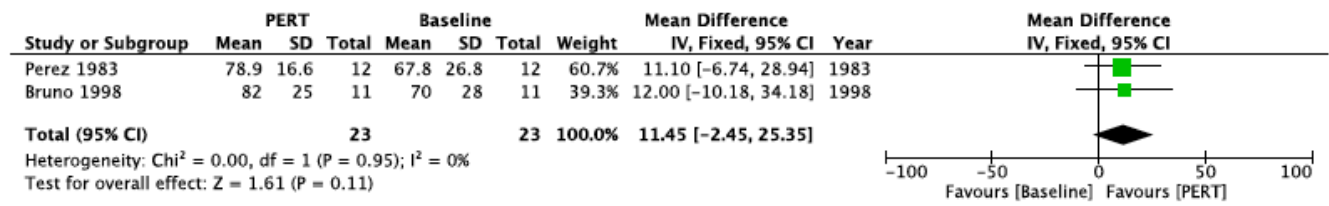
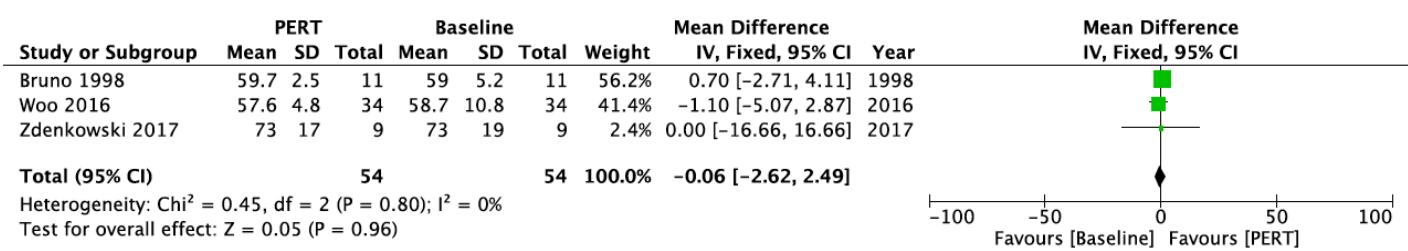


