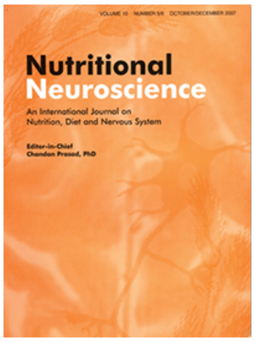

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Principal component analysis identifies differential gender-specific dietary patterns that may be linked to mental distress in human adults

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ABSTRACT: Independent reports describe the structural differences between the human male and female brains and the differential gender-susceptibility to mood disorders. Nutrition is one of the modifiable risk factors that has been reported to impact brain chemistry and affect mental health. **Objectives:** To study dietary patterns in adult men and women in relation to mental distress. Another aim was to develop evidence-based prototypes using System Dynamic Modeling methodology to better describe our findings. **Methods:** An anonymous internet-based survey was sent through social media platforms to different social and professional networks. Multivariate analyses were used for data mining. Data were stratified by gender and further by tertiles to capture the latent variables within the patterns of interest. **Results:** Mental distress in men associated with a consumption of a Western-like diet. In women, mental wellbeing associated with a Mediterranean-like diet and lifestyle. No other patterns in both genders were linked to mental distress. Based on the generated prototypes, men are more likely to experience mental wellbeing until nutritional deficiencies arise. However, women are less likely to experience mental wellbeing until a balanced diet and a healthy lifestyle are followed. In men, dietary deficiencies may have a profound effect on the limbic system; whereas dietary sufficiency in women may potentiate the mesocortical regulation of the limbic system. **Discussion and conclusion:** Our results may explain the several reports in the literature that women are at a greater risk for mental distress when compared to men and emphasize the role of a nutrient-dense diet in mental wellbeing.

KEYWORDS: Mental wellbeing, mental distress, mood, gender, multivariate analysis, principal component analysis, common factorial analysis

Introduction

The gender-specific structural differences in the human brain are linked to behavioral traits as well as to differential susceptibility to mood disorders.[1,2] Particularly, women are twice as likely to be diagnosed with depression or anxiety disorders compared to men.[1,2,3] Moreover, anxiety in women, tend to be co-morbid with depressive symptoms.[3] Women are also more susceptible to longer depressive episodes and to relapses when compared to men.[4] The differential susceptibility to mental disease may be related to the morphological differences in the brain of men and women. According to several reports, men tend to have a larger total brain volume (TBV) compared to women.[5–7] However, conflicting reports exist in the literature describing the actual neuroanatomical region volumes of the human male and female brains. These discrepancies could be attributed to small sample sizes and/or inconsistency of age range of the sample across individual studies.[8] Additionally, it appears that there is a lack of consensus on the level of gray and white matter densities between gender. Gray matter (GM) is concentrated in information-processing regions like the hippocampus (HC) and the amygdala of the limbic system. White matter (WM) represents the network connectivity with the processing regions. It appears, that women tend to have almost twice the GM and WM in the frontal lobes than men, mostly in areas that support impulse controls and emotion.[9] Specifically, females have thicker

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cortices, temporal and parietal, independent of brain size differences.[10] In fact, Luders and colleagues reported a negative correlation between brain volume and GM proportions; suggesting that larger brains tend to have relatively smaller proportions of GM.[11] To correct for the sex-related brain volume, imaging studies matched for TBV revealed that women exhibit larger GM volumes in many brain regions than men.[12] Therefore, identification of gender-specific risk factors that account for the anatomical differences in the human brain may provide valuable tools to support a therapeutic approach. Nutrition is one of the modifiable risk factors that may influence brain structure and its chemistry, which may impact mental health.[13] Conventionally, studies of the association between diet and mental distress have focused on single nutrients;[14,15] however, the current trend in nutritional epidemiology research is striding toward analyzing dietary patterns (DP) in relation to comorbidities. DP analysis considers the complexity of nutrient interactions and the difference in the daily dietary intake. Additionally, the build-up of nutrients and their metabolites, rather than a one-time consumption, plays a substantial role in mental health.[16] The goal of DP analysis is to compare the frequency of food intake to a health outcome, which has a translational significance for public health.

