Accepted author's manuscript. Published in final edited form as: Journal of Nutrition 2021 (in press). Publisher DOI: <u>10.1093/jn/nxab003</u>

# Menopausal transition is not associated with dietary change in Swiss women

Running head: Menopause status and diet

Giorgia Grisotto<sup>1,2,3</sup>, Peter Francis Raguindin<sup>1,2,4</sup>, Marija Glisic<sup>1,4</sup>, Lia Bally<sup>5</sup>, Arjola Bano<sup>1</sup>,

Oscar H. Franco<sup>1</sup>, Pedro Marques-Vidal<sup>6\*</sup>, Taulant Muka<sup>1\*</sup>

<sup>1</sup>Institute of Social and Preventive Medicine (ISPM), University of Bern, Switzerland

<sup>2</sup>Graduate School for Health Sciences, University of Bern, Switzerland

<sup>3</sup>Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston,

Massachusetts, USA

<sup>4</sup>Swiss Paraplegic Research, Nottwil, Switzerland

<sup>5</sup>Department of Diabetes, Endocrinology, Clinical Nutrition & Metabolism, Bern University

Hospital, Bern, Switzerland

<sup>6</sup>Department of Medicine, Internal Medicine, Lausanne University Hospital (CHUV) and

University of Lausanne, Lausanne, Switzerland

\*Denotes equal contribution

Giorgia Grisotto Giorgia.grisotto@ispm.unibe.ch ORCID: 0000-0002-8284-3225

Peter Francis Raguindin Peter.raguindin@ispm.unibe.ch

Marija Glisic Marija.glisic@ispm.unibe.ch

Lia Bally Lia.Bally@insel.ch

Arjola Bano Arjola.bano@ispm.unibe.ch

Oscar H. Franco Oscar.franco@ispm.unibe.ch

Pedro Marques-Vidal <u>Pedro-Manuel.Marques-Vidal@chuv.ch</u> Taulant Muka Taulant.muka@ispm.unibe.ch

# Sources of support

The CoLaus study was and is supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science Foundation (grants 33CSCO-122661, 33CS30-139468 and 33CS30-148401).

# **Conflict of interest**

Authors have no conflicts of interest to declare

Corresponding author: Taulant Muka, MD, MPH, PhD; Institute of Social and Preventive

Medicine (ISPM), University of Bern, Mittelstrasse 43, 3012, Bern, Switzerland.

taulant.muka@ispm.unibe.ch.

Abstract word count: 300

Word count (without abstract and references): 3744 (from Introduction to Conclusion)

Number of figures: 1

Number of Tables: 3

**Supplementary data submitted:** 10 Supplementary tables are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents available <u>on the Journal homepage</u>.

**List of abbreviation:** SD, standard deviation; IQR, interquartile range; OR, odd ratio; TEI, total energy intake; CVD, cardiovascular disease; T2D, type 2 diabetes; HT, hormone therapy; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; FFQ, food frequency questionnaire; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; BMI, body mass index.

# 1 ABSTRACT

Background: Adherence to a healthy diet could contribute to maintaining adequate health
throughout the menopausal transition but data are scarce.

4 Objective: We evaluated the association between menopausal status and changes in dietary
5 intake in Swiss adult women.

6 Methods: Cross-sectional (n=2,439) and prospective analyses (n=1,656) were conducted 7 between 2009 and 2012 (first follow-up) among women (mean age  $\pm$  standard deviation [SD] 8 58.2±10.5 years) living in Lausanne, Switzerland. In both visits, dietary intake was assessed 9 using a validated food frequency questionnaire (FFQ) and menopausal status was classified 10 based on presence or absence of menstruations. Multivariable linear and logistic regression 11 models were used to investigate the cross-sectional association of menopausal status 12 (postmenopausal vs. premenopausal) at the first follow-up with food intake and dietary 13 recommendations. To examine whether menopausal status (premenopausal as reference group, 14 menopausal transition and postmenopausal) during 5 years of follow-up was associated with 15 longitudinal changes in diet, including adherence to dietary Swiss recommendations, we 16 applied multivariable linear and logistic mixed models adjusted for several covariates.

17 **Results:** At the first follow-up, postmenopausal women consumed less (P value < 0.002) meat 18 (median, interquartile range [IQR] 57.2 [35-86.2] vs. 62.5 [41.2-95.2] gram/day), pasta (61.8 [37.5-89.2] vs. 85 [57.8-128] gram/day), added sugar (0.1 [0-4] vs. 0.7 [0-8] gram/day), and 19 more dairy products (126 [65.4-214] vs. 109 [64.5-182] gram/day), fruits (217 [115-390] vs. 20 21 174 [83.2-319] gram/day) than premenopausal women. However, linear regression analysis 22 adjusted for potential confounding factors showed no independent (cross-sectional) 23 associations of menopausal status with total energy intake (TEI) and individual macro- or 24 micronutrient intakes. In the prospective analysis, compared to women who remained 25 premenopausal during follow-up (n=244), no differences were found in changes in TEI, dietary intakes, or in adherence to the Swiss dietary recommendations in women transitioning from
premenopausal to postmenopausal (*n*=229) and who remained postmenopausal (*n*=1168). **Conclusion**: The menopausal transition is not associated with changes in dietary habits among
Swiss women.

- 30
- 31 Keywords: Menopause transition; dietary recommendation; dietary habits; Switzerland;
- 32 cross-sectional; population-based study.

#### 33 Introduction

34 Menopause marks the end of a physiological process after which, women face a drastic drop 35 in oestrogen levels, an increase in iron levels, appearance of menopausal symptoms, and an 36 increase in the incidence and mortality rates for cardiovascular disease (CVD) [1, 2]. Menopausal transition is associated with adverse changes in sleep and mood [3], body 37 38 composition as weight gain and accumulation of central body fat [4], a shift towards a more 39 atherogenic lipid profile and impairment of glucose homeostasis, and higher depression, all important risk factors for CVD and overall mortality [5, 6, 7]. Numerous postmenopausal 40 41 women also live with type 2 diabetes (T2D), which confers a greater risk of CVD in women compared to men [8, 9, 10]. Furthermore, the menopausal transition has an adverse impact on 42 43 overall musculoskeletal health, including osteoporosis, osteoarthritis and sarcopenia [11].

