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1 Title:

2 **Low adherence to dietary recommendations in adult childhood cancer survivors**

3

4 **Fabiën Belle^{a, b}, Laura Wengenroth^c, Annette Weiss^a, Grit Sommer^a, Maja Beck Popovic^d,**
5 **Marc Ansari^e, Murielle Bochud^b, Claudia Kuehni^{a*} for the Swiss Paediatric Oncology**
6 **Group (SPOG)****

7

8 ^a Swiss Childhood Cancer Registry, Institute of Social and Preventive Medicine, University of
9 Bern, Finkenhubelweg 11, 3012 Bern, Switzerland. Email: fabien.belle@ispm.unibe.ch,
10 annette.weiss@ispm.unibe.ch, grit.sommer@ispm.unibe.ch, claudia.kuehni@ispm.unibe.ch

11 ^b Division of Chronic Diseases, Institute of Social and Preventive Medicine, Lausanne
12 University Hospital CHUV, Route de la Corniche 10, 1010, Lausanne, Switzerland. Email:
13 murielle.bochud@chuv.ch

14 ^c Institute for Occupational, Social and Environmental Medicine, Ludwig-Maximilians-
15 Universität, Munich, Germany. Email: laura.wengenroth@med.uni-muenchen.de

16 ^d Paediatric Haematology-Oncology Unit, Lausanne University Hospital CHUV, Bugnon 46,
17 1011, Lausanne, Switzerland. Email: maja.beck-popovic@chuv.ch

18 ^e Department of Paediatrics, Onco-Haematology Unit, Geneva University Hospital HUG, Rue
19 Willy-Donzé 6, 1211, Geneva 14, Switzerland. Email: marc.ansari@hcuge.ch

20

21 * Corresponding author. Institute of Social and Preventive Medicine, University of Bern,
22 Finkenhubelweg 11, 3012 Bern, Switzerland. E-mail: claudia.kuehni@ispm.unibe.ch

23

24 ** Swiss Paediatric Oncology Group (SPOG) Scientific Committee: Prof. Dr. med. R.
25 Ammann, Bern; Dr. med. R. Angst, Aarau; Prof. Dr. med. M. Ansari, Geneva; PD Dr. med. M.
26 Beck Popovic, Lausanne; Dr. med. E. Bergstraesser, Zürich; Dr. med. P. Brazzola, Bellinzona;

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29 F. Niggli, Zürich; PD Dr. med. J. Rischewski, Lucerne; Prof. Dr. med. N. von der Weid, Basel.

30

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32 diseases, Swiss Childhood Cancer Registry, Europe

33

34 **Abbreviations**

35	ACS	American Cancer Society
36	CCS	childhood cancer survivors
37	CNS	central nervous system
38	CVD	cardiovascular disease
39	FFQ	food frequency questionnaire
40	SCCSS	Swiss Childhood Cancer Survivor Study
41	SCCR	Swiss Childhood Cancer Registry
42	SHS	Swiss Health Survey

43

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71

72 **ABSTRACT**

73 **Background & aims:** Poor diet may increase the risk that childhood cancer survivors (CCS)
74 will suffer from chronic disease. We compared adherence to national dietary recommendations
75 between CCS, their siblings and the Swiss population, identified determinants of adherence,
76 and assessed the association of adherence with cardiovascular disease (CVD) risk profiles.

77 **Methods:** As part of the Swiss Childhood Cancer Survivor Study (SCCSS), a questionnaire
78 was sent to all Swiss resident CCS aged <21 years at diagnosis, who survived ≥ 5 years and
79 were 16-45 years old at the time of the survey. We compared dietary adherence between CCS,
80 their siblings and participants in the Swiss Health Survey (SHS), a representative survey of the
81 general population. A multivariable logistic regression was used to assess characteristics
82 associated with dietary adherence. We sorted CCS into four kinds of CVD risk groups based
83 on type of treatment (anthracyclines, chest irradiation, a combination, or neither).

84 **Results:** We included 1'864 CCS, 698 siblings and 8'258 participants of the general population.
85 Only 43% of the CCS met the recommended dietary intakes for meat, 34% for fruit, 30% for
86 fish, 18% for dairy products, 11% for vegetables, and 7% for combined fruit and vegetables.
87 Results were similar for both control groups. In all groups, dietary adherence was associated
88 with gender, parental education, migration background, language region in Switzerland,
89 smoking, alcohol consumption and sport participation. CCS with a higher CVD risk profile
90 because of cardiotoxic treatment had no better adherence.

91 **Conclusions:** CCS have similar food patterns as their siblings and the general population, and
92 poorly adhere to current recommendations. Awareness of the importance of a healthy diet
93 should be raised among CCS, to prevent chronic diseases like CVD.

94 **1. INTRODUCTION**

95 Cancer or the late effects of its treatment cause more than two-thirds of childhood cancer
96 survivors (CCS) to develop chronic diseases later in life. Chronic diseases reduce quality of
97 life, and increase morbidity and premature mortality [1, 2]. CCS are up to 15 times more likely
98 to develop heart failure than their siblings, and almost 13 times more likely to die from
99 circulatory diseases than their peers in the general population [1, 3]. This increased risk could
100 be the result of cardiotoxic therapy effects due to anthracycline-containing chemotherapy and
101 radiation therapy involving the heart. Unhealthy lifestyles, including unbalanced diets, physical
102 inactivity and being overweight or obese, could also each significantly increase the risk of
103 cardiovascular disease (CVD) [4].

104 Excess calorie intake, and consuming too little fish, fruit and vegetables are associated with
105 higher risk of CVD in the general population. Better dietary habits may improve cardiovascular
106 health [4, 5]. Unbalanced diet is a major modifiable risk factor for CVD, Type II diabetes,
107 metabolic syndrome, and osteoporosis [4-7]. But a recent review that included 14 observational
108 studies showed that childhood cancer patients and survivors in the US, Australia, Germany,
109 Canada, and the UK rarely adhere to dietary recommendations [8]. CCS do not eat enough fruit
110 and vegetables [9-11], dairy products [10, 11], whole grains [11, 12], or the micronutrients
111 calcium and vitamin D [12]. They also eat too much sodium and meat [9].