The purpose of this study was to depict gender-specific dietary factors and socio-demographic characteristics in relation to mental distress using multivariate analyses. Mounting evidence suggests that the differential anatomical and functional differences in men's and women's brain dictate susceptibility to mental disease.[17–20] However, little is known about the role of DP in gender-specific psychological wellbeing. This gap in the literature is an area in need of further research. To our knowledge, no studies have explored this association in adult men and women using a multivariate analysis approach.

Method

Study design

The study protocol was reviewed and approved by the Institutional Review Board at Binghamton University. An anonymous internet-based questionnaire was built in Google Sheets. Data were collected between March and April 2014. Dietary and nutrient consumption patterns were assessed using a validated Food-Mood Questionnaire (FMQ) which includes questions on food groups that constituents have been linked to mental distress, neurotransmitter biosynthesis and associated receptor activity.[21] FMQ assesses average weekly servings of nine different food groups (whole grain, fruits, vegetables, meat, beans, nuts, dairy, fish and high glycemic index (HGI) foods). Frequency of breakfast consumption, use of multivitamins (MV) and fish oil (FO) supplements, eating fast food and drinking caffeinated beverages were also included. Mental distress was assessed using the individual item and the total scores of Kessler-6 Psychological Distress Scale (K-6) to account for the spectrum of psychological distress.[22]

Participants

Participants, 18 years and older, were invited via social media to complete the questionnaire. FMQ was distributed in English to social and professional groups where English is the primary language of communication. Participants consented to the study by agreeing to access the survey. DP, exercise frequency and socio-demographic information such as age, gender, level of education and region were collected. There was no incentive or compensation provided for completing the questionnaire. The anonymous survey was sent through Facebook and Twitter platforms. The targeted groups included Facebook social and professional groups, Facebook personal profiles and Twitter personal profiles. Facebook social and professional groups were chosen based on a high number of followers (more than 100,000 followers) with no focus on specific regions. Groups were randomly selected if they perceptibly had no overlap of potential members, met the number of followers and used the English language as the main language of communication. A post describing the purpose of the study was made public and was posted on each platform. The selection of arbitrary social and professional pages was made to diminish ascertainment bias. To minimize attempts to take the survey more than twice, a few measures were undertaken. First, the survey was posted for a limited time on each platform. Second, based on recommendations by Kramer et al.[23], data were examined for back-to-back entries using date and time stamps to identify respondents who completed the questionnaire faster than expected. If a double-entry was suspected, the second entry was eliminated. Prior to analyzing the data, a 'Duplicate' function in R (from the base package) was performed to identify potential duplicate responses based on observations for both groups of men and women (see supplemental Table 1). We also performed a sensitivity analysis on responses to identify highly unlikely response patterns. For this purpose, we ran the codes from caret packages in R to explore which responses have zero variance predictors (see supplemental Figure 1).

