Childhood body mass index and risk of adult pancreatic cancer

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Abbreviations:

BMI: body mass index

CI: confidence intervals

HR: hazard ratios

NIH-AARP: American National Institutes of Health-AARP Diet and Health Study Cohort
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Running title: Child body size and pancreatic cancer risk

MeSH keywords: body mass index, childhood, cohort, height, pancreatic cancer
Abstract

Background: Excess weight in adulthood is one of the few modifiable risk factors for pancreatic cancer, and height has associations as well. This leads to question whether body weight and height in childhood are associated with adult pancreatic cancer.

Objective: To examine if childhood body mass index (BMI; kg/m²) and height are associated with pancreatic cancer in adult life.

Methods: We linked 293,208 children born from 1930-1982 in the Copenhagen School Health Records Register who had measured values of weights and heights at ages 7-13 years with the Danish Cancer Registry to identify incident pancreatic cancer cases from 1968-2012. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional hazard regressions.

Results: During 8,207,015 person-years of follow-up, 1,268 pancreatic cancer cases were diagnosed. Childhood BMI z-scores at ages 7-13 years were positively and significantly associated with pancreatic cancer in men and women up to age 70 years; beyond age 70 the associations diminished. The HRs of pancreatic cancer were 1.13 (95% CI: 1.05-1.21) and 1.18 (95% CI: 1.09-1.27) per BMI z-score at ages 7 and 13 years, respectively. A BMI ≥ 1.5 z-score at ages 7, 10 and 13 years was positively and significantly associated with pancreatic cancer; however, the effect did not differ from having a BMI z-score ≥ 1.5 at only one of these ages. Positive, albeit non-statistically significant, associations were identified with height.

Conclusions: BMI at all ages from 7-13 years is positively and linearly associated with adult pancreatic cancer; the higher the BMI, the higher the risk. Excess childhood BMI may be indicative of processes initiated early in life that lead to this cancer. Prevention of childhood adiposity may decrease the burden of pancreatic cancer in adults.
Keywords: cancer, children, growth, height, obesity, pancreas, weight
INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer death in the United States (1), and it ranks in the top ten leading causes of cancer death in Denmark (2). Pancreatic cancer is highly fatal; 65% of patients die within one year of diagnosis and the current 5-year survival rate is 7.7% (3). Whereas overall cancer incidence and deaths are declining, incidence and death rates for pancreatic cancer have increased (1). One hypothesis that may explain these increasing rates is the current obesity and diabetes epidemic.

Adult obesity has emerged as a consistent risk factor for pancreatic cancer over the past decade (4-10). Recent studies have shown overweight and obesity during late adolescence and early adulthood associated with an elevated risk of this disease (9-12). Evidence also suggests that there is a cumulative effect of adult overweight; the longer an adult is overweight or obese, the greater the risk of pancreatic cancer (12). Further, as with many forms of cancer, a greater adult attained height is also associated with increased pancreatic cancer risk but the exact mechanisms remain speculative (4, 13).

Childhood obesity is a global public health issue with an estimated 155 million school-aged children currently classified as overweight or obese (14). Overweight and obesity in childhood are associated with a variety of diseases in adulthood (9, 11, 12, 15-18). The World Cancer Research Fund reported greater childhood growth as a probable risk factor for pancreatic cancer, however this was based on attained height and BMI during early adulthood (4). The majority of the studies that have examined body size during adolescence or early adulthood relied on recalled weight and height (9, 11, 12). Hence, we examined whether childhood BMI and height as determined from measures during childhood health examinations are associated with subsequent pancreatic cancer in adulthood in a Danish population.
METHODS

Study Population

In this prospective cohort study, 372,636 subjects from the Copenhagen School Health Records Register who were born from 1930-1989 underwent mandatory health examinations at public and private schools from ages 7-13 years annually through 1983 after which time the health examinations were performed only at school entry and exit unless a child had special health needs (19). During the examinations, school doctors and nurses measured the height and weight of the children using equipment provided by the schools and standard procedures. Each child was assigned a health card with the child’s name, year of birth, height and weight. This information has been computerized.

