



HAL
open science

The role of overweight in the association between the Mediterranean diet and the risk of type 2 diabetes mellitus: a mediation analysis among 21 585 UK biobank participants

Perrine André, Gordon Proctor, Bénédicte Driollet, Esther Garcia-Esquinas, Esther Lopez-Garcia, David Gomez-Cabrero, Eric Neyraud, Fernando Rodriguez-Artalejo, Martine Morzel, Catherine Feart

► To cite this version:

Perrine André, Gordon Proctor, Bénédicte Driollet, Esther Garcia-Esquinas, Esther Lopez-Garcia, et al.. The role of overweight in the association between the Mediterranean diet and the risk of type 2 diabetes mellitus: a mediation analysis among 21 585 UK biobank participants. *International Journal of Epidemiology*, 2020, 49 (5), pp.1582-1590. 10.1093/ije/dyaa103 . hal-02969294

HAL Id: hal-02969294

<https://hal.science/hal-02969294>

Submitted on 16 Oct 2020

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 **Int J Epidemiol 2020** doi: 10.1093/ije/dyaa103.

2 **TITLE:**

3 The role of overweight on the association between Mediterranean diet and risk of type 2
4 diabetes mellitus: a mediation analysis among 21 585 UK Biobank participants

5 **Running title :** Mediterranean diet, overweight and type 2 diabetes

6 **Authors:**

7 Perrine André*¹, Gordon Proctor², Bénédicte Driollet¹, Esther Garcia-Esquinas³, Esther
8 Lopez-Garcia³⁻⁴, David Gomez-Cabrero², Eric Neyraud⁵, Fernando Rodriguez-Artalejo³⁻⁴,
9 Martine Morzel⁵, Catherine Féart¹

10 **Affiliations:**

11 ¹ *Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team Lifelong*
12 *Exposure Health and Aging, U1219, Bordeaux, France*

13 ² *Centre for Host Microbiome Interactions, Faculty of Dentistry, Oral & Craniofacial*
14 *Sciences, King's College, London, UK*

15 ³ *Department of Preventive Medicine and Public Health, Universidad Autónoma de*
16 *Madrid/IdiPaz, and CIBERESP Spain*

17 ⁴ *IMDEA-Food Institute, Madrid. Spain.*

18 ⁵ *Centre des Sciences du Goût et de l'Alimentation, AgroSup Dijon, CNRS, INRA, Université*
19 *de Bourgogne Franche-Comté, Dijon, France.*

20

21 **Corresponding author:** Perrine André

22 Address: Team "Lifelong Exposures, Health and Aging"

23 INSERM U1219 - Bordeaux Population Health Research Center, Bordeaux University

24 ISPED 146 rue Léo-Saignat

25 33076 Bordeaux Cedex–France

26 E-mail: perrine.andre@u-bordeaux.fr

27 Phone: + (33) 05 57 57 12 9

28

29 **ABSTRACT**

30

31 **Background.** There is growing evidence that the Mediterranean (Medi) diet may lower the
32 risk of type 2 diabetes mellitus (T2DM). Whether this association is due to the Medi by itself
33 or is mediated by a diet-associated lower overweight is uncertain. The aim was to disentangle
34 these relationships among UK adults.

35 **Methods.** Based on 21 585 participants from the UK Biobank cohort, the adherence to the
36 Medi diet (high fruits, vegetables, legumes, cereals, fish, olive oil; low meat, dairy products
37 and intermediate alcohol intakes) was assessed (range 0-18). Data on diabetes was self-
38 reported, and overweight was defined as a BMI ≥ 25 kg/m². A mediation analysis was
39 implemented to disentangle the role of overweight on the Medi- T2DM relationship.

40 **Results.** The average baseline Medi score was 8.8 (SD 2.6). During a mean follow-up of 6.1
41 years, 473 individuals developed T2DM. A higher adherence to a Medi diet (+1 point) was
42 associated with 14% decreased risk of T2DM (Hazard Ratio HR: 0.86, 95%CI: 0.82–0.90).
43 This association was splitting into an indirect effect of 10%, mediated by lower odds of
44 overweight (HR: 0.90, 95%CI: 0.87 – 0.92), and a direct effect of the Medi of 4% (HR: 0.96,
45 95%CI: 0.93 – 0.99), regardless of the effect mediated by overweight.

46 **Conclusions.** Considered as a single mediator, reduced overweight mainly contributes to the
47 association between greater Medi adherence and lower risk of T2DM on this British
48 subsample. However, the direct effect of the diet on the risk of T2DM, even weaker, should
49 not be overlooked.

50

51 **Keywords:** BMI, Diabetes, mediation analysis, Mediterranean diet, overweight, type 2
52 diabetes mellitus

53

54 **Key messages:**

- 55 • It is still poorly elucidated to what extent the contribution of the Mediterranean diet to
56 the risk of type 2 diabetes could be explained by a mediated-effect of overweight
- 57 • This large population-based study provides evidence that the beneficial effect of a
58 higher adherence to a Mediterranean diet on the risk of type 2 diabetes is mostly (10%
59 out of 14% lower risk of diabetes), but not totally, explained by a mediated effect on
60 the odds of developing overweight.
- 61 • Although weaker, a specific effect of the Mediterranean diet on type 2 diabetes (4%
62 out of 14% lower risk of diabetes), regardless of the overweight, should not be
63 overlooked.
- 64 • These findings, combined with evidence of other health benefits of higher adherence
65 to a Mediterranean diet, encourage a Mediterranean-like pattern adoption in order to
66 prevent type 2 diabetes, even if it does not lead to weight loss.