44 As a preventive approach, balanced nutrition and correct dietary changes during the 45 menopausal transition could have substantial positive effects on cardiometabolic risk, 46 musculoskeletal health and psychological health. To date, there are few studies examining 47 changes in dietary intake during the menopausal transition [12], with inconsistent results, and with smaller sample sizes (i.e., below 1000 participants). Some studies report no change and 48 49 some a decrease in TEI and carbohydrates [13, 14]. For health promotion and disease 50 prevention in women transitioning in menopause, it is important to understand whether dietary 51 changes occur. Furthermore, examining possible changes in dietary intake during menopause 52 can also provide more information on whether the observed adverse metabolic changes during 53 menopause can be attributed to dietary changes.

54 Therefore, we studied the changes in dietary intake in women before and after menopause using 55 data from the CoLaus study. We compared cross-sectionally the dietary intake between pre-56 and postmenopausal women, and then we examined whether the change in menopausal status was prospectively associated with 5-years changes in dietary intake compared to women who
remained premenopausal during the follow-up or were postmenopausal across the study period.

# 60 Methods

#### 61 *Study population*

62 The study was carried out within the framework of CoLaus study, a population-based cohort study conducted in Lausanne, Switzerland. The details of the study have been reported 63 elsewhere [15]. Briefly, the baseline study was conducted between June 2003 and May 2006 64 65 and included 6733 participants, of which 5064 attended the first follow-up, April 2009 and 66 September 2012. The second follow-up included 4750 participants and was conducted between 67 May 2014 and March 2017. During each visit, information on medical conditions, use of 68 medications, and lifestyle were collected, and each participant was extensively evaluated 69 regarding cardiovascular risk factors and blood characterisation was performed.

70 *Ethical statement* 

The institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of Canton Vaud (www.cer-vd.ch) approved the baseline CoLaus study (reference 16/03, decisions of 13<sup>th</sup> January and 10<sup>th</sup> February 2003). The approval was renewed for the first (reference 33/09, decision of 23<sup>rd</sup> February 2009) and the second (reference 26/14, decision of 11<sup>th</sup> March 2014). The study was performed in agreement with the Helsinki declaration and its former amendments, and in accordance with the applicable Swiss legislation. All participants gave their signed informed consent before entering the study.

78 Selection criteria

The present study used data from the first and the second follow-up visit of the CoLaus study.
A total of 2707 women were included in the first follow-up of CoLaus. Of these, 46 were
excluded because there was no information on their menopause status and 222 women were

excluded due to no information on dietary intake, leaving 2,439 women for the cross-sectional analysis (**Figure 1**). Among them, 271 did not participate in the second follow-up visit of the study, and a further 527 women were excluded because there was no information on menopause status (n = 57), unreliable (women reporting being postmenopausal at the first follow-up and premenopausal at the second follow-up) menopause status (n = 15) or dietary intake was not known (n = 455), leaving 1,641 women for the prospective analysis (**Figure 1**).

# 88 Menopause status

Women participating in the study were asked whether they were still having menses. Women reporting "No" were classified as postmenopausal, and as premenopausal if they answered "Yes". Based on the self-reported menopausal status at the first and second follow-up visits, women were classified as being (i) *premenopausal-premenopausal* if they remained premenopausal, (ii) *premenopausal-postmenopausal* if they changed their status, (iii) and otherwise as *postmenopausal-postmenopausal*.

95 Dietary assessment

96 Dietary intake of 4 weeks prior to the interview was assessed using a self-administered, semi-97 quantitative FFQ that also included portion size [16]. This FFQ has been validated among 626 volunteers from the Geneve population [16, 17]. The FFQ consisted of 97 different food items 98 99 accounting for more than 90% of the intake of calories, proteins, fats, carbohydrates, alcohol, cholesterol, vitamin D and retinol, and 85% of fibre, carotene and iron. For each item, 100 101 consumption frequencies ranging from "less than once during the last 4 weeks" to "2 or more 102 times per day" were provided, and the participants indicated the average serving size (smaller, 103 equal, or bigger) compared to a reference size. To calculate nutrient intakes, frequency of intake 104 was multiplied by the nutrient composition of the specified portion size. Nutrient estimates 105 were based on the French CIQUAL food composition table. Two values of TEI were computed: 106 one including alcohol consumption, the other not. Carbohydrates (total and subtypes such as 107 disaccharides), proteins (total, plant and animal derived) and fats (total, saturated fatty acids 108 SFAs, monounsaturated fatty acids MUFAs and polyunsaturated fatty acids PUFAs) were 109 expressed as percentage of TEI (alcohol excluded). All food items were reported in g/day. 110 Participants were further dichotomised based on whether they adhered to dietary guidelines 111 recommendations of the Swiss Society of Nutrition including (i) 2 and 3 portions of fruits and 112 vegetables per day, (ii) less than 3 portions of meat per week, (iii) more than 1 portion of fish 113 per week, (iv) 3 portions of dairy products per day (milk, yogurt, hard and soft cheese) [18]. 114 For each food item recommendations (fruits, vegetables, meat, fish, dairy products), a binary 115 variable (1=yes, 0=no) was computed, classifying participants on whether they adhered or not 116 to the recommendation per item. We also further divided participants into adhering to 3 or more 117 recommendations.

118 *Covariates* 

Based on biological plausibility and previous literature we selected the potential confounding
factors namely age, marital status, education level, body mass index (BMI), history of CVD
and diabetes, serum lipids, antihypertensive, hypolipidemic and antidiabetic treatments [19,
20].

123 Sociodemographic and lifestyle data were collected by self-administered questionnaires. 124 Sociodemographic data included age, marital status (married, divorced, single or widowed) 125 and education level (university education, high school, apprenticeship and mandatory 126 education). Health characteristics included BMI calculated and categorized in three groups 127 (normal 18.5 to < 25 kg/m<sup>2</sup>; overweight 25 to < 30 kg/m<sup>2</sup>; obese  $\ge$  30 kg/m<sup>2</sup>) based on the 128 World Health Organization recommendations [21]. CVD was defined as a history of 129 myocardial infarction, coronary artery bypass surgery, or percutaneous transluminal coronary 130 angioplasty. T2D mellitus was diagnosed if fasting serum glucose level was  $\geq 7 \text{ mmol/L}$  or if the participants used glucose-lowering medication. Participants also indicated whether theyused antihypertensive medications or lipid-lowering medications.