112 Most studies that investigated dietary adherence had low sample sizes (N<500) [9-13], no
113 control group [9, 10, 12, 14], and did not investigate the association between dietary adherence
114 and CVD risk profiles based on received type of therapy [9, 10, 12-14]. Therefore, we analysed
115 data from the Swiss Childhood Cancer Survivor Study (SCCSS) to (1) compare adherence to
116 national dietary recommendations among CCS, their siblings and the general population, (2)
117 identify socio-demographic and clinical factors associated with adherence to national dietary

118 recommendations, and (3) determine if adherence to dietary recommendations in CCS differed
119 by cardiovascular risk profiles.

120

121 **2. METHODS**

122 *2.1. Sampling*

123 *2.1.1 The Swiss Childhood Cancer Survivor Study (SCCSS)*

124 The SCCSS is a nationwide long-term follow-up study of all ≥ 5 -year CCS registered in the
125 Swiss Childhood Cancer Registry (SCCR), diagnosed between 1976 and 2005, and alive at the
126 time of the study [15]. The SCCR registers children and adolescents under age 21, who are
127 diagnosed in Switzerland with leukaemia, lymphoma, central nervous system (CNS) tumours,
128 malignant solid tumours or Langerhans cell histiocytosis [16, 17].

129 From 2007 to 2012, we traced all addresses of eligible survivors for the SCCSS and sent
130 them a long questionnaire. Non-responders were sent a second copy of the questionnaire four
131 to six weeks later. Non-responders to the second copy were contacted by phone. We used
132 questionnaires similar to those used in US and UK CCS studies [18, 19], but added questions
133 about health behaviours and socio-demographic measures from the Swiss Health Survey 2007
134 (SHS) [20] and the Swiss Census 2000 [21]. The main domains covered by the questionnaire
135 were quality of life, somatic health, fertility, use of current medication and health services,
136 psychological distress, health behaviours, and socio-economic status. Detailed information on
137 our study design was published previously [15].

138 The Ethics Committee of the Canton of Bern gave ethical approval to the SCCR and the
139 SCCSS.

140

141 *2.1.2 Sibling controls*

142 From 2007 to 2012, when we sent out the questionnaire to CCS, we asked them to give us
143 consent to contact their siblings and to provide sibling contact information. Beginning in 2010,

144 we sent siblings the same questionnaire as CCS, but omitted questions about cancer history.
145 Siblings who did not respond were sent another copy of the questionnaire four to six weeks
146 later, but were not contacted by phone.

147

148 *2.1.3 General population controls (Swiss Health Survey)*

149 The second control group consisted of participants in the 2007 SHS survey. The SHS is a
150 national representative telephone survey repeated every five years. The SHS compiled a
151 randomly selected representative sample of 28'332 Swiss households with telephone land lines
152 and attempted to contact one person per household. Of households called, 6'185 did not answer,
153 and 3'414 refused to participate. The final sample included 18'760 participants (66% response
154 rate) [20]. Sampling was stratified by region and conducted stepwise. Households were selected
155 first, and then the survey was administered to anyone 15 or older who answered the phone.

156

157 *2.2 Measurements*

158 *2.2.1 Dietary intake and adherence to dietary recommendations*

159 In CCS and control groups, dietary intake was assessed with standardised open and closed
160 questions. The same standard units and serving sizes for each food item were used in the CCS
161 and sibling surveys. They were also the same in the SHS survey for the general population. The
162 questionnaire to survivors and siblings offers a choice of six responses to describe frequency of
163 intake, ranging from “never” to “several times per day”. It also offers open questions where
164 participants can indicate the portions they consume per day (**Supplemental Fig S1**). The SHS
165 survey offers similar options, though questions about frequency of fruit and vegetable intake
166 were phrased slightly differently. We thus transformed the SHS questions on fruit and vegetable
167 intake into the following daily consumption frequencies: “never”=0; “less than 1/day”=0.5; “1-
168 2/day”=1.5; “3-4/day”=3.5 and “5+/day”=5.5. From the SHS survey, we obtained fruit and
169 vegetable consumption by summing up fresh and conserved fruit or vegetable products and fruit

170 or vegetable juices. The questionnaire to CCS and siblings assessed only fruit and vegetable
171 products. Questions about fish intake also differed slightly. In the SHS survey, the general
172 population could indicate the exact number of days per week they consumed fish, but CCS and
173 siblings could only select from categories that specified a range.

174 We used current recommendations from the Swiss Society of Nutrition (SSN) to
175 determine adequate intake of fruit, vegetable, meat, fish, and dairy products [22]. SSN
176 recommendations are in line with those of other European countries [23-25]. We determined
177 failure to comply with these dietary recommendations by calculating the proportion of
178 participants who did not eat the minimum recommended daily number of servings of each food
179 group. The lowest values of the following recommended ranges were our cut-off values: two
180 portions of fruit (120g) per day; three portions of vegetable (120g) per day; one portion of fish
181 (100-120g) per week, and three portions of dairy (2dl milk, 150-200g yoghurt or 30-60g cheese)
182 per day. We used the maximum cut-off value for meat: three portions of meat (100-120g) per
183 week.

184

185 ***2.2.2 Explanatory variables from the Swiss Childhood Cancer Survivor Study (SCCSS)***

186 We assessed the following explanatory variables from the questionnaires submitted by CCS,
187 siblings, and the general population: socio-demographic data (gender; age at survey; education
188 level; parents' education level; migration background; and, language region in Switzerland) and
189 lifestyle factors (body mass index [BMI]); smoking; sport participation; and, alcohol
190 consumption). Participants who were not Swiss citizens at birth, not born in Switzerland, or had
191 at least one parent who was not a Swiss citizen were designated to have a migration background.
192 We classed education into four categories, according to the Swiss Census: compulsory
193 schooling only (≤ 9 years); vocational training (10-13 years); upper secondary education (higher
194 vocational training or college); and, university degree. We divided highest education level of
195 parents into three categories: primary schooling (compulsory schooling only [≤ 9 years]);

196 secondary education (vocational training [10-13 years]; higher vocational training or college);
197 and, tertiary education (university degree). We calculated BMI from self-measured height and
198 weight, dividing weight by height in meters squared (kg/m^2). For adolescents (16–19 years at
199 survey), we standardized BMI into z-scores for age and gender using the Swiss references [26].
200 BMI was classified as underweight (>19yrs: $<18\text{kg}/\text{m}^2$; $\leq 19\text{yrs}$: <-2 Z-scores), normal weight
201 (>19yrs: $\geq 18 - <25\text{kg}/\text{m}^2$; $\leq 19\text{yrs}$: $\geq -2 - \leq 1$ Z-scores), overweight (>19yrs: $\geq 25 - <30\text{kg}/\text{m}^2$;
202 $\leq 19\text{yrs}$: $>1 - \leq 2$ Z-scores), and obese (>19yrs: $\geq 30\text{kg}/\text{m}^2$; $\leq 19\text{yrs}$: >2 Z-scores). Sport
203 participation was classified as “sports” if respondents reported engaging at least somewhat
204 intensely in a targeted gym or sport for at least one hour per week, or “no sports” if
205 participation was lower.