67

68 INTRODUCTION

69 According to the International Diabetes Federation, about 8.8% of adults have diabetes (1).
70 Worldwide, the prevalence and incidence of type 2 diabetes mellitus (T2DM) has increased,
71 with a subsequent increase in health complications (1). In the United Kingdom (UK),
72 prevalence rates raised from 3.2% in 2004 to 5.3% in 2014 (2). T2DM is a long-term
73 metabolic disorder, mainly characterized by insulin resistance (IR) and pancreatic beta-cell
74 dysfunction (3). Excessive body weight represents one of the main risk factors of T2DM.
75 Therefore, concomitantly with the increased prevalence of diabetes over time, the prevalence
76 of excessive weight has substantially increased: worldwide, the proportion of overweight or
77 obese (*i.e.* body mass index BMI $\geq 25\text{kg/m}^2$) adults increased from 29% to 37% in men, and
78 from 30% to 38% in women, during the period from 1980 to 2013 (4). In 2015, 58% of
79 women and 68% of men were overweight or obese in the UK (5). Gray *et al.* observed that
80 higher BMI was consistently associated with a higher risk of developing T2DM among older
81 adults, even for participants who were only moderately overweight ($25\text{ kg/m}^2 \leq \text{BMI} \leq 27.49$
82 kg/m^2) with a 14% to 31% higher risk of diabetes for men and women respectively (6).
83 Because of the epidemic of obesity, expected trends regarding the incidence of T2DM are
84 alarming and today most public health strategies to counteract both obesity and diabetes
85 emphasize modifiable risk factors, such as avoiding unhealthy diet, sedentary lifestyle,
86 smoking and excessive alcohol intake. Regarding diet, the plant-based Mediterranean diet
87 (Medi Diet) is widely recognized as a healthy dietary pattern (7). Accumulated evidence has
88 supported a beneficial effect of higher adherence to this healthy dietary pattern on the risk of
89 diabetes (8–12). Specifically, in a recent review and meta-analysis based on 6 studies (2 out
90 of 6 included non-Mediterranean populations), Jannasch *et al.* observed a 13% lower risk of
91 T2DM for the upper quantile of Medi Diet (9). Esposito *et al.* found that 5 out of 8 meta-
92 analyses showed a favorable effect of the Medi Diet compared with other dietary patterns on
93 weight loss. Moreover among 2 meta-analyses selected, up to 23% lower risk of T2DM was
94 observed with greater adherence to a Medi Diet (11). Regarding interventional studies, a
95 review and meta-analysis on 16 randomized clinical trials (RCTs) suggested that after 6
96 months of a dietary intervention, the Medi Diet induced a significant mean weight loss of
97 -1.84 kg , compared with other diets for which weight loss remained non-significant (13).
98 Hamman *et al.* found a 16% lower risk of diabetes for every kilogram of weight loss,
99 suggesting a dose-response effect (14). In this context, we hypothesized that the contribution
100 of the Medi Diet to the reduced risk of T2DM in previous studies could be explained by (i) a
101 direct effect of Medi Diet on T2DM independent of overweight (whatever the role of diet on
102 overweight), (ii) the above effect jointly with an effect of Medi Diet on T2DM mediated by
103 overweight, (iii) a single effect of Medi Diet on overweight, this latter being then favorable to
104 the glycemic control or insulin resistance, for instance, and therefore for the risk of diabetes.
105 Elucidating the role of overweight in this association is important because it can help resolve
106 the controversy on whether the Medi Diet can prevent T2DM even among those in which the
107 Medi Diet fails to reduce weight. The aim of the present analysis was to disentangle these
108 relationships among UK adults using a mediation approach with diet as a major determinant
109 of diabetes and changes in overweight as potential mediators in the relation between
110 adherence to a Medi Diet and T2DM.

111

112 SUBJECTS AND METHODS

113 The UK Biobank

114 The UK Biobank is a prospective cohort initiated in 2007 that included more than 500 000
115 UK participants recruited between 2007 and 2010, aged 40 to 71 years and who registered for

116 primary health-care provision under the National Health Service (see UK Biobank’s online
117 protocol <http://www.ukbiobank.ac.uk>). The UK Biobank obtained ethical approvals from the
118 North West Multi-Centre Research Ethics Committee, the Community Health Index Advisory
119 Group, the Patient Information Advisory Group, and the National Health Service National
120 Research Ethics Service. All participants gave written informed consent.

121 At baseline participants provided information on lifestyle, health and socioeconomic factors,
122 and underwent a complete physical examination. Follow-ups were conducted between 2012
123 and 2013 (F1, approximately 4% of baseline participants were followed-up) and between
124 2014 and 2017 (F2, approximately 4.7% of baseline participants were followed-up).

125

126 **Study sample**

127 This research has been conducted using the UK Biobank resource under application number
128 3028. Analyses were based on a selected sample from the UK Biobank cohort with available
129 dietary data and diabetic status. **Figure 1** describes the sample selection for the present
130 analysis. From the initial sample of 502 591 UK Biobank participants, we identified 38 027
131 participants with at least one follow-up data and without secondary withdrawal of consent.
132 Among these 38 027 participants, we excluded those without data on diabetic status at
133 baseline (n= 62) or at least at one follow-up after baseline (n= 202) or with prevalent diabetes
134 (n= 1 319). Moreover, we excluded women who had gestational diabetes, as well as
135 participants with transient diabetes (*i.e.* those reporting incident diabetes at F1 but not at F2,
136 n= 17). Then, we excluded participants without nutritional data (n= 13 181) or nutritional data
137 not reflecting the usual diet (usual diet is defined in the Diet section, n= 1 662), leading to a
138 final sample of 21 585 participants.

139

140 **Assessment of type 2 diabetes**

141 At baseline and each follow-up, participants were invited to answer the following question:
142 “Has a doctor ever told you that you have diabetes?” and women with a positive answer were
143 also asked whether they had been diagnosed with diabetes only during pregnancy. The type of
144 diabetes (type 1 or 2 diabetes) was not available, but, as type 1 diabetes most often appears in
145 children or young adults, we considered that most incident cases in this study were T2DM.

146 As the self-reported age of T2DM diagnosis included many missing or unlikely data, we
147 determined this as the mean age between the two follow-up intervals for all participants.

148

149 **Diet**

150 Between baseline and F1, participants were invited to answer up to five dietary surveys at
151 regular intervals over the previous 24h as described previously (15). Dietary information was
152 collected via the Oxford WebQ, a web based 24h recall developed for use in large population
153 studies (16,17). The following question was added to ensure that responses reflected usual
154 diet: “Would you say that what you ate and drank yesterday was fairly typical for you?”. Most
155 (around 82%) of 24h dietary recalls were considered as reflecting typical diet. These latter
156 (*i.e.* dietary surveys reflecting the usual diet) were used in all the analyses, in order to select
157 participants with stable diet over time. We calculated average food, drink and energy intakes
158 (derived from food composition tables) with an average of 2.2 dietary surveys reflecting the
159 usual diet per participant.