Statistical analysis

Principal component analysis (PCA) analysis was done to confirm the variability of DP among respondents. Common factor analysis (CFA) was performed on data stratified by gender and further by tertiles of factors to capture latent variables within each group. The tertile approach was adopted from Thorpe et al.[24]. PCA and CFA are powerful multivariate data analysis methods used for data mining to extract interesting patterns and latent variables, respectively. PCA employs a correlational matrix to identify common patterns in association with a condition or biomarkers. It simplifies a multidimensional data set into a two-dimensional system while retaining the characteristics that contribute most to the variance. This property makes it a valuable method in DP research.[25] CFA shares many of PCA characteristics; however, unlike PCA, it identifies the least number of factors that account for the common variance within a pattern. Furthermore, CFA considers the covariance between variables; thus, latent factors may reflect actual phenomena.[26] To account for mental distress level between both genders, K-6 individual items and total K-6 scores were computed. Individual K-6 items describe specific mental distress symptoms such as being anxious, restless, feeling depressed, hopeless or worthless. The total K-6 scores were calculated to assess the spectrum of mood.[27] All scores were converted into standardized z-scores to improve interpretation of results. Sampling adequacy and inter-correlation of variables were assessed using the Kaiser–Meyer-Olkin (KMO) test and Bartlett's test of sphericity, respectively. To determine the number of principal components (PCs) retained, eigenvalue >1.0 criterion was used. Additionally, the number of PCs selected was confirmed by visually examining the scree plot (see supplemental Figures 2(a,b)). PCs were then orthogonally rotated (varimax) to simplify and enhance their interpretability.[28] Variables with the loading of ≥ 0.2 were considered significant contributors to DP and were included in the PC solution.[29] Positive and negative loadings indicate a direct and inverse relationship with PCs, respectively. All criteria used for PCA (factor retention, rotation and minimal factor loading value) were retained for CFA when data were classified by gender. Tucker's congruence coefficient was used to assess the level of similarity of factor interpretation between men and women grouping to confirm proportionality of categories (see supplemental Table 2).[30] For data partitioning into tertiles, age was divided into young adults (18–29) and older adults (≥30). This segregation was based on brain maturation timeframe which may impact mental health.[31] DP were classified into Western, Mediterranean, Eastern and Asian. Education was subdivided into high school, undergraduate and graduate. Region partitioning included NA, Europe, MENA, Africa and Asia. Mental distress partitioning was based on the suggested cut-off scores: K-6 sum score between 0 and 7 reflects 'No Psychological Distress', a score between 8 and 12 refers to 'Mild/Moderate Psychological Distress.' A score between 13 and 24 reveals 'Serious Psychological Distress'.[27] Pearson's Chi-square test was used to assess equality of tertiles (refer to Table 4). All analyses were performed using the R software (Version 1.0.136).[32]

Results

A total sample of 563 participants, of which 272 (48%) men and 291 (52%) women, completed the questionnaire. Descriptive statistics and characteristics of participants are presented in Table 1. Questionnaire respondents were from North America (NA), Europe, Middle East/North Africa (MENA), Africa and Asia. Mean age for men was 26.45 ± 7.63 and for women 26.53 ± 8.12. KMO test for Sampling Adequacy score was 0.739. Barlett's test of sphericity was statistically significant ($P < .001$). Using ANOVA and Chi-square analyses, a region of residency and DP between genders were statistically significant ($P < .001$) and P ($< .05$), respectively. Women were more likely to be living in NA and men were more likely than women to follow MD. However, levels of mental distress between men and women were not statistically significant. Sensitivity analysis revealed that none of the predictors had zero

Table 1. Participant characteristics. ANOVA and Chi-square.

	Men	Women	*P* value
Gender	272 (48%)	291 (52%)	
Mean Age (Standard Deviation)	26.45 (7.63)	26.53(8.12)	.06
Education			
High school	45	63	.12
Undergraduate	152	165	
Graduate	73	60	
Dietary Pattern			
Mediterranean	163	137	.04*
Western	49	72	
MENA	28	46	
Asia	31	35	
Region of Residency			
North America	34	83	.00**
Europe	41	21	
MENA	150	117	
Asia	40	66	
Africa	7	4	
Exercise (strength or cardiovascular)			
None (per week)	104	109	.50
Less than three times a week	92	98	
Three of more times a week	76	84	
Mental distress			
No mental distress	3	0	.38
Low mental distress	219	228	
High mental distress	50	63	

*$P < .05$.
**$P < .001$.

variances, which indicated that none of the responses exhibited an unlikely response pattern (see Figure 2).

Principal component analysis

PCA analysis identified five different PCs accounting for a total of 51.22% of the variance. PC1 explained 17% of variance and describes a 'Fast food and Mental Distress Pattern', PC2 explained 14% of variance and resembles a 'Western Diet Pattern', PC 3 explained 8% of variance and describes a 'MENA Pattern', PC 4 explained 7% of variance and reflects a 'Supplement Use Pattern' and PC 5 explained 5% of variance and describes a 'Mediterranean Diet (MD) Pattern' (Table 2).

