



HAL
open science

Short-term weight change and fluctuation as risk factors for type 2 diabetes in Finnish male smokers

Merja Kataja-Tuomola, Jari Sundell, Satu Männistö, Mikko J. Virtanen,
Jukka Kontto, Demetrius Albanes, Jarmo Virtamo

► **To cite this version:**

Merja Kataja-Tuomola, Jari Sundell, Satu Männistö, Mikko J. Virtanen, Jukka Kontto, et al.. Short-term weight change and fluctuation as risk factors for type 2 diabetes in Finnish male smokers. *European Journal of Epidemiology*, 2010, 25 (5), pp.333-339. 10.1007/s10654-010-9444-6. hal-00581004

HAL Id: hal-00581004

<https://hal.science/hal-00581004>

Submitted on 30 Mar 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1

2

3 **Short-term Weight Change and Fluctuation as Risk Factors for Type 2 Diabetes**
4 **in Finnish Male Smokers**

5

6 Merja Kataja-Tuomola¹, Jari Sundell¹, Satu Männistö¹, Mikko J. Virtanen¹, Jukka
7 Kontto¹, Demetrius Albanes², Jarmo Virtamo¹

8

9 WORD COUNT: abstract: 246

10 text: **2986**

11 NUMBER OF FIGURES: **2**

12 NUMBER OF TABLES: 2

13 KEYWORDS: Cohort study; diabetes; weight change; weight fluctuation

14

15 Conflict of interest: Merja Kataja-Tuomola¹, Jari Sundell¹, Satu Männistö¹, Mikko
16 J. Virtanen¹, Jukka Kontto¹, Demetrius Albanes², Jarmo Virtamo¹: no conflicts of
17 interest.

18

19 Affiliations of authors:

20 ¹Chronic Disease Epidemiology and Prevention Unit

21 National Institute for Health and Welfare

22 Helsinki, Finland

24 ²National Cancer Institute, NIH

25 Bethesda, MD, USA

26 Corresponding author:

27Merja Kataja-Tuomola, MD

28Chronic Disease Epidemiology and Prevention Unit

29National Institute for Health and Welfare

30PL 30

3100271 Helsinki

32Finland

33

34Phone +358-206108739

35Fax +358-206108742

36E-mail: merja.kataja-tuomola@thl.fi

37

38Abbreviations:

39ATBC Study Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

40BMI Body mass index

41HDL High density lipoprotein

42RR Relative risk

43RMSE Root mean square error

4495% CI 95% Confidence interval

45

46

47Abstract

48Risk of weight change and fluctuation for type 2 diabetes was studied in a prospective
49study among 20,952 Finnish male smokers aged 50 to 69 years. Baseline data on
50lifestyle and medical history were collected, and height and weight measured. Weight
51was measured thrice after the baseline, one year apart. Weight change was defined as
52the slope of the regression line fitted to the four measurements and weight fluctuation
53as the root-mean-square-error deviation from this line. Incident cases of diabetes were
54identified from a national medication reimbursement register; 535 cases up to 9 years'
55follow-up. The Cox proportional hazards model served to estimate relative risk (RR,
5695% confidence interval [CI]). Weight gain and fluctuation associated with higher
57risk for diabetes, multivariate RR = 1.77, 95% CI 1.44-2.17, for weight gain of at least
584 kg compared with those of weight change less than 4 kg, and RR = 1.64, 95% CI
591.24-2.17 in the highest weight fluctuation quintile compared to the lowest. These
60RRs remained similar when weight change and fluctuation were adjusted for each
61other. Large weight fluctuation increased the risk of diabetes both in men who gained
62weight (≥ 4 kg), had stable weight ($\pm < 4$ kg), and lost weight (≥ 4 kg); RR = 2.17, 95%
63CI 1.60-2.94, RR = 1.47, 95% CI 1.14-1.91, and RR = 2.04, 95% CI 1.47-2.83,
64respectively, compared to those with stable weight and moderate fluctuation. Short-
65term weight gain and large weight fluctuation are independent risk factors for
66diabetes.

67

68

69

70

71

72

73Introduction

74Obesity, physical inactivity and smoking are established and modifiable risk factors
75for type 2 diabetes [1-10]. The risk for developing type 2 diabetes also increases with
76age [3, 4, 6]. When dietary and lifestyle factors were analysed simultaneously in the
77Nurses' Health Study, the most important risk factor for type 2 diabetes was a higher
78body mass index (BMI, weight (kg)/ height (m)²) [11].

79Weight gain has been associated with the risk for type 2 diabetes [10, 12-15].

80Weight loss can prevent or delay the progression to diabetes in obese patients [16,17],

81though some studies have linked weight loss to increased risk for diabetes [18, 19].