160 Adherence to the Medi Diet was assessed as described by Sofi *et al.* (18), using literature-
161 based thresholds of selected food groups and alcohol, in order to avoid sample-dependent data
162 analysis (*i.e.* food consumption based on median sample (19)). The term “literature-based
163 Medi Diet score” was used in this article to refer to this Medi Diet score (18). We computed
164 this score, which ranged from 0 (poor adherence) to 18 (highest adherence), using the portion
165 size of 8 food groups (*i.e.* fruits, vegetables, legumes, cereals, fish and olive oil, for which the
166 higher, the better; meat and meat products, and dairy products, for which the lower, the better)
167 and alcohol (a moderate consumption of 1 to 2 units per day was considered as beneficial).
168 The literature-based Medi score was used as a continuous variable (+1 point) in the present
169 study.

170

171 **Overweight**

172 Body mass index (BMI) was measured at baseline and at each follow-up, and expressed in
173 kg/m². For the present analyses we only used data on BMI collected after inclusion (at F1 or
174 F2 if missing at F1). This strategy enabled us to account for the temporality of mediation
175 analyses requiring the mediator (*i.e.* overweight) to be measured after the main exposure (*i.e.*
176 Medi Diet). Overweight was considered as a BMI ≥ 25 kg/m², those with lower BMI being
177 considered not overweighted.

178

179 **Covariates**

180 Sociodemographic, lifestyle and health characteristics were collected at baseline, including
181 age, sex, educational level (considered as A-level, college or university versus less or other
182 qualification), tobacco use (non-smoker, ex-smoker or current smoker), physical activity
183 (defined as less than 210 min walking/week or 150 min moderate activity/week or 75 min
184 intense activity/week, based on World Health Organization recommendations for people aged
185 18 to 64 (20)), number of comorbidities (defined as the number of comorbidities among the
186 following: cancer, heart attack, angina, stroke, hypertension, blood clot, chronic bronchitis,
187 asthma, eczema, allergic rhinitis or hay fever) and number of drugs taken regularly.

188

189 **Statistical analyses**

190 Quantitative and qualitative variables were expressed as means \pm standard deviation (SD) or
191 number (percentages), and were compared using Student’s t test or Chi2 test according to
192 T2DM status, respectively.

193 Logistic regressions were performed to evaluate the association between adherence to a Medi
194 Diet and the odds of overweight (Path α , **Figure 2**). Cox proportional hazards models, with
195 age considered as the time scale, were used to analyze the association between overweight
196 and risk of T2DM (Path β , **Figure 2**). The hypotheses of log-linearity and proportionality of
197 risks were tested. Based on the non-significant interaction between Medi Diet and overweight
198 (p -value 0.61) and between Medi Diet and sex (p -value 0.46), we decided not to stratify the
199 analyses. The covariates considered as confounding factors, selected according to the DAG
200 (Directed Acyclic Graph) process and using data from the literature, included sex, educational
201 level, energy intake, inactive lifestyle, tobacco use and overweight. Additional adjustment for
202 age at baseline in the logistic regression model (Path α), or literature-based diet adherence
203 score in the Cox proportional hazards model (Path β) were performed.

204 Regression-based mediation analyses (21) were fitted to distinguish the Direct effect of
205 adherence to a Medi Diet on risk of T2DM, and the Indirect effect mediated by overweight. It
206 results in three estimates (**Figure 2**):

207 - Total effect, *i.e.* the whole association between adherence to the Medi Diet and the risk of
208 T2DM, including the one mediated by the odds of overweight;

209 - Direct effect, *i.e.* the association between adherence to the Medi Diet and the risk of T2DM,
210 adjusted for overweight;

211 - Indirect effect, *i.e.* the association between adherence to the Medi Diet and the risk of
212 T2DM, mediated by the overweight.

213 Secondary analyses were carried out for exploratory purposes and performed (i) by removing
214 the alcohol item from the literature-based Medi Diet score, in order to avoid an association
215 between Medi Diet T2DM which could be excessively driven by alcohol intake (22), (ii) by
216 excluding non-whole grains from the cereal item, given that whole but not refined grains
217 could protect from diabetes (23,24) (iii) and by using each food group of the literature-based
218 Medi Diet score separately, simultaneously adjusting for other food groups, to evaluate if the
219 association could be driven by a particular food group than another.

220 In supplementary analyses, we assessed the robustness of our main analysis by implementing
221 an alternative Medi Diet adherence score. We chose to compute a score already proposed by
222 Panagiotakos *et al* (25), which considered the same 9 food groups as the literature-based Medi
223 score, with some modifications (emphasis is done on non-refined cereals and full fat dairy
224 products), but that also considered consumption of potatoes (the higher, the better) and
225 poultry (the lower, the better). This score ranges from 0 (low adherence) to 55 (high
226 adherence) points, each of the 11 food groups being marked from 0 to 5 points depending on
227 the level of consumption. This alternative Medi score was considered as a continuous variable
228 (+5 points) in the present study.

229 Missing data represented less than 3% of the analytical sample, we thus imputed missing
230 values using the reference category for qualitative variables or the median value for
231 quantitative variables. Statistical analyses were performed using SAS software version 9.4
232 (SAS Institute Inc., Cary, 134 NC, USA) and R software version 3.3.2 (R Foundation for
233 Statistical Computing, Vienna, Austria).

234

235 **RESULTS**

236 Overall, the participants included in our study sample (n= 21 585) exhibited similar
237 characteristics than those non-included (n= 481 006) regarding age at baseline (56.5y for
238 included participants *versus* 57.1y for non-included participants), BMI at baseline (26.5 kg/m²
239 for included participants *versus* 27.5 kg/m² for non-included participants), sex (proportion of
240 women 52% in the present studied sample *versus* 54% for non-included participants) and the
241 average number of drug consumed at baseline, as proxy of comorbidities (2.0 for included
242 participants *versus* 2.5 for non-included participants).

