32;5	Ref.		
	55-65	56;7	2.02	[0.17;24.06]	0.58	117;50	1.81	[1.06;3.08]	0.03	56;7	NA		

	>65	112;15	10.48	[0.41;270.43]	0.16	91;44	3.15	[1.74;5.69]	0	112;15	NA		
Educational level	<5 y	61;9	Ref.			74;40	Ref.			61;9	Ref.		
	6 to 9 y	70;16	0.39	[0.11;1.4]	0.15	78;60	0.57	[0.32;1.01]	0.06	70;16	0.49	[0.19;1.28]	0.15
	10 to 13 y	70;13	0.78	[0.18;3.34]	0.74	120;44	0.97	[0.51;1.84]	0.93	70;13	0.65	[0.23;1.85]	0.42
	≥14 y	63;8	1.52	[0.29;7.96]	0.62	66;27	1.17	[0.59;2.30]	0.65	63;4	0.92	[0.29;2.87]	
BMI 2 years before[2]	normal	45;2	Ref.			79;49	Ref.			66;8	Ref.		
	over	109;17	0.2	[0.04;0.99]	0.05	165;80	1.59	[0.97;2.62]	0.07	141;24	0.57	[0.24;1.4]	0.22
	obese	46;8	0.17	[0.03;0.94]	0.04	94;42	1.62	[0.93;2.84]	0.09	57;14	0.38	[0.14;1.03]	0.06
BMI at age 20	normal	163;21	Ref.			274;147	Ref.			218;37	Ref.		
	over	31;6	0.64	[0.22;1.88]	0.42	53;19	1.48	[0.81;2.69]	0.2	38;7	0.79	[0.33;1.92]	0.61
	obese	6;0	NA		NA 1	11;5	1.22	[0.38;3.89]	0.74	8;2	0.94	[0.10;8.55]	0.96
BMI at age 50	normal	39;9	Ref.			66;44	Ref.			60;17	Ref.		
	over	100;8	3.62	[1.12;11.75]	0.03	164;77	1.29	[0.78;2.13]	0.33	129;13	2.48	[1.07;5.74]	0.03
	obese	61;10	1.28	[0.43;3.79]	0.66	108;50	1.09	[0.62;1.89]	0.77	75;16	1	[0.44;2.29]	0.99
Weight gain >5kg	no	26;1	Ref.			39;19	Ref.			39;7	Ref.		
	yes	174;26	0.24	[0.03;1.95]	0.18	299;152	0.9	[0.48;1.68]	0.74	225;39	0.97	[0.39;2.39]	0.94
Weight gain >10kg	no	62;10	Ref.			102;53	Ref.			90;20	Ref.		
	yes	138;17	1.17	[0.47;2.89]	0.74	236;118	0.81	[0.53;1.25]	0.35	174;26	1.27	[0.65;2.47]	0.49
Weight loss since age 50	yes	135;21	Ref.			217;116	Ref.			175;36	Ref.		
	no	65;6	0.4	[0.13;1.21]	0.1	121;55	0.72	[0.45;1.15]	0.17	89;10	0.43	[0.2;0.96]	0.04

[1]Odds ratios (ORs) adjusted for age (<55, 55-65, 65-75, ≥75 years), gender, country, pack years (never-smokers and tertiles of pack-years) and BMI (<25, 25-30, ≥30 kg/m^2), except: sex in analyses stratified by sex, BMI in analyses stratified by obesity and pack-years in analyses stratified by smoking status.
[2]Obesity status defined based on BMI 2 years before recruitment.
[3]The association with PC risk could not be evaluated in reclassified NODM for diabetes-related variables due to lack of information on these variables.

Supplemental Table 10: Estimates for the observational and causal association between T2DM and PC and *viceversa*, applying different MRA methods, conducted among 1,162 cases and 752 controls with epidemiological and genetic data. T2DM status based on self-reported (SR) data.

	SR-based classification of T2DM status					SR-based classification of T2DM status				
	LSDM (N=289)[1]		NODM (N=136)[1]			LSDM (N=289)[1]		NODM (N=136)[1]	
Diabetes-->PC	**OR [95%CI][2]**	***p-value***	**OR [95%CI][2]**	***p-value***	**PC-->Diabetes**	**OR [95%CI][2]**	***p-value***	**OR [95%CI][2]**	***p-value***
Observational association study					**Observational association study**				
T2DM and PC	1.43 [1.09;1.88]	0.011	6.10 [3.45;10.8]	5.40E-13	PC and T2DM	1.45 [1.10;1.91]	0.008	6.08 [3.44;10.7]	4.80E-10
T2DM-allele score[3] and T2DM in controls	1.15 [1.09;1.21]	1.20E-05	1.31 [1.15;1.47]	0.0007	PC-allele score[4] and PC (without T2DM)	1.10 [1.06;1.13]	9.30E-09	1.10 [1.06;1.14]	4.10E-09
T2DM-allele score[3] and PC	1.01 [0.98;1.04]	0.5	1.02 [0.98;1.05]	0.315	PC-allele score[4] and T2DM	1.03 [0.99;1.06]	0.121	1.09 [1.04;1.14]	0.0002
Causal estimates: MR study					**Causal estimates: MR study**				
MRA_Wald	1.08 [0.86;1.29]	0.5	1.06 [0.95;1.17]	0.315	MRA_Wald	1.32 [0.97;1.67]	0.121	2.52 [2.07;3.03]	0.0002
TSLS Estimates	1.08 [0,87;1.33]	0.5	1.07 [0.96;1.20]	0.239	TSLS Estimates	1.31 [0.97;1.66]	0.123	2.52 [2.18;2.88]	0.0002
Inverse-variance weighted method (IVW)	0.90 [0.77;1.07]	0.238	0.98 [0.96;1.02]	0.692	Inverse-variance weighted method (IVW)	1.12 [0.89;1.41]	0.326	1.57 [1.13;2.12]	0.007
Mr-Egger regression	0.98 [0.74;1.30]	0.918	0.98 [0.96;1.02]	0.694	Mr-Egger regression	1.09 [0.78;1.51]	0.614	0.94 [0.57;1.55]	0.804
Mr-Egger Intercept	-0.022 (0.030)	0.468	0.006 (0.018)	0.964	Mr-Egger Intercept	0.007 (0.028)	0.807	0.090 (0.042)	0.027
Weighted median	0.94 [0.73;1.22]	0.649	0.99 [0.98;1.02]	0.905	Weighted median	1.18 [0.85;1.65]	0.323	1.36 [0.85;2.16]	0.197
Simple median	0.83 [0.60;1.06]	0.117	1.03 [0.94;1.13]	0.496	Simple median	1.50 [1.00;2.26]	0.049	2.37 [1.78;2.96]	<0.001