82Unintentional weight regain frequently follows intentional weight loss, thus leading

83easily to weight cycling, which appears to enhance subsequent weight gain and may

84predispose one to obesity [20-23]. Findings concerning the association between

85weight fluctuation or cycling and the risk for type 2 diabetes remain controversial;

86three studies have found weight fluctuation to increase the risk for diabetes [16, 18,

8724], but other three studies have found no significant association [23, 25, 26].

88We studied the association of various weight change patterns, specified as weight

89gain, weight loss, and weight fluctuation, with the risk for type 2 diabetes in Finnish

90male smokers who participated in the Alpha-Tocopherol, Beta-Carotene Cancer

91Prevention Study (ATBC Study).

92

93Methods

94The ATBC Study

95The primary aim of the ATBC Study was to examine whether supplementation with

96alpha-tocopherol, beta-carotene, or both would reduce the incidence of lung cancer

97and other cancers. The study was a randomized, double-blind, placebo-controlled
98clinical trial with a 2x2 factorial design [27, 28]. The participants were screened from
99among the total male population between the ages of 50 and 69 living in south-
100western Finland ($n = 290,406$). Men were excluded if they smoked fewer than 5
101cigarettes per day, had prior cancer or a serious disease limiting long-term
102participation or used vitamin E, vitamin A or beta-carotene supplements in excess of
103predefined doses or anticoagulants. A total of 29,133 eligible men were enrolled from
1041985 through 1988, and the trial continued until April 1993 (median intervention
105time: 6.1 years), with the cohort followed up through national registers thereafter. The
106institutional review boards of the National Public Health Institute, Finland, and the
107U.S. National Cancer Institute approved the ATBC Study. All subjects provided their
108written, informed consent prior to randomization.

109**Subjects and case ascertainment**

110In Finland, patients needing medical treatment for diabetes are entitled to
111reimbursement for the cost of medication according to the sickness insurance
112legislation. This requires a medical certificate from the attending physician. The
113certificate of every case is verified to fulfill the diagnostic criteria for diabetes at the
114Social Insurance Institution which maintains a central register of all patients receiving
115drug reimbursement.

116This study included those men ($n = 20,952$) who had their weight measured at
117baseline and three times thereafter, one year apart after which the follow-up for
118diabetes began [Fig.1]. During a follow-up period of up to 9 years, 535 incident cases
119of diabetes were diagnosed.

120Data collection

121At baseline, data on medical history, smoking, alcohol consumption and physical
122activity were collected with questionnaires. Height and weight were measured, and
123BMI was calculated. Blood pressure was measured with a mercury
124sphygmomanometer from the right arm with the subject sitting, and the lower reading
125of the two measurements taken at least one minute apart was recorded. A blood
126sample was drawn and serum stored at -70°C . Serum glucose was determined with the
127enzymatic hexokinase method using an Optima analyzer (ThermoFischer, Vantaa,
128Finland). Serum total and high-density lipoprotein (HDL) cholesterol concentrations
129were determined enzymatically [29, 30].

130The participants made a follow-up visit three times annually, and weight was
131measured once a year.

132Statistics

133Person years were calculated from the date of the fourth annual weight measurement
134to the date of diabetes occurrence, death, or the end of the follow-up period
135(December 1997), whichever came first. The average trend in weight change was
136assessed through the slope of the regression line fitted to four weight measurements
137taken one year apart. The slope was categorized into three classes: below -1.33
138(kg/year) for weight loss, between -1.33 and 1.33 for stable weight, and over 1.33 for
139weight gain. The 1.33 kg/year corresponded to an average weight change of 4 kg over
140three years. This was similar to a two-year net weight reduction of 2.7 kg, which
141associated with a 58% reduction in diabetes risk in the Finnish Diabetes Prevention
142Study [31].

143To examine the association of risk for diabetes with weight fluctuation, we calculated
144the root mean square error (RMSE) using annual weight deviations from the

145corresponding estimated regression line [18, 32, 33]. This variable was divided into
146quintiles. Weight fluctuation and weight change were also considered as combined
147variable, in which case the weight fluctuation was categorized into two classes: Q1-
148Q4 for **minor** fluctuation and Q5 for large fluctuation.

149The association between weight indicators (short-term weight change and weight
150fluctuation) and the incidence of type 2 diabetes was estimated with the Cox
151proportional hazards regression as relative risks (RR) and 95% confidence intervals
152(CI). The basic model was adjusted for age and supplementation group. The model
153was further adjusted for BMI, years of smoking, number of cigarettes smoked daily,
154systolic and diastolic blood pressure, serum total and HDL cholesterol, alcohol
155consumption and leisure time physical activity (sedentary and moderate-heavy).
156Stratified analysis was performed in order to assess the possible effect modifications,
157and the significance of interactions was tested using the likelihood ratio test.
158Differences between the groups were tested using analysis of variance (ANOVA).
159Analyses were carried out with the R statistical program [34]. All *p* values were two-
160sided.