243

244 **Characteristics of the included participants**

245 The studied sample consisted of 21 585 participants. Mean age at baseline was 56.5 years
246 (range: 40.2 - 71.0), and there was a slightly lower proportion of men (48%) than women.
247 During a mean follow-up time of 6.1 years (range: 1.3 – 10.9), 473 participants developed
248 incident diabetes.

249 The average BMI (SD) was 30.7 (5.5) kg/m² for incident cases of T2DM and 26.4 (4.3) kg/m²
 250 for participants without T2DM, representing 85.6% and 57.0% of overweight, respectively.

251 Overall, T2DM incident cases were older, more often men, and were more likely to present a
 252 more inactive lifestyle, a higher prevalence of drugs consumption, and a higher prevalence of
 253 comorbidities than their counterparts (**Table 1**). However, there was no difference on average
 254 energy intake between groups.

255 [Table 1 here]

256 The literature-based Medi Diet score was normally distributed with 8.8 out of 18 points on
 257 average among the 21 585 participants. Incident T2DM cases had a lower score than those
 258 who did not develop diabetes (-0.7 point on average).

259 Regarding the consumption of each food included in the Medi Diet, participants who
 260 remained free from T2DM over time consumed more fruits, more vegetables and olive oil,
 261 and less meat and meat products than participants who developed T2DM (**Table S1**).

262

263 **Regression-based mediation analysis between the literature-based Medi score,** 264 **overweight and risk of T2DM.**

265 In multivariate analyses, each 1-point increase of adherence to the Medi Diet was associated
 266 with a 8% lower odds of overweight (Path α , odds ratio OR: 0.92, 95% CI: 0.91–0.93) (**Table**
 267 **2**). Moreover, being overweight was associated with a higher risk of T2DM (Path β , hazard
 268 ratio HR: 3.89, 95% CI: 3.00 – 5.04).

269 Regarding the whole association between Medi Diet adherence and risk for T2DM, we
 270 observed that each additional point of the Medi Diet score was associated with a 14%
 271 decreased risk of T2DM (HR: 0.86, 95%CI: 0.82 – 0.90); 10% of this association (HR: 0.90,
 272 95% CI: 0.87 – 0.92) was mediated by the reduced overweight associated with each additional
 273 point of the Medi Diet score, and 4% (HR: 0.96, 95% CI: 0.93 – 0.99) was due to the Direct
 274 effect of the Medi Diet on the risk of T2DM. After additional adjustment for comorbidities
 275 and number of drugs consumed, these results were virtually unchanged.

276 [Table 2 here]

277

278 **Secondary analyses**

279 When (i) alcohol item was removed from the literature-based Medi Diet score or when (ii)
 280 considering only whole cereals, results were unchanged. None of the food groups were
 281 directly associated with the risk of T2DM (*i.e.* Direct effect). However, higher intake of fruits,
 282 vegetables and olive oil, and lower intake of meat and dairy products were indirectly
 283 associated with a lower risk of T2DM by a lower odds of overweight (*i.e.* Indirect effect
 284 mediated by BMI) (data not shown).

285

286 **Supplementary analyses**

287 Using the alternative Medi Diet adherence score proposed by Panagiotakos *et al.*, we
 288 observed similar findings which reinforced the robustness of the results. Each 5-additional
 289 point of the alternative Medi Diet was associated with a 28% decreased risk of T2DM (HR:
 290 0.72, 95% CI: 0.67 – 0.79) as a whole; a 18% (HR: 0.82, 95% CI: 0.77 – 0.85) decreased risk
 291 of T2DM explained by an indirect association mediated by overweight, and a 10% (HR: 0.90,

292 95%CI: 0.84 – 0.96) decreased risk of T2DM only explained by a higher adherence to this
293 dietary pattern (**Table S2**).

294

295 **DISCUSSION**

296 In the present study with participants from the UK Biobank prospective cohort, a higher
297 adherence to a Medi Diet was associated with a lower risk of T2DM over time. This
298 association was mostly mediated by the lower odds of being overweight or obese among the
299 highest Medi Diet adherents, although direct effect of Medi diet on the risk of T2DM,
300 independent of overweight, was also observed.

301 This overall result appears consistent with existing literature, agreeing with a beneficial role
302 of the Medi Diet in the prevention of T2DM. Specifically, in a meta-analysis based on 122
303 810 subjects, Schwingshackl *et al.* found a pooled risk ratio of 0.81 for T2DM comparing
304 individuals in the highest vs. lowest adherence of Medi Diet (26). In 2014, based on 22
305 relevant studies including RCTs, meta-analyses and systematic reviews, Khemayanto *et al.*
306 concluded that the combination and interaction of Medi Diet food groups was essential for the
307 prevention and management of T2DM (27). Specifically, these food groups (*i.e.* such as fruits,
308 vegetables, legumes, olive oil or fish) provided health promoting properties such as lower
309 body weight, hemoglobin A1C, density lipoprotein (LDL) and oxidative stress, and improved
310 HDL, these latter being beneficial for the improvement of the prevention and prognosis of
311 T2DM (27). According to our exploratory results, when each food group part of the Medi
312 Diet was considered separately in mediation models none was directly associated with T2DM
313 (*i.e.* Direct effect, not mediated by the odds of developing overweight), suggesting that the
314 synergistic effect that occurs in a Medi Diet might brings superior benefits compared to each
315 isolated nutrient (28).

316 The vast majority of previous studies only adjusted for BMI or the waist circumference (*i.e.*
317 Direct effect), while our innovative approach took into account both the direct and the indirect
318 effect of the Medi Diet on the risk of T2DM mediated by overweight. Our mediation analysis
319 indicated that the association between Medi Diet adherence and risk of T2DM was mostly
320 mediated through overweight ($\approx 10\%$ out of 14%). Specifically, a higher adherence to the
321 literature-based Medi Diet was inversely associated with a lower odds of developing
322 overweight, this latter being positively associated with a higher risk of T2DM. Interestingly,
323 using an alternative Medi Diet definition, based on 11 food groups and different cut-off
324 points, the present results were confirmed which reinforced the robustness of our findings.