Supplementary Figure 1 A

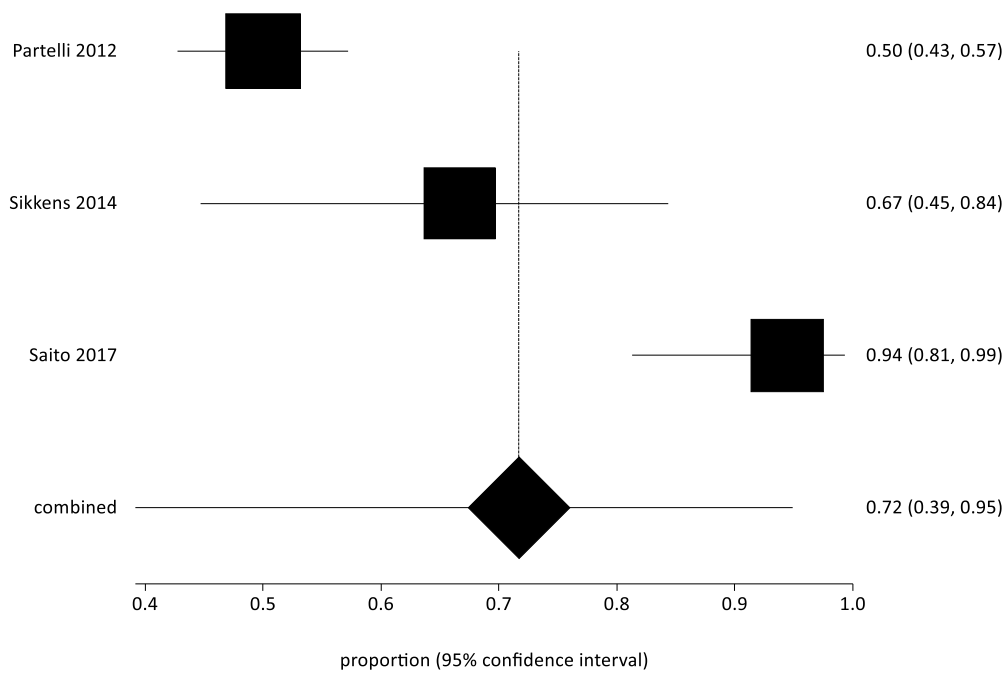


Supplementary Figure 1 B

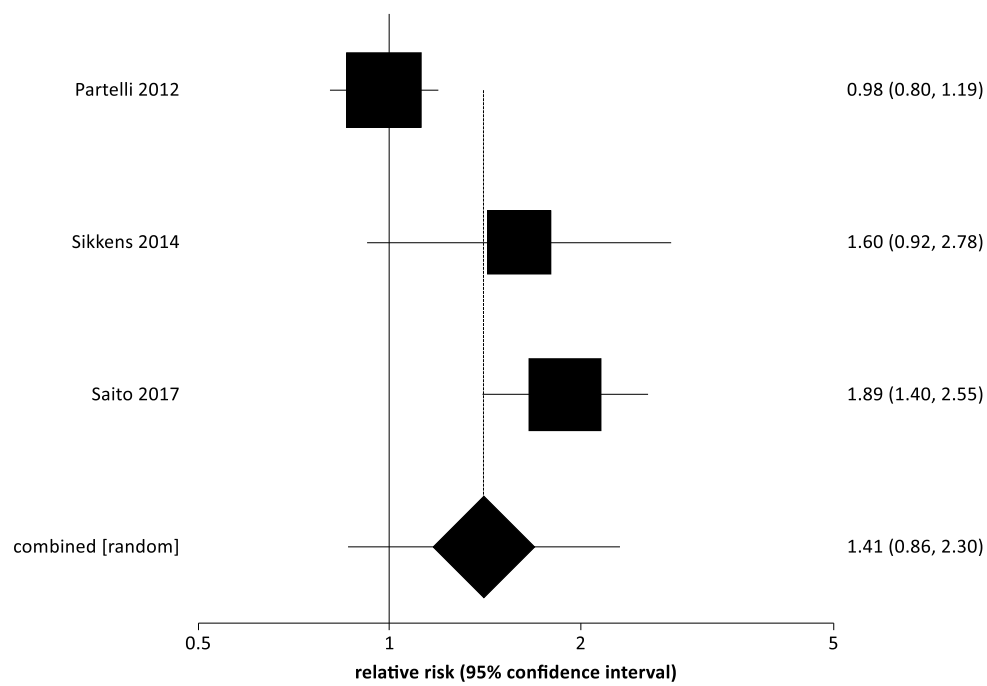


Supplementary Figure 2

A

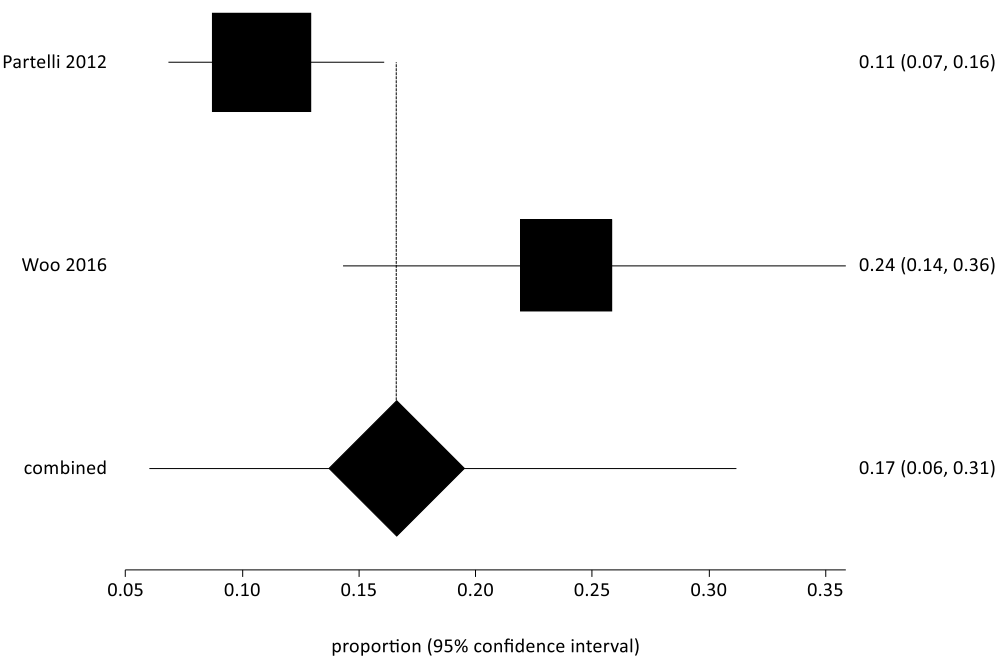


B

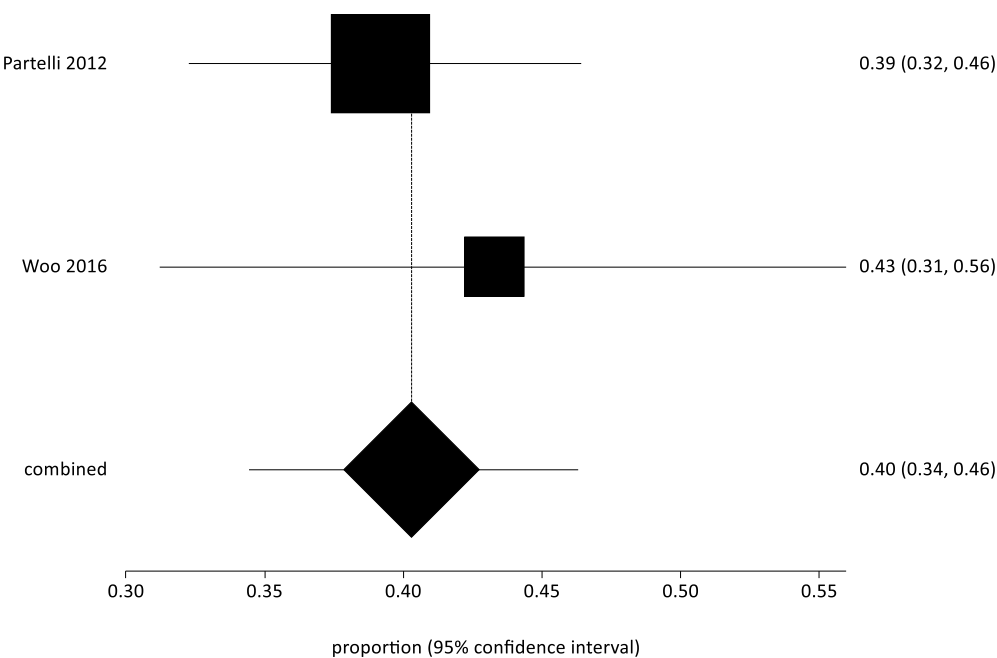


Supplementary Figure 3

A

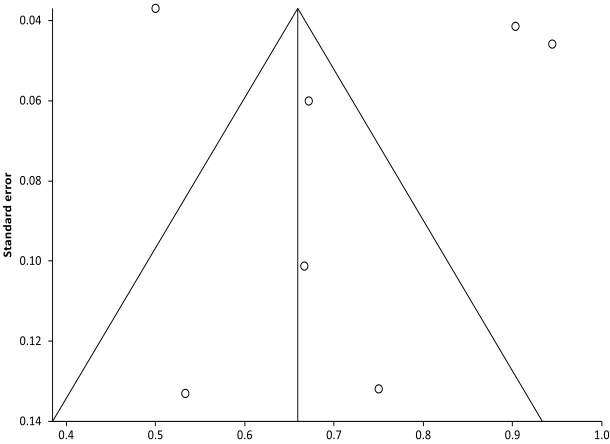


B

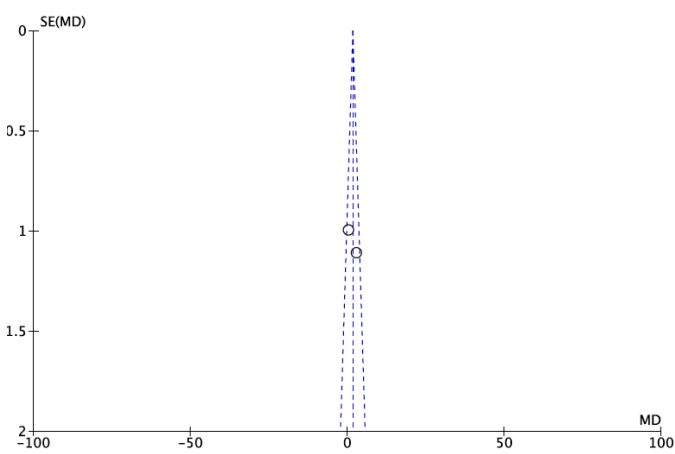


Supplementary Figure 4

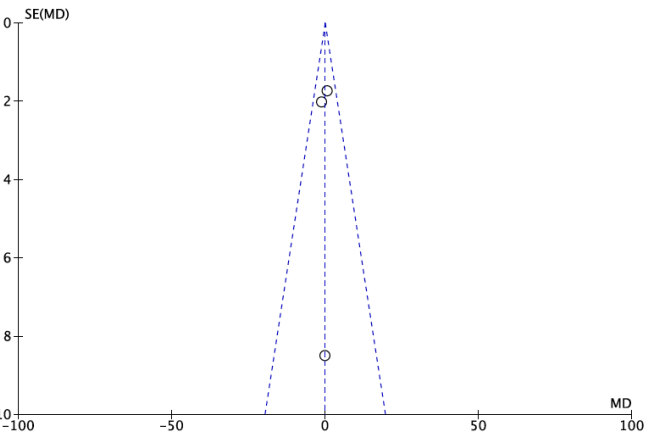
A



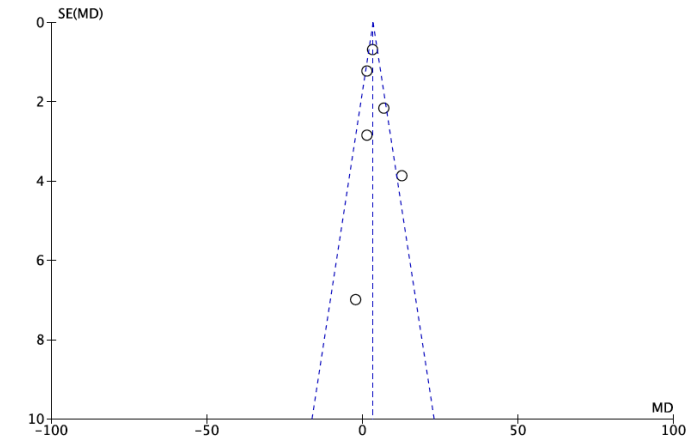
D



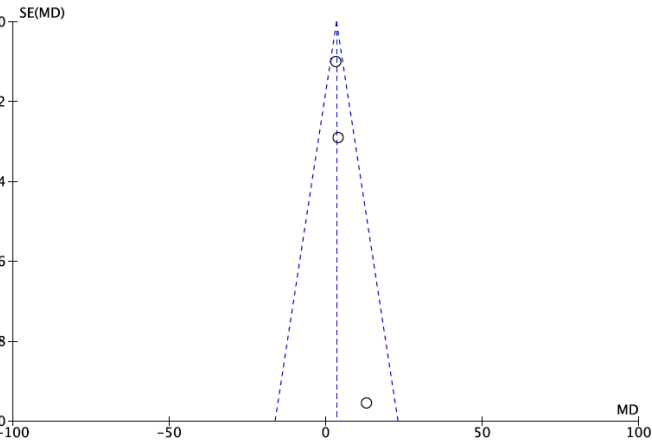
B



E



C



Supplementary Table 1A. Quality assessment of included cohort studies by the Newcastle-Ottawa scale

| | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts |
|---------------------------------|--|-------------------------------------|---------------------------|--|---|-----------------------|---|----------------------------------|
| Dominguez-Munoz 2018 | + | + | + | ? | + | + | + | ? |
| Landers 2019 | + | + | + | ? | + | + | + | + |
| Partelli 2012 | + | + | + | + | + | + | + | + |
| Salto 2017 | + | + | + | + | + | + | + | ? |
| Sikkens 2014 | + | + | + | ? | ? | + | + | + |
| Witvliet-van Nierop 2018 | + | + | + | ? | ? | + | ? | ? |

Risk of bias of included cohort studies. Risk of bias were assessed base on Newcastle-Ottawa Scale. Green dots indicate low risk of bias; yellow dots indicate unclear risk of bias and red dots indicate high risk of bias.

Supplementary Table 1B. Quality Assessment of Included Randomized Controlled Trials by the Jadad Score

| | Randomization | Double blinding | Drop-out or withdrawal | Allocation concealment |
|------------------------|---------------|-----------------|------------------------|------------------------|
| Bruno 1998 | ? | + | - | ? |
| Salto 2018 | + | - | + | ? |
| Woo 2016 | ? | + | + | ? |
| Zdenkowski 2017 | + | + | - | ? |

Risk of bias of included randomized clinical trials. Risk of bias were assessed based on Jada scale. Green dots indicated low risk of bias (2 points in Jadad scale); yellow dots indicate unclear risk of bias (1 point in Jadad scale) and red dots indicate high risk of bias (0 point in Jadad scale)