An unique personal identification number was assigned to all Danish residents who were alive or born after April 1968, when the Central Person Register was established (20). Children who were in school at that time or later had their identification number recorded on their health cards and children who attended school prior to this time had their identification numbers retrieved from the register on the basis of their name and date of birth (21). These numbers were identified for >88% of the children in the register. The process of retrieving the numbers was conservative (19), and the main reasons for not identifying the number were death, emigration prior to 1968 or misspellings in names that precluded the unique identification of the child.

BMI was calculated by dividing weight in kilograms (kg) by height in meters (m) squared. BMI values were transformed to z-scores based on an internal age- and sex-specific reference that was computed using the Lambda Median Sigma (LMS) method (22). The reference population was chosen from a period when the prevalence of obesity was low and...
stable and z-scores were interpolated to the exact age if two measurements were available or extrapolated if only one was available, but always within a ±12 month timeframe (15).

The identification number enabled linkage to the Danish Cancer Registry (23) from which information on pancreatic cancer was obtained. The cancer registry has collected information on all cancer diagnoses in Denmark since 1943. Pancreatic cancer was defined according to the modified Danish version of the International Classification of Diseases (ICD) versions 7 (157.0) and 10 (C25.0-C25.4, C25.7-C25.9).

The first diagnosis of pancreatic cancer, regardless of a previous cancer diagnosis, was used in the analyses. Follow-up began in 1968, corresponding to when the computerized vital statistics register was established. We followed subjects from 30 years of age, corresponding to the birth years of 1930 to 1982. From the population of 348,974 individuals available for this study, 42,480 did not have a personal identification number and from the remaining individuals, with the identification numbers 2,309 died, 6,281 emigrated and 196 were lost to follow-up before the age of 30 years (Supplementary Figure S1). Therefore the eligible population for inclusion in the study consisted of 297,708 individuals who were alive and living in Denmark at 30 years of age. Exclusions were made for individuals who had pancreatic cancer prior to 30 years of age (n=1) and individuals with missing (n=4,492) or outlying (z-score < -4.5 or > 4.5) height or BMI values at all ages (n=7) (Supplementary Figure S1). Of the 293,208 individuals included in the study, 6,152 individuals emigrated, 166 individuals were lost to follow-up, and 56,147 died before the end of the study period. Follow-up ended on the date of a pancreatic cancer diagnosis, death, emigration, or December 31st 2013, whichever came first.
The analyses were conducted on anonymous data and the study was approved by the Danish Data Protection agency. According to the Danish Act of Processing of Personal Data, informed consent is not required for register-based research of pre-existing personal data.

**Statistical analyses**

Associations between BMI and height z-scores at each age from 7 through 13 years were estimated using Cox proportional hazard regression models with age as the underlying time metric. We conducted the sensitivity analyses adjusting BMI for height, and vice versa, since they are correlated in childhood. To examine if there was a cumulative effect of excess BMI in childhood, we examined if children who were heavy, defined as having a BMI z-score $\geq 1.5$ (equivalent to the 93.3rd percentile), at ages 7, 10 and/or 13 years had a different risk of pancreatic cancer compared with children who had a BMI z-score $<1.5$ at these ages. Due to how the z-scores were calculated, the ages of 7, 10 and 13 were chosen for analysis as they were calculated independently of each other. Children who never had a BMI z-score $\geq 1.5$ at any of these ages formed the reference group. Further we examined if children who were heavier at 13 years irrespective of their body size history had a different risk of pancreatic cancer compared with children who were not large at age 13 years. For these analyses, the reference group was children with a BMI z-score $<1.5$ at age 13 years only.

As the cohort spans many years of birth, all analyses were stratified by birth cohort (5-year intervals from 1930-1975 and 1976-1982). Interactions of the BMI and height z-scores associations with pancreatic cancer by sex and birth cohort were also tested using log likelihood ratio tests. No interactions were detected (all p-values $>0.40$); however, as the sex-specific results may be of interest, these are presented as well. The linearity of the associations was assessed by restricted cubic splines (5 knots) and notable violations were not detected. The
proportional hazards assumption was tested in each model by the inclusion of a time-varying
effect of BMI and height, respectively, in the Cox regression models. Violations were detected
such that the associations with BMI changed around 70 years of age (p-value range: 0.005-
0.035). Therefore, we present analyses stratified by <70 and ≥70 years of age.