325 The biological plausibility of our results is strong. Hamman *et al.* found a 16% lower risk of
326 diabetes for every kg of weight loss, suggesting a dose-response effect (14). Also, a previous
327 study observed that weight loss among overweight or obese patients with T2DM was
328 consistently associated with a reduction of hemoglobin A1C, in a dose-dependent manner
329 (29). A reduction of an average 16.7% in the homeostasis model assessment of IR (HOMA-
330 IR) and 23.3% in leptin, both involved in the pathogenesis of T2DM, was also observed
331 following a mean weight loss of 5.6 kg among 35 overweight or obese subjects (30).

332 Moreover, evidence has accumulated suggesting that greater adherence to a Medi Diet results
333 in significant weight loss. In a RCT over 12 months, Medi Diet led to a similar weight loss
334 than the American Diabetes Association diet (whose its composition in fiber is lower than the
335 Medi Diet), but with a greater weight loss compared to a low-fat diet (ranging from -4.1 to -
336 10.1 kg across studies for the Medi Diet) (31).

337 Therefore, the inverse association between higher adherence to a Medi Diet and lower risk of
338 T2DM observed in the literature may be, at least in part, explained by the preventive role of
339 the Medi Diet on the odds of developing overweight or obesity.

340 In our study, the whole effect of the Medi Diet (*i.e.* Direct & Indirect effects) on the risk of
341 T2DM resulted in a higher impact than each effect alone (*i.e.* Direct or Indirect effect only),
342 suggesting that better adherence to a Medi Diet would have a synergistic impact on both the
343 lower odds of overweight and the reduced risk for developing T2DM. This latter result
344 suggests a beneficial effect of the Medi Diet preventing T2DM even among those who do not
345 reduce their weight. These results can be attributed to a higher intakes of nutrients and food
346 groups associated with anti-inflammatory properties, polyphenols, vitamins, minerals as well
347 as other antioxidants, which are found in typical Medi Diet food groups such as fruits,
348 vegetables, fish, olive oil, legumes, red wine and nuts (32–34). Other potential beneficial
349 effects of a Medi Diet on glucose metabolism and insulin sensitivity include in contrast lower
350 intake of pro-inflammatory nutrients such as saturated fatty acids, refined sugars and a low-to
351 moderate consumption of alcohol (35–37).

352 Some limitations of the present work should be emphasized. First, the rate of participant loss
353 to follow-up was high, which could lead to a selection bias, although minimized as observed
354 in the present study. Therefore, the obtained results may not be generalizable to the whole UK
355 biobank cohort, and further investigations, in other population-based cohorts, are needed to
356 confirm such results. Second, longer follow-up time would allow increasing the duration
357 between nutritional assessment (Medi Diet) and assessment of the mediator (BMI). However,
358 to limit inverse causation due to dietary changes over time that would occur at the time of the
359 diagnosis of T2DM, and to have the most accurate and representative assessment of usual
360 diet, analyses were focused only on participants who reported a typical diet in nutritional
361 questionnaires. Third, the diagnosis of diabetes was self-declared and we have considered that
362 all incident cases of diabetes, except for gestational diabetes, were T2DM, which increased
363 the risk of exposure misclassification.

364 Our study also has important strengths including its large sample size, its sampling among a
365 population-based cohort and the use of a literature-based non-sample-dependent Medi Diet
366 score which will allow comparison across further studies. Moreover, only dietary
367 questionnaires reflecting the usual diet were used to determine usual food consumption. The
368 robustness of our results were tested and confirmed with another different Medi Diet score,
369 highlighting that these results are robust even with the use of another definition of the Medi
370 Diet. Finally, we take into account a large range of sociodemographic, lifestyle and clinical
371 factors to minimize the possibility of potential confounding.

372 **Conclusion**

373 In this study, we found that overweight may have a crucial mediated-effect in the relationship
374 between higher adherence to a Medi Diet score and lower risk of T2DM. Interestingly, we
375 also found a direct effect of the Medi Diet, regardless of the overweight, suggesting that this
376 dietary pattern can prevent T2DM even if it does not lead to lower weight. These results seem
377 to be clinically relevant for public health, in particular for encouraging a Mediterranean-like
378 dietary pattern adoption for primary prevention of T2DM and overweight/obesity.

379

380

381 **Acknowledgments and fundings:** This work was supported by the Joint Programming
382 Initiative (JPI) Healthy diet for healthy life (HDHL). The SALAMANDER project is funded
383 by the French National Research Agency (ANR, France), the Research Council for
384 Biotechnology and Biological Sciences (BBSRC, UK) and the Ministry of Economy and
385 Competitiveness (MINECO, Spain). This specific analysis was agreed by the UK Biobank
386 Steering Committee (application #3028).

387

388 **Declaration of interest:** The authors declare that they have no conflicts of interests.

