Intentional weight loss as a predictor of type 2 diabetes occurrence in a general adult population

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Supplemental File S1: Evaluation of potential reasons for discrepancies in the results between the present study and other weight loss studies

Reliability and validity of the IWL used

The reliability of the intentional weight loss (IWL) at baseline was relatively good when compared to a weight loss of 5% or more, a common measure of IWL.[1 2] Previous studies have shown that those currently dieting have more previous IWL episodes than current non-dieters[3 4] and, thus, it is apparent that, in general, dieting seldom is a one-time effort. Unfortunately, we have no direct data on the repeatability of the IWL measure during the 15-year long follow-up. The relatively consistently elevated type 2 diabetes (T2D) risk in the IWL group during the follow-up does, however, give indirect evidence of the representative measure values.

Unfortunately, the validity of the IWL measure could not be evaluated owing to a lack of an external reference and available information on possible misreporting. IWL was defined as IWL during the last year before baseline. Therefore, information on dieting history over a longer period or the earlier consequences of dieting was not available. Accordingly, we were unable to comprehensively investigate whether the group with IWL was overrepresented by individuals with a long-lasting need for weight loss (e.g. due to undiagnosed diabetes or pre-diabetes possibly inducing weight loss without information on intentionality (WLW), other mental or somatic disorders predicting diabetes, or an unhealthy lifestyle) or repeated weight loss attempts, elevating the risk of T2D. In accordance with this suspicion, we found that the group with IWL had more pathological values in the metabolic syndrome (MetS) indicators and that adjustment for these indicators eliminated the elevated relative risk during the first 5 years of follow-up. In contrast, a study of possible effect modification by other health conditions (e.g. severe MetS, mental health, self-perceived heath, and osteoarthritis) in persons with overweight revealed no significant interactions, suggesting that the prediction of IWL on the incidence of T2D did not differ by health status. Overall, it cannot fully be excluded that individuals with IWL were already at a greater risk of T2D at baseline. In addition, weight loss may be an activity that is susceptible to misreporting. Individuals with obesity, in particular, may report IWL due to social pressure or due to a recommendation from a doctor or a family member, albeit not actually having lost weight. Such false IWL among those already at higher risk of T2D may partly account for the direct association found in our study.

Differences in the definition of the dieting variables

In the present study, IWL was limited to the year prior to baseline, whereas in another cohort study using IWL and giving an inverse association with T2D risk, the Cancer Prevention Study, the time interval of the weight loss was not limited to a specific time interval. [5-7] In cohort studies with WLW, i.e. giving no information on the intentionality of the weight change, weight loss has usually been measured or retrospectively self-reported as the weight change from a specific prior time point to baseline.[8-10] The time intervals varied from 5 to 27 years and an inverse association with

T2D risk was mainly seen for studies with intervals up to 10 years.[9-12] It is thus possible that weight loss during a longer time interval may refer to a more earnest and hence long-term weight loss. In our study, however, using higher cut off values for IWL, which could represent more earnest weight loss, did not notably affect the results.

The decades in which the data was collected may have affected the prevalence of weight loss efforts and also the answering of questions related to this. A recent meta-analysis suggested that the prevalence of weight loss attempts has increased over time.[13] In the Cancer Prevention Study (during 1959-1972) and in the San Antonio Heart Study,[14] as well as in most of the studies with opposite finding to our own and WLW as an exposure,[8 10-12 15 16] data on changes in weight was collected from the 1940s, to the 1980s, when the prevailing health consciousness and dieting culture may have been different than in the year 2000. As one of the previous studies includes data from the 21st century,[9] however, this does not entirely explain the differences in the results.

In cohort studies using WLW as an exposure, the variable may comprise intentional weight-losers but also unintentional weight-losers potentially having a health condition inducing weight loss. Thus, heterogeneity within the variable may influence the results of these studies.

In contrast to individuals usually self-initiating weight loss in cohort studies and with common weight regain,[17] individuals within intervention groups received support to achieve their goals and usually tools to help maintain the results, too. Accordingly, studies with long follow-up after the intervention period have shown the preventive effect to last long after the actual intervention. [18-20]

In addition to the preventive effect of the actual weight loss, the supported longer-term lifestyle changes, including increased physical activity and healthier eating habits, may partly explain the preventive effect found in intervention studies. Thus, the results from the intervention studies would not appear to be comparable with our results.

Differences in study populations

In our study, the study sample represented a general population, including the whole BMI distribution, and the majority of individuals not at high risk of T2D.[21] The cohort studies with significant findings of an inverse association between WLW and T2D occurrence were mainly based on large population studies: the Health Professionals Follow-up Study (HPFS),[8 12] Nurses' Health Study (NHS),[15] the National Health and Nutrition Examination Survey (NHANES),[11 16] the Korean National Health Insurance Service, National Sample Cohort (NHIS-NSC),[9] and the British Regional Heart Study.[10] Thus, the populations in most of the WLW studies were relatively similar to our own.

In contrast, in the previous cohort studies with IWL, the participants were restricted to persons who had overweight or obesity.[5-7 14] Likewise, the target groups in the intervention studies consisted of persons with overweight/obesity and/or otherwise at high risk of T2D. High-risk individuals in intervention studies presumably take their weight loss and weight maintenance efforts more seriously, on average, than individuals in the general population. Moreover, motivation for dieting (i.e. health or appearance reasons) has been suggested to influence the outcome of dieting; disinhibition and relapses are associated with appearance related motivation to dieting but not with health-related motivation.[22] Accordingly, as populations with more obesity or health-related problems presumably diet more often for

health-related reasons than individuals in a general population, it is possible that the preventive effects found in intervention studies partly derive from this. The divergence between our results and findings from intervention studies and the few cohort studies with IWL may thus partly derive from the different study populations.