161

162**Results**

163At baseline, men who gained on average at least 4 kg of weight during the subsequent
164three years, were slightly younger and had a lower serum total cholesterol
165concentration than did those whose weight was stable or who lost at least 4 kg of
166weight (Table 1). Men whose weight fluctuated the most during the subsequent three
167years (fifth quintile) were younger and less physically active during leisure time, had
168a higher BMI, but lower serum total cholesterol and HDL cholesterol levels than did
169men of the four lowest quintiles.

170The multivariate-adjusted risk for diabetes was higher in men who gained at least 4 kg
171during three years than in those whose weight was stable (RR = 1.77, 95% CI 1.44-
1722.17) [Fig.2]. When compared to those with stable weight, weight loss of at least 4kg
173was not associated with the risk for diabetes (RR = 1.17, 95% CI 0.90-1.53). Neither
174BMI, number of cigarettes, years of smoking, alcohol consumption nor physical
175activity modified the association between short-term weight change and the risk for
176diabetes. Age, however, did modify the risk for diabetes ($p = 0.0067$ for weight gain
177and $p = 0.0036$ for weight loss). Among those 60 and older at baseline, weight gain as
178well as weight loss were associated with higher risk for diabetes than among those of
179stable weight (RR = 3.42, 95% CI 1.70-6.88, and 2.07, 95% CI 1.08-3.99,
180respectively), whereas among those younger than 60, no association was observed
181(RR = 1.25, 95% CI 0.90-1.73 and RR = 0.74, 95% CI 0.55-1.01, respectively).

182

183 The risk for diabetes in the four lowest quintiles of weight fluctuation was similar,
184whereas in the highest quintile the risk was higher than in the lowest quintile (RR =
1851.64, 95% CI 1.24-2.17) [Fig.2]. Neither age, BMI, nor number of cigarettes
186significantly modified the association between short-term weight fluctuation and the
187risk for diabetes. Leisure time physical activity did modify the risk of diabetes with
188weight fluctuation ($p = 0.02$); among those of light leisure time physical activity, large
189weight fluctuation was associated with increased risk for diabetes (RR = 1.95, 95% CI
1901.28-2.98 for the highest vs. lowest quintile), whereas among those with moderate or
191heavy leisure time physical activity we found no such association (RR = 1.38, 95% CI
1920.95-2.00). In addition, years of smoking modified the risk for diabetes ($p = 0.04$);
193among those who had smoked less than 36 years, large weight fluctuation increased
194the risk for diabetes (RR = 1.91, 95% CI 1.27-2.88), whereas among those who had

195 smoked at least 36 years, the association was weaker (RR = 1.43, 95% CI 0.98-2.09).
196 Finally, the association of weight fluctuation to diabetes risk was stronger in men
197 who consumed on average 11g or more of alcohol daily (RR = 2.17, 95% CI 1.36-
198 3.45) than in men consuming less alcohol (RR = 1.58, 95% CI 1.10-2.28; $p =$
199 0.0001).

200

201 Both short-term average weight change (slope) and weight fluctuation remained
202 independent risk factors for diabetes when simultaneously adjusted for in the
203 multivariate model: RR = 1.69, 95% CI 1.37-2.07, for a weight increase of at least 4
204 kg compared with stable weight, and RR = 1.55, 95% CI 1.17-2.06, for the highest vs.
205 lowest weight fluctuation quintile, respectively. Weight gain of at least 4kg in three
206 years, either steady or fluctuating, increased significantly the risk of diabetes about
207 two-fold compared with those whose weight changed less than 4kg and fluctuated
208 only moderately (Table 2). Among men whose weight changed less than 4kg, large
209 weight fluctuation increased the risk of diabetes 1.47-fold, 95% CI 1.14-1.91. Steady
210 loss of weight of at least 4kg was associated non-significantly with decreased risk of
211 diabetes, RR = 0.73, 95% CI 0.47-1.15. However, if weight loss was associated with
212 large weight fluctuation, the risk of diabetes was two-fold compared with those of
213 stable weight and moderate fluctuation, RR = 2.04, 95% CI 1.47-2.83 (Table 2).

214

215 Discussion

216 Short-term weight gain and fluctuation associated with a higher risk for diabetes. **The**
217 **observation is in line with those of other epidemiological studies [10, 15].** In the
218 Health Professionals Follow-up Study, weight gain during the preceding ten years was
219 associated with a 1.9 times higher risk for diabetes (95% CI 1.4-2.7) **among those**

220who gained 9 kg or more of weight than among those with a stable weight (± 2 kg)
221[15]. A parallel observation resulted in the National Health and Nutrition Examination
222Survey Epidemiologic Follow-up Study, where participants who gained weight at
223least 5 kg during 9 years had up to 3.85 times the risk for diabetes compared with
224participants whose weights remained relatively stable [10].