# 133 Statistical analysis

Statistical analyses were performed using Stata version 15.1 for Windows (Stata corp, College
Station, TX, USA). Continuous variables were reported as mean ± SD if normally distributed,
and as median and IQR if not normally distributed; categorical variables were presented as
numbers and percentages [%]. The normality of continuous variables was checked using a
histogram and the Shapiro-Wilk test.

139 Cross-sectional analysis

140 We compared the sociodemographic, diet and other lifestyle variables between pre- and 141 postmenopausal women included in the cross-sectional analysis (Supplementary table 1), 142 using the Student's t-test, Wilcoxon rank-sum test and chi-square test, as appropriate 143 (Supplementary table 2). Age and multivariable-adjusted linear and logistic regression 144 models were performed to examine whether menopause status (premenopausal vs. 145 postmenopausal) was cross-sectionally associated with TEI, food intake and dietary 146 recommendations (Table 2). Factors for multivariable analyses were selected based on current 147 knowledge and literature, and were adjusted for age, education level, civil status, BMI, 148 prevalent CVD and diabetes, and use of medications including lipid-lowering medications and 149 antihypertensive treatment.

150 Longitudinal analysis

We used repeated measures analysis to analyse dietary changes during the follow-up among (i) women who transitioned from premenopausal to menopausal, and among women who remained (ii) pre- or (iii) postmenopausal. To examine whether changing menopausal status during the follow-up was independently associated with changes in TEI and dietary intake, we performed linear mixed model with random effects of menopausal categories; (i) 156 premenopausal during the follow-up (as reference), (ii) women who transitioned to menopause, 157 and (iii) women who were postmenopausal during the all study period (Table 3). The models 158 were adjusted for age, education level, civil status, BMI, prevalent CVD and diabetes, and use 159 of medications including lipid-lowering medications and antihypertensive treatment. Similarly, 160 to investigate whether menopause status would affect changes over time in adherence with the 161 dietary guidelines, we applied mixed-effects logistic regression (Table 3). Sensitivity analyses 162 were performed by repeating all analyses censoring the nutrition data at the 0.5 and 99.5 163 percentiles to account for the influence of outliers. Sociodemographic and clinical 164 characteristics comparison among included women at the first follow-up and second follow-up 165 after 5 years are reported in Table 1.

166 *Sensitivity analysis* 

167 As sensitivity analysis, to investigate the possibility of selection bias, we examined whether 168 there were differences in sociodemographic characteristics between included and excluded 169 women from the cross-sectional analysis, by using chi-square or Student's t-test. Since some 170 of the dietary variables were not normally distributed, we also reran the main linear regression 171 and linear mixed analyses using natural log-transformed values, and for longitudinal analysis, 172 we also did a sensitivity analysis applying a generalized linear mixed model, which does not 173 require the response variable to be normally distributed. To explore the impact of BMI, we 174 stratified the main cross-sectional and longitudinal analyses by BMI categories (normal (<25 175 kg/m<sup>2</sup>) vs. overweight/obese ( $\geq 25$  kg/m<sup>2</sup>)). To evaluate a possible over-adjustment for age or 176 the impact of TEI without alcohol, we ran a sensitivity analysis excluding age as covariate and 177 using TEI without alcohol as variable instead of TEI with alcohol. Since, physical activity and 178 weight changes during menopausal transition could be related to diet [22], in the longitudinal 179 analysis we included BMI at both visits as covariate and also baseline physical activity 180 (expressed as total time min/day). To examine the impact of dietary supplements, we ran the main analyses (i) adjusting for supplements use (vitamins and minerals, calcium and vitamin
D) or (ii) excluding women reporting dietary supplements. Additionally, we explored whether
menopause status in the cross-sectional and longitudinal analyses was associated with
supplement intake.

185 To account for multiple testing, we applied a conservative Bonferroni corrected P < 0.002 (0.05)186 divided by the number of diet variables (n = 30)).

- 187
- 188 Results

**189** *Sample characteristics* 

190 The characteristics of the study sample of women included in the cross-sectional and 191 longitudinal analyses are shown in **Table 1**. After 5 years, women reported higher use of 192 antidiabetic medications, and were less frequently current smokers.

193 Cross-sectional analysis: Menopausal status and dietary intake at first follow-up

194 Compared to premenopausal women, postmenopausal women were older, had higher BMI and 195 more prevalent CVD and T2D (Supplementary table 1). No differences were found in TEI 196 between non-menopausal and menopausal women (mean  $\pm$  SD; 1686  $\pm$  638 vs. 1633  $\pm$  649 197 kcal/day). Compared to premenopausal women, postmenopausal women reported consuming 198 less meat, pasta, added sugar, polysaccharides, MUFAs, and cholesterol, but more dairy 199 products, fruits, monosaccharides, and retinol. (Supplementary table 2). However, the 200 multivariable linear regression analysis showed no association between menopause status, TEI 201 and the intake of micro- and macronutrients (Table 2). With no adjustments for potential 202 confounding factors, compared to premenopausal women, postmenopausal women showed 203 higher adherence to the dietary guidelines on fruits intake (n [%] 809 [33.2] vs. 253 [19.4]) and 204 meat (769 [31.5] vs. 248 [10.2]), but no difference was found between the two women-groups 205 for other dietary components (Supplementary table 2). The multivariable logistic regression analysis showed no association between menopause status and adherence to Swiss dietary
guidelines related to intake of fruits, neither for vegetables, meat, or dairy products (Table 2). *Longitudinal analysis: Changes in menopausal status and changes in dietary intake*

During the follow-up, there were 244 women who remained premenopausal, and 229 women transitioned from premenopausal to menopause; the rest (n = 1168) were postmenopausal women at both first and second follow-up. TEI and dietary intake according to different menopausal status at the first follow-up and after 5 years are summarised in **Supplementary table 3**.