[1] LSDM and NODM was evaluated in comparison to non-diabetics (1,489 subjects: 851 PC cases and 638 controls), with subjects classified as either NODM (N=136) or LSDM (N=289) being removed, respectively.
[2] All estimates were adjusted for age (<55, 55-65, 65-75, ≥75 years), gender, BMI (<25, 25-30, ≥30 kg/m2), smoking (never-smokers and tertiles of pack-years), country and the first five principal components for population ancestries.
[3] From the 57 T2DM-SNPs, 16 were excluded due to high LD with other SNPs (r2>0.8) (Supplementary Table 1), and 6 SNPs were excluded due to their association with BMI (rs10830963, rs4430796) and smoking (rs2641348, rs13234407, rs1111875, rs2334499). The allele score, as instrumental variable, included the remaining 35 SNPs.
[4] From the 40 PC-SNPs, 2 were excluded due to high LD (r2>0.8) (Supplementary Table 1), and 5 SNPs were excluded due to their association with BMI (rs1747924.64538961, rs2816938.199985368, rs2736098.1294086, rs17688601.40866663) and smoking (rs6537481.148396094). The allele score, as instrumental variable, included the remaining 33 SNPs.

Supplemental Table 11: Estimates for the causal association between T2DM and PC and *viceversa,* applying different Multivariable MRA methods, conducted among 1,162 cases and 752 controls with epidemiological and genetic data. T2DM status based on self-reported (SR) data.

	SR-based classification of T2DM status			
	Single MRA		Multivariable MRA	
	OR [95%CI][1]	OR [95%CI][1]	OR [95%CI][1]	OR [95%CI][1]
Diabetes-->PC	**LSDM (N=289)[2]**	**NODM (N=136)[2]**	**LSDM[2] (X1) + BMI (X2) -> PC**	**NODM[2] (X1) + BMI (X2) -> PC**
TSLS Estimates	1.08 [0,87;1.33]	1.07 [0.96;1.20]	1.08 [0.84;1.41]	1.06 [0.95;1.19]
Inverse-variance weighted method (IVW)	0.90 [0.77;1.07]	0.98 [0.96;1.02]	0.94 [0.80;1.10]	1.00 [0.99;1.01]
Mr-Egger regression	0.98 [0.74;1.30]	0.98 [0.96;1.02]	1.00 [0.76;1.30]	1.00 [0.99;1.01]
Mr-Egger Intercept	´-0.022; p=0.468	0.006; p=0.964	´-0.014; p=0.54	0.001; p=0.93
PC-->Diabetes			**PC (X1) + BMI (X2) -> NODM**	**PC (X1) + BMI (X2) -> LSDM**
TSLS Estimates	1.03 [0.99;1.06]	2.52 [2.05;3.03]	1.05 [0.90;1.20]	1.31 [1.10;1.52]
Inverse-variance weighted method (IVW)	1.12 [0.89;1.41]	1.57 [1.13;2.12]	1.20 [0.98;1.48]	1.58 [1.15;2.17]
Mr-Egger regression	1.09 [0.78;1.51]	0.94 [0.57;1.55]	1.21 [0.87;1.69]	1.19 [0.72;1.96]
Mr-Egger Intercept	0.007; p=0.81	0.090; p=0.027	´-0.002; p=0.93	0.063; p=0.14
PC-->Diabetes (without outliers)[3]			**PC (X1) + BMI (X2) -> NODM**	**PC (X1) + BMI (X2) -> LSDM**
TSLS Estimates	1.38 [0.95;1.99]	2.85 [2.04;3.98]		
Inverse-variance weighted method (IVW)	1.18 [0.93;1.51]	1.52 [1.08;2.13]	1.19 [0.97;1.42]	1.77 [1.46;2.08]
Mr-Egger regression	1.18 [0.84;1.66]	1.36 [0.80;2.32]	1.28 [0.87;1.87]	1.65 [0.98;2.77]
Mr-Egger Intercept	0.001; p=0.96	0.023; p=0.6	´-0.01; p=0.645	0.01; p=0.73

From the 57 T2DM-SNPs, 16 were excluded due to high LD with other SNPs (r2>0.8) (Supplementary Table 1), and 4 SNPs was excluded due to its association with smoking (rs2641348, rs13234407, rs1111875, rs2334499). The allele score, as instrumental variable, included the remaining 37 SNPs. SNPs associated with obesity were not excluded.

From the 40 PC-SNPs, 2 were excluded due to high LD (r2>0.8) (Supplementary Table 1), and 1 SNPs was excluded due to its association with smoking (rs6537481.148396094). The allele score, as instrumental variable, included the remaining 37 SNPs. SNPs associated with obesity were not excluded.

[1] All estimates were adjusted for age (<55, 55-65, 65-75, ≥75 years), gender, BMI (<25, 25-30, ≥30 kg/m2), smoking (never-smokers and tertiles of pack-years), country and the first five principal components for population ancestries.

[2] LSDM and NODM was evaluated in comparison to non-diabetics (1,489 subjects: 851 PC cases and 638 controls), with subjects classified as either NODM (N=136) or LSDM (N=289) being removed, respectively. BMI to define obesity (yes, no) two years before recruitment.

[3] Outliers removed: "rs1747924:64538961:C:A", "rs1486134:67639769:G:T", "rs17688601:40866663:C:A" for LDSM and "rs6971499" and "rs7310409" for NODM

Supplemental Table 12: Estimates for the observational and causal association between obesity measures and PC, applying different MRA methods, conducted among 1,162 cases and 752 controls with epidemiological and genetic data.