225

226An average weight loss of 4 kg in three years was not associated with a lower risk for
227incident diabetes. This differs from the findings of several prospective cohort and
228intervention studies where even modest weight loss was associated with a
229significantly reduced risk for diabetes [12, 31, 35-39]. In the Finnish Diabetes
230Prevention Study a net loss of 3.5 ± 5.5 kg by the end of the second year decreased
231risk of diabetes for 58 % [31]. In the Nurse's Health Study women who lost more than
2325.0 kg reduced their risk for diabetes at least 50% compared to those who maintained
233a steady weight [12]. In the Diabetes Prevention Program (DPP) study, a 5 kg weight
234loss accounted for a 55 % reduction in risk of incident diabetes over the mean of 3.2
235years of follow-up [38]. Participants with intentional weight loss in the Cancer
236Prevention Study had a reduction of incident diabetes of about 25% compared with
237participants with no-intentional weight loss [39]. The unintentional weight loss may
238be an effect of diabetes per se, not a cause of diabetes.

239

240We found that age **did modify** significantly the association between weight loss and
241risk of diabetes. Among men 60 years or older weight loss **is** associated with
242increased risk, whereas among **men** younger **than 60 years** no such an association was
243evident. In the Iowa Women's Health Study of women aged 55-69 years and in a

244Swedish study of middle-aged women, weight loss associated with increased risk of
245diabetes, but effect modification by age was not studied in these materials [18, 19].

246

247The association of weight loss in our study was, however, different depending on
248whether the weight decreased smoothly or fluctuating. If the weight diminished
249smoothly, the risk of diabetes was decreased, though not significantly (RR = 0.73,
25095% CI 0.47-1.15), which is in line with other studies. The small number of men with
251smooth weight loss may be the reason why the decrease in risk remained non-
252significant. If the weight loss was associated with large weight fluctuation, it was
253associated with increased risk of diabetes.

254

255Our results support the hypothesis that weight fluctuation is associated with higher
256risk for diabetes. In the Iowa Women's Health Study, weight cycling (an increase of
257 $\geq 10\%$ of body weight during a ten-year period and a loss of $\geq 10\%$ of weight during
258another ten-year period, regardless of order) increased significantly the risk for
259diabetes (RR = 1.70, 95% CI 1.25-2.29) [18]. A similarly increased risk was found in
260an adult community where the adjusted rate ratio for diabetes risk was 1.7 ($p < 0.01$)
261for the weight fluctuation (both weight gain and losses of 4.5kg between ages 40 to 60
262vs. all others) [16]. In an other cohort study among women, an index of weight
263fluctuation based on weights in different phases of life associated with diabetes with
264standardized odds ratio of 1.10 (95% CI 1.07-1.14) [24]. Supportive evidence comes
265from the Baltimore Longitudinal Study of Aging, where body weight variability
266associated with a decrease in glucose tolerance [32].

267Some studies, however, have found no association between weight fluctuation and the
268risk for diabetes. In a six-year follow-up of the Nurses' Health Study II, neither mild

269nor severe weight cycling predicted diabetes [23]. In a prospective study among Pima
270Indians in Arizona, weight fluctuation was not associated with the incidence of
271diabetes in either sex [25]. In the Johns Hopkins Precursors Study the variability in
272BMI before age 50 predicted incident diabetes only marginally [26].

273

274Leisure time physical activity modified the association between weight fluctuation
275and risk of diabetes. Large weight fluctuation increased the risk of diabetes two-fold if
276only light exercise were taken during leisure time whereas no association was found if
277exercise was moderate or heavy. This is in keeping with the knowledge that physical
278activity can prevent diabetes. Regular exercise **induces** various adaptations in the
279body resulting in improved muscle and whole body insulin sensitivity, fuel
280partitioning and cardiovascular function leading to prevention of metabolic disease
281[40, 41].

282The strengths of our study include the prospective study design, with up to 9-year
283follow-up for incident diabetes, and data available for several possible risk factors.
284Weight and height were measured by trained staff at study centres, not self-reported.
285The cases were retrieved from a nationwide register with strict criteria for inclusion.
286**The trial supplementation had no effect on the incidence of diabetes [42].**

287Some limitations should be kept in mind, however, when interpreting these results.
288We were able to identify only patients receiving medication for treatment of diabetes,
289not individuals treating their disease with dietary changes. This will attenuate our
290estimate between weight indicators and risk of diabetes towards unity. The drug
291reimbursement register for diabetes contains no data on the type of diabetes.
292However, almost all of our diabetes cases would be of type 2 diabetes based on the
293age of the participants at baseline: 50 to 69 years [43]. **Some [44, 45] but not all**

294studies [46] suggest that smoking cessation may associate with lower risk of diabetes.
295About 21 % of the ATBC participants stopped smoking during the trial [28]. But we
296do not have smoking data from drop-outs and post-trial follow-up. Thus the possible
297effects of smoking cessation on our results remain unclear.