Differences in length of follow-up

In the intervention studies, intervention periods have varied between 6 months and 4 years. With a few exceptions with 10–14-year follow-ups after the intervention period,[18-20] most of the studies have only published immediate results after the intervention period, and the sustainability of the effects remains unknown. In our study, after controlling for the effect of various potential pre-existing metabolic conditions during the first five years of the follow-up, IWL did not predict an elevated risk of T2D, which suggests that IWL may endure for a such period of time and does not seem to have immediate negative consequence. After a longer period of time, however, it is possible that, in parallel with weight regain, the preventive effect of IWL fades out and is reversed. In the previous cohort studies with IWL or WLW showing contradictory results, the follow-up periods varied from three years[23] to up to 36 years,[24] with most of the follow-ups being approximately 10-15 years. The most consistent inverse associations were found for follow-up intervals up to 15 years. Thus, it would appear that the discrepant results are not due to differences in length of follow-up.

Differences in control for confounding

Because of the randomisation as a part of the intervention study design, no confounding was expected. In the present cohort, the most apparent risk factors of T2D (i.e. sex, age, education, several modifiable lifestyle factors, adiposity, metabolic factors, and indicators of poor health) were confirmed to predict T2D occurrence. These, and also some dietary factors, were appropriately controlled for in the statistical analyses. The elevated risk of T2D among individuals with IWL consistently remained, suggesting that our results are plausible from this point of view. In other cohort studies with IWL or WLW and finding an opposite association than in our study, the variables adjusted for came from the same groups but, generally, the coverage of variables was smaller. The only risk factor adjusted for in some of the studies and missing from our data was 'family history of diabetes'.[8 9 12 16] Despite the fact that we carried out a comprehensive control for confounding, possible residual confounding cannot be fully excluded.

Differences in definition of the outcome variable (T2D diagnosis)

The T2D incidence variable, used in this study, and considered valid and reliable, was formed with daily information on medication use, hospitalisation, and cause of death, all of which were drawn from national registers and linked to the study participants with unique social security numbers identifying each Finnish citizen.[25] In addition to T2D, the ICD-10 codes used (E10 to E14) included type 1 diabetes (T1D), and other types of diabetes, excluding gestational diabetes. We decided, however, to include all new cases, as incidence of T1D and other types of diabetes in adults of this age is extremely rare.[26] Patients treated with diet only and individuals with undiagnosed diabetes were included among non-cases, resulting in conservative estimates.

In the first Cancer Prevention Study, a cohort study with IWL, non-fatal incident T2D cases were determined using self-report of T2D on questionnaires completed 2, 4, 6, and 13 years after baseline, and T2D related deaths were determined using death certificates with diabetes as an underlying or contributing cause of death.[5-7] In the San Antonio Heart Study,[14] incident T2D cases were determined based on fasting plasma glucose and glucose load determinations and self-reports on insulin or oral antidiabetic drugs at study endpoint of the 8-year follow-up.

In cohort studies with WLW and with opposite result to our own, there has been variation in the diagnostics of T2D. In the HPFS[8 12] and the NHS,[15] biennial questionnaires gave information on symptoms, plasma glucose, and glycaemic medication during the last follow-up period. Those patients satisfying the National Diabetes Data Group Criteria were considered incident cases of T2D. A validity study in the NHS was carried out in which the diagnosis of T2D was confirmed by medical records.[15] In The NHANES T2D cases were based on self-reports of physician diagnosis on T2D or antidiabetic medication in interviews with 5- or 2-year intervals.[11 16] Moreover, of those with self-reported overnight-stays in hospital during the follow-up, discharge diagnoses were collected from health care facility records.[11] Additionally, information from death certificates was used. In the NHIS-NSC[9] T2D cases were based on biannual glucose measurements and information on the prescription of antidiabetic medication from medical records. In the British Regional Heart Study,[10] information for T2D cases was drawn from biennial interviews and further confirmed with primary care records.

In intervention studies with significant inverse results, diagnoses of T2D cases were based on biochemical measurements and determined according to established criteria and definitions (by the American Diabetes Association and the World Health Organization).[27-36] In part of the studies, the diagnoses were confirmed by a second test[27-30 32] and, in the Finnish Diabetes Prevention Study, [27] they were additionally confirmed by an independent end-points committee. In one study, participants who were known to have begun treatment for diabetes were also diagnosed as having T2D.[31] The time intervals between which T2D was determined ranged from every 3 months to every 2 years, with the most common intervals being 0.5 to 1 years.

In studies with only self-reports of incident T2D or with biochemical measurements to determine the disease without verification from other sources, the validity of the diagnoses may be lower compared to that in studies with confirmed information on diagnosis from ascertained linkage to a registry or medical record or verifying information from several sources. Moreover, follow-up at only certain timepoints with retrospective information on the preceding time periods versus continuous real-time follow-up from e.g. medical records generate differences in the variables.

Summary

This evaluation suggested that, despite differences in study populations, length of follow-up, control for confounding, and definition of T2D, the discrepant results between the present study and other weight loss studies would appear to potentially be explained by two issues. First, the group with IWL may, due to poor health or a pronounced health consciousness, have been overrepresented by individuals with an elevated risk of T2D or an elevated risk to be diagnosed with T2D. Second, self-implemented IWL during the short, one-year period may not have worked properly for all individuals, resulting in weight regain or weight cycling and later in an elevated risk of T2D.

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