Common factorial analysis based on gender

CFA was conducted on data stratified by gender to identify latent variables with the most significant weights that describe the gender-specific patterns (Table 3). In men, the highest factor loading generated factor 1 'Supplement Use Pattern' and includes MV and FO supplements. Factor 2, identified as a 'Partially Healthy Diet', comprises of beans, HGI food, nuts, coffee, fruits and leafy vegetables. Factor

Table 2. Principal component analysis – PC loadings for food groups (>0.2) with varimax rotation.

	Fast food and mental distress pattern	western pattern	MENA pattern	Supplement pattern	Mediterranean pattern
Eigenvalue	3.64	2.89	1.66	1.41	1.14
Variance explained	17%	14%	*8%*	7%	5%
Mental Distress	0.56				
Fast foods	0.21	0.25			
Rice/pasta		0.33			
Meat /chicken		1			
Breakfast			0.27		
Wholegrain			0.28		
Coffee			0.42		
Fruits			0.44		0.44
Dairy			0.79		
Fish oil				0.43	
Multivitamin				0.98	
Nuts					0.27
Fish					0.27
Bean					0.34
Exercise					0.37
Leafy Vegetables					0.56

Table 3. Factor loadings for food groups that loaded highly in varimax (> 0.2) rotated principal components for men and women.

Men					Women				
	Factor1 Supplement Use	Factor2 Partially healthy diet	Factor3 Unhealthy diet	Factor4 Healthy diet and lifestyle		Factor1 Unhealthy diet	Factor2 Partially healthy diet	Factor3 Healthy diet and lifestyle	Factor4 Supplement Use
Eigenvalue	1.18	1.16	1.14	1.04	Eigenvalue	1.31	1.26	1.21	1.16
Variance explained	7%	7%	7%	6%	Variance explained	8%	8%	8%	7%
Multivitamin	0.58				Rice/pasta	0.33			
Fish oil	0.83				Meat	0.99			
Beans		0.24			Breakfast		0.20		
Rice/pasta		0.28			Wholegrain		0.31		
Nuts		0.30			Fruits		0.49		
Coffee		0.38			Coffee		0.53		
Fruits		0.50			Dairy		0.74		
Leafy vegetables		0.58			Mental distress			−0.22	
Fast food			0.98		Nuts			0.29	
Mental distress			0.27		Fish			0.35	
Dairy				0.55	Beans			0.4	
Wholegrain				0.26	Exercise			0.43	
Fish				0.27	Leafy vegetables			0.52	
Exercise				0.30	Multivitamin				0.4
Breakfast				0.52	Fish oil				0.9

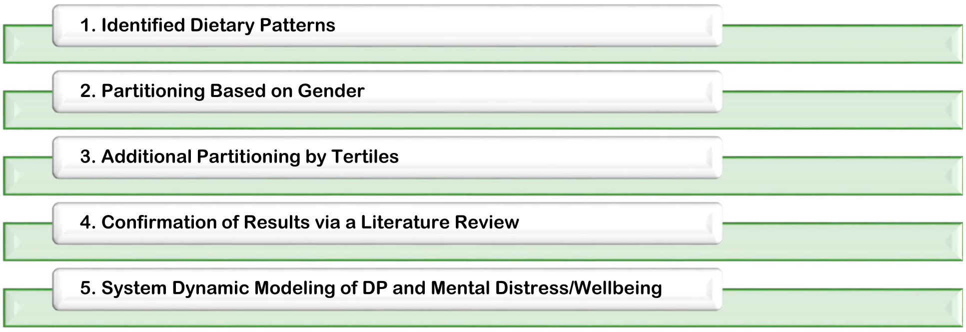

Figure 1. Study design and rationale.

3, identified as 'Unhealthy Diet' pattern, encompasses fast food and mental distress. Factor 4, recognized as a 'Healthy Dietary and Lifestyle Practice', comprises of daily breakfast, exercise, fish, wholegrain and dairy. In women, Factor 1, recognized as an 'Unhealthy Diet', has the highest loading for HGI food and meat. Factor 2, which was recognized as a 'Partially Healthy Diet', includes breakfast, whole grain, coffee, dairy and fruits. Factor 3 resembles a 'Healthy Diet and Lifestyle' and comprises of nuts, fish, beans, leafy vegetables and exercise. Interestingly, this pattern negatively associates with mental distress. Factor 4, identified as 'Supplement Use Pattern', includes MV and FO supplements.