298For short-term weight change, we had only four weight measurements at intervals of
299one year and were thus unable to detect weight variations occurring over a shorter
300period of time. No information on intentionality of weight changes was recorded. In
301addition, RMSE may have misclassified participants with continuous non-linear
302weight gain without real weight fluctuation [47].

303 The ATBC Study was designed to test whether alpha-tocopherol or beta-carotene
304could reduce the incidence of lung or other cancers in male smokers, thus our results
305may not be generalizable to women or non-smokers.

306

307Globally, over one billion adults are overweight, of whom at least 300 million are
308obese [48]. If epidemic obesity increases worldwide, the disease burden of type 2
309diabetes and cardiovascular diseases will be enormous. Our results confirm that even
310a short-term weight gain is a risk factor for type 2 diabetes. They also contribute to
311previous work by demonstrating a significant association between weight fluctuation
312and higher risk for diabetes. The association between weight fluctuation and risk for
313diabetes may raise concerns about health-promoting weight-control programs that
314could result in such cycling. A key target could then be to maintain not only a normal,
315but a stable body weight in order to optimally lower the risk for diabetes.

316

317

318This ATBC Study was supported by U.S. Public Health Service contracts N01-CN-
31945165, N01-RC-45035, and N01-RC-37004 from the National Cancer Institute, NIH,
320and the Department of Health and Human Services.

321

322

323

324References

325

3261. Paffenbarger RS, Jr., Wing AL. Chronic disease in former college students.
327 XII. Early precursors of adult-onset diabetes mellitus. *Am J Epidemiol.* 1973;
328 97:314-23.
3292. Modan M. Effect of past and concurrent body mass index on prevalence of
330 glucose intolerance and Type 2 (non-insulin-dependent) diabetes and on
331 insulin response. *Diabetologia.* 1986;29:82-9.
3323. Burchfiel CM, Curb JD, Rodriguez BL, Yano K, Hwang LJ, Fong KO, et al.
333 Incidence and predictors of diabetes in Japanese-American men. The Honolulu
334 Heart Program. *Ann Epidemiol.* 1995;5:33-43.
3354. Medalie JH, Papier CM, Goldbourt U, Herman JB. Major factors in the
336 development of diabetes mellitus in 10,000 men. *Arch Intern Med.* 1975;135:
337 811-17.
3385. Wilson PW, Anderson KM, Kannel WB. Epidemiology of diabetes mellitus in
339 the elderly. The Framingham Study. *Am J Med.* 1986;80:3-9.
3406. Feskens EJ, Kromhout D. Cardiovascular risk factors and the 25-year
341 incidence of diabetes mellitus in middle-aged men. The Zutphen Study. *Am J*
342 *Epidemiol.* 1989;130:1101-8.
3437. Ohlson LO, Larsson B, Björntorp P, Eriksson H, Svärdsudd K, Welin L, et al.
344 Risk factors for type 2 (non-insulin-dependent) diabetes mellitus. Thirteen and
345 one-half years of follow-up of the participants in a study of Swedish men born
346 in 1913. *Diabetologia.* 1988;31:798-805.

3478. Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS, Jr. Physical activity
348 and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J*
349 *Med.* 1991;325:147-52.
3509. Manson JE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC,
351 Hennekens CH A prospective study of exercise and incidence of diabetes
352 among US male physicians. *JAMA.* 1992;268:63-7.
35310. Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence:
354 findings from a national cohort of US adults. *Am J Epidemiol.* 1997;146:214-
355 22.
35611. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, et al. Diet,
357 lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med.*
358 2001;345:790-97.
35912. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk
360 factor for clinical diabetes mellitus in women. *Ann Intern Med.* 1995;122:
361 481-6.
36213. Schienkiewitz A, Schulze MB, Hoffmann K, Kroke A, Boeing H. Body mass
363 index history and risk of type 2 diabetes: results from the European
364 Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study.
365 *Am J Clin Nutr.* 2006;84:427-33.
36614. Oguma Y, Sesso HD, Paffenbarger RS, Jr., Lee IM. Weight change and risk of
367 developing type 2 diabetes. *Obes Res.* 2005;13:945-51.
36815. Koh-Banerjee P, Wang Y, Hu FB, Spiegelman D, Willett WC, Rimm EB.
369 Changes in body weight and body fat distribution as risk factors for clinical
370 diabetes in US men. *Am J Epidemiol.* 2004;159:1150-9.