389

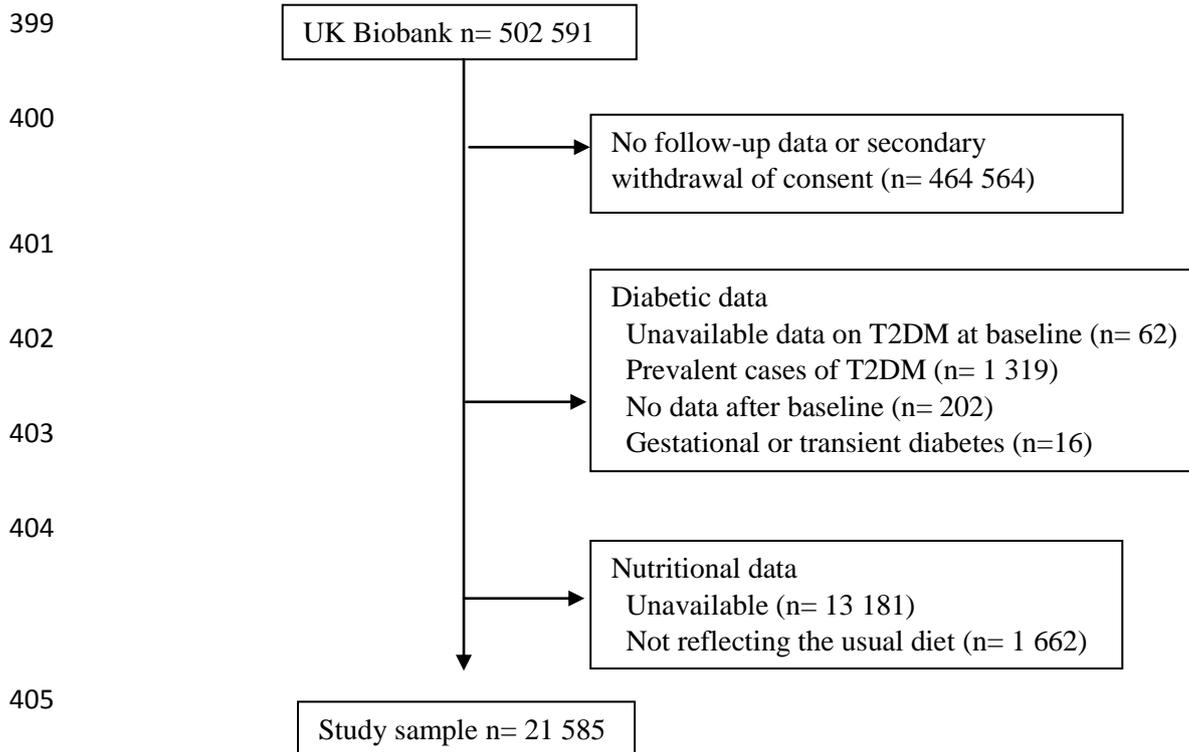
390 **Authors' contribution:** All authors contributed to study concept and design. PA and BD
391 performed statistical analysis and interpretation of data. PA prepared the manuscript. All
392 authors critically reviewed the manuscript for important intellectual content. All authors read
393 and approved the final manuscript.

394

395 **Guarantors:** MM, CF, FRA and GP.

396

397

398 **FIGURES****AND TABLES**

408 **Figure 1.** Flow chart of the research study design, UK Biobank. Abbreviations: T2DM Type
409 2 Diabetes Mellitus.

416

417

418

419

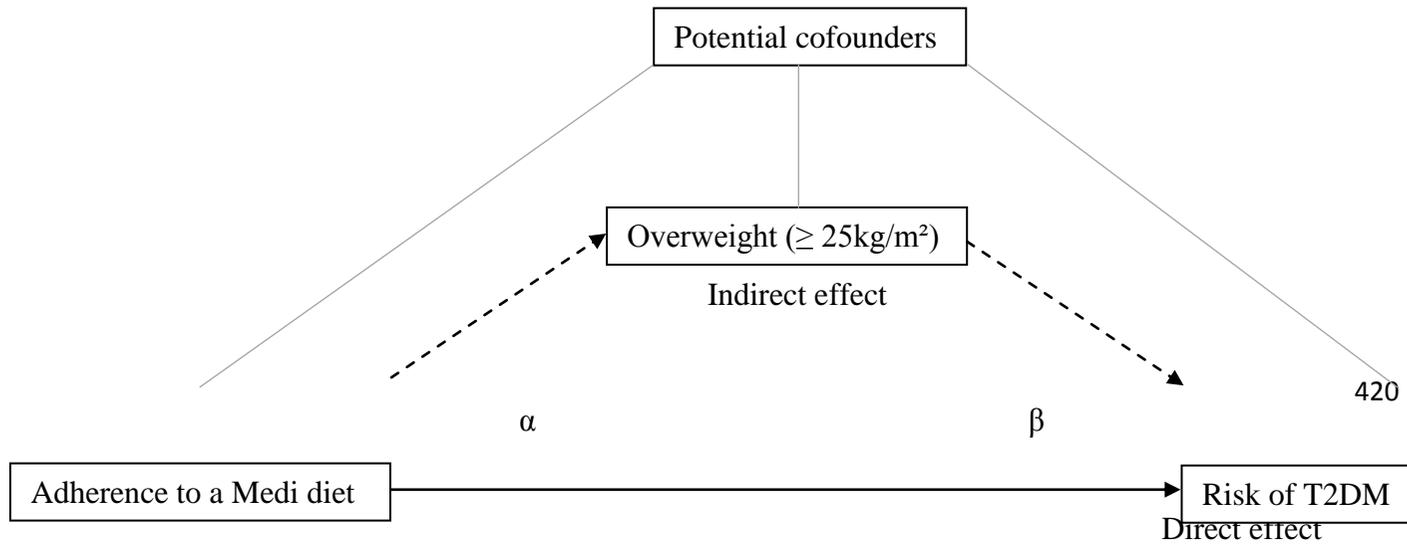
421

422

423

424

425 **Figure 2.** Mediation analysis model of associations between adherence to a Mediterranean diet and risk of Type 2 Diabetes Mellitus mediated by
 426 overweight. Path α represents the regression coefficient for the association between the literature-based Mediterranean score and overweight.
 427 Path β represents the regression coefficient for the association between overweight and the risk of T2DM. The indirect effect is represented by
 428 dotted arrows and the direct effect by continuous arrow. Potential confounders selected from i) a directed acyclic graph, ii) literature, iii)
 429 available data among the whole dataset. Abbreviations: Medi Mediterranean; T2DM Type 2 Diabetes Mellitus.



430 **Table 1.** Baseline characteristics of the participants according to the T2DM, study sample from the UK Biobank (n= 21 585).