We calculated the unadjusted population attributable fraction (PAF) (24) to estimate the
percentage of pancreatic cancer cases before age 70 years that would potentially be eliminated if
children were not overweight or obese at age 13 years. Overweight and obesity were defined
using the Centers for Disease Control 2000 classifications (25). For these calculations, we used
the HRs for boys and girls at age 13 years in our Danish study population and the proportions of
overweight or obese girls and boys at age 12½ to 13½ years in the United States, National
Health and Nutrition Examination Survey (NHANES, all ethnicities) between 2003 and 2014
(26).

RESULTS

At least one BMI and height z-score were available for 144,826 girls and 148,382 boys.

As previously published and expected, height and BMI increased with age in this study
population (18). The analyses included 8,207,015 person-years of follow-up after age 30 years.
During follow up there were 1,268 cases of pancreatic cancer (699 in men and 569 in women).
The incidence rate of pancreatic cancer increased with advancing age, and was slightly higher in
the men compared to women (Figure 1).

Positive and statistically significant associations between childhood BMI z-scores and
adult pancreatic cancer were found at all ages (Figure 2, Supplementary Table S1). Childhood
BMI z-scores at each age from 7 to 13 years were significantly associated with pancreatic cancer
risk in adult men and women up until the age of 70 years (Figure 2, Supplementary Table S1). Beyond 70 years of age, the associations were no longer statistically significant. No notable violations of linearity were detected; the pancreatic cancer risk was greatest with the highest childhood BMI z-scores. Adjustment for height in the model had no effect on the hazard ratios of pancreatic cancer (Supplementary Table S2). Height was positively, albeit non-significantly associated with adult pancreatic cancer (Table 1).

In the sub-analysis of 119,799 men and 119,080 women who had BMI values at 7, 10 and 13 years of age, we examined if there was an effect of repeatedly high BMI or if it was only size at 13 years that mattered for later pancreatic cancer.

Compared with the reference group of children who had a BMI < 1.5 z-scores at all ages of 7, 10 and 13 years, having a BMI ≥ 1.5 z-score once, twice, or three times at any of these ages (7, 10 or 13 years) was associated with an increased risk of pancreatic cancer until age 70 years (Table 2). Even though the hazard ratios for children who had a BMI z-score of ≥ 1.5 at all three ages were higher than for other combinations of BMI z-scores, these differences were not statistically significant compared to having a z-score >1.5 at only one age (P= 0.88) or at two ages (P=0.67). Compared with the reference group of 225,606 children with a BMI z-score <1.5 at age 13 years (823 pancreatic cancer cases), the 13,273 children who had a BMI z-score ≥1.5 at the same age (61 pancreatic cancer cases) had a hazard ratio for pancreatic cancer before age 70 years of 1.51 (95% CI, 1.16 to 1.96).

Using the pooled data from NHANES and the Centers for Disease Control criteria, among 13-year-old US children, 14.8% of boys and 17.2% of girls are classified as overweight and 21.7% of boys and 21.5% of girls are classified as obese. Based on these US prevalence data and the pancreatic cancer HRs for BMI at age 13 from the continuous model from our Danish
study, we estimated that the Population attributable fractions of pancreatic cancer before age 70
years will be 12.7% and 11.4% for men and women, respectively.

DISCUSSION

In this large prospective population-based study using measured heights and weights in
childhood, we found that BMI at each age from 7 to 13 years was significantly and positively
associated with pancreatic cancer in adulthood diagnosed up until age 70 years; beyond this age
there were no associations. Repeatedly having a high BMI at ages 7, 10 and 13 years was not
significantly different from having a high BMI once. Associations were similar for men and
women and consistent for cancer diagnosis from 30 to 70 years of age. Associations between
child height and pancreatic cancer although positive, were not statistically significant. Our study
is novel as it examines child body size in relation to the risk of pancreatic cancer in adulthood as
other investigations focused on body size at older ages.