37116. Holbrook TL, Barrett-Connor E, Wingard DL. The association of lifetime
372 weight and weight control patterns with diabetes among men and women in an
373 adult community. *Int J Obes*. 1989;13:723-9.
37417. Pi-Sunyer FX. How effective are lifestyle changes in the prevention of type 2
375 diabetes mellitus? *Nutr Rev*. 2007;65:101-10.
37618. French SA, Folsom AR, Jeffery RW, Zheng W, Mink PJ, Baxter JE. Weight
377 variability and incident disease in older women: the Iowa Women's Health
378 Study. *Int J Obes Relat Metab Disord*. 1997;21:217-23.
37919. Noppa H. Body weight change in relation to incidence of ischemic heart
380 disease and change in risk factors for ischemic heart disease. *Am J Epidemiol*.
381 1980;111:693-704.
38220. Blackburn GL, Wilson GT, Kanders BS, Stein LJ, Lavin PT, Adler J, et al.
383 Weight cycling: the experience of human dieters. *Am J Clin Nutr*. 1989; 49
384 (Suppl):1105-9.
38521. Saarni SE, Rissanen A, Sarna S, Koskenvuo M, Kaprio J. Weight cycling of
386 athletes and subsequent weight gain in middleage. *Int J Obes*. 2006;30:1639-
387 44.
38822. Kroke A, Liese AD, Schulz M, Bergmann MM, Klipstein-Grobusch K,
389 Hoffmann K, et al. Recent weight changes and weight cycling as predictors of
390 subsequent two year weight change in a middle-aged cohort. *Int J Obes Relat*
391 *Metab Disord*. 2002;26:403-9.
39223. Field AE, Manson JE, Laird N, Williamsson DF, Willett WC, Colditz GA.
393 Weight cycling and the risk of developing type 2 diabetes among adult women
394 in the United States. *Obes Res*. 2004;12:267-74.

39524. Morris RD, Rimm AA. Long-term weight fluctuation and non-insulin-
396 dependent diabetes mellitus in white women. *Ann Epidemiol.* 1992;2:657-64.
39725. Hanson RL, Narayan KM, McCance DR, Pettitt DJ, Jacobsson LT, Bennett
398 PH, et al. Rate of weight gain, weight fluctuation, and incidence of NIDDM.
399 *Diabetes.* 1995;44:261-6.
40026. Brancati FL, Wang NY, Mead LA, Liang KY, Klag MJ. Body weight patterns
401 from 20 to 49 years of age and subsequent risk for diabetes mellitus: the Johns
402 Hopkins Precursors Study. *Arch Intern Med.* 1999;159:957-63.
40327. The ATBC Cancer Prevention Study Group. The Alpha-Tocopherol, Beta-
404 Carotene Lung Cancer Prevention Study: design, methods, participant
405 characteristics and compliance. *Ann Epidemiol.* 1994;4:1-10.
40628. The ATBC Cancer Prevention Study Group. The effect of vitamin E and beta-
407 carotene on the incidence of lung cancer and other cancers in male smokers. *N*
408 *Engl J Med.* 1994;330:1029-35.
40929. Kattermann R, Jaworek D, Möller G, Assmann G, Björkhem I, Svensson L, et
410 al. Multicentre study of a new enzymatic method of cholesterol determination.
411 *J Clin Chem Clin Biochem.* 1984;22:245-51.
41230. Kostner G. Enzymatic determination of cholesterol in high density lipoprotein
413 fractions prepared by polyanion precipitation. *Clin Chem.* 1976;22:695.
41431. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-
415 Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle
416 among subjects with impaired glucose tolerance. *N Engl J Med.* 2001;344:
417 1343-50.
41832. Lissner L, Andres R, Muller DC, Shimokata H. Body weight variability in
419 men: metabolic rate, health and longevity. *Int J Obes.* 1990;14:373-83.

42033. Iribarren C, Sharp DS, Burchfiel CM, Petrovitch H. Association of weight loss
421 and weight fluctuation with mortality among Japanese American men. *N Engl*
422 *J Med.* 1995;333:686-92.
42334. Ihaka R, Gentleman R. A language for data analysis and graphics. *J Comput*
424 *Graph Stat.* 1996;5:299-314.
42535. Wannamethee SG, Shaper AG, Walker M. Overweight and obesity and weight
426 change in middle aged men: impact on cardiovascular disease and diabetes. *J*
427 *Epidemiol Community Health.* 2005;59:134-39.
42836. Resnick HE, Valsania P, Halter JB, Lin X. Relation of weight gain and weight
429 loss on subsequent diabetes risk in overweight adults. *J Epidemiol Community*
430 *Health.* 2000;54:596-602.
43137. Davey Smith G, Bracha Y, Svendsen KH, Neaton JD, Haffner SM, Kuller LH.
432 Incidence of type 2 diabetes in the randomized multiple risk factor
433 intervention trial. *Ann Intern Med.* 2005;142:313-22.
43438. Hamman RF, Wing RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L, et
435 al. Effect of weight loss with lifestyle intervention on risk of diabetes.
436 *Diabetes Care.* 2006;29:2102-7.
43739. Will JC, Williamson DF, Ford ES, Calle EE, Thun MJ. Intentional weight loss
438 and 13-year diabetes incidence in overweight adults. *Am J Public Health.*
439 2002;92:1245-8.
44040. Christ-Roberts CY, Pratipanawatr T, Pratipanawatr W, Berria R, Belfort R,
441 Kashyap S, et al. Exercise training increases glycogen synthase activity and
442 GLUT4 expression but not insulin signaling in overweight nondiabetic and
443 type 2 diabetic subjects. *Metabolism.* 2004;53:1233-42.
44441. Perseghin G, Price TB, Petersen KF, Roden M, Cline GW, Gerow K, et al.