	SR-based classification of obesity status			
	BMI 2 years (N=343 obese)		BMI 50 years (N=401 obese)	
BMI-->PC	**OR [95%CI][1]**	***p-value***	**OR [95%CI][1]**	***p-value***
Observational association study				
BMI and PC	0.89 [0.69;1.14]	0.356	0.83 [0.64;1.07]	1.41E-01
BMI-allele score[2] and BMI in controls	1.11 [1.08;1.15]	3.06E-09	1.16 [1.12;1.21]	1.71E-11
BMI-allele score[2] and PC	1.01 [0.98;1.02]	0.927	1.01 [0.99;1.03]	0.311
Causal estimates: MR study				
MRA_Wald	1.01 [0.98;1.03]	0.927	1.07 [0.94;1.21]	0.311
TSLS Estimates	1.01 [0,85;1.20]	0.927	1.09 [0.95;1.25]	0.293
Inverse-variance weighted method (IVW)	1.01 [0.90;1.15]	0.828	1.03 [0.93;1.14]	0.542
Mr-Egger regression	0.98 [0.74;1.30]	0.794	0.97 [0.82;1.15]	0.705
Mr-Egger Intercept	0.009(0.015)	0.573	0.016 (0.017)	0.343
Weighted median	0.96 [0.80;1.32]	0.688	1.03 [0.88;1.20]	0.728
Simple median	1.10 [0.92;1.32]	0.278	1.05 [0.90;1.22]	0.554

[1] All estimates were adjusted for age (<55, 55-65, 65-75, ≥75 years), gender, smoking (never-smokers and tertiles of pack-years), country and the first five principal components for population ancestries.
[4] From the 126 obesity-SNPs, 30 were excluded due to high LD (r2>0.8) (Supplementary Table 1), and 11 SNPs were excluded due to their association with T2DM and smoking. The allele score, as instrumental variable, included the remaining 85 SNPs.
There were few obese subjects at age 20 years; BMI at this age was therefore not considered.

Supplemental Table 13: Results of causal mediation analyses evaluating mediator effects of T2DM on the obesity and PC association considering different obesity measures, and mediator effects of obesity on the T2DM and PC association. Estimates are derived from counterfactual models (2,018 cases and 1,540 controls) and MRA (1,162 cases and 752 controls with epidemiological and genetic data).

	OR[1]	[95%CI]	OR[1]	[95%CI]	OR[1]	[95%CI]	OR[1]	[095%CI]	OR[1]	[95%CI]	OR[1]	[95%CI]
Counterfactual model	**NDE**		**NIE**		**TE**		**NDE**		**NIE**		**TE**	
NODM mediator							**LSDM**	**mediator**				
Obese[2]	0.90	[0.73;1.10]	**1.04**	**[1.01;1,11]**	0.94	[0.77;1.17]	0.95	[0.80;1.15]	**1.05**	**[1.02;1.10]**	1.00	[0.84;1.22]
Overweight/obese[2]	**0.83**	**[0.71;0.98]**	**1.09**	**[1.08;1,13]**	0.91	[0.79;1.11]	0.92	[0.80;1.08]	**1.03**	**[1.01;1.06]**	0.95	[0.82;1.11]
Weight gain > 5 kg[3]	**0.82**	**[0.66;0.97]**	**1.08**	**[1.07;1.10]**	0.89	[0.72;1.07]	0.86	[0.70;1.03]	**1.05**	**[1.03;1.08]**	0.89	[0.74;1.08]
Weight loss[3]	1.04	[0.85;1.38]	0.95	[0.73;1.02]	1.00	[0.83;1.19]	0.98	[0.82;1.15]	**1.02**	**[1.00;1.04]**	1.00	[0.84;1.17]
Obese at age 50[3]	0.83	[0.67;1.01]	**1.07**	**[1.04;1,13]**	0.89	[0.73;1.08]	0.88	[0.72;1.07]	**1.07**	**[1.04;1.15]**	0.94	[0.78;1.14]
Overweight/obese at age 50[3]	**1.21**	**[1.01;1.44]**	1.03	[0.98;1.08]	**1.25**	**[1.07;1.51]**	**1.18**	**[1.01;1.37]**	**1.04**	**[1.03;1.07]**	**1.23**	**[1.06;1.43]**
Obese[2] mediator							**Overweight/obese[2] mediator**					
NODM	**5.92**	**[3.69;9.14]**	0.97	[0.78;1.01]	**5.72**	**[3.76;9.11]**	**10.14**	**[5.48;22.69]**	**0.55**	**[0.23;0.92]**	**5.58**	**[3.65;8.92]**
LSDM	**1.65**	**[1.34;2.03]**	1.02	[0.99;1.07]	**1.68**	**[1.37;2.06]**	**1.61**	**[1.31;2.00]**	**1.03**	**[1.01;1.08]**	**1.67**	**[1.35;2.06]**
Obese at age 50[3] mediator							**Overweight/obese at age 50[3] mediator**					
NODM	**4.99**	**[2.54;10.87]**	0.87	[0.43;1.04]	**4.35**	**[2.35;9.65]**	**4.27**	**[2.14;8.08]**	**1.08**	**[1.03;1.12]**	**4.63**	**[2.66;10.82]**
LSDM	**1.53**	**[1.13;2.09]**	0.99	[0.87;1.07]	**1.50**	**[1.14;2.17]**	**1.38**	**[1.08;1.94]**	**1.09**	**[1.03;1.15]**	**1.49**	**[1.17;2.02]**
Counterfactual IV	**NDE**		**NIE**		**TE**		**NDE**		**NIE**		**TE**	
NODM mediator							**LSDM**	**mediator**				
Obese[2]	0.83	[0.63;1.15]	1.03	[1.00;1.11]	0.85	[0.68;1.24]	0.88	[0.63;1.27]	1.02	[0.99;1.04]	0.89	[0.68;1.27]
Overweight/obese[2]	0.93	[0.72;1.12]	1.05	[1.00;1.08]	0.97	[0.81;1.26]	0.98	[0.81;1.27]	1.01	[0.99;1.02]	0.98	[0.79;1.27]
Weight gain > 5 kg[3]	1.15	[0.68;1.53]	1.03	[1.00;1.07]	1.19	[0.68;1.56]	1.16	[0.94;1.58]	1.02	[1.00;1.03]	1.18	[0.95;1.78]
Weight loss[3]	1.20	[0.96;1.69]	**0.94**	**[0.90;0.98]**	1.13	[0.92;1.48]	1.13	[0.88;1.35]	1.01	[0.99;1.02]	1.14	[0.88;1.39]
Obese at age 50[3]	0.82	[0.66;1.22]	1.06	[1.00;1.12]	0.87	[0.70;1.31]	0.84	[0.66;1.12]	1.02	[1.00;1.06]	0.86	[0.68;1.13]
Overweight/obese at age 50[3]	**1.44**	**[1.18;1.89]**	1.03	[1.00;1.06]	**1.49**	**[1.23;1.96]**	**1.47**	**[1.17;1.88]**	**1.02**	**[1.01;1.03]**	**1.49**	**[1.19;1.90]**
Obese[2] mediator							**Overweight/obese[2] mediator**					
NODM	**5.06**	**[3.15;13.19]**	0.92	[0.40;1.01]	**4.67**	**[2.97;9.77]**	**8.21**	**[6.64;11.58]**	**0.53**	**[0.38;0.75]**	**4.37**	**[3.02;7.75]**
LSDM	**1.46**	**[1.02;1.91]**	1.02	[0.97;1.07]	**1.47**	**[1.07;2.01]**	**1.45**	**[1.12;2.18]**	1.01	[0.94;1.04]	**1.46**	**[1.22;2.29]**
Obese at age 50[3] mediator							**Overweight/obese at age 50[3] mediator**					
NODM	**5.01**	**[3.02;12.20]**	0.86	[0.37;1.06]	**4.32**	**[2.78;8.77]**	**4.28**	**[2.72;9.79]**	**1.09**	**[1.05;1.20]**	**4.68**	**[3.04;11.49]**
LSDM	**1.51**	**[1.24;2.20]**	0.98	[0.87;1.04]	**1.49**	**[1.25;2.32]**	**1.37**	**[0.88;1.81]**	**1.08**	**[1.03;1.16]**	**1.48**	**[1.07;2.15]**