Our findings are consistent with previous studies that have examined adolescent or early
adulthood BMI and pancreatic cancer (11, 27). Within a cohort of 720,000 Israeli men with BMI
measured at ages 16 to 19 years, adolescent overweight as defined by BMI Z-score >1, compared
to Z-score ≥ -1 to ≤ 1, showed a significant 2-fold pancreatic cancer risk (27). One case-control
study found significant increase in risk associated with 5 unit increase in recalled BMI during
adolescence and early adulthood (11). The American National Institutes of Health-AARP Diet
and Health Study Cohort (NIH-AARP), and two pooled analyses of cohort studies showed
adolescent or early adulthood body size obtained by recall to be positively associated with
pancreatic cancer (8, 9, 11). The associations were independent of BMI at an older age,
suggesting that the risk was established to a certain extent in earlier life. In a study of American
retired adults (50-71 years of age) in the NIH-AARP, adolescent body size obtained by recall had a positive association with pancreatic cancer (12). The effect was not attenuated by including adult size, thus suggesting that the risk was established to a certain extent in earlier life. Since adult body size was not available in the current study, we could not conduct a fully comparable analysis. When BMI was analyzed as a continuous variable using recalled height and weight at age 50 from participants in the NIH-AARP study, the HRs for the association between BMI and pancreatic cancer were 1.18 (1.07, 1.32) for males and 1.02 (0.94, 1.12) for women per z-score (unpublished). Interestingly, these associations were of a smaller magnitude than those observed in the current study per BMI z-score, which suggests that tracking of childhood BMI whereby heavy children become heavy adults is not the only explanation for the observed results.

Prospective studies have also shown that BMI gain during adulthood and after age 50 years is associated with an elevated pancreatic cancer risk (9, 10, 12). Given that we did not observe an association between childhood BMI and pancreatic cancer diagnosed after age 70 years it is possible that childhood adiposity contributes to pancreatic cancer diagnosed at younger ages, whereas adiposity related to weight gain during adulthood contributes more to occurrence of cancer diagnosis later at older ages.

Our results suggest that there is not a cumulative effect of excess adiposity during childhood associated with adult pancreatic cancer. In our study, the association between having a high BMI value more than once from the ages of 7 to 13 years and subsequent pancreatic cancer did not differ significantly from the association observed for having a high BMI only once (Table 2). In contrast, the NIH-AARP study showed that longer absolute and cumulative years of being overweight or obese (BMI ≥ 25.0 kg/m²) were significantly associated with pancreatic cancer (12). It is possible that we examined too few years during childhood to detect a
cumulative effect, that we had too few cases to distinguish such patterns, or that it is body size change across many years during mid- to late adult life that is important for pancreatic cancer development.

Despite evidence from several studies suggesting that adult height has a positive association with pancreatic cancer (4, 13) there is great heterogeneity in the literature, with later reports pointing towards the association being very modest in magnitude (28). In our study, the HRs for the associations between childhood height and pancreatic cancer were positive, but weak and not statistically significant. Given that the confidence intervals around the estimates were small, it is unlikely that our study was under powered to detect an effect, but this cannot be ruled out. Nonetheless, our findings are in accord with the majority of the adult literature.

Body mass index is not a perfect indicator of adiposity in either adults or children. In childhood it is correlated with height, and this reflects that the body composition of healthy tall children has a greater amount of lean and adipose tissue (29). However, even when we accounted for the effects of height beyond what is captured by BMI in the models, the associations between childhood BMI and pancreatic cancer remained virtually unchanged. These results suggest that some aspect of body composition, presumably the adipose tissue component, is contributing to our observed associations. Adipose tissue is an endocrinologically active tissue that is known to be linked to pancreatic inflammation, beta-cell dysfunction, insulin resistance, and diabetes (30). These processes have been suggested to play an etiologic role in adulthood pancreatic cancer (31) and may likewise contribute to our association between childhood BMI and pancreatic cancer. Excess childhood weight may also be linked to later pancreatic cancer through correlations between child and adult size or through independent processes that stimulate early steps of carcinogenesis. Genes involved in the embryonic development of pancreas have been
associated with BMI, diabetes, as well as, pancreatic adenocarcinoma (32-34) which lend support to early life exposures that affect the pancreas having a role in the pathways that lead to the development of pancreatic cancer later in life. Future research is warranted to determine whether the association between childhood excess weight and risk of pancreatic cancer later in life is mediated through adult adiposity and to understand the biologic mechanisms that explain the associations that we observe.