Common factorial analysis based on tertiles and subcategorization of variables

CFA of tertiles generated a new set of additional findings (Table 4). Men, in the third tertile of factor 3, are more likely to be 30 years or older and following a WD pattern. No other significance was detected for men. Women, in the third tertile of factor 2, are more likely to be 30 years or older, with a high school degree and resides in Asia. Those in the third tertile of factor 3 are more likely to have a graduate degree and live in NA. Women, in the third tertile of factor 4, are more likely to be 30 years or older.

Discussion

The main purpose of this study was to assess gender-specific DP in relation to mental distress in a heterogeneous population with broad socio-geographical demographics. The literature describes symptomatological differences between men and women as well as brain morphological discrepancies that potentially describe susceptibility to mental disease.[18,19] However, no study has looked holistically at the effect of DP on psychological distress in both sexes. Based on this necessity, we wished to identify potential causal factors that may contribute to the gender-specific associations with mental distress. As a first step, we confirmed variability of DP within the dataset. PCA identified three DP pertaining to geographical regions (Western, Mediterranean and MENA) and two patterns describing trends such as consuming fast food and mental disease and supplement use. Next, using CFA, significant factors that account for the common variance within the gender-specific patterns were extracted. The overall patterns were nearly similar between both groups (unhealthy, partially healthy, healthy and supplement use). Subdivision of data into tertiles captured the latent variables within each factor. Using evidence from the literature, we wished to confirm the validity of our findings and subsequently model the potential link between diet, brain structures and functions and mental health to better explain our results (Figure 1).

PCA: the identified dietary patterns

The combination of fast food and mental distress pattern supports previous findings.[16] Consuming fast food on a regular basis may trigger a deficiency of key neurotransmitters and structural precursors that increase the risk of mental disease. All other patterns generated were expected as well. WD pattern includes meat, HGI food as well as fast food and lacks exercise.[33] MENA pattern comprises of daily breakfast,[34] which typically includes substantial dairy.[35] MENA cuisine is rich in whole grain dishes made with durum wheat.[36] Coffee drinking is a traditional daily practice. Fruits are consumed after lunch instead of dessert and between meals as snacks.[35] Therefore, these variables grouped together confirmed the MENA pattern. Supplement Use pattern bundled MV and FO supplements together which may reflect a pattern of use potentially extending to other supplements. MD pattern includes food that is best grown in the Mediterranean climate such as green leafy vegetables, beans, fruits and nuts. Fish consumption is high and dates back to the Roman Empire.[37] The Mediterranean lifestyle is known to promote physical activity. Mild climate and proximity to sea favor leisure-time activities from walking to swimming and cycling.[38] Consequently, these variables that loaded together support the MD pattern notion. Therefore, PCA analysis identified and confirmed the different dietary patterns within the data (Table 2).

Table 4: Common factorial analysis.