CI, confidence interval; TE, marginal total effect; NDE, natural direct effect; NIE, natural indirect effect;
[1] All estimates were adjusted for age (<55, 55-65, 65-75, ≥75 years), gender, smoking (never-smokers and tertiles of pack-years), country, and the first five principal components for population ancestries in network MRA
[2] Obesity status defined based on BMI 2 years before recruitment
[3] Obesity-related variables based on information collected at age 50 years, such as weight gain from age 20 to 50 and weight loss since age 50 years
Significant estimates are marked in bold.

Supplemental Table 14: Association between diabetes-related variables and PC risk in the PanGenEU study (2,018 cases and 1,540 controls). Unimputed data.

	Cases N=2,018		Controls N=1,540			Model1		Model2	
	N	%	N	%	p-value[1]	OR	[95%CI]	OR	[95%CI]
Diabetes status					<0.001				
no diabetes	1479	73.30	1340	87.00		Ref.		Ref.	
yes	498	24.70	184	11.90		2.60	[2.13;3.18]	2.55	[2.04;3.18]
Missing	41	2.03	16	1.04					
Diabetes status by subtype					<0.001				
no diabetes	1479	73.30	1340	87.00		Ref.		Ref.	
yes, ≤ 2 years (NODM)	200	9.91	27	1.75		6.41	[4.2;9.79]	6.43	[4.06;10.2]
yes, > 2years (LSDM)	265	13.10	152	9.87		1.82	[1.45;2.3]	1.77	[1.37;2.28]
Missing	74	3.67	21	1.36					
Family history of diabetes[2]									
no diabetes	1069	58.0	821	65.7		Ref.		Ref.	
yes	594	32.2	357	28.6		1.24	[1.04;1.49]	1.14	[1.00;1.38]
Missing	182	9.9	72	5.8					
Diabetes by age at diagnosis[3]					<0.001				
no diabetes	1479	73.30	1340	87.00		Ref.		Ref.	
≤ 55 years	141	6.99	72	4.68		1.66	[1.21;2.28]	1.59	[1.12;2.26]
55 to ≤ 65 years	138	6.84	50	3.25		2.48	[1.74;3.55]	2.48	[1.69;3.64]
> 65 years	197	9.76	58	3.77		3.97	[2.88;5.54]	3.79	[2.67;5.44]
Missing	63	3.12	20	1.30	*p-trend*	2E-16		2E-16	
Diabetes by time since diagnosis[3]					<0.001				
no diabetes	1479	73.30	1340	87.0		Ref.		Ref.	
≤1	159	7.88	12	0.78		10.98	[6;20.09]	9.39	[5.08;17.34]
1 to ≤2	41	2.03	15	0.97		2.64	[1.4;4.97]	3.19	[1.56;6.52]
2 to ≤5	71	3.52	32	2.08		2.38	[1.54;3.75]	2.43	[1.52;3.94]
5 to ≤10	86	4.26	36	2.34		2.43	[1.60;3.73]	2.41	[1.52;3.86]
10 to ≤20	56	2.78	40	2.60		1.50	[0.96;2.33]	1.38	[0.85;2.25]
>20	52	2.58	44	2.86		1.21	[0.78;1.90]	1.11	[0.67;1.81]
Missing	74	3.67	21	1.36	*p-trend*	1.5E-06		4.5E-05	
Diabetes control measures									
Diet					<0.001				
no diabetes	1479	73.30	1340	87.00		Ref.		Ref.	
yes	297	14.70	133	8.64		2.50	[1.98;3.15]	2.44	[1.9;3.14]
no use	118	5.85	49	3.18		2.41	[1.68;3.46]	2.38	[1.6;3.55]
Missing	124	6.14	18	1.17					
Use of oral medication					<0.001				
no diabetes	1479	73.30	1340	87.00		Ref.		Ref.	
yes	304	15.10	130	8.44		2.36	[1.86;2.99]	2.24	[1.73;2.9]
no use	140	6.94	50	3.25		3.00	[2.12;4.24]	3.21	[2.17;4.74]
Missing	95	4.71	20	1.30					
Use of insulin					<0.001				
no diabetes	1479	73.30	1340	87.00		Ref.		Ref.	
yes	236	11.70	59	3.83		4.26	[3.12;5.81]	4.18	[2.97;5.89]
no use	195	9.66	119	7.73		1.77	[1.37;2.28]	1.77	[1.34;2.35]
Missing	108	5.35	22	1.43					

[1] Differences between groups evaluated by the Chi-square test

[2] Information on family history of diabetes was not collected in Ireland; results are based on data for 1,845 cases and 1,250 controls

[3] Linear association for age since T2DM diagnosis and nonlinear association for time since T2DM (Supplemental Figure 1)

Model 1: adjusted for age (<55, 55-65, 65-75, ≥75 years), gender, country.

Model 2: Model 1 also adjusted for pack years (never-smokers and tertiles of pack-years) and BMI (<25, 25-30, ≥30 kg/m^2)

Supplemental Table 15: Estimates for the observational and causal association between T2DM and PC and *vice versa*, applying different MRA methods, conducted among 1,162 cases and 752 controls with epidemiological and genetic data. T2DM status based on self-reported (SR) and biomarker data.