214 For the women remaining premenopausal during follow-up, there was an increase in intakes of 215 total fat and MUFAs, and a decrease in intakes of pastries, pasta, added sugar, total 216 carbohydrate and monosaccharides. Premenopausal women transitioning to menopause, during 217 the follow-up, consumed less milk, pasta and more MUFAs, whereas no differences were found 218 for the other dietary components. Menopausal women from the first to second follow-up 219 showed a reduction in intakes of milk, bread and cereals, pasta, vegetable proteins, total 220 carbohydrate, monosaccharides, polysaccharides and fibre, but increases in fish, total fat, 221 SFAs, MUFAs, cholesterol, and vitamins (Supplementary table 3). The multivariable linear 222 mixed model analysis showed that, compared to women remaining premenopausal during the 223 follow-up, women transitioning to menopause or being postmenopausal had no significant 224 differences in changes in dietary intake over 5 years (P value < 0.002). Similarly, women 225 transitioning to menopause or being postmenopausal, compared to women remaining 226 premenopausal during the follow-up, showed no differences in changes in adherence to Swiss 227 dietary guidelines [18] (Table 3).

228 *Sensitivity analysis* 

Supplementary table 4 summarises the characteristics of women included in the final crosssectional analysis (n = 2439) and of those excluded (n = 268). Compared to women included

231 in the cross-sectional analysis, excluded women were less frequently married, single and 232 more divorced or widowed, had a lower education level, and mostly were current smokers 233 with a higher prevalence of history of diabetes. Stratification analyses by BMI categories did 234 not show a role of BMI in the cross-sectional (Supplementary table 5) and longitudinal (Supplementary table 6) associations between menopause status and dietary intake. 235 236 Restricting the analyses to nutrition data within 0.5 and 99.5 percentiles and using natural 237 log-transformed values of dietary variables yielded similar results to the main analyses (data 238 not shown). Also, applying generalized linear mixed models (Supplementary table 7) did 239 not significantly change the main results. Unlike the results reported in the main analyses, by 240 removing age as covariate, we found in the cross-sectional analysis menopause status was 241 associated with pasta, added sugar and adherence to fruits dietary recommendations (P value 242 < 0.002) (Supplementary table 8), while in the longitudinal analysis postmenopausal 243 women, compared to postmenopausal women after five years, significantly reported higher 244 intakes of dairy products and fruits, lower intake of pasta and higher adherence to fruits and 245 meat dietary recommendations (P value < 0.002) (Supplementary table 9). While 246 performing the longitudinal analysis with adjustment for BMI at two time points, and 247 additionally for baseline physical activity (Supplementary table 10) or using TEI without 248 alcohol, did not materially change the results (data not shown). Also, the cross-sectional and 249 longitudinal analyses adjusted for supplements use (vitamins and minerals, calcium and 250 vitamin D) or excluding women reporting dietary supplements did not materially change the 251 results. Finally, menopause status was not associated with supplements intake at baseline or 252 with changes in supplements intake during the five years of follow-up (data not shown). 253

254 Discussion

To our knowledge, this is the first large study to comprehensively investigate the associations of menopause status and transition to menopause with dietary changes. We observed that among adult Swiss women, there are changes in diet over time, but these changes are independent of the level and changes in menopause status.

259 In our study, menopause per se was not a period of marked changes in TEI and dietary intake 260 even after stratification by BMI. This is in line with a study of 898 women which reported that 261 nutrient intakes over a period of 5 to 6 years were similar across menopausal status, menopause 262 not being independently associated with changes in diet [12]. Also, a small study of 94 women 263 showed no role of menopausal status on any of macronutrients investigated during 5 years of 264 follow-up, except for an increase in carbohydrates intake in the menopausal transition group 265 compared to women being postmenopausal for over 12 months. However, in the later study, 266 the premenopausal women and women transitioning into menopause were grouped together, 267 making the interpretation of the results challenging [13].

# 268 Cross-sectional analysis

269 In the cross-sectional analysis, postmenopausal women consumed more fruits and retinol but 270 less meat, pasta and added sugar compared to non-menopausal women. Adherence to dietary 271 guidelines was higher in postmenopausal women. A possible explanation for these differences 272 could be that postmenopausal women as they age, could have a higher health awareness due to 273 a higher number of diagnosed conditions, as well a higher purchasing power. This is also 274 supported by our results which, after adjusting for cardiovascular risk factors and chronic 275 conditions, showed no differences between pre- and postmenopausal women on all food items. 276 Also, after removing age as a covariate from the analyses, some of these results remained 277 significant.

278 Longitudinal analysis

279 In the prospective analysis, the menopause transition was not associated with changes in TEI 280 and diet, except for a decrease in milk consumption and pasta. The decrease in milk and pasta 281 consumption over a period of 5 years was also observed in premenopausal and postmenopausal 282 women, albeit the decline in milk intake was non-significant in premenopausal women. This 283 suggests that the decrease in milk and pasta intake might not be due to the changes in 284 menopause status, but could be related to other factors. For instance, the decrease in milk 285 consumption could be due to increased awareness of lactose intolerance and/or due to the large 286 availability in the last years of plant-based types of milk in the market. Many marketing 287 campaigns advertise the use of different types of milk deriving from soya, coconut, almond, 288 rice etc., rather than cow and other animals, which were constituting the milk component 289 included in our analyses.

290 Considering age and menopause are correlated, it is difficult to understand the contribution of 291 each of the two factors in impacting dietary changes. Removing age from our analyses, 292 postmenopausal women at the first follow-up compared to postmenopausal women after five 293 years, showed higher intakes of dairy products and fruits, lower intake of pasta and higher 294 adherence to fruits and meat dietary recommendations, but not on other dietary factors 295 considered in the current study. Future research is needed to understand the independent effects 296 of menopause and age (**Supplementary tables 8 and 9**).