Several strengths of our study should be noted including the prospective design and availability of measured, instead of recalled, height and weight during childhood. Furthermore, selection bias is unlikely to be present in our study, since it includes virtually all children born from 1930 to 1982 who attended school in Copenhagen and we were able to follow these individuals from 1977 onwards with the Danish Registers. Pancreatic cancer diagnoses were obtained from the national Cancer Registry, which has a high coverage due to the mandatory reporting of all malignant neoplasms. In Denmark, healthcare is universal and paid for by taxation, so it is unlikely that this study is affected by access bias. Further, there was minimal loss to follow-up as all subjects could be efficiently tracked through the Danish register system. Information on family history of pancreatic cancer, childhood diet and second hand smoke, adult body size, and other adult health conditions (e.g. diabetes and pancreatitis) and exposures (e.g. adult smoking history) was not available. Exposures in adulthood, however, are unlikely confounders of measured childhood height and weight. Further, some of these factors may be mediating factors on the causal pathway from obesity and pancreatic cancer. There may also be other unknown exogenous exposures as well as genetic susceptibility (35) contributing to the pancreatic cancer associations that we observe that cannot be controlled in our present analysis. Our Danish population is primarily Caucasian and our results might not be generalizable to other
ethnicities. Nonetheless, our results along with those of others suggest that childhood BMI is associated with future pancreatic cancer and that body size across the lifespan contributes to this disease (8, 9, 11).

Levels of childhood overweight and obesity in children have increased in Denmark (36) and across the globe (14). Our results show that risks are significantly elevated even at BMI z-scores of 1.0 (84.1 percentile) in our study population. For example, when compared with the contemporary US reference for 13-year-old children, our BMI z-scores of 1.0 (20.9 kg/m$^2$ in girls, 20.3 kg/m$^2$ in boys) are equivalent to BMI values that fall just below the 75$^{th}$ percentiles. Thus elevated risks are being observed at BMI values far below those which are currently classified as “overweight” by the Centers for Disease Control reference. To place our results in perspective, we calculated Population attributable fractions using the prevalence of overweight and obesity in contemporary American children (>36% among 13-year-old boys and girls). If contemporary children moved from overweight (including obesity) to normal-weight at age 13 years, 12.7% and 11.4% of cases of pancreatic cancer before age 70 years might be avoided among men and women, respectively. These estimations, even with the limitations of their assumptions of causality, underscore that there is cause for concern about the future risk of pancreatic cancer in children of today.

In conclusion, we find that childhood BMI has a strong and positive association with pancreatic cancer in adulthood before age 70 years. The association between having a high childhood BMI repeatedly during the ages 7 to 13 years and pancreatic cancer did not statistically differ from just having a high BMI at only one age during this age period. Associations between child height and pancreatic cancer were not statistically significant. These
results support the hypothesis that excess BMI in childhood contributes to the future risk of pancreatic cancer before 70 years of age.
Acknowledgements:

The Copenhagen School Health Records Register was built in collaboration between the Department of Clinical Epidemiology and the Copenhagen City Archives in Denmark.

Author Contribution: T.I.A.S. and J.L.B. acquired data. L.N., R.S., M.G., T.I.A.S., J.L.B. designed research, L.N., R.S., M.G., J.L.B. conducted research, M.G. analyzed data and L.N., R.S., and J.L.B. wrote the paper. J.L.B. had primary responsibility for final content. All authors read and approved the final manuscript.
References


Table 1. Childhood Height Z-score at Ages 7 through 13 Years and Pancreatic Cancer Risk in Adulthooda  

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Individuals, No.</th>
<th>Cases, No.</th>
<th>Hazard ratio (95% CI)</th>
<th>Individuals, No.</th>
<th>Cases, No.</th>
<th>Hazard ratio (95% CI)</th>
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<td>922</td>
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<td>58,475</td>
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<td>1.10 (0.97, 1.24)</td>
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<td>270</td>
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<td>930</td>
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<td>11</td>
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<td>59,898</td>
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<td>59,043</td>
<td>264</td>
<td>1.09 (0.96, 1.23)</td>
</tr>
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aAnalyses stratified by sex and birth cohort
Table 2. Patterns of Repeatedly High BMI Values (≥1.5 z-score) at Ages 7, 10 and 13 Years and Pancreatic Cancer Risk in Adulthood by Age at Diagnosis\textsuperscript{a}