	SR + biomarker-based classification of T2DM status					SR + biomarker -based classification of T2DM status				
	LSDM (N=289)[1]		NODM (N=190)[1]			LSDM (N=289)[1]		NODM (N=190)[1]	
Diabetes-->PC	**OR [95%CI][2]**	***p-value***	**OR [95%CI][2]**	***p-value***	**PC-->Diabetes**	**OR [95%CI][2]**	***p-value***	**OR [95%CI][2]**	***p-value***
Observational association study					**Observational association study**				
T2DM and PC	1.50 [1.14;1.98]	0.003	5.08 [3.27;7.90]	4.40E-13	PC and T2DM	1.51 [1.15;2.00]	0.003	5.15 [3.31;8.00]	3.22E-13
T2DM-allele score[3] and T2DM in controls	1.11 [1.05;1.16]	3.73E-04	1.23 [1.13;1.33]	4.74E-05	PC-allele score[4] and PC (without T2DM)	1.10 [0.75;1.45]	1.54E-08	1.09 [1.07;1.13]	1.54E-08
T2DM-allele score[3] and PC	1.02 [0.99;1.05]	0.146	0.99 [0.96;1.02]	0.461	PC-allele score[4] and T2DM	1.03 [0.99;1.06]	0.119	1.07 [1.03;1.11]	0.0014
Causal estimates: MR study					**Causal estimates: MR study**				
MRA_Wald	1.21 [0.95;1.47]	0.146	0.95 [0.96;1.02]	0.461	MRA_Wald	1.32 [0.97;1.67]	0.12	2.01 [1.58;2.43]	0.0014
T2LS Estimates	1.19 [0.92;1.54]	0.194	0.95 [0.84;1.08]	0.461	T2LS Estimates	1.03 [0.99;1.06]	0.12	2.86 [2.07;3.97]	2.37E-10
Inverse-variance weighted method (IVW)	1.06 [0.79;1.42]	0.708	0.99 [0.93;1.05]	0.725	Inverse-variance weighted method (IVW)	1.12 [0.89;1.41]	0.316	1.29 [0.98;1.70]	0.078
Mr-Egger regression	1.31 [0.80;2.15]	0.278	1.00 [0.94;1.06]	0.921	Mr-Egger regression	1.05 [0.76;1.47]	0.756	0.83 [0.55;1.26]	0.382
Mr-Egger Intercept	´-0.049 (0.045)	0.283	´-0.019 (0.029)	0.538	Mr-Egger Intercept	0.015 (0.028)	0.604	0.095 (0.034)	0.005
Weighted median	0.97 [0.72;1.30]	0.823	1.00 [0.96;1.04]	0.812	Weighted median	1.22 [0.88;1.17*	0.238	1.16 [0.78;1.75]	0.446
Simple median	1.20 [0.86;1.70]	0.284	1.00 [0.85;1.17]	0.95	Simple median	1.55 [1.00;2.32]	0.05	1.56 [0.96;2.54]	0.075

[1] LSDM and NODM was evaluated in comparison to non-diabetics after reclassifying T2DM status with the biomarker data (obtained for 654 subjects with epidemiological and genetic data), with subjects reclassified as either NODM (N=190) or LSDM (N=289) being removed, respectively.
[2] All estimates were adjusted for age (<55, 55-65, 65-75, ≥75 years), gender, BMI (<25, 25-30, ≥30 kg/m2), smoking (never-smokers and tertiles of pack-years), country and the first five principal components for population ancestries.
[3] From the 57 T2DM-SNPs, 16 were excluded due to high LD with other SNPs (r2>0.8) (Supplementary Table 1), and 6 SNPs were excluded due to their association with BMI (rs10830963, rs4430796) and smoking (rs2641348, rs13234407, rs1111875, rs2334499). The allele score, as instrumental variable, included the remaining 35 SNPs.
[4] From the 40 PC-SNPs, 2 were excluded due to high LD (r2>0.8), and 5 SNPs were excluded due to their association with BMI (rs1747924.64538961, rs2816938.199985368, rs2736098.1294086, rs17688601.40866663) and smoking (rs6537481.148396094). The allele score, as instrumental variable, included the remaining 33 SNPs.

Removal of SNPs potentially associated with other traits (at p-value 10-8) according to PhenoScanner database led to similar results.

Supplemental Table 16: Estimates for the observational and causal association between T2DM and PC and *vice versa*, after removing other potential pleiotropic variants and outliers (based on Cook´s distances) and applying different MRA methods, conducted among 1,162 cases and 752 controls with epidemiological and genetic data. T2DM status based on self-reported (SR) data.

	SR-based classification of T2DM status					SR-based classification of T2DM status				
Diabetes-->PC	**LSDM (N=289)[1] OR [95%CI][2]**	***p-value***	**NODM (N=136)[1] OR [95%CI][2]**	***p-value***		**PC-->Diabetes**	**LSDM (N=289)[1] OR [95%CI][2]**	***p-value***	**NODM (N=136)[1] OR [95%CI][2]**	***p-value***
Observational association study						**Observational association study**				
T2DM and PC	1.43 [1.09;1.88]	0.011	6.10 [3.45;10.8]	<0.001		PC and T2DM	1.45 [1.10;1.91]	0.008	6.08 [3.44;10.7]	4.80E-10
T2DM-allele score[3] and T2DM in controls	1.16 [1.09;1.22]	1.42E-05	1.32 [1.15;1.48]	0.001		PC-allele score[4] and PC (without T2DM)	1.10 [1.06;1.13]	4.10E-08	1.10 [1.06;1.13]	3.10E-08
T2DM-allele score[3] and PC	1.00 [0.97;1.03]	9.93E-01	1.01 [0.98;1.05]	0.389		PC-allele score[4] and T2DM	1.03 [1.00;1.06]	0.09	1.08 [1.03;1.13]	0.0023
Causal estimates: MR study						**Causal estimates: MR study**				
MRA_Wald	1.00 [0.79;1.22]	0.273	1.05 [0.99;1.09]	0.389		MRA_Wald	1.38 [0.99;1.74]	0.09	2.47 [1.71;2.74]	0.00053
TSLS Estimates	0.98 [0.79;1.22]	0.864	1.05 [0.93;1.19]	0.39		TSLS Estimates	1.38 [0.95;1.99]	0.09	2.85 [2.04;3.98]	2.80E-09
Inverse-variance weighted method (IVW)	0.92 [0.79;1.08]	0.315	1.00 [0.96;1.02]	0.538		Inverse-variance weighted method (IVW)	1.18 [0.93;1.51]	0.16	1.52 [1.08;2.13]	0.016
Mr-Egger regression	1.00 [0.77;1.20]	0.992	0.98 [0.96;1.02]	0.534		Mr-Egger regression	1.18 [0.84;1.66]	0.348	1.36 [0.80;2.32]	0.251
Mr-Egger Intercept	0.019 (0.025)	0.448	0.001 (0.018)	0.936		Mr-Egger Intercept	0.001 (0.028)	0.963	0.023 (0.043)	0.06
Weighted median	0.96 [0.74;1.24]	0.481	1.01 [0.95;1.04]	0.966		Weighted median	1.18 [0.84;1.67]	0.321	1.43 [0.88;2.33]	0.15
Simple median	0.86 [0.69;1.07]	0.174	1.02 [0.92;1.11]	0.735		Simple median	1.51 [1.00;2.27]	0.052	2.84 [2.27;3.41]	<0.001