297 *Menopause, cardiometabolic changes and diet* 

While women undergo menopause, they experience various symptoms, including hot flashes, night sweats, depression, irritability and anxiety which might increase the risk of CVD and hamper quality of life. The decline on oestrogen levels and accumulation of iron during menopause can negatively impact metabolism, potentially leading to weight gain and repercussions on cholesterol levels and carbohydrate digestion [23]. Additionally, the hormonal changes during menopause can lead to decreased bone density and adverse metabolic 304 changes, which can, in turn, increase the risk of fractures [24] and overall mortality. These 305 adverse metabolic changes in menopause, including weight gain, can also be due to adverse 306 changes in dietary intake in women transitioning into menopause, or due to increases in energy 307 intake because of increased appetite [13, 25]. Future research is needed to explore dietary 308 factors that could counteract the adverse metabolic changes women experience after 309 menopause, and improve women's overall health.

## 310 *Public health implications*

Healthier eating habits (e.g., more vegetables and fruits) and specific educational campaigns throughout women's life could be important in maintaining optimal health and reducing the development of several medical complications during the menopausal years. Yet, there is little research examining the effect of changes in diet during menopausal transition on metabolic changes and cardiovascular health. Future studies should examine which dietary components or dietary patterns are associated with better health during menopausal transition, and whether the identified dietary components/patterns have beneficial and long term effects in women.

318 *Study limitations* 

This study has several limitations. First, the food questionnaire is based on self-reported data, with the possibility of inaccurate reporting and recall bias. While FFQ can be used to estimate TEI, the overall TEI would be less accurate estimate, and therefore our results on TEI should be interpreted with caution [26]. The food questionnaire also is focused on a limited number of food items (97 overall) and some foods groups were missing.

We had no information on type of carotene intakes but only on total intake of carotene, and therefore, we cannot exclude the possibility that women may have changed the consumption of different types of carotenoids. Also, food frequency questionnaires may not be very sensitive in detecting dietary changes, despite studies have demonstrated that food frequency questionnaire, compared to 24-hour dietary recalls, have greater reproducibility in detecting

329 differences in self-reported dietary intake over time [27]. Further, our study included only the 330 population of Lausanne and Caucasian women, and it might not be generalised for all Swiss 331 people, other population, and other ethnicities. A misclassification of menopause status might 332 be due to self-reported data and missing information regarding the absence of menstruations in 333 the last 12 months. Also, because the diet in the longitudinal analysis was assessed 334 prospectively, the subjective measure of menopause would probably lead to non-differential 335 misclassification with respect to the outcome, and would therefore bias estimates toward the 336 null. Yet, when exploring the women reporting the age of menopause, 100% of them had 337 reported no menses, suggesting that the misclassification is unlikely to have happened. Future 338 studies with better definition of menopause status are needed to replicate our findings. For 339 instance, self-reported menopause status should capture the lack of menstruations in the last 12 340 months. Also, use of biomarkers as follicle-stimulating hormone (FSH) is helpful if the 341 diagnosis is in doubt in women with suspected premature ovarian failure, but levels of FSH do 342 not predict when the last menstrual period will occur. Measurement of thyroid-stimulating 343 hormone (TSH) and prolactin are also useful in investigating menstrual irregularity [28]. 344 Finally, some differences have been reported between included and excluded women regarding 345 smoking status, educational level, marital status, history of diabetes and antidiabetic treatment, 346 and therefore, the possibility of selection bias cannot be excluded.

347

# 348 Conclusion

In this Swiss population-based study, menopause *per se* was not associated with changes in
TEI and dietary habits, or with changes in adherence to dietary guidelines.

351

#### 352 Acknowledgment

353 *Author contributions* 

- TM conceived the study. GG, PMV and TM designed the study. TM supervised the study. GG,
- 355 PFR, MG, LB, AB, PMV, OHF and TM participated in data acquisition, collection, analysis or

356 interpretation. GG and PFR performed the statistical analyses. GG and TM drafted the

357 manuscript; PFR, MG, LB, AB, PMV and OHF critically revised the manuscript for intellectual

- 358 content. All authors approved the final version of the manuscript. TM is the guarantor of the
- 359 study and is responsible for the integrity of the work as a whole.

360 *Data availability* 

- 361 The study participants of CoLaus have not provided consent to publicly share the individual
- 362 level data underlying this study. Information related to data access is available to qualified,
- 363 interested researchers at <u>https://www.colaus-psycolaus.ch/professionals/how-to-collaborate/</u>.
- 364 All responses to data sharing requests must comply with the ethical and legal constraints of

365 Switzerland.

366

367

#### References

1. Roa Diaz ZM, Muka T and Franco OH. Personalized solutions for menopause through artificial intelligence: Are we there yet? Maturitas. 2019;129:85-86. DOI:

10.1016/j.maturitas.2019.07.006. PubMED PMID: 31371237

 Jaspers L, Daan NM, van Dijk GM, Gazibara T, Muka T, Wen KX, Meun C, Zillikens MC, Roeters van Lennep JE, Roos-Hesselink JW, et al. Health in middle-aged and elderly women: A conceptual framework for healthy menopause. Maturitas. 2015;81:93-8. DOI: 10.1016/j.maturitas.2015.02.010. PubMED PMID: 25813865

 Caretto M, Giannini A and Simoncini T. An integrated approach to diagnosing and managing sleep disorders in menopausal women. Maturitas. 2019;128:1-3. DOI: 10.1016/j.maturitas.2019.06.008. PubMED PMID: 31561815

4. Karvonen-Gutierrez C and Kim C. Association of Mid-Life Changes in Body Size, Body Composition and Obesity Status with the Menopausal Transition. Healthcare MDPI.
2016;4:42.

5. Brand JS, Onland-Moret NC, Eijkemans MJ, Tjonneland A, Roswall N, Overvad K, Fagherazzi G, Clavel-Chapelon F, Dossus L, Lukanova A, et al. Diabetes and onset of natural menopause: results from the European Prospective Investigation into Cancer and Nutrition. Human Reproduction. 2015;30:1491-8. DOI: 10.1093/humrep/dev054. PubMED PMID: 25779698

6. Coylewright M, Reckelhoff JF, Ouyang P. Menopause and hypertension - an age-old debate. Hypertension. 2008;51:952-959. DOI:

10.1161/HYPERTENSIONAHA.107.105742. PubMED PMID: 18259027

7. Daan NM, Muka T, Koster MP, Roeters van Lennep JE, Lambalk CB, Laven JS, Fauser CG, Meun C, de Rijke YB, Boersma E, et al. Cardiovascular Risk in Women With Premature Ovarian Insufficiency Compared to Pre-menopausal Women at Middle Age.