206

207 ***2.2.3 Explanatory variables from the Swiss Childhood Cancer Registry (SCCR)***

208 Clinical information was extracted from the SCCR. We recorded diagnosis and the age at which
209 cancer was diagnosed. Diagnosis was classified according to the International Classification of
210 Childhood Cancer – 3rd Edition [27]. Chemotherapy was divided into “anthracyclines”; “other
211 chemotherapeutic agents” or “no chemotherapy”. Radiotherapy was classified as “chest
212 radiotherapy” if direct radiation was applied to the chest, “other radiotherapy” or “no
213 radiotherapy”. Chest radiotherapy included total body irradiation, mantlefield irradiation or
214 irradiation to the thorax, mediastinum, or thoracic spine. There was a record if a CCS had
215 relapsed during follow-up time.

216

217 ***2.3 Statistical Analysis***

218 Our analysis included all participants in the SCCSS (CCS and siblings) and the SHS (general
219 population), aged 16-45 years at time of survey. Both control groups included more women and
220 older persons than the CCS. Migrants and non-German speakers were less frequent among
221 siblings, but more frequent in the general population. To increase the validity of the comparison

222 between CCS and the control groups, we standardised both control groups for gender, age,
223 migration background, and language region, according to the distribution in CCS (**Table I**).
224 Standardisation was applied in all analyses, and was used as in previous publications [28, 29].

225 The first step in our analysis was to compare socio-demographic and clinical
226 characteristics and adherence to national dietary recommendations in CCS and control groups
227 using χ^2 tests.

228 Second, we used logistic regressions to determine factors associated with dietary
229 adherence by estimating crude and adjusted odds ratios (OR) and 95% confidence intervals
230 (95%CI). In univariable analyses, we tested each individual socio-demographic and lifestyle
231 variable. If variables were significant on a p-value of <0.05 , we included them in the
232 multivariable analyses. We performed Wald tests to calculate global p-values. We used
233 interaction terms to formally test differences in effects of risk factors between CCS and
234 controls. We selected potential confounders and effect modifiers based on the literature.

235 Third, and in CCS only, we investigated associations between adherence to dietary
236 recommendations and different CVD risk profiles (the profiles were based on type of
237 treatment). CVD risk profiles were categorized as “no chemo- and radiotherapy”, “other chemo-
238 and/or radiotherapy” (no anthracyclines and no chest radiotherapy), “either anthracyclines or
239 chest radiotherapy”, and “both anthracyclines and chest radiotherapy”. We conducted tests for
240 linear trend for the ordered categorical CVD risk profiles.

241 We performed sensitivity analyses to compare standardised data for gender, age,
242 migration background and language region in both control groups according to the distribution
243 in CCS to non-standardised data. We used Stata software (version 14, Stata Corporation,
244 Austin, Texas) for all statistical analysis. All statistical significance tests were two-sided with
245 a significance level of 5%.

246

247 **3. RESULTS**

248 **3.1.Characteristics of study population**

249 We traced and contacted 3'593 of 4'116 eligible CCS. Of those we contacted, 2'527 (70%)
250 returned the full questionnaire. We excluded 520 participants who were younger than 16 or
251 older than 45 years, and 143 participants who did not provide data on diet. We thus included
252 1'864 CCS in the analysis (**Supplemental Fig S2**). We had consent to contact 1'295 siblings,
253 of whom 733 returned the questionnaire; 32 were outside the age range, and three did not
254 provide data on diet. Of 28'332 households surveyed, one person per each of 18'760 households
255 (66%) replied to the survey. Of these, 8'258 were between 16-45 years old.

256 More CCS than controls had completed compulsory schooling only (12% vs. 7%
257 siblings and 5% general population) and fewer CCS had earned a university degree (7% vs.
258 11% siblings and 10% general population; all $p<0.001$) (**Table I**). Mean BMI did not differ
259 between groups, but BMI categorisation was significantly different: CCS were more likely to
260 be underweight (4% vs. 1% siblings and 2% general population) or obese (7% vs. 4% siblings;
261 and 4% general population; $p_{\text{siblings}}=0.001$ and $p_{\text{SHS}}<0.001$). CCS were less likely to smoke than
262 the general population (24% vs. 34%, $p_{\text{SHS}}<0.001$). We found no significant difference between
263 CCS and siblings for smoking. More CCS than controls consumed never or rarely alcohol (51%
264 vs. 36% siblings and 44% general population; all $p<0.001$). CCS were less likely to engage in
265 sports than both control groups (55% vs. 65% siblings and 64% general population; all
266 $p<0.001$).

267 Among CCS, the largest diagnostic group was leukaemia (32%), followed by lymphoma
268 (20%) and CNS tumours (14%) (**Table II**). When we divided CCS into CVD risk profiles, 17%
269 did not receive chemo- and radiotherapy (lowest risk category), 37% had received other
270 chemotherapeutic agents than anthracyclines and/or other radiotherapy than chest radiotherapy,
271 39% either anthracyclines or chest radiotherapy, and 7% had both anthracyclines and chest

272 radiotherapy (highest risk category). Mean age at diagnosis was 8.8 ± 5.5 years and mean time
273 since diagnosis was 17.2 ± 6.9 years. Twelve percent had experienced a relapse.

274

275 *3.2 Dietary adherence in CCS and control groups*

276 Overall dietary adherence was low (**Fig I, Supplemental Table S1**). The highest scores on
277 adherence were for meat (37-43%), fish (26-55%) and fruit (24-39%). The lowest scores for
278 adherence were for the combination of two servings of fruit/day and three servings of
279 vegetables/day (6-7%). We saw no large differences between CCS, their siblings, and the
280 general population. CCS were slightly less adherent than their siblings to fruit intake
281 recommendations ($p_{\text{siblings}}=0.011$), more adherent to recommendations for eating meat
282 ($p_{\text{siblings}}=0.011$), and tended to adhere better to recommendations for eating fish ($p_{\text{siblings}}=0.075$).
283 CCS were more adherent than the general population to recommendations for fruit
284 ($p_{\text{SHS}}<0.001$), meat ($p_{\text{SHS}}=0.003$) or dairy products ($p_{\text{SHS}}<0.001$), but less adherent to
285 recommendations for vegetables ($p_{\text{SHS}}=0.009$) or fish ($p_{\text{SHS}}<0.001$). Although these differences
286 were statistically significant, the absolute differences between the groups were small and
287 clinically irrelevant.