[1] LSDM and NODM was evaluated in comparison to non-diabetics (1,489 subjects: 851 PC cases and 638 controls), with subjects classified as either NODM (N=136) or LSDM (N=289) being removed, respectively.
[2] All estimates were adjusted for age (<55, 55-65, 65-75, ≥75 years), gender, BMI (<25, 25-30, ≥30 kg/m2), smoking (never-smokers and tertiles of pack-years), country and the first five principal components for population ancestries.
[3] From the 57 T2DM-SNPs, 16 were excluded due to high LD with other SNPs (r2>0.8) (Supplementary Table 1), and 6 SNPs were excluded due to their association with BMI (rs10830963, rs4430796) and smoking (rs2641348, rs13234407, rs1111875, rs2334499). In addition, 3 SNPs potentially being outliers were removed (rs2191348, rs13266634, rs7965349). The allele score, as instrumental variable, included the remaining 32 SNPs.
[4] From the 40 PC-SNPs, 2 were excluded due to high LD (r2>0.8) (Supplementary Table 1), and 5 SNPs were excluded due to their association with BMI (rs1747924.64538961, rs2816938.199985368, rs2736098.1294086, rs17688601.40866663) and smoking (rs6537481.148396094). In addition, 2 SNPs potentially being outliers were removed (chr12_121454622, chr16_75263661). The allele score, as instrumental variable, included the remaining 31 SNPs.

Supplemental Table 17: Magnitudes of the E-value for different combinations of the Exposure-Confounder Association RREU and the Confounder-Outcome Association RRUD for the estimation of the causal effect of NODM on PC (OR=6.39 (4.18;9.78)) and of LSDM on PC (OR=1.86 (1.49;2.32)).

NODM

E-value		RR_{UD}								
		3.5	**6.5**	**9.5**	**12.5**	**15.5**	**18.5**	**21.5**	**24.5**	**27.5**
RR_{EU}	**3.5**	2,04	2,53	2,77	2,92	3,01	3,08	3,14	3,18	3,21
	6.5	2,53	3,52	4,12	4,51	4,80	5,01	5,18	5,31	5,42
	9.5	2,77	4,12	5,01	5,65	6,14	6,51	6,81	7,05	7,26
	12.5	2,92	4,51	5,65	6,51	7,18	7,71	8,14	8,51	8,81
	15.5	3,01	4,80	6,14	7,18	8,01	8,69	9,26	9,74	10,15
	18.5	3,08	5,01	6,51	7,71	8,69	9,51	10,20	10,79	11,31
	21.5	3,14	5,18	6,81	8,14	9,26	10,20	11,01	11,71	12,32
	24.5	3,18	5,31	7,05	8,51	9,74	10,79	11,71	12,51	13,21
	27.5	3,21	5,42	7,26	8,81	10,15	11,31	12,32	13,21	14,00

LSDM

E-value		RR_{UD}									
		1.5	**2.5**	**3.5**	**4.5**	**5.5**	**6.5**	**7.5**	**8.5**	**9.5**	**10.5**
RR_{EU}	**1.5**	1,13	1,25	1,31	1,35	1,38	1,39	1,41	1,42	1,43	1,43
	2.5	1,25	1,56	1,75	1,88	1,96	2,03	2,08	2,13	2,16	2,19
	3.5	1,31	1,75	2,04	2,25	2,41	2,53	2,63	2,70	2,77	2,83
	4.5	1,35	1,88	2,25	2,53	2,75	2,93	3,07	3,19	3,29	3,38
	5.5	1,38	1,96	2,41	2,75	3,03	3,25	3,44	3,60	3,73	3,85
	6.5	1,39	2,03	2,53	2,93	3,25	3,52	3,75	3,95	4,12	4,27
	7.5	1,41	2,08	2,63	3,07	3,44	3,75	4,02	4,25	4,45	4,63
	8.5	1,42	2,13	2,70	3,19	3,60	3,95	4,25	4,52	4,75	4,96
	9.5	1,43	2,16	2,77	3,29	3,73	4,12	4,45	4,75	5,01	5,25
	10.5	1,43	2,19	2,83	3,38	3,85	4,27	4,63	4,96	5,25	5,51

Supplemental Figure 1: Directed acyclic graphs illustrating the single MR and multivariable and network MR approaches used to explore causal associations and mediation in the causal pathways between T2DM, obesity and PC.