- 445 Increased glucose transport-phosphorylation and muscle glycogen synthesis
446 after exercise training in insulin-resistant subjects. *N Engl J Med.* 1996;335:
447 1357-62.
- 448 42. Kataja-Tuomola M, Sundell JR, Männistö S, Virtanen MJ, Kontto J, Albanes
449 D, et al. Effect of alpha-tocopherol and beta-carotene supplementation on the
450 incidence of type 2 diabetes. *Diabetologia.* 2008;51:47-53.
- 451 43. Laakso M, Pyörälä K. Age of onset and type of diabetes. *Diabetes Care.* 1985;
452 8:114-7.
- 453 44. Manson JE, Ajani UA, Liu S, Nathan DM, Hennekens CH. A prospective
454 study of cigarette smoking and the incidence of diabetes mellitus among US
455 male physicians. *Am J Med.* 2000;109:538-42.
456
457
458
- 459 45. Will JC, Galuska DA, Ford ES, Mokdad A, Calle EE. Cigarette smoking and
460 diabetes mellitus: evidence of a positive association from a large prospective
461 cohort study. *Int J Epidemiol.* 2001;30:540-6.
462
463
464
- 465 46. Beziaud F, Halimi JM, Lecomte P, Vol S, Tichet J. Cigarette smoking and
466 diabetes mellitus. *Diabetes Metab.* 2004;30:161-6.
467
468
- 469 47. Vergnaud A-C, Bertrais S, Oppert J-M, Maillard-Teyssier L, Galan P,
470 Hercberg S, et al. Weight fluctuations and risk for metabolic syndrome in an
471 adult cohort. *Int J Obesity.* 2008;32:315-21.
- 472 48. World Health Organization. Obesity and overweight Geneva: WHO, 2004
473 Available:
474 <http://www.who.int/dietphysicalactivity/publications/facts/obesity/en/>
475
476
477