Supplementary Table 2. Results of Subgroup Analyses

| Subgroups | No. of studies | No. of patients | No. of PEI | Effect estimate | Heterogeneity | |
|----------------------|----------------|-----------------|------------|--------------------------------|-------------------------|----------------|
| | | | | Pool prevalence, % (95% CI) | <i>I</i> ² % | <i>P</i> value |
| High quality studies | 7 | 410 | 265 | 72 (55-86) | 90 | < .0001 |
| Sample size ≥ 30 | 4 | 359 | 232 | 77 (53-94) | 95 | < .0001 |
| Western population | 4 | 245 | 130 | 57 (46-67) | 35 | .198 |
| Eastern population | 3 | 165 | 135 | 85 (66-97) | 87 | .0004 |
| RCT studies | 2 | 129 | 101 | 79 (53-96) | 91 | < .0001 |

PEI, pancreatic exocrine insufficiency; CI, confidence interval; RCT; randomized control trial

Supplementary Table 3. Results of Sensitivity Analyses

| Variables | No. of studies | No. of patients | No. of PEI | Effect estimate | Heterogeneity | |
|------------------------------------|----------------|-----------------|------------|--------------------------------|-------------------------|----------------|
| | | | | Pool prevalence, % (95% CI) | <i>I</i> ² % | <i>P</i> value |
| Studies used direct test for EPI | 4 | 310 | 179 | 65 (50-79) | 81 | < .0013 |
| Studies used indirect test for EPI | 4 | 125 | 107 | 81 (64-94) | 77 | < .0051 |
| Studies used only FE-1 test | 3 | 285 | 158 | 60 (46-72) | 72 | .027 |

PEI, pancreatic exocrine insufficiency; CI, confidence interval; FE-1, fecal elastase-1.

Supplementary Table 4. Results of Meta-regression Analyses

| | Pooled prevalence (95% CI), <i>P</i> value ^a | | | | | | |
|---------------------------|---|--------------------------------|--------------------------------|----------------------------------|-------------------------------|-------------------------------|-------------------------------------|
| | Year of publication | Sex (men, %) | Age (year) | Population (Western) | Population > 30 | Type of PEI test | Adjusted R-squared ^b (%) |
| Univariate | 0.003 (-0.022 to 0.028), 0.782 | 0.008 (-0.031 to 0.048), 0.598 | 0.044 (-0.001 to 0.09), 0.055 | -0.286 (-0.549 to -0.023), 0.038 | 0.074 (-0.421 to 0.57), 0.716 | 0.297 (0.018 to 0.576), 0.041 | |
| Multivariate ^c | | | 0.022 (-0.001 to 0.045), 0.054 | -0.139 (-0.309 to 0.031), 0.080 | | 0.167 (0.008 to 0.324), 0.044 | 87 |

CI, confidence interval; PEI, pancreatic exocrine insufficiency.

^aTwo-sided *P* value.

^bProportion of variability between studies explained.

^cIncluded covariates in the full model which have more influence in the heterogeneity.

Pubmed:

((pancreatic cancer[Title/Abstract]) OR (pancreatic neoplasm[Title/Abstract]) OR (carcinoma, pancreatic ductal [MeSH])) AND ((pancreatic function[Title/Abstract]) OR (exocrine pancreatic function[Title/Abstract]) OR (pancreatic insufficiency[MeSH Terms]) OR (exocrine pancreatic insufficiency[MeSH Terms]) OR (pancreas function[Title/Abstract]) OR (pancreas dysfunction[Title/Abstract]) OR (enzyme replacement therapy [MeSH Terms]) OR (Exocrine Pancreatic Insufficiency/drug therapy[MAJR]) OR (Enzyme Therapy[MAJR]))

Scopus:

(TITLE-ABS-KEY (pancreas PRE/3 cancer OR "pancreatic cancer" OR "pancreas neoplasm") AND TITLE-ABS-KEY ("exocrine pancreatic funct*" OR "exocrine insuffien*" OR "exocrine pancreatic insufficien*" OR "pancrea* insufficien*" OR "pancrea* funct*" OR "pancrea* dysfunct*" OR "enzyme replacement therap*")) AND (LIMIT-TO(EXACTKEYWORD, "Human"))

Embase:

((pancreas adj3 cancer).ti,sh. or (pancreatic adj3 cancer).ab,ti,sh. or (pancreas adj3 neoplasm).ab,ti,sh.) and ((exocrine pancreatic function or exocrine pancreatic insufficiency).ab,ti,sh. or pancrea* insufficien*.ab,sh,ti. or pancrea* funct*.ab,ti,sh. or pancrea* dysfunct*.ab,ti,sh. or enzyme replacement therapy.ti,sh.) and human.sh.