A: Observational association between T2DM (Exposure) and PC (Outcome)

B: Single Mendelian Randomization (MR) between T2DM (Exposure) and PC (Outcome)

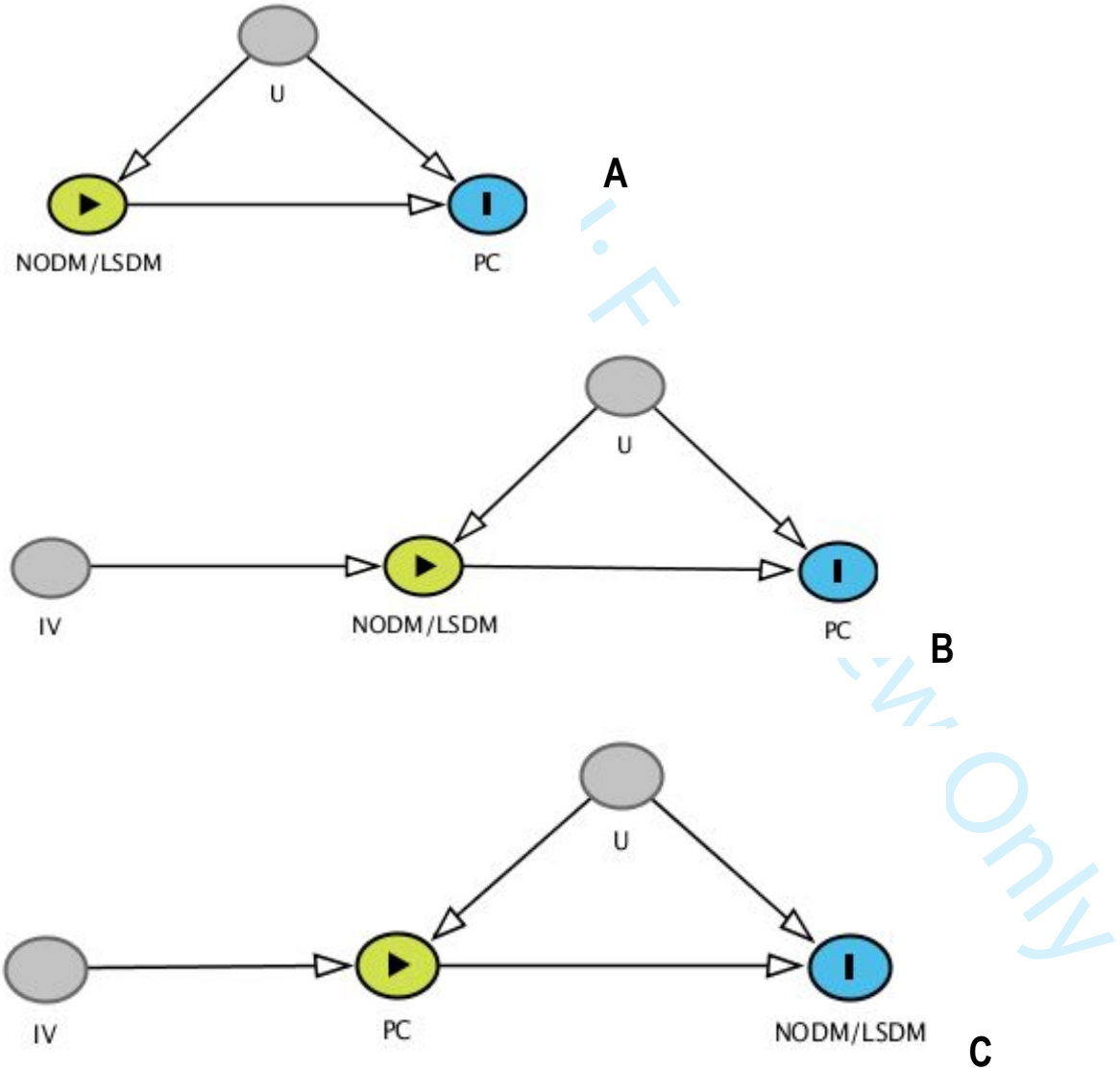
C: Single Mendelian Randomization (MR) between PC (Exposure) and T2DM (Outcome) – bidirectional MR

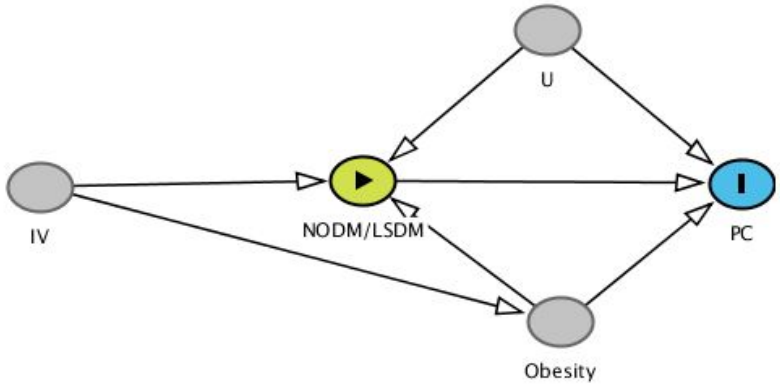
D: Multivariable Mendelian Randomization (MR) between T2DM (Exposure) and PC (Outcome)

E: Multivariable Mendelian Randomization (MR) between PC (Exposure) and T2DM (Outcome) – bidirectional MR

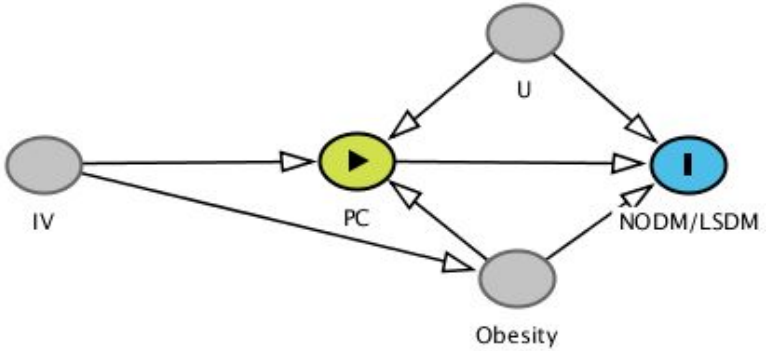
F: Network Mendelian Randomization (MR) between T2DM (Exposure), Obesity (Mediator) and PC (Outcome)

G: Network Mendelian Randomization (MR) between Obesity (Exposure), T2DM (Mediator) and PC (Outcome)