431

Baseline characteristics	Incident T2DM cases (n=473)	Non incident T2DM (n=21 112)	p-value
Age (years)	58.1 ± 7.2	56.4 ± 7.5	<0.0001
Sex (men)	313 (66.1)	10 033 (47.5)	<0.0001
Educational level (/ A level, college or university)	242 (51.1)	8 241 (39.0)	<0.0001
BMI (overweight or obesity)	405 (85.6)	12 033 (57.0)	<0.0001
Smoking status			
Non-smoker	238 (50.3)	12 882 (61.0)	<0.0001
Ex-smoker	196 (41.4)	7 039 (33.3)	
Current smoker	39 (8.3)	1 191 (5.6)	
Inactive lifestyle	80 (16.9)	2 093 (9.9)	<0.0001
Number of drugs	3.2 ± 3.0	2.0 ± 2.3	<0.0001
Comorbidities	2.5 ± 2.2	1.8 ± 1.8	<0.0001
Energy intake (Kjoules)	8879.3 ± 2412	8870.7 ± 2555	0.997
Literature-based Medi score (/18 points)	8.1 ± 2.7	8.8 ± 2.6	<0.0001
Alternative Medi score (/55 points)	25.4 ± 7.4	27.3 ± 7.1	<0.0001

432

433 Values are mean ± standard deviation or number (%). Abbreviations: T2DM Type 2 Diabetes Mellitus; BMI Body Mass Index, overweight being
434 defined as BMI >25 kg/m².

435

436 **Table 2.** Mediation analysis of the association between adherence to a literature-based
 437 Mediterranean diet (+ 1 point, /18 points) and the risk of T2DM mediated by overweight,
 438 study sample from the UK Biobank (n= 21 585).

439

Literature-based Medi diet score	Effect scale: Hazard Ratio [95%CI]	p-value
Path α (Medi Diet \rightarrow overweight)	0.92 [0.91 – 0.93] *	<0.0001
Path β (Overweight \rightarrow T2DM)	3.89 [3.00 – 5.04]	<0.0001
Direct effect (Medi Diet \rightarrow T2DM)	0.96 [0.93 – 0.99]	0.0197
Indirect effect (Medi Diet \rightarrow T2DM mediated by overweight)	0.90 [0.87 – 0.92]	<0.0001
Total effect (Medi Diet \rightarrow Overweight \rightarrow T2DM)	0.86 [0.82 – 0.90]	<0.0001

440

441 Path α represents the regression coefficient (*Odds Ratio) for the association between
 442 adherence to a Medi-diet and overweight. Path β represents the regression coefficient for the
 443 association between overweight and the risk of T2DM (supplementary adjustment for Medi
 444 diet). Abbreviations: Medi Mediterranean; T2DM Type 2 Diabetes Mellitus. Models were
 445 adjusted for sex, educational level, average intake of calorie, sedentary lifestyle, tobacco use
 446 (supplementary adjustment for age at baseline for the path α model, and adherence to the
 447 Medi-diet for path β).

448

449 **REFERENCES**

- 450
- 451 1. International Diabetes Federation. IDF Diabetes Atlas [Internet]. 8th ed. Brussels, Belgium;
452 2017. Available from: <http://diabetesatlas.org/resources/2017-atlas.html>
- 453 2. Zghebi SS, Steinke DT, Carr MJ, Rutter MK, Emsley RA, Ashcroft DM. Examining trends in
454 type 2 diabetes incidence, prevalence and mortality in the UK between 2004 and 2014. *Diabetes*
455 *Obes Metab.* 2017;19(11):1537–45.
- 456 3. DeFronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for
457 the treatment of type 2 diabetes mellitus. *Diabetes.* 2009 Apr;58(4):773–95.
- 458 4. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and
459 national prevalence of overweight and obesity in children and adults during 1980-2013: a
460 systematic analysis for the Global Burden of Disease Study 2013. *Lancet Lond Engl.* 2014 Aug
461 30;384(9945):766–81.
- 462 5. Statistics on Obesity, Physical Activity and Diet - England, 2017 - NHS Digital [Internet]. [cited
463 2019 Mar 14]. Available from:
464 [https://webarchive.nationalarchives.gov.uk/20180328133908/http://digital.nhs.uk/catalogue/PUB](https://webarchive.nationalarchives.gov.uk/20180328133908/http://digital.nhs.uk/catalogue/PUB23742)
465 [23742](https://webarchive.nationalarchives.gov.uk/20180328133908/http://digital.nhs.uk/catalogue/PUB23742)
- 466 6. Gray N, Picone G, Sloan F, Yashkin A. The Relationship between BMI and Onset of Diabetes
467 Mellitus and its Complications. *South Med J.* 2015 Jan;108(1):29–36.
- 468 7. Martinez-Gonzalez MA, Bes-Rastrollo M, Serra-Majem L, Lairon D, Estruch R, Trichopoulou
469 A. Mediterranean food pattern and the primary prevention of chronic disease: recent
470 developments. *Nutr Rev.* 2009 May;67 Suppl 1:S111-116.
- 471 8. Khazrai YM, Defeudis G, Pozzilli P. Effect of diet on type 2 diabetes mellitus: a review.
472 *Diabetes Metab Res Rev.* 2014 Mar;30 Suppl 1:24–33.
- 473 9. Jannasch F, Kröger J, Schulze MB. Dietary Patterns and Type 2 Diabetes: A Systematic
474 Literature Review and Meta-Analysis of Prospective Studies. *J Nutr.* 2017;147(6):1174–82.
- 475 10. Esposito K, Giugliano D. Mediterranean diet and type 2 diabetes. *Diabetes Metab Res Rev.* 2014
476 Mar;30 Suppl 1:34–40.
- 477 11. Esposito K, Maiorino MI, Bellastella G, Chiodini P, Panagiotakos D, Giugliano D. A journey
478 into a Mediterranean diet and type 2 diabetes: a systematic review with meta-analyses. *BMJ*
479 *Open.* 2015 Aug 10;5(8):e008222.
- 480 12. Koloverou E, Esposito K, Giugliano D, Panagiotakos D. The effect of Mediterranean diet on the
481 development of type 2 diabetes mellitus: a meta-analysis of 10 prospective studies and 136,846
482 participants. *Metabolism.* 2014 Jul;63(7):903–11.
- 483 13. Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary
484 approaches to the management of type 2 diabetes. *Am J Clin Nutr.* 2013 Mar;97(3):505–16.
- 485 14. Hamman RF, Wing RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L, et al. Effect of weight
486 loss with lifestyle intervention on risk of diabetes. *Diabetes Care.* 2006 Sep;29(9):2102–7.
- 487 15. Bradbury KE, Young HJ, Guo W, Key TJ. Dietary assessment in UK Biobank: an evaluation of
488 the performance of the touchscreen dietary questionnaire. *J Nutr Sci [Internet].* 2018 Feb 1 [cited
489 2019 Apr 11];7. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5799609/>
- 490 16. Liu B, Young H, Crowe FL, Benson VS, Spencer EA, Key TJ, et al. Development and
491 evaluation of the Oxford WebQ, a low-cost, web-based method for assessment of previous 24 h
492 dietary intakes in large-scale prospective studies. *Public Health Nutr.* 2011 Nov;14(11):1998–
493 2005.
- 494 17. Anderson J, Celis-Morales C, Mackay D, Iliodromiti S, Lyall D, Sattar N, et al. Adiposity among
495 132 479 UK Biobank participants; contribution of sugar intake vs other macronutrients. *Int J*
496 *Epidemiol.* 2017 Apr;46(2):492–501.
- 497 18. Sofi F, Macchi C, Abbate R, Gensini GF, Casini A. Mediterranean diet and health status: an
498 updated meta-analysis and a proposal for a literature-based adherence score. *Public Health Nutr.*
499 2014 Dec;17(12):2769–82.
- 500 19. Féart C, Samieri C, Allès B, Barberger-Gateau P. Potential benefits of adherence to the
501 Mediterranean diet on cognitive health. *Proc Nutr Soc.* 2013 Feb;72(1):140–52.