478 Title to Figure 1.

479

480 **Figure 1.** Diagram of flow of participants through the study

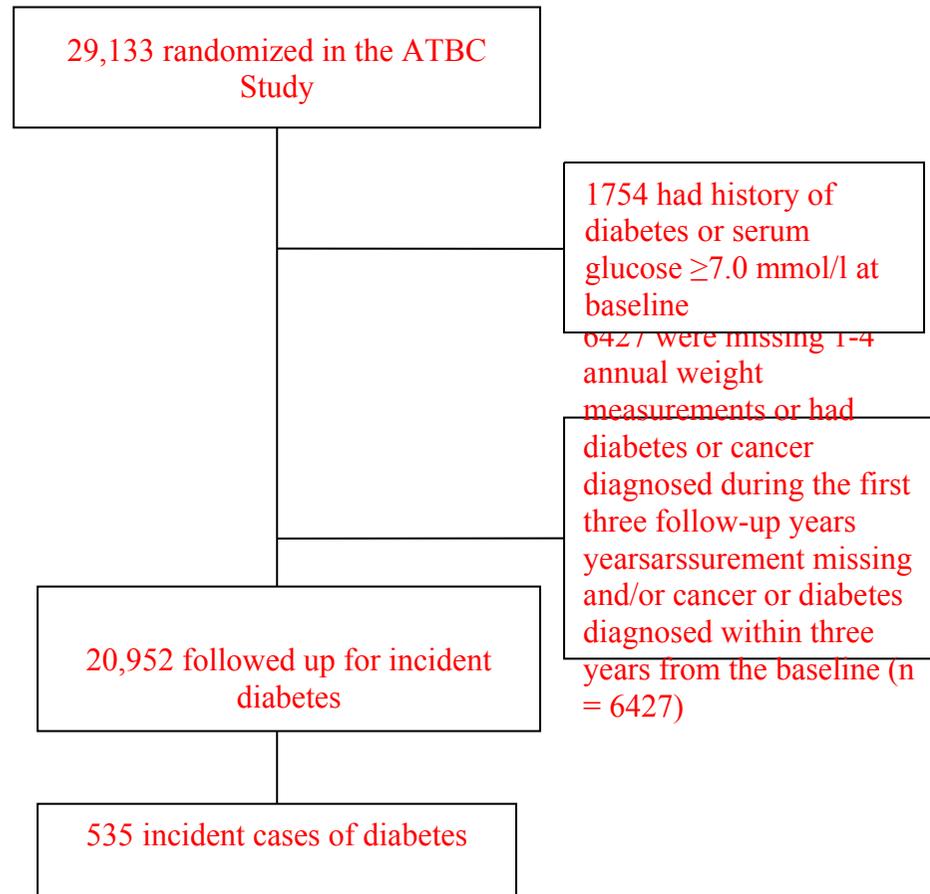
481

482

483

484

485



487 Title to Figure 2

488 **Figure 2.** Relative risk and 95% confidence interval for diabetes by average weight change and weight fluctuation (RMSE) during
489 three subsequent years in the ATBC Cancer Prevention Study cohort.

490

491 Footnote to Figure 2

492 Adjusted for age, intervention (alpha-tocopherol, beta-carotene, both, and placebo), body mass index, smoking, blood pressure, serum total and
493 high density lipoprotein cholesterol, alcohol consumption and leisure time physical activity.

494 The root mean square error (RMSE) is calculated using annual weight deviations from the corresponding estimated regression line and this
495 variable is divided into quintiles (Q). Q1: -0.54, Q2: 0.55-0.84, Q3: 0.85-1.17, Q4: 1.18-1.67, Q5: 1.68.

496

497

498

499

500

501

502

503

504

505

506

507

508 Title to Table 1.

509 **Table 1** Trial baseline characteristics by weight changes during the subsequent three years in the ATBC Cancer Prevention Study

510 cohort

511

512

513

514

515

516

517

518

519

520

521

522 Characteristic^aAverage weight change^b (kg)Quintile of weight fluctuation^c (kg)

523

524

525

	Loss (≥ 4)	Stable ($\pm < 4$)	Gain (≥ 4)	-0.54	0.55-0.84	0.85-1.17	1.18-1.67	1.68-
527 ⁿ	2,108	15,347	3,497	4,248	4,244	4,224	4,163	4,073
Age, y	57.6	56.9	56.2	57.1	56.9	57.2	56.8	56.4
Weight, kg	82.5	77.1	79.5	75.6	76.5	76.9	78.9	82.8
BMI, kg/m ²	27.1	25.6	26.2	25.3	25.5	25.6	26.0	27.1
Number of cigarettes/day	20	20	20	20	20	20	20	20
Smoking years	37	36	35	36	36	36	36	35
Systolic blood pressure, mmHg	142	140	140	140	140	140	140	140
Diastolic blood pressure, mmHg	90	88	88	86	88	86	88	88
Serum cholesterol, mmol/l	6.30	6.20	6.08	6.21	6.20	6.20	6.18	6.16
Serum HDL cholesterol, mmol/l	1.11	1.16	1.16	1.17	1.17	1.16	1.15	1.11
Alcohol consumption, g/day	11	11	11	10	11	11	11	11
Leisure time physical activity, moderate or heavy, %	55	62	57	62	63	62	59	56

528Footnote to Table 1

529^a Medians or proportions

530^b Weight change is based on the slope of the regression line fitted to the four weight measurements taken one year apart

531^c Weight fluctuation is the RMSE around the slope

532
533
534 Title to table 2
535
536 **Table 2.** Risk for diabetes by weight change and weight
537
538 fluctuation in three years, in the Alpha-Tocopherol, Beta-Carotene
539
540 (ATBC) Cancer Prevention Study cohort.
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565

566

567

568

Weight change

Weight fluctuation

569

570

Stable (quintiles 1-4^a)

Large (quintile 5^a)

571

	<u>cases</u>	<u>person years</u>	<u>RR</u>	<u>95% CI</u>	<u>cases</u>	<u>person years</u>	<u>RR</u>	<u>95% CI</u>
572 Stable ($\pm < 4\text{kg}$)	226	93,816	1.00 (reference)		84	16,283	1.47	1.14-1.91
573 Gain ($\geq 4\text{kg}$)	91	17,408	1.86	1.45-2.39	63	7,281	2.17	1.60-2.94
574 Loss ($\geq 4\text{kg}$)	23	9,451	0.73	0.47-1.15	48	4,874	2.04	1.47-2.83

572

Stable ($\pm < 4\text{kg}$)

573

Gain ($\geq 4\text{kg}$)

574

Loss ($\geq 4\text{kg}$)

575

576

577

578

579

580

581

582

583

584

585

586

587Footnote to table 2.

588

589Adjusted for baseline age, intervention (alpha-tocopherol, beta-carotene, both and

590

591placebo), BMI, smoking, blood pressure, serum total and HDL cholesterol, alcohol

592

593consumption and leisure time physical activity

594^a The total number of participants is 20,952 divided in quintiles.