Journal of Clinical Endocrinology & Metabolism. 2016;101:3306-15. DOI:

10.1210/jc.2016-1141. PubMED PMID: 27300572

Muka T, Asllanaj E, Avazverdi N, Jaspers L, Stringa N, Milic J, Ligthart S, Ikram MA, Laven JSE, Kavousi M, Dehghan A and Franco OH. Age at natural menopause and risk of type
 diabetes: A prospective cohort study. Diabetologia. 2017;60:1951-1960. DOI: 10.1007/s00125-017-4346-8. PubMED PMID: 28721436

 Asllanaj E, Bano A, Glisic M, Jaspers L, Ikram MA, Laven JSE, Volzke H, Muka T and Franco OH. Age at natural menopause and life expectancy with and without type 2 diabetes. Menopause. 2019;26:387-394. DOI: 10.1097/GME.000000000001246. PubMED PMID: 30300301

10. Masana L, Ros E, Sudano I, Anqoulvant D and lifestyle expert working group. Is there a role for lifestyle changes in cardiovascular prevention? What, when and how?
Atherosclerosis supplements. 2017; 26: 2-15. DOI: 10.1016/S1567-5688(17)30020-X.
PubMED PMID: 28434481

11. Khadilkar SS. Musculoskeletal Disorders and Menopause. The Journal of Obstetrics and Gynecology of India. 2019; 69(2):99-103.

12. Macdonald HM, New SA and Reid DM. Longitudinal changes in dietary intake in Scottish women around the menopause: changes in dietary pattern result in minor changes in nutrient intake. Public Health Nutrition. 2004; 8(4): 409-416. DOI: 10.1079/phn2005705. PubMED PMID: 15975187

13. Duval K, Prud'homme D, Rabasa-Lhoret R, Strychar I, Brochu M, Lavoie JM and Doucet E. Effects of the Menopausal Transition on Dietary Intake and Appetite. A MONET Group Study. European Journal of Clinical Nutrition. 2014; 68(2): 271-276. DOI:

10.1038/ejcn.2013.171. PubMED PMID: 24065065

14. Marlatt KL, Beyl RA and Redman LM. A qualitative assessment of health behaviors and experiences during menopause: A Cross-sectional, observational study. Maturitas.
2018; 116: 36-42. DOI: 10.1016/j.maturitas.2018.07.014. PubMED PMID: 30244777
15. Firmann M, Mayor V, Vidal PM, Bochud M, Pécoud A, Hayoz D, Paccaud F, Preisig M, Song KS, Yuan X, et al. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. BMC Cardiovascular Disorders. 2008; 8:6. DOI: 10.1186/1471-2261-8-6.
PubMED PMID: 18366642

16. Bernstein L, Huot I and Morabia A. Amélioration des performances d'un questionnaire alimentaire semi-quantitatif comparé à un rappel des 24 heures. Santé Publique. 1995; 7(4): 403-413.

17. Morabia A, Bernstein M, Heritier S and Ylli A. Community-based surveillance of cardiovascular risk factors in Geneve : methods, resulting distribution, and comparisons with other populations. Preventive Medicine. 1997; 26(3):311-319. DOI:

10.1006/pmed.1997.0146. PubMED PMID: 9144755

Swiss Society of Nutrition. Swiss pyramid food. In: Swiss Society of Nutrition, editor.
 Swiss Society of Nutrition. 2016.

19. Hardy R, Kuh D and Wadsworth M. Smoking, body mass index, socioeconomic status and the menopausal transition in a British national cohort. International Journal of Epidemiology. 2000; 29:845-851. DOI: 10.1093/ije/29.5.845

20. Bittner V. Menopause and cardiovascular risk. Journal of the American College of Cardiology. 2006; 47:10. DOI: 10.1016/j.jacc.2006.02.032

21. World Health Organization. Regional Office for Europe. The challenge of obesity in the WHO European Region and the strategies for response: summary. 2007. https://apps.who.int/iris/handle/10665/328775

22. Greendale GA, Sternfeld B, Huang M, Han W, Karvonen-Gutierrez C, Ruppert K, Cauley JA, Finkelstein JS, Jiang SF and Karlamangla AS. Changes in body composition and weight during the menopause transition. JCI Insight. 2019; 4(5):e124865.

23. Lizcano F and Guzmán G. Estrogen deficiency and the origin of obesity during menopause.
Hindawi Publishing Corporation BioMed Research International. 2014; Article ID757461.
24. Sullivan SD, Lehman A, Nathan NK, Thomas CA and Howard BV. Age of menopause and fracture risk in post-menopausal women randomized o calcium + vitamin D, hormone therapy, or the combination: Results from the Women's Health Initiative Clinical Trials.
Menopause. 2017; 24(4): 371-378. DOI: 10.1097/GME.00000000000775. PubMED PMID: 27801706

25. Macdonald HM, New SA, Campbell MK and Reid DM. Longitudinal changes in weight in perimenopausal and early post-menopausal women: effects of dietary energy intake, energy expenditure, dietary calcium intake and hormone replacement therapy. International Journal of Obesity. 2003; 27: 669-676. DOI: 10.1038/sj.ijo.0802283. PubMED PMID: 12833110

26. Anderson LF, Tomten H, Haggarty P, Løvø and Hustvedt BE. Validation of energy intake estimated from a food frequency questionnaire: a doubly labelled water study.
European Journal of Clinical Nutrition. 2003; 57:279-284. DOI: 10.1038/sj.ejcn.1601519
27. Thomson CA, Giuliano A, Rock CL, Ritenbaugh CK, Flatt SW, Faerber S, Newman V, Caan B, Graver E, Hartz V et al. Measuring dietary change in a diet intervention trial: comparing food frequency questionnaire and dietary recalls. American Journal of Epidemiology. 2002; 157:8. DOI: 10.1093/aje/kwg025

28. Brockie J, Lambrinoudaki I, Ceausu I, Depypere H, Erel CT, Pérez-López FR, Schenck-Gustafsson K, Van der Schouw YT, Simoncini T, Tremollieres F and Rees M. EMAS position statement: Menopause for medical students. Maturitas. 2014; 78:67-69.

 Table 1. Demographic and clinical characteristics of women at the first and second follow-up

 (after 5 years) of the CoLaus study<sup>1</sup>

	First follow-up	Second follow-up
Sample size	<i>n</i> = 2,439	<i>n</i> = 1,656
Age (years)	$58.2\pm10.5$	$62.9 \pm 9.9$
BMI (kg/m <sup>2</sup> )	$25.5\pm4.9$	$25.7{\pm}~4.9$
BMI category <sup>2</sup> , $n$ (%)		
Normal	1284 (53.1)	832 (50.3)
Overweight	753 (31.1)	550 (33.2)
Obese	383 (15.8)	272 (16.4)
Waist circumference (cm)	$87.4\pm12.8$	$86.3\pm12.6$
Smoking status, n (%)		
Former	826 (33.9)	593 (36.7)
Never	1126 (46.3)	752 (46.6)
Current	482 (19.8)	269 (16.7)
Educational level, $n$ (%)		
University education	443 (18.2)	322 (19.4)
High school	659 (27)	477 (28.8)
Apprenticeship	881 (36.1)	618 (37.3)
Mandatory education	455 (18.7)	239 (14.4)
Marital status, <i>n</i> (%)		
Single	413 (16.9)	288 (17.4)
Married/cohabitating	1207 (49.5)	774 (46.7)
Divorced	593 (24.3)	410 (24.8)
Widowed	226 (9.3)	182 (11)
Menopause status, $n$ (%)		
Pre menopause	677 (27.8)	254 (15.3)
Post menopause	1762 (72.2)	1397 (84.4)
History of CVD, <i>n</i> (%)		
Yes	76 (3.1)	78 (4.7)
No	2363 (96.9)	1578 (95.3)
History of diabetes, $n$ (%)		
Yes	137 (5.6)	94 (5.7)
No	2295 (94.4)	1562 (94.3)
Serum lipids, mmol/L		
HDL cholesterol	$1.8\pm0.4$	$1.8\pm0.4$
LDL cholesterol	$3.4 \pm 0.9$	$3.2\pm 0.9$
Triglycerides	$1.2\pm0.6$	$1.2\pm0.8$
Treatments, $n$ (%)		
Antihypertensive	584 (23.9)	474 (28.6)
Hypolipidemic	371 (15.2)	272 (16.4)
Antidiabetic	69 (2.8)	73 (4.4)

<sup>1</sup>Values are mean  $\pm$  SD unless otherwise indicated.

<sup>2</sup>BMI categories: normal 18.5 to < 25 kg/m<sup>2</sup>, overweight 25 to < 30 kg/m<sup>2</sup>, obese  $\ge$  30 kg/m<sup>2</sup>.

# Table 2. Multivariable cross-sectional association between menopausal status

(postmenopausal versus premenopausal women) and dietary intake at the first follow-up of

CoLaus study <sup>1</sup>	
---------------------------	--

	β (95% CI)	P value
Sample size	<i>n</i> = 2,439	
Total energy (kcal/d)	-36.6 (-116 ; 43.1)	0.37
Daily intake, animal products (g/day)		
Meat	9.4 (0.6 ; 18.1)	0.04
Fish	-0.06 (-4.8 ; 4.7)	0.98
Milk	-9.9 (-22.4 ; 2.5)	0.12
Dairy products	0.2 (-18.9 ; 19.3)	0.98
Daily intake, other foods (g/day)		
Bread and cereals	-3.7 (-11.8 ; 4.3)	0.36
Pastries	0.09 (-2.2 ; 2.1)	0.80
Pasta	-9.8 (-16.8 ; -2.7)	0.01
Added sugar	-0.4 (-1.3 ; 0.5)	0.41
Vegetable oils	0.3 (-0.6 ; 1.2)	0.58
Fruits	13.7 (-18.8 ; 46.2)	0.41
Vegetables	-0.2 (-17.8 ; 17.4)	0.98
Dietary intake (% of TEI)		
Total proteins	0.4 (-0.02 ; 0.8)	0.06
Vegetable proteins	-0.1 (-0.2 ; 0.05)	0.17
Animal proteins	0.5 (0.03;1)	0.04
Total carbohydrate	-0.8 (-1.9 ; 0.4)	0.18
Monosaccharides	0.5 (-0.6 ; 1.6)	0.36
Polysaccharides	-1.2 (-2.2 ; -0.3)	0.01
Total fat	-0.1 (-0.9 ; 0.8)	0.88
SFAs	-0.2 (-0.6 ; 0.2)	0.39
MUFAs	0.04 (-0.4 ; 0.5)	0.85
PUFAs	0.05 (-0.1 ; 0.2)	0.63
Daily nutrient intake ( <i>per</i> day)		
Alcohol (g)	5.6 (-3.8; 15.1)	0.24
Fibre (g)	-0.04 (-1.2; 1.1)	0.95
Cholesterol (mg)	0.2 (-17.4 ; 17.9)	0.98
Ca (mg)	-18.2 (-81.2 ; 44.8)	0.57
Fe (mg)	0.04 (-0.5; 0.5)	0.88
Retinol (µg)	13 (-76.3 ; 102)	0.78
Carotene (µg)	-14.7 (-447 ; 417)	0.95
Vitamin D (µg)	0.2 (-0.1 ; 0.4)	0.30
Adherence to dietary guidelines	OR (95% CI)	P value
Fruits	1.0 (0.7 ; 1.2)	0.70
Vegetables	1.2 (0.8 ; 1.9)	0.35

Meat <sup>2</sup>	0.9 (0.7; 1.2)	0.66
Fish <sup>3</sup>	1.1 (0.8; 1.4)	0.64
Dairy products	0.9 (0.6 ; 1.2)	0.46
Guidelines adherence score		
At least 3 recommendations	1.0 (0.7 ; 1.4)	0.84

<sup>1</sup>Values are coefficients  $\beta$  (95% CI) for each food item and as OR (95% CI) for dietary guidelines [18], comparing postmenopausal to non-menopausal women. TEI, total energy intake; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.

<sup>2</sup>Included poultry.

<sup>3</sup>Included fresh and fried/baked fish.

<sup>4</sup>Obtained from linear or logistic regression models adjusted for age, body mass index, education level, civil status, prevalent cardiovascular and diabetes, and use of antihypertensive and hypolipidemic treatments have been applied.

# **Table 3.** Multivariable longitudinal association between menopausal categories

(premenopausal as reference group, menopausal transition and postmenopausal) and dietary

intake in the first a	nd second follow-up	(after 5 years)	of the CoLaus study <sup>1</sup>
	1		

	Pre - post menoj	oause	Post - post menopause	
	β (95% CI)	P value	β (95% CI)	P value
Sample size	<i>n</i> = 229		<i>n</i> = 1,168	
Total energy (kcal/d)	-36.6 (-136 ; 62.7)	0.47	-34.8 (-136 ; 66.3)	0.50
Daily intake, animal products (g/day)				
Meat	-1.4 (-10 ; 7.2)	0.74	5.1 (-3.6 ; 13.9)	0.25
Fish	-0.7 (-5.5 ; 4.0)	0.76	0.9 (-3.9 ; 5.7)	0.72
Milk	-6.8 (-21.9 ; 8.2)	0.38	-9.6 (-24.9 ; 5.8)	0.22
Dairy products	-1.8 (-23.7 ; 20.1)	0.87	4.9 (-17.4 ; 27.2)	0.67
Daily intake, other foods (g/day)				
Bread and cereals	3.2 (-6.9 ; 13.3)	0.54	-1.4 (-11.6 ; 8.9)	0.79
Pastries	-1.8 (-5.4 ; 1.8)	0.34	0.1 (-3.6 ; 3.8)	0.94
Pasta	-3.8 (-12.8 ; 5.2)	0.41	-10.6 (-20.8 ; -2.5)	0.01
Added sugar	-0.9 (-2.0 ; 0.2)	0.11	-0.7 (-1.8 ; 0.4)	0.20
Vegetable oils	0.4 (-0.7 ; 1.6)	0.44	0.6 (-0.6 ; 1.7)	0.34
Fruits	4.8 (-34 ; 43.5)	0.81	20.2 (-19.3 ; 59.6)	0.32
Vegetables	-3 (-22.6; 16.6)	0.76	2.4 (-17.5 ; 22.3)	0.81
Dietary intake (% of TEI)				
Total proteins	-0.1 (-0.6 ; 0.4)	0.65	0.4 (-0.1 ; 0.9)	0.16
Vegetable proteins	0.1 (-0.1 ; 0.3)	0.33	-0.04 (-0.2; 0.1)	0.63
Animal proteins	-0.2 (-0.8 ; 0.4)	0.47	0.4 (-0.2 ; 1)	0.15
Total carbohydrate	0.01 (-1.4 ; 1.4)	0.99	-0.8 (-2.2 ; 0.6)	0.28
Monosaccharides	-0.5 (-1.8 ; 0.8)	0.42	0.02 (-1.3 ; 1.3)	0.97
Polysaccharides	0.5 (-0.6 ; 1.7)	0.38	-0.8 (-2.0 ; 0.4)	0.20
Total fat	0.1 (-0.9 ; 1.2)	0.81	0.1 (-1; 1.1)	0.90
SFAs	-0.2 (-0.7 ; 0.3)	0.42	-0.3 (-0.8 ; 0.2)	0.26
MUFAs	0.3 (-0.3 ; 0.9)	0.33	0.2 (-0.3 ; 0.8)	0.41
PUFAs	0.1 (-0.1 ; 0.3)	0.49	0.1 (-0.1; 0.3)	0.21
Daily nutrient intake ( <i>per</i> day)				
Alcohol (g)	-1.5 (-13.1;10)	0.79	2.1 (-9.7 ; 13.9)	0.73
Fibre (g)	0.3 (-1.0 ; 1.7)	0.63	0.3 (-1.1 ; 1.7)	0.68
Cholesterol (mg)	-7.1 (-28.5 ; 14.2)	0.51	-7.4 (-29.2 ; 14.3)	0.50
Ca (mg)	-48 (-122 ; 26)	0.20	-16.2 (-91.5 ; 59.1)	0.67
Fe (mg)	-0.1 (-0.7 ; 0.5)	0.68	-0.1 (-0.7 ; 0.5)	0.78
Retinol (µg)	-41 (-129 ; 46.7)	0.36	-9.2 (-98.5 ; 80.1)	0.84
Carotene (µg)	-254 (-786; 278)	0.35	-195 (-737; 346)	0.48
Vitamin D (µg)	-0.2 (-0.4 ; 0.1)	0.31	0.1 (-0.2 ; 0.4)	0.62
Adherence to dietary guidelines	OR (95% CI)	P value	OR (95% CI)	P value
Fruits	-0.1 (-0.6 ; 0.4)	0.75	-0.1 (-0.6 ; 0.4)	0.64

Vegetables	0.1 (-0.5 ; 0.8)	0.70	0.1 (-0.5 ; 0.8)	0.69
Meat <sup>2</sup>	0.4 (-0.1; 0.9)	0.15	0.2 (-0.3 ; 0.7)	0.48
Fish <sup>3</sup>	0.1 (-0.5 ; 0.7)	0.75	0.2 (-0.3 ; 0.8)	0.43
Dairy products	-0.3 (-2; 1.4)	0.70	-0.3 (-1.9 ; 1.3)	0.68
Guidelines adherence score				
At least 3 recommendation	0.2 (-0.3 ; 0.7)	0.41	0.1 (-0.4 ; 0.6)	0.72

<sup>1</sup>Values are coefficients  $\beta$  (95% CI) for each food item and as OR (95% CI) for dietary guidelines [18], between menopausal categories with women being premenopausal at both first and second follow-up as reference category. TEI, total energy intake; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.

<sup>2</sup>Included poultry.

<sup>3</sup>Included fresh and fried/baked fish.

<sup>4</sup>Obtained from linear or logistic mixed effect models adjusted for age, body mass index, civil status, prevalent cardiovascular and diabetes, and use of hypertensive and hypolipidemic treatments have been applied.

Figure 1. Selection of participants for the present study