- 502 20. OMS | Recommandations mondiales en matière d'activité physique pour la santé [Internet].
503 WHO. [cited 2019 Mar 14]. Available from:
504 https://www.who.int/dietphysicalactivity/factsheet_recommendations/fr/
- 505 21. VanderWeele TJ. Causal mediation analysis with survival data. *Epidemiol Camb Mass*. 2011
506 Jul;22(4):582–5.
- 507 22. Trichopoulou A, Bamia C, Trichopoulos D. Anatomy of health effects of Mediterranean diet:
508 Greek EPIC prospective cohort study. *BMJ*. 2009 Jun 23;338:b2337.
- 509 23. Aune D, Norat T, Romundstad P, Vatten LJ. Whole grain and refined grain consumption and the
510 risk of type 2 diabetes: a systematic review and dose-response meta-analysis of cohort studies.
511 *Eur J Epidemiol*. 2013 Nov;28(11):845–58.
- 512 24. Della Pepa G, Vetrani C, Vitale M, Riccardi G. Wholegrain Intake and Risk of Type 2 Diabetes:
513 Evidence from Epidemiological and Intervention Studies. *Nutrients*. 2018 Sep;10(9):1288.
- 514 25. Panagiotakos DB, Pitsavos C, Arvaniti F, Stefanadis C. Adherence to the Mediterranean food
515 pattern predicts the prevalence of hypertension, hypercholesterolemia, diabetes and obesity,
516 among healthy adults; the accuracy of the MedDietScore. *Prev Med*. 2007 Apr;44(4):335–40.
- 517 26. Schwingshackl L, Missbach B, König J, Hoffmann G. Adherence to a Mediterranean diet and
518 risk of diabetes: a systematic review and meta-analysis. *Public Health Nutr*. 2015
519 May;18(7):1292–9.
- 520 27. Khemayanto H, Shi B. Role of Mediterranean diet in prevention and management of type 2
521 diabetes. *Chin Med J (Engl)*. 2014;127(20):3651–6.
- 522 28. Martínez-González MA, Gea A. Mediterranean diet: the whole is more than the sum of its parts.
523 *Br J Nutr*. 2012 Aug;108(4):577–8.
- 524 29. Gummesson A, Nyman E, Knutsson M, Karpefors M. Effect of weight reduction on glycated
525 haemoglobin in weight loss trials in patients with type 2 diabetes. *Diabetes Obes Metab*.
526 2017;19(9):1295–305.
- 527 30. Wang T-N, Chang W-T, Chiu Y-W, Lee C-Y, Lin K-D, Cheng YY, et al. Relationships between
528 changes in leptin and insulin resistance levels in obese individuals following weight loss.
529 *Kaohsiung J Med Sci*. 2013 Aug;29(8):436–43.
- 530 31. Mancini JG, Filion KB, Atallah R, Eisenberg MJ. Systematic Review of the Mediterranean Diet
531 for Long-Term Weight Loss. *Am J Med*. 2016 Apr;129(4):407–415.e4.
- 532 32. Pérez-Jiménez J, Neveu V, Vos F, Scalbert A. Identification of the 100 richest dietary sources of
533 polyphenols: an application of the Phenol-Explorer database. *Eur J Clin Nutr*. 2010 Nov;64
534 Suppl 3:S112–120.
- 535 33. Martínez-González MA, Salas-Salvadó J, Estruch R, Corella D, Fitó M, Ros E, et al. Benefits of
536 the Mediterranean Diet: Insights From the PREDIMED Study. *Prog Cardiovasc Dis*. 2015
537 Aug;58(1):50–60.
- 538 34. Schwingshackl L, Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial
539 function: a systematic review and meta-analysis of intervention trials. *Nutr Metab Cardiovasc*
540 *Dis NMCD*. 2014 Sep;24(9):929–39.
- 541 35. Riserus U, Willett WC, Hu FB. Dietary fats and prevention of type 2 diabetes. *Prog Lipid Res*.
542 2009 Jan;48(1):44–51.
- 543 36. Chandalia M, Garg A, Lutjohann D, von Bergmann K, Grundy SM, Brinkley LJ. Beneficial
544 effects of high dietary fiber intake in patients with type 2 diabetes mellitus. *N Engl J Med*. 2000
545 May 11;342(19):1392–8.
- 546 37. Bonnet F, Disse E, Laville M, Mari A, Hojlund K, Anderwald CH, et al. Moderate alcohol
547 consumption is associated with improved insulin sensitivity, reduced basal insulin secretion rate
548 and lower fasting glucagon concentration in healthy women. *Diabetologia*. 2012
549 Dec;55(12):3228–37.
- 550