<table>
<thead>
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<th>Age at diagnosis</th>
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<th>≥ 70 years</th>
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<tr>
<td><strong>BMI z-score ≥ 1.5</strong></td>
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<td>Cases</td>
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<tr>
<td>Never</td>
<td>217,721</td>
<td>789</td>
</tr>
<tr>
<td>7 years only</td>
<td>3,839</td>
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<td>2,131</td>
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<td>4,243</td>
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<tr>
<td>7 and 10 years</td>
<td>1,915</td>
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<td>7 and 13 years</td>
<td>830</td>
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<tr>
<td>10 and 13 years</td>
<td>2,996</td>
<td>13</td>
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<tr>
<td>7, 10 and 13 years</td>
<td>5,204</td>
<td>24</td>
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</tbody>
</table>

\textsuperscript{a}Analyses stratified by sex and birth cohort. Compared with a child with a BMI z-score ≥1.5 at 7, 10 and 13 years, the HR did not statistically differ from children who had a BMI z-score ≥1.5 at only one age (\(P=0.88\)) or at two ages (\(P=0.67\)).
Figure legends

Figure 1. Incidence Rate of Pancreatic Cancer among Men and Women from 30 to 83 years of age.

Figure 2. Childhood Body Mass Index Z-score and Pancreatic Cancer Risk by Diagnosis at Ages < 70 years and ≥ 70 years *

*Analyses stratified by sex and birth cohort.
Figure 2

![Graph illustrating hazard ratio (95% CI) with age (years) with symbols and error bars for different age groups: <70 years and >=70 years.](image_url)
Supplemental data

The supplemental material includes a flowchart of individuals from the Copenhagen School Health Records Register included in the study, and two tables of childhood BMI Z-scores at ages 7 through 13 years (without and with adjustment for height) and risk of pancreatic cancer in adulthood by age at diagnosis.
Supplemental Figure 1. Flowchart of individuals from the Copenhagen School Health Records Register included in the study.

Total population of individuals in the CSHRR
Born 1930 to 1989
n=372,636
188,360 men / 184,276 women

Population of available for this study
Born 1930 to 1982
n=348,974
176,287 men / 172,687 women

Do not have a personal identification number
n=42,480
20,838 men / 21,642 women

Starting population
n=306,494
155,449 men / 151,045 women

Emigrated, deceased or lost to follow-up prior to 30 years
n=8,786
4,591 men / 4,195 women

Eligible population alive and living in Denmark at 30 years
n=297,708
150,858 men / 146,850 women

Age at diagnosis <30 years
n=1
1 woman

Height or BMI measures outlier at all ages
n=7
4 men / 3 women

Missing values of height and/or BMI at all ages
n=4,492
2,472 men / 2,020 women

Included sample
n=293,208
148,382 men / 144,826 women
**Supplemental Table 1. Childhood Body Mass Index Z scores at ages 7 through 13 Years and Pancreatic Cancer Risk in Adulthood by Age at Diagnosis**

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>&lt; 70 years</th>
<th>≥ 70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Individuals, No.</td>
<td>Cases, No.</td>
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<td></td>
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<td>7</td>
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<td><strong>Men &amp; Women</strong></td>
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<tr>
<td>7</td>
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<td>266,091</td>
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<tr>
<td>12</td>
<td>263,328</td>
<td>929</td>
</tr>
<tr>
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<td>259,342</td>
<td>927</td>
</tr>
</tbody>
</table>

*aAnalyses stratified by birth cohort
bAnalyses additionally stratified by sex*
### Supplemental Table 2. Childhood Body Mass Index Z-scores at ages 7 through 13 Years with Adjustment for Height and Pancreatic Cancer Risk by Age at Diagnosis

<table>
<thead>
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<th>Age at diagnosis</th>
<th>&lt;70 years</th>
<th>≥ 70 years</th>
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<tr>
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<td>Age (years)</td>
<td>Individuals, No.</td>
<td>Cases, No.</td>
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<tr>
<td><strong>Women</strong></td>
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<tr>
<td>Age (years)</td>
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<td>Cases, No.</td>
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<tr>
<td>9</td>
<td>135,305</td>
<td>411</td>
</tr>
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</tbody>
</table>

*a* Analyses stratified by birth cohort  
*b* Analyses stratified by sex