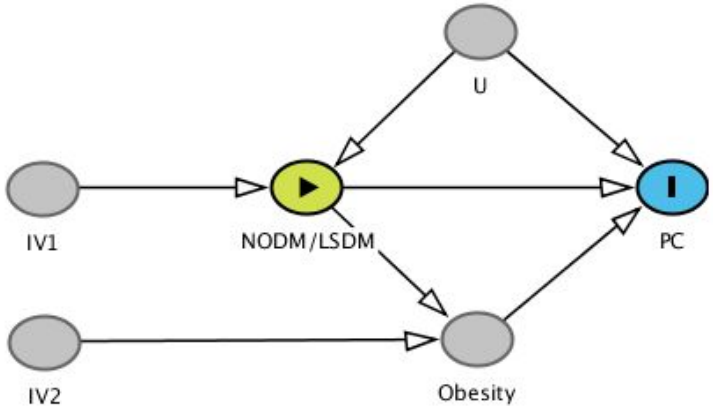



U
IV
NODM/LSDM
PC
Obesity

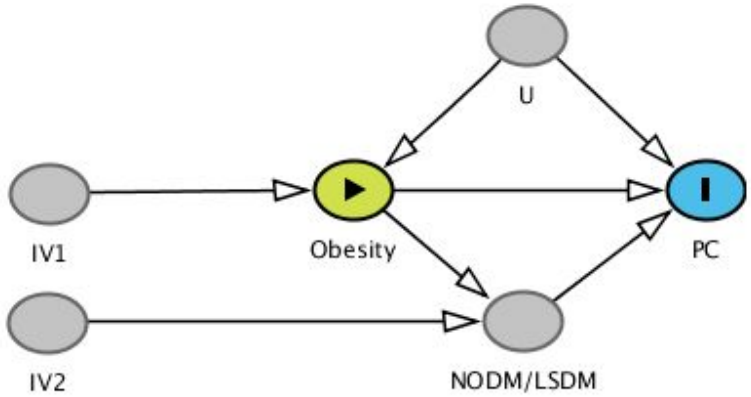
D


U
IV
PC
NODM/LSDM
Obesity

E

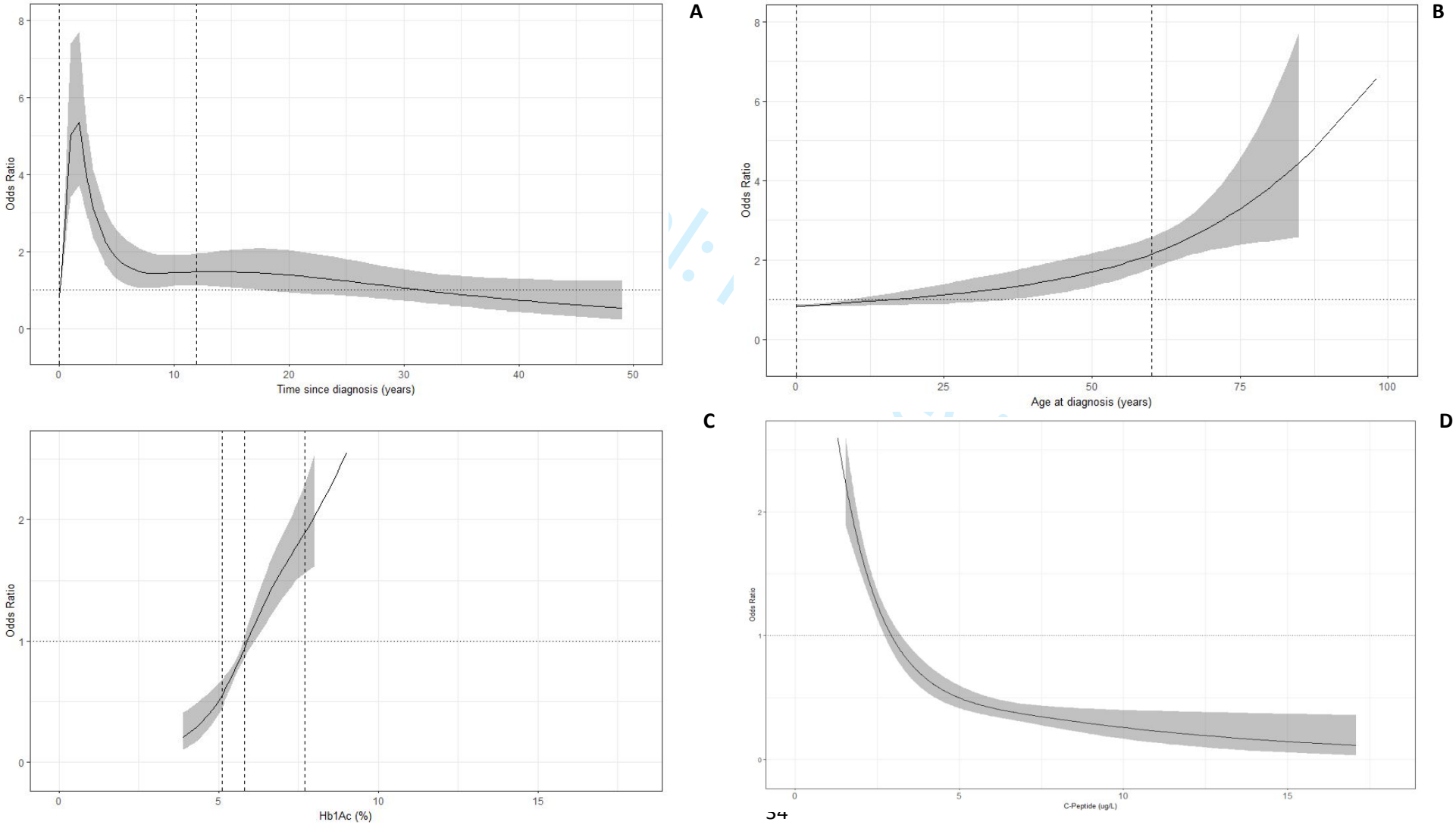

U
IV1
NODM/LSDM
PC
IV2
Obesity

F


U
IV1
Obesity
PC
IV2
NODM/LSDM

G

Supplemental Figure 2: Linear and Non-linear association between T2DM-related continuous variables and pancreatic cancer risk, with non-diabetics as a reference group: (A) time since T2DM diagnosis; (B) age at T2DM diagnosis; (C) Hb1Ac levels and (D) C-Peptide levels with the minimum value (Hb1Ac=4; C-Peptide=0.05) as the reference group.



Supplemental Figure 3: Pleiotropy visualization plots regarding the directional association between PC and NODM risk.

A: funnel plot for IV made up of SNPs without SNPs in LD and SNPs associated with obesity and smoking. **B:** funnel plot for IV excluding further SNPs that were outliers (based on Cooks distances). Y-axes represent SNP to outcome effect corrected by SNP to exposure standard error of the effect. X-axes (SNP to exposure effect) are in logarithmic scale. **C:** Correlation plot of per-allele associations (genetic score of the IV) with the outcome and exposure. **D:** Forest plot of per-allele MR effect size for exposure on outcome and **E:** leave-one-out analyses.