288

289 *3.3 Determinants of dietary adherence in CCS and control groups*

290 In univariable logistic regressions, factors associated with better adherence to dietary
291 recommendations were female gender, age (depending on the food group), higher education,
292 higher parental education, migration background, residence in the French or Italian speaking
293 part of Switzerland, being underweight or having a healthy BMI, not a smoker, no-to-rarely
294 alcohol consumption (those who ate enough fish tended to consume more alcohol), and sport
295 participation (**Results available upon request**). Since all socio-demographic and lifestyle
296 variables were significant for at least one outcome, we included all of them in the multivariable

297 models when we investigated CCS (**Table III, Supplemental Table S2**), their siblings (**Results**
298 **available upon request**), and the general population (**Supplemental Table S3**), and when we
299 looked at cancer-related determinants in CCS only (**Supplemental Table S5**).

300 **Socio-demographic and lifestyle determinants.** In CCS, several socio-demographic
301 and lifestyle factors were related to adherence to dietary recommendations in multivariable
302 logistic regressions (**Table III, Supplemental Table S2**). CCS who ate enough fruit and
303 vegetables were more often female, had more educated parents, a migration background,
304 residence in the French-speaking part of Switzerland, participated in sports, and tended to have
305 higher BMI. Meat adherence was associated with female gender, older age, a migration
306 background, residence in the French- or Italian-speaking part of Switzerland, current smoking,
307 never-to-rare alcohol consumption, and sports participation. As with adherence to
308 recommendations for meat intake, CCS who ate enough fish were older; had a migration
309 background, were from the French- or Italian-speaking part of Switzerland, and participated in
310 sports. More highly educated participants and non-smokers were more likely to eat enough fish.
311 The opposite was true for the intake of dairy products. Maleness, younger age, and no migration
312 background were associated with adherence to recommendations for dairy intake.

313 After we performed interaction tests (**Supplemental Table S4**), we found no evidence
314 that the effect of risk factors differed between CCS and their siblings (all interaction p-values
315 >0.05). This means that the same socio-demographic and lifestyle factors were associated with
316 dietary adherence in both CCS and siblings. However, the strength of the associations between
317 some risk factors and dietary adherence differed between CCS and the general population
318 (interaction p-values <0.05) (**Supplemental Table S4**). When comparing effect sizes between
319 CCS (**Table III, Supplemental Table S2**) and the general population (**Supplemental Table**
320 **S3**), differences were small and hardly clinically relevant.

321 **Cancer-related determinants.** After controlling for socio-demographic and lifestyle
322 factors, we found that cancer-related factors among CCS were not significantly associated with

323 adherence to dietary recommendations (**Supplemental Table S5**). CCS diagnosed at age 5-9
324 were less likely to adhere to combined fruit and vegetables and vegetable recommendations
325 than CCS diagnosed younger than five years.

326 We found no important differences in the sensitivity analyses that compared
327 standardised data to non-standardised data. Both types of analyses led to the same conclusions.

328

329 **3.4 Dietary adherence among different CVD risk profiles**

330 There was no relevant difference in adherence to dietary recommendations between CVD risk
331 profiles based on type of chemo- and radiotherapy and p-values for trend were insignificant
332 ($p>0.10$) (**Figure 2**). We did see a trend for adherence to meat recommendations, which was
333 slightly higher in all risk groups than in the group of CCS who had not received chemo- and
334 radiotherapy.

335

336 **4. DISCUSSION**

337 **4.1 Principal findings**

338 We found that CCS poorly adhered to dietary recommendations, but that adherence of siblings
339 and the general Swiss population was equally poor. Predictors of adherence in CCS were similar
340 in siblings, but differed somewhat from the general population. Adherence to dietary
341 recommendations was not better among CCS with a higher CVD risk because of cardiotoxic
342 treatment.

343

344 **4.2 Dietary adherence in Switzerland and the rest of the world**

345 Ours is the largest study to compare the adherence of adolescents and young adult CCS and
346 control groups to national dietary recommendations. Our findings on low adherence are in line
347 with data from the 6th Swiss Nutrition Report [30] and the population-based cross-sectional

348 study of de Abreu et al. 2013 in the French-speaking part of Switzerland, which reported only
349 39% of the participants adhered to Swiss recommendations for fruit intake, 7% for vegetables,
350 61% for meat, 66% for fish and 8% for dairy products [31]. We found adherence for meat was
351 lower, probably because national recommendation guidelines for consumption of meat dropped
352 from ≤ 5 days per week to $\leq 1-3$ days per week [22] between de Abreu's and our study. Our
353 findings also concord with the few studies that reported dietary adherence among CCS.
354 Demark-Wahnefried et al. found that only 20% of the 209 US CCS consumed the recommended
355 five servings of fruit and vegetables per day [32]. Similar poor adherence levels for fruit and
356 vegetables were observed in more recent and larger US studies [13, 14]. Although meat
357 recommendations were different in previous studies, overall meat adherence was low in CCS.
358 Only 10% adhered to the World Cancer Research Fund/American Institute for Cancer Research
359 guidelines to consume less than 80 grams of red meat per day [14]. A study from the US CCSS
360 also found that less than half of CCS met the American Cancer Society (ACS) recommendations
361 to eat less than 18 oz (+/-500g) of red and processed meat per week [13].

362

363 **4.3 Dietary adherence among CCS compared to control groups**

364 CCS and siblings had similar levels of dietary adherence, as also found by a US study based on
365 Healthy Eating Index-2005 (HEI) scores [11]. However, our comparison of CCS to the general
366 population revealed more significant differences in adherence. When we looked at the
367 proportion of CCS and the general population that adhered to dietary recommendations (e.g.,
368 18% adherence for dairy products among CCS vs. 12% among the general population) we found
369 the observed differences were, although statistically significant, clinically irrelevant. A cross-
370 sectional study between CCS and the general US population came to similar conclusions,
371 finding no relevant differences after basing their analyses on adherence criteria from the ACS
372 Guidelines on nutrition [13].