	Men												Women											
	Factor 1			Factor 2			Factor 3			Factor 4			Factor 1			Factor 2			Factor 3			Factor 4		
	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3
Factor score	−0.7 to −0.3	−0.3 to −0.2	−0.2 to 4	−1.8 to −0.3	−0.3 to 0.4	0.4 to 2.3	−1.7 to −0.6	−0.6 to 0.5	0.5 to 2.6	−1.8 to −0.3	−0.3 to 0.4	0.4−2	−2.6 to −0.2	−0.2−0.6	0.6−1.4	−2 to −0.4	−0.4−0.6	0.6−1.4	−1.5 to −0.4	−0.4−0.3	0.3−2.8	−0.6 to −0.3	−0.3 to −0.2	−0.2 to 3.9
Age groups																								
Young	75	74	73	73	74	75	65	73	84	69	80	73	82	84	75	84	87	70	84	82	75	88	83	70
Old	16	16	18	18	18	14	25	18	7*	22	11	17	15	15	20	12	11	27*	13	15	22	9	14	27*
Dietary Pattern																								
Western	10	18	21	21	13	15	12	9	28*	17	11	21	29	16	27	22	26	24	22	25	25	22	20	30
East	9	11	8	7	16	5	7	13	8	13	8	7	11	23	12	19	16	11	15	19	12	20	12	14
Asia	9	10	12	8	10	13	13	13	5	10	13	8	12	14	9	19	9	7*	14	16	5	11	12	12
Mediterranean	63	51	49	55	53	55	58	56	49	51	58	54	44	44	49	36	46	55	46	48	43	43	52	42
Education Level																								
High school	14	12	19	22	13	10	14	18	13	14	17	14	27	17	19	26	27	10*	19	16	28	19	23	21
some college	49	51	52	48	48	56	45	55	52	55	55	42	40	58	58	55	52	58	65	54	46	54	57	54
graduate	28	25	20	21	29	23	31	18	24	22	18	33	19	20	21	16	17	27	12	26	22*	22	17	21
Region																								
Africa	1	2	4	2	2	3	2	4	1	2	3	2	1	2	1	3	1	0	2	2	0	1	2	1
Asia	13	15	12	17	10	12	18	12	10	18	14	8	19	23	24	31	17	18	23	25	18	18	27	21
Europe	18	11	12	16	11	14	14	13	14	6	15	20	8	5	8	5	8	8	3	8	10	10	3	8
Middle East/ North Africa	52	53	45	44	57	49	45	51	54	52	49	49	37	48	32	33	41	43	56	39	22	47	37	33
North America/ Central America	7	9	19	12	9	13	11	8	15	13	10	11	33	18	32	26	29	28	15	21	47**	23	25	35

Notes: Participants characteristics based on gender further subdivided into tertiles. All tests are Chi-square analysis.
*$P < .05$.
*$P < .001$.

CFA: results and significance of findings

The generated CFA variables described patterns comprised of a spectrum of unhealthy and healthy diets. However, mental distress in men only associates with the least healthy pattern (fast food). Conversely, mental distress in women negatively associates with the healthiest diet and lifestyle (described as a Mediterranean-like diet and lifestyle (MDL)). When data were further subdivided into tertiles, mental distress associates with men typically over the age of 30 and who consume WD, which aligns with fast food consumption. In women, factor 3 subdivision into tertiles connects MDL and mental wellbeing to a graduate degree and living in NA (Table 3). However, this finding might be influenced by the fact that women in our study are more likely to be living in NA.

It appears that mental health in men ensues from severe nutritional deficiencies. In women, there was an inverse pattern. Mental distress negatively associates with a range of healthy food groups and with exercise. Although many components of the 'partially healthy diets' identified in this study (along with MV and FO) have been described to support mental health,[39–42] these single or combined dietary factors did not reveal any significance for women in our results. Anecdotally, it appears that individual nutrients do not provide an inverse strong association with mental distress; therefore, a threshold of beneficial nutrients may be needed to reach mental wellbeing in women.

Interpretation of results based on evidence from the literature

We hypothesized that the differential mental health-dietary patterns depicted in this study were due to differences in brain morphology between men and women. A literature review was performed to identify the potential links to better explain our results. MRI imaging of 68 brain regions of 2750 females and 2466 males reported that men inherently have larger brain volume in all subcortical regions including HC and amygdala, after adjusting for age.[20] On the other hand, women tend to have significantly thicker cortices than men. A meta-analysis comparing hippocampal volume in men and women, reported that men of all ages exhibit a larger HC volume than women. However, after adjusting for TBV, it appears that the difference is negligible.[43] Additionally, activation of the amygdala has a differential pattern in men and women.[44] The male amygdala is significantly larger than the female counterpart, after adjustment for TBV.[45] Nevertheless, women tend to recall negative emotional memories faster while men tend to be more sensitive to positive stimuli. This discrepancy suggests differences in topological connectivity and control.[44] Combining all findings together, it appears that women may have a higher level of GM in the cortices, potentially more WM connecting with subcortical regions and smaller amygdala volume compared to men. On the other hand, men tend to possess more GM in the subcortical regions including the amygdala. Although HC is not sