Nutrients, Manuscript Revisions: nutrients-1904378

Table of Changes:

Editor Comment	**Response/ Revision to manuscript**	**Location of change**
Dear authors, Thank you for responding to the insightful comments of reviewer 2. Both editors have additional comments to add that we feel should be addressed. However, at this time we have suggested rejection with the opportunity of resubmission. We have come to this decision based on the totality of the review along with the additional comments below.	Thank you very much for providing additional peer review that has supplemented the reviewer's comments. We have undertaken significant revisions to address the valid concerns you raise and appreciate the opportunity to resubmit these for further consideration.	
Point 1. We feel the manuscript needs more clarity. It is also not clear what the primary message of the paper is. While negative results are as important as positive results, we still need to see clarity and critical thought in light of the data presented. Please feel free to resubmit the paper if you feel you can address these comments.	To improve the clarity, we have: - reviewed and added further pertinent literature, - undertaken extensive English language editing, - undertaken a further critical analysis of our findings, and - revised sections of the texts in the methods, results, and discussion accordingly. • The primary message of this paper now reads that there is no significant relationship between diet quality (DQ), measured using the AHEI-2010, and NCDs in a younger cohort of Australian women aged 25-40 years. Nevertheless, looking at modifiable risk factors at an earlier age is important since Australian reports have shown that 43% of women aged 45 and younger have experienced one or more NCDs. Exploring NCD risk factors and considering which NCDs are most prevalent at different life stages are important for developing appropriate primary prevention strategies. We have revised this in the discussion (Page 13, Line 531-538) to read; *The selected NCDs are characterized by increasing incidence with age, which makes it difficult to obtain results based on clinical endpoints like CHD and DM. However, looking*	Line 531-538

	at modifiable risk factors early, even prior to disease onset is important given that Australian reports have shown 43% of women aged 45 and younger were affected by one or more NCDs [11,12]. Exploring NCD risk factors and considering which NCDs are most prevalent at different life stages [142,143] are important for developing appropriate primary prevention strategies. We would like to resubmit our revisions for further consideration.	
Point 2. Table 2 in the supplementary files omits some important factors such as the total fat and total protein in the diet that are important to include.	Thank you for the opportunity to clarify this important point. Healthy Eating Index (HEI), and Alternative Healthy Eating Index (AHEI) are different diet quality indices. HEI, one of the earliest diet quality indices (DQIs), was constructed based on the Dietary Guidelines for Americans, where total fat and protein (meat and beans) were included as components of fat and protein respectively (https://doi.org/10.1016/S0002-8223(95)00300-2). AHEI, an alternative to HEI, was developed later, based on foods and nutrients for the prevention of chronic or non-communicable diseases (https://doi.org/10.1093/ajcn/76.6.1261). AHEI included trans-fat and a ratio of polyunsaturated fatty acid to saturated fatty acids in the fat component, and a ratio of white to red meat, nuts, and soy protein in the protein component (https://doi.org/10.1093/ajcn/76.6.1261). Since their inception, both HEI and AHEI have been updated: HEI-2005 (https://doi.org/10.1016/j.jada.2008.08.016), HEI-2010 (https://doi.org/10.1016/j.jand.2012.12.016.), HEI-2015 (https://doi.org/10.1016/j.jand.2018.05.021) and HEI-2020 (https://doi.org/10.1093/cdn/nzac054.047) for HEI; and AHEI-2010 (https://doi.org/10.3945/jn.111.157222) for AHEI. In the updated versions of HEI, total protein foods has been included as a separate component in HEI-2010 and HEI-2015, however, total fat intake (% of energy) was not included in the updated versions. In our previously published systematic review and critical appraisal of diet quality indices used in Australian and New Zealand adults, we have described the origin of AHEI as from HEI (https://doi.org/10.3390/nu12123777). A comparative summary of HEI and AHEI is as follows;	

	HEI	AHEI
Established in	1995	2002
Based on	American Dietary Guidelines	Food and nutrients for NCD prevention
Components (protein foods)	Meat and beans are included as component of protein foods and typically reported in scoring of total HEI.	Ratio of white to red meat, nuts and soy protein are included as component of protein foods and typically reported in scoring of AHEI.
Components (fat)	Total fat intake is included as component of fats and typically reported in scoring of total HEI.	Trans-fat, ratio of polyunsaturated fatty acid to saturated fatty acid are included as component of fats and typically reported in scoring of total AHEI.