373

374 **4.4 Gender and migration background differences**

375 Females adhered better to fruit, vegetable, and meat recommendations. Males were more
376 adherent to dairy products recommendations. These match previous Swiss [31, 33] and
377 European [34] findings. The reasons for these gender differences are unclear. Males and
378 females may be socialized differently, and exposed to different amounts of information about
379 diet and health. It is also possible that males and females have different tastes, different levels
380 of interest in healthy diets, and different eating goals. Although women were almost twice as
381 likely to adhere to dietary recommendations for fruit, vegetable and meat intake than men were,
382 adherence levels were still far from ideal for either gender and both need improvement.

383 Migration background was associated with higher adherence to recommendations for all
384 food groups except dairy products. Much of the Swiss population with a migration background
385 is from Southern Europe, where people commonly eat a Mediterranean diet already rich in fruit,
386 vegetables and fish, and poor in meat and dairy products [35].

387

388 **4.5 Dietary adherence and CVD risk profiles**

389 Low intake of fruit, vegetable, fish and dairy products are already a concern in the general
390 population, but may have a more deleterious effect on CCS. Better adherence to dietary
391 recommendations lowers the risk of all-cause mortality, CVD mortality, cancer incidence and
392 mortality, and Type II diabetes mellitus among adults by 15 to 22% [6]. Since CCS are up to
393 15 times more likely to have heart failure than their siblings [1], risk factors like poor diet may
394 exacerbate this [4-6]. CCS with baseline risk elevated by cancer treatment may strongly benefit
395 from a good diet, but we found no differences in adherence levels among CCS for different
396 CVD risk profiles. As in our study, Landy et al. found little to no difference between dietary
397 intake and cancer diagnosis and therapy, except for exposure to cranial irradiation, which was
398 related to even poorer adherence [11].

399

400 **4.6 Implications for clinical practice**

401 The national organisation Swiss Cancer League (www.liguecancer.ch) emphasizes in cancer
402 prevention campaigns to increase fruit and vegetable consumption and reduce alcohol, red and
403 processed meat intake. This could partly explain the higher levels of fruit and meat adherence
404 in CCS. However, it is unclear to which extent CCS are aware of these dietary recommendations
405 and if diet is perceived as a risk factor for late effects. Current CCS guidelines do not
406 specifically focus on diet [8].

407 We performed a short survey among the nine Swiss paediatric oncology clinics to assess
408 whether they discussed diet issues during follow-up visits. Six replied that they discuss diet in
409 case CCS suffer from nutritional related late effects, and three indicated to discuss it routinely
410 during each follow-up visit (personal communication). Given the strong evidence about diet
411 and health in general and the increasing data for CCS, focus should be placed on the importance
412 of good eating habits during annual long-term follow up visits. Follow-up visits are especially
413 recommended for CCS with moderate to severe late health effects or high risk cancer treatment,
414 a group which could benefit of dietary counselling [36].

415 General dietary recommendation campaigns are equally widespread between language
416 regions within Switzerland. As regional differences in adherence are seen, campaigns should
417 be adapted to federal state and regional level, which will not only benefit CCS but also the
418 general population.

419

420 **4.7 Strengths and limitations**

421 Our study is limited by the fact that all available data were self-reported; so social desirability
422 bias and subjective interpretation could have favourably biased the results. The different survey
423 designs (questionnaire in CCS and siblings, telephone interviews in the general population)
424 might have influenced the results. For example, respondents might list alcohol consumption
425 more moderately in a telephone interview than a written survey. Differences in level of

426 adherence to recommendations for fruit and fish intake between CCS and the general population
427 may have been a product of differently worded survey answers. Our study was strengthened by
428 its national coverage of the SCCSS, our large sample size, and the high response rate among
429 CCS, which made our results representative. We had access to high quality clinical information
430 extracted from the SCCR. The questionnaires gave us access to a wide variety of socio-
431 demographic, and lifestyle factors. We compared adherence of CCS with both siblings (who
432 share environmental factors with CCS) and a representative population-based study performed
433 simultaneously in Switzerland (so we could account for different environmental factors).

434

435 **5. CONCLUSION**

436 Large-scale studies with systematic and standardised dietary assessments, such as 24h recalls
437 and validated food frequency questionnaires would help more precisely assess nutritional intake
438 among CCS, and determine if food intake patterns are associated with cancer diagnoses,
439 treatments, patient characteristics, adverse somatic late effects, and survival outcomes. Finding
440 these connections would provide incentive for CCS to eat a balanced diet because it could lessen
441 their chance of suffering adverse late effects. Poor eating habits may predispose CCS to chronic
442 comorbidities or increase the likelihood they will develop a secondary neoplasm [4-6, 8, 14].
443 More focus should be placed on improving dietary adherence during clinical follow up,
444 especially for CCS with high CVD risk profiles.

445 Though no worse than their siblings or the general population, CCS adhere poorly to
446 nutritional recommendations, and may be more susceptible to health problems caused by poor
447 nutrition.

448

449 **STATEMENT OF AUTHORSHIP**

450 FB conducted the statistical analyses and wrote the article; LW and CK gave support in the
451 statistical analyses and revised critically the manuscript; All authors have critically revised and
452 approved the final article.

453

454 **CONFLICT OF INTEREST STATEMENT**

455 The authors report no conflict of interest.

456

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465

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582

583 TABLES

584 Table I. General characteristics of childhood cancer survivors (CCS), their siblings and
585 the general population (Swiss Health Survey)

Characteristics	CCS	Siblings ^a	General population ^a		
	(n=1864)	(n=698)	(n=8258)		
	n (%)	n (% _{std})	<i>p-value</i> ^b	n (% _{std})	<i>p-value</i> ^c
Gender					
Male	978 (52)	288 (53)	<i>n.a.</i>	3886 (53)	<i>n.a.</i>
Female	886 (48)	410 (47)		4372 (47)	
Age at survey (years)					
<20	449 (24)	110 (24)	<i>n.a.</i>	747 (25)	<i>n.a.</i>
20-29	886 (48)	331 (48)		1959 (47)	
30-39	438 (24)	201 (23)		3246 (23)	
≥40	91 (5)	56 (5)		2306 (5)	
Education (highest degree)					
Compulsory schooling	230 (12)	45 (7)	<0.001	596 (5)	<0.001
Vocational training	872 (47)	292 (42)		4668 (63)	
Upper secondary education	632 (34)	286 (40)		1924 (22)	
University education	130 (7)	75 (11)		1070 (10)	
Parents' education (highest degree)					
Primary schooling	169 (9)	59 (7)	0.214	n.a. ^d	<i>n.a.</i>
Secondary education	1351 (73)	513 (73)			
Tertiary education	344 (19)	126 (20)			
Migration					
No migration background	1423 (76)	561 (77)	<i>n.a.</i>	4901 (77)	<i>n.a.</i>
Migration background	441 (24)	137 (23)		3357 (23)	
Language region of Switzerland					
German speaking	1310 (70)	565 (71)	<i>n.a.</i>	5068 (70)	<i>n.a.</i>
French speaking	495 (27)	112 (26)		2580 (27)	

Italian speaking	59 (3)	21 (3)		610 (3)	
BMI^e					
Underweight	72 (4)	11 (1)	0.001	178 (2)	<0.001
Normal	1324 (71)	508 (75)		5702 (76)	
Overweight	347 (19)	146 (20)		1907 (18)	
Obese	121 (7)	33 (4)		471 (4)	
Smoking					
Current smoker	443 (24)	155 (23)	0.491	2688 (34)	<0.001
Stopped smoking	210 (11)	101 (13)		1209 (10)	
Never smoked	1211 (65)	442 (64)		4361 (56)	
Alcohol					
Never/rarely	956 (51)	275 (36)	<0.001	3728 (44)	<0.001
Weekly, ≥ 1 std drink/week	747 (40)	358 (52)		4012 (53)	
Daily, 1 std drink/day	65 (3)	22 (3)		435 (3)	
Frequently, >1 std drink/day	96 (5)	43 (9)		83 (6)	
Sports					
Yes	1016 (55)	447 (65)	<0.001	4722 (64)	<0.001
No	848 (46)	251 (35)		3536 (36)	

586 BMI: body mass index; n.a.: not applicable; std: standard alcoholic drink;

587 ^a: Standardized on gender, age at survey, migration background and language region according to
588 the CCS population;

589 ^b: p-value calculated from Chi-Square statistics comparing CCS to siblings (2-sided test);

590 ^c: p-value calculated from Chi-Square statistics comparing CCS to general Swiss population (2-
591 sided test);

592 ^d: No data on parental education within the Swiss Health Survey available;

593 ^e: BMI Z-scores were calculated for subjects ≤ 19 years, BMI scores (kg/m^2) were calculated for
594 adults (>19 years).

595 **Table II. Clinical characteristics of childhood cancer survivors (CCS)**

Characteristics	CCS	
	(n=1864)	
	n	(%)
Clinical treatment		
Paediatric cancer centre ^a	1590	(85)
Other clinic	274	(15)
ICCC3 diagnosis		
I: Leukaemia	600	(32)
II: Lymphoma	371	(20)
III: CNS tumour	261	(14)
IV: Neuroblastoma	76	(4)
V: Retinoblastoma	40	(2)
VI: Renal tumour	108	(6)
VII: Hepatic tumour	11	(1)
VIII: Bone tumour	81	(4)
IX: Soft tissue sarcoma	112	(6)
X: Germ cell tumour	89	(5)
XI & XII: Other tumour	47	(3)
Langerhans Cell Histiocytosis	68	(4)
CVD risk profile		
No chemo- and RT	314	(17)
Other chemo- and/or RT (no anthracyclines and no chest RT) ^b	694	(37)
Either anthracyclines or chest RT ^c	718	(39)
Both anthracyclines and chest RT	138	(7)
Age at diagnosis (years)		
<5	604	(32)
5-9	455	(24)
10-14	521	(28)
15-20	284	(15)

Time since diagnosis (years)

<15	746 (40)
≥15	1118 (60)

History of relapse

No	1636 (88)
Yes	228 (12)

596 CNS: central nervous system; CVD: cardiovascular disease; ICC3: International Classification of
597 Childhood Cancer, 3rd edition; RT: radiotherapy;
598 ^a: Including the following clinics with paediatric oncology units Kantonsspital Aarau AG,
599 Universitäts-Kinderspital Basel, Ospedale S. Giovanni Bellinzona, Universitäts-Kinderklinik Bern,
600 Hôpital des Enfants Genève, CHUV Lausanne, Kantonsspital Luzern, Ostschweizer Kinderspital St.
601 Gallen, Universitäts-Kinderspital Zurich;
602 ^b: Other chemotherapeutic agents and radiotherapy than anthracyclines and chest radiotherapy;
603 ^c: Chest radiotherapy includes direct radiation applied to the chest, including total body irradiation,
604 mantlefield irradiation or irradiation to the thorax, mediastinum, or thoracic spine.

605 **Table III. Adherence to dietary recommendations among childhood cancer survivors, and socio-**
606 **demographic predictors for adherence (retrieved from multivariable logistic regressions)**

	Fruit/vegetable ≥ 5 portions/day			Fruit ≥ 2 portions/day			Vegetable ≥ 3 portions/day		
	(n=123)			(n=624)			(n=196)		
	% ^a	OR (95% CI) ^b	p-value ^c	% ^a	OR (95% CI) ^b	p-value ^c	% ^a	OR (95% CI) ^b	p-value ^c
Gender									
Male	5	1.00 (ref)	0.051	26	1.00 (ref)	<0.001	8	1.00 (ref)	0.002
Female	8	1.48 (1.00; 2.18)		42	2.18 (1.77; 2.69)		13	1.67 (1.21; 2.29)	
Age at survey (years)									
<20	7	1.00 (ref)	0.512	35	1.00 (ref)	0.938	11	1.00 (ref)	0.542
20-29	7	1.23 (0.75; 2.02)		34	1.02 (0.78; 1.34)		11	1.18 (0.79; 1.76)	
30-39	7	1.26 (0.70; 2.25)		32	0.97 (0.70; 1.33)		9	0.91 (0.56; 1.48)	
≥ 40	3	0.56 (0.16; 1.96)		31	0.89 (0.53; 1.50)		9	0.83 (0.36; 1.89)	
Education (highest degree)									
Compulsory schooling	9	1.44 (0.83; 2.52)	0.138	36	1.20 (0.87; 1.65)	0.416	13	1.33 (0.84; 2.10)	0.379
Vocational training	6	1.00 (ref)		32	1.00 (ref)		10	1.00 (ref)	
Upper secondary education	8	1.16 (0.75; 1.79)		35	1.02 (0.81; 1.29)		12	1.19 (0.83; 1.69)	
University education	3	0.39 (0.13; 1.18)		31	0.78 (0.50; 1.21)		8	0.75 (0.36; 1.58)	
Parents' education (highest degree)									
Primary schooling	6	1.00 (ref)	0.022	31	1.00 (ref)	0.055	13	1.00 (ref)	0.141
Secondary education	6	1.53 (0.75; 3.12)		32	1.15 (0.79; 1.67)		10	0.91 (0.54; 1.53)	
Tertiary education	9	2.64 (1.19; 5.88)		39	1.55 (1.00; 2.39)		13	1.35 (0.74; 2.46)	
Migration									
No migration background	6	1.00 (ref)	<0.001	32	1.00 (ref)	0.034	9	1.00 (ref)	<0.001
Migration background	10	2.07 (1.37; 3.14)		37	1.31 (1.02; 1.68)		16	1.92 (1.36; 2.70)	
Language region									
German speaking	6	1.00 (ref)	0.423	32	1.00 (ref)	0.032	10	1.00 (ref)	0.629
French speaking	8	1.29 (0.85; 1.95)		38	1.31 (1.04; 1.65)		12	1.13 (0.80; 1.59)	
Italian speaking	5	0.79 (0.24; 2.63)		27	0.75 (0.41; 1.37)		9	0.75 (0.29; 1.95)	
	Meat $\leq 1-3$ days/week			Fish ≥ 1 day/week			Dairy ≥ 3 portions/day		

	(n=807)			(n=554)			(n=330)		
Gender									
Male	29	1.00 (ref)	<0.001	31	1.00 (ref)	0.616	20	1.00 (ref)	<0.001
Female	59	3.09 (2.52; 3.79)		28	0.95 (0.76; 1.18)		15	0.63 (0.49; 0.82)	
Age at survey (years)									
<20	38	1.00 (ref)	0.021	26	1.00 (ref)	0.001	25	1.00 (ref)	0.004
20-29	45	1.41 (1.08; 1.85)		27	1.14 (0.85; 1.53)		17	0.66 (0.48; 0.90)	
30-39	45	1.62 (1.18; 2.22)		38	1.76 (1.26; 2.45)		14	0.56 (0.38; 0.83)	
≥40	45	1.58 (0.95; 2.63)		37	1.76 (1.05; 2.95)		10	0.34 (0.16; 0.72)	
Education (highest degree)									
Compulsory schooling	51	1.50 (1.09; 2.06)	0.096	30	1.37 (0.97; 1.93)	0.022	21	1.01 (0.69; 1.48)	0.517
Vocational training	40	1.00 (ref)		25	1.00 (ref)		19	1.00 (ref)	
Upper secondary education	45	1.10 (0.88; 1.39)		32	1.25 (0.98; 1.60)		16	0.87 (0.66; 1.16)	
University education	45	1.05 (0.68; 1.60)		48	1.77 (1.17; 2.68)		11	0.66 (0.36; 1.22)	
Parents' education (highest degree)									
Primary schooling	48	1.00 (ref)	0.356	37	1.00 (ref)	0.231	11	1.00 (ref)	0.548
Secondary education	42	0.98 (0.68; 1.41)		28	0.83 (0.58; 1.20)		16	1.10 (0.68; 1.78)	
Tertiary education	46	1.20 (0.78; 1.83)		35	1.03 (0.67; 1.59)		24	1.29 (0.74; 2.24)	
Migration									
No migration background	41	1.00 (ref)	0.002	27	1.00 (ref)	<0.001	19	1.00 (ref)	0.032
Migration background	50	1.49 (1.16; 1.90)		40	1.72 (1.34; 2.21)		15	0.70 (0.51; 0.97)	
Language region									
German speaking	42	1.00 (ref)	0.023	24	1.00 (ref)	<0.001	19	1.00 (ref)	0.196
French speaking	46	1.18 (0.94; 1.49)		42	1.98 (1.57; 2.49)		14	0.76 (0.57; 1.03)	
Italian speaking	59	2.08 (1.17; 3.69)		44	2.25 (1.30; 3.90)		15	0.80 (0.38; 1.68)	

607 CI: confidence interval; OR: odds ratio;

608 ^a: Column percentages are given;

609 ^b: Adjusted for: 1) socio-demographic variables: gender, age category, education level, migration

610 background, and language region in Switzerland and 2) lifestyle factors: BMI category, smoking

611 status, alcohol intake, and sport participation;

612 ^c: global p-value for an association between adherence to national dietary recommendations and
613 the variable as a whole (Wald test comparing models with and without the variable).

614 **FIGURES**

615

616 **Figure 1. Adherence to dietary recommendations among childhood cancer survivors**

617 **(CCS), their siblings and the general population (Swiss Health Survey)**

618 Data are proportions with 95% confidence intervals. Siblings and the general population (SHS)

619 are standardised on gender, age, migration background and language region according to the

620 CCS population. P-values were calculated from Chi-Square statistics comparing CCS to siblings

621 or CCS to the general population (SHS) (2-sided test), *: p-value<0.05, **: p-value<0.001

622

623 **Figure 2. Adherence to dietary recommendations among childhood cancer survivors**

624 **over 4 cardiovascular disease risk profiles**

625 Dots are OR's and whiskers 95% CI. CI: confidence interval; CVD: cardiovascular disease;

626 OR: odds ratio; RT: radiotherapy not including chest. Multivariable analysis for adherence to

627 nutritional recommendations per CVD risk profile were adjusted for: 1) socio-demographic

628 variables: gender, age category, education level, parental education level, migration

629 background, and language region in Switzerland and 2) lifestyle factors: BMI category,

630 smoking status, alcohol intake, and sport participation; All p-values for trend were

631 insignificant (p-value>0.10) between the different CVD risk profiles for adherence to dietary

632 recommendations;

633 Other chemo- and/or RT indicates other chemotherapeutic agents and radiotherapy than

634 anthracyclines and chest radiotherapy.

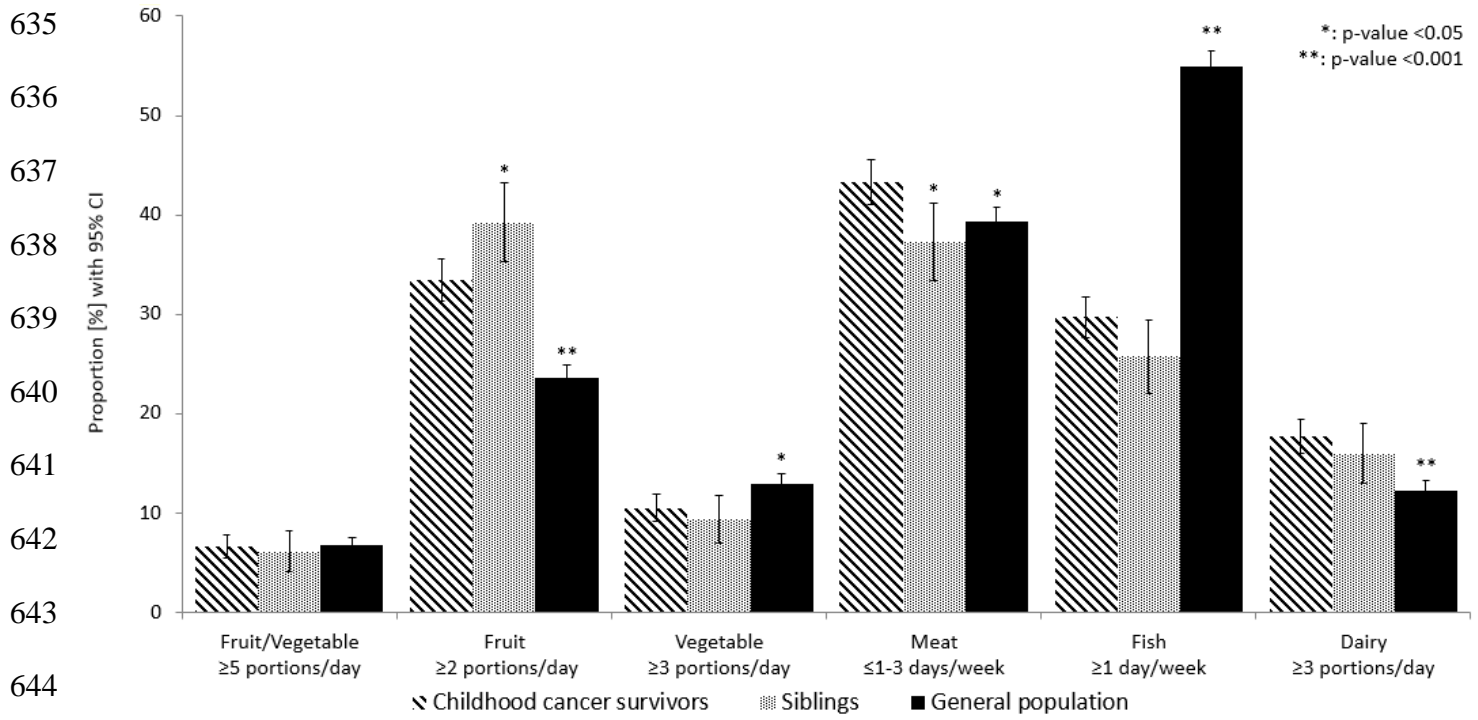
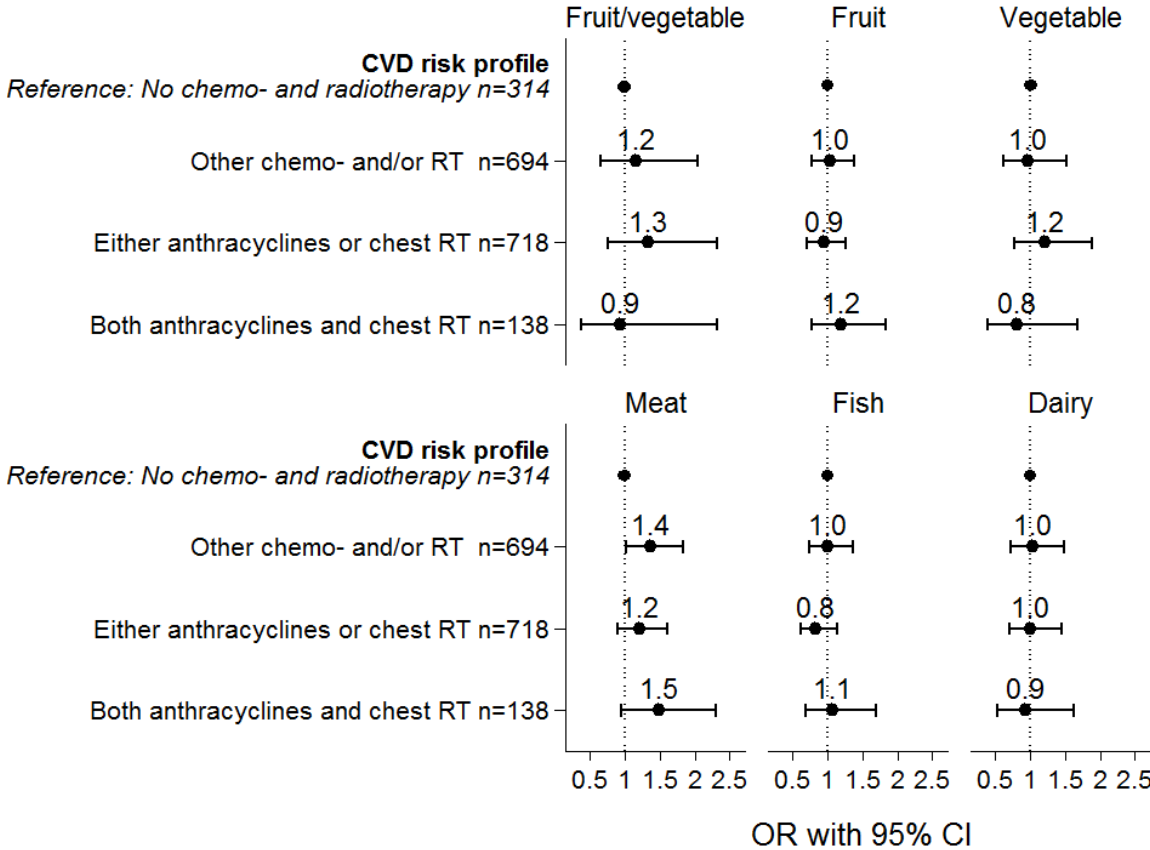


Figure 1.



646

647 **Figure 2.**