We have also updated the text in Introduction (Page 2, Line 61-77) to read;

A higher score on a DQI generally represents better diet quality (DQ) or closer adherence to dietary recommendations [25]. The original DQIs such as Healthy Eating Index (HEI), Diet Quality Index and Diet Quality Index-Revised were constructed based on the Dietary Guidelines for Americans [26-28], whereas the Mediterranean Diet Score was based on Mediterranean dietary pattern [29]. More recently, DQIs have been developed based on country-specific dietary guidelines (e.g., Dietary Guideline Index [30], China Dietary Guideline Index [31], and Healthy Dietary Habits Index [32], etc), or modified based on earlier indices (e.g., Recommended Food Score [33], Australian Recommended Food Score [34], alternative Mediterranean Diet [35], etc). Additionally, the Alternative Healthy Eating Index (AHEI), based on the original HEI, was created based on extensive epidemiological evidence for NCD prevention [33]. Although both HEI and AHEI are measurements of DQ, there were differences in scoring (e.g., the original HEI included total fat and protein (meat and beans) for fat and protein components [26], whereas AHEI included trans-fat and ratio of polyunsaturated fatty acid (PUFA) to saturated fatty acid (SFA) in the fat component, and ratio of

Line 61-77

	white to red meat, nuts and soy protein in the protein component [33]. Both HEI and AHEI have been regularly updated (HEI-2005 [37], HEI-2010 [38], HEI-2015 [39], HEI-2020 [40] for HEI; AHEI-2010 [36] for AHEI).	
Point 3. There could be further review of the evidence for the benefits of AHEI-2010 in the US and in Australia, maybe by using a table. It would be important to show that this index has been found inversely correlated with some health outcomes. There is some important literature out there that could be incorporated to further support your findings. Here are some suggestions that you may/may not find relevant: https://doi.org/10.3945/jn.113.183079 https://doi.org/10.1017/S0007114517001908 https://doi.org/10.1016/j.jand.2012.12.016	Thank you for your suggestion and the links. Since HEI is a different diet quality tool, we have omitted evidence relating to this and instead focused exclusively on AHEI. Evidence for the benefits of AHEI and/or AHEI-2010 on NCDs is extensively conducted (https://doi.org/10.1016/j.jand.2020.08.076) and has been revised as follows in our manuscript, which now reads (Line 81-85); *Previous evidence has shown that high level of DQ assessed by AHEI and/or AHEI-2010 were associated with reduced risk of CVD, cancer, DM, neurodegenerative disease and all-cause mortality[41]. However, in term of clustering of NCDs, evidence on the relationship between overall diet and NCD multimorbidity is very limited [49].* Regarding the references you suggested, the first and third ones are references for HEI-2010. The second reference is AHEI-2010 and all-cause mortality. We have added the third reference to show the original HEI has been updated regularly aligned with the latest Dietary Guidelines for Americans and it reads; *Both HEI and AHEI have been regularly updated (HEI-2005 [37], HEI-2010 [38], HEI-2015 [39], HEI-2020 [40] for HEI; AHEI-2010 [36] for AHEI).* Most of the studies investigating the relationship between AHEI and/or AHEI-2010 and NCDs were conducted in the US (https://doi.org/10.1016/j.jand.2020.08.076), however, there is limited evidence in Australia. We have discussed this in the text and have also revised this in the Discussion (Page 13, Line 504-508) to read; *However, most of the studies were conducted in the United States [41]. A few Australian studies used AHEI-2010 as a measurement of diet quality [136-140], and only two studies were related to NCDs such as urothelial cell carcinoma [140] and ovarian cancer survival [136]. Hence this study adds to the body of evidence related with DQ.* In our systematic review (https://doi.org/10.3390/nu12123777) which critically appraised the DQIs based on construction criteria developed by Burggraf et.al. and Trijsburg el. al., AHEI-2010 was	Line 81-85 Line 76-77 Line 504-508

	found as a DQI having perferrable features. In one of our previous studies we also showed AHEI-2010 was the most sensitive of 3 DQIs in predicting NCDs in the ALSWH 1946-51 cohort (https://doi.org/10.3390/ijerph182111375). We have described the AHEI as the most sensitive DQI in our previous study, and now state (Page 2, Line 85-92); *Previously, we have examined the relationship between DQ (measured as Healthy Eating Index for Australian Adults-2013 (HEIFA-2013), Mediterranean Diet Score (MDS), and Alternative Healthy Eating Index-2010 (AHEI-2010)) and incidence of NCDs, including multimorbidity among a cohort of women born between 1946-51 that was drawn from the Australian Longitudinal Study on Women's Health (ALSWH) [50]. Data showed that mid-aged women with higher DQI scores had reduced odds of NCDs in later surveys (9 to 15 years later), and AHEI-2010 was the most sensitive DQI for prediction of NCDs [50].* As described on Page 2, Line 81-83 and 502-507 in the Discussion (responses in above comments), we have described that AHEI and/or AHEI-2010 were mostly applied in the United States (US) (https://doi.org/10.1016/j.jand.2020.08.076) and limited in Australia (we have responded above). Looking at the studies conducted in the US only (https://doi.org/10.1016/j.jand.2020.08.076), reduced risk of all-cause mortality and AHEI and/or AHEI-2010 were reported. There were mixed results for cardiovascular disease mortality or incidence, cancer mortality or incidence, type 2 diabetes mellitus and neurodegenerative disease in US studies. Among the limited Australian studies that used AHEI-2010 as a measure of DQ, only 2 studies were related to NCDs (urothelial cell carcinoma https://doi.org/10.1002/ijc.30175, and ovarian cancer survival https://doi.org/10.1158/1055-9965.EPI-20-1036). We have revised the text in the Discussion (Line 505-507) to now read; *A few Australian studies used AHEI-2010 as a measurement of diet quality [136-140], and only two studies were related to NCDs such as urothelial cell carcinoma [140] and ovarian cancer survival [136].*	Line 85-92 Line 505-507

A comparative summary of studies conducted in US and Australia is as follow;

	US	Australia
All-cause mortality	Reduced	No evidence
Cardiovascular disease mortality or incidence	Mixed	No evidence
Cancer mortality or incidence	Mixed	No association between AHEI-2010 and urothelial cell carcinoma incidence and survival of ovarian cancer patients.
Type 2 diabetes mellitus	Mixed	No evidence
Neurodegenerative disease	Mixed	No evidence

Point 4. A better description of the order and timing of surveys between 2006-2018 (S4-S8) is required in the methods. It is not clear in terms of time the surveys were conducted and how the findings of these surveys relate to each other longitudinally. It might be worth including these in figure 1 also.

We have added a simplified figure (Page 4, Figure 1) to show the order and timing of surveys between 2006-2018 (S4-S8).

Figure 1

Survey (S)	S1	S2	S3	S4	S5	S6	S7	S8
Year	1996	2000	2003	2006	2009	2012	2015	2018
1973–78 cohort								
Age (yrs)	18–23	22–27	25–30	28–33	31–36	34–39	37–42	40–45
Key Data			Baseline; Diet quality, Covariates	NCD outcomes	NCD outcomes	NCD outcomes	NCD outcomes	NCD outcomes
Exclusions	History of NCD	History of NCD	History of NCD					

Figure 1. Study overview: Data from the Australian Longitudinal Study on Women's Health (ALSWH) for women born between 1973 and 1978

	We also have amended the text to read; *Figure 1 shows the simplified description of the ALSWH 1973-78 data for analysis.* *The sampling strategy with exclusion criteria is presented in Figure 2.*	Line 161-162 Line 163
Point 5. Line 20 – the mean what?	This has been clarified and now reads; *The AHEI-2010 mean (±sd) for participants (n=8017) was 51.6 ±11.0 (range: 19-91).*	Line 20
Point 6. Line 325 – physically	Thank you for detecting this inaccuracy. We have amended this in the text (Page 8, Line 338-341) which now reads; *Women with higher AHEI-2010 score were more likely to be married/de facto, living in urban area, have a university/ higher degree, had paid employment, had the ability to manage income easily, and were more physically active than women with lower DQ (Table 1).*	Line 338-341
Point 7. Line 336 – delete space	Thank you. We have corrected this (now Page 9, Line 356).	
Point 8. Line 389 – ensure this is correct.	We can see the previous sentences in our Discussion may have introduced confusion. We have taken this information out to make the text clearer. Moreover, after reviewing our analysis, we have amended the texts. We have revised the texts in the Methods (Section 2.6, Page 8, Line 331-335) to read; *To check the robustness of the findings, sensitivity analyses were performed. We performed multiple testing, applying the Bonferroni correction in the logistic regression models to account for the covariates whose 95% CIs were near 1. Analyses that used taking prescribed medicine as a covariate (Supplementary Table 5) and changes of childbearing variables (Supplementary Table 6) were performed.* We have revised the texts in the Results (Page 8, Line 348-352) to now read; *After the Bonferroni correction was applied to the univariate model (asthma at S4) and multivariate model (asthma at S4 without a history of asthma variable) (Table 2) the odds of asthma in S4 (2006)*	Line 331-335 Line 348-352

	when compared to the highest vs lowest quintile of AHEI-2010, p-value=0.41 and 0.42, respectively, resulted in a non-significant association (Table 2, footnote). We have amended the footnote under Table 2 (Page 10, Line 369-372) to read; *The main results presented were ORs (95% CI) obtained from respective models. Bonferroni correction was applied to logistic regression models where 95% CIs were near 1. [§] Inverse association became non-significant after Bonferroni correction was applied (p-value=0.41 for univariate model and p-value=0.42 for multivariate model without a history of asthma variable respectively).* In the Discussion on Page 11, Line 406, we have taken out the potentially confusing information to make the text clearer; *There was no association between AHEI-2010 and HT in multivariate models.* On Page 11, Line 417-421, we have revised the Discussion to read: *In the present study, women with the highest quintile of AHEI-2010 had a 25% reduction in odds of asthma at S4 (2006) compared to the lowest quintile. Yet, the association attenuated and was not statistically significant when applying a Bonferroni correction in the multivariate logistic regression models. Current evidence on DQ and asthma outcome is inconclusive, and studies investigating the role of diet in adults were limited [103].*	Line 369-372 Line 406 Line 417-421
Point 9. Line 417 – or indeed the diets themselves, an arbitrary score is not the full picture	Thank you for your comment. We have reviewed again the literature on diet and asthma and revised the text accordingly to read; *Preventive roles of fruits, vegetables, and vitamin E [104,105], fiber [106]; and deleterious roles of red processed meat [107,108] and SSB [109] on asthma were documented in observational studies.* We have also discussed further, the nature of DQIs, with the amended text reading; *In assessing dietary intake, FFQs, like the DQES-v2, are useful in providing relative ranking more so than absolute values of intake [144]. Calculating a DQI from FFQs introduces further uncertainty in the dietary measure, and by no means represents a complete picture of diet [145].*	Line 421-424 Line 538-542

	Instead it provides a simple summary that performs well across large-scale studies, national and international [23].	
Point 10. Line 421 – something missing here?	Thank you for detecting this inaccuracy. We have added one word (Page 11, Line 440-441) so the text now reads; *In our study, we did not find any association between DQ and cancer (excluding skin cancer).*	Line 440-441
Point 11. Some of the studies used to draw comparisons within the results and discussion sections used mixed cohorts. Should you only compare with females in these cohorts? For example, references 99 and 100. This is important because of the differences in risk profiles between males and females as pointed out in the introduction.	Thank you for your constructive suggestion. We have discussed mostly women studies and where the studies were mixed we have used the percentage of women in the specific studies (where reported). We have revised the Discussion about AHEI-2010 and hypertension to read; *Significant reduction of SBP, not DBP, was demonstrated among people with quartile 4 of AHEI-2010 compared to quartile 1 in the 2007-2010 National Health and Nutrition Examination Survey (NHANES) (n=4097, aged ≥20 years) [99].* *Nevertheless, there was no association between AHEI-2010 and HT or BP in a nested case-control study conducted within the Singapore Chinese Health Study (SCHS) (n=1994, aged 45-75 years, 35% women) [98].* We have revised the Discussion about AHEI-2010 and asthma to read; *A favourable effect of DQ on asthma was observed in the French prospective Epidemiological study on the Genetics and Environment and Asthma Study (n=969, mean age=43 years, 51% women), indicating a 10-unit increase in AHEI-2010 was associated with improved asthma symptom score, which measured the number of respiratory symptoms during the last 12 months [110]. In another French cohort study (n=26197 women, aged ≥18 years), a 21% reduced odds of asthma symptom in women and AHEI-2010 was also observed [111]. By contrast, no association between AHEI-2010 and adult onset asthma among 73,228 participants from NHS [112], nor among 12,687 adult participants (60.2% women) from the Hispanic Community Health Study/ Study of Latinos [113].* We have revised the Discussion about AHEI-2010 and cancer to read;	Line 408-411 Line 414-416 Line 424-433

	With regard to overall cancer and DQ, inverse association between AHEI-2010 and overall cancer was observed in 71,495 women aged 38-63 years from the NHS over 24 years of follow-up [36] and 41,543 participants from the NNS study over 9 years of follow-up (aged ≥40 years, 73.5% women) [114]. We have revised the Discussion about AHEI-2010 and diabetes mellitus to read; *Previous studies have demonstrated a significant inverse association between AHEI-2010 and risk of DM: among participants from the NHS over 24 years of follow-up (n=71495, aged 38-63 years) [36], among white women from the MEC study (aged 45-74 years, 53% women) [117], among participants from the Women's Health Initiative Observational Study (aged 50-79 years) [118], among women from the Singapore Chinese Health Study (aged 45-74 years) [119], and among the ALSWH 1946-51 cohort (n=5350, aged 50-55 years) [50]. However, these findings were not replicated in the present study or in a recent analysis of the ARIC Study over a median follow-up of 22 years (n=10808, aged 45-64 years, 56.1% women) [94].* We have revised the Discussion about AHEI-2010 and depression and/or anxiety to read; *The preventive potential of diet quality assessed by AHEI-2010 on depression and/or anxiety was observed among Iranian adults (n=3363, mean age=36 years, 58.3% women) [125], and Spanish adults (n=15093, aged ≥18 years, 59% women) [126]. However, we did not find any association between AHEI-2010 and depression and/or anxiety in the present study, nor in a French cohort (n=26225, aged 18-86 years, 76% women) [127]. Compared to our results, reported prevalence or incidence of depression were higher in the Iranian study (30% in total participants, 35% in women) [125], but lower in the Spanish (~7%) [126] and French (~8.3%) [127] studies. Given that incidence of depression and/or anxiety in our participants (~15%) was lower than Iranian women (35%) it might be underpowered to detect the difference.* We have revised the Discussion about AHEI-2010 and NCD multimorbidity to read; *Regarding the relationship between dietary factors and NCD multimorbidty, the literature is limited and inconclusive [50,128-135]. Potential benefits of vegetable and fruits consumption for NCD*	Line 437-440 Line 450-458 Line 472-481

	multimorbidity have been observed in cross-sectional [129,130] and prospective [131-133] studies. Harmful effect of soft drink consumption on multimorbidity was reported in an Australian study (n=36663, aged ≥ 16 years, 51.1% women) [128]. In exploring the relationship between overall diet assessed by DQIs and multimorbidity, decreased relative odds were observed among European adults who adhered to the Mediterranean diet (n=291778, aged 43-58 years, 64% women vs n=1140, aged 18 years, 56% women) [134,135] and Australian women who adhered to Australian Dietary Guideline and AHEI-2010 (n=5350, aged 50-55 years) [50], when compared to those who did not. By contrast to the previous findings [50], there was no association between AHEI-2010 and NCD multimorbidity in this study. Potential explanation for the lack of association could be the differences between AHEI-2010 scores amongst the ALSWH 1946-51 cohort (mean (±sd): 56.01±10.32, range: 26-93.75) and this study cohort (mean (±sd): 51.6±11.0, range: 19-91). We have added a reference (reference 50) to the text and it reads; *Descriptive summaries of AHEI-2010 have been reported in previous studies: similar to [36,93,118], higher than [50,94,97,117,126] or smaller than [112] the present study.*	Line 482-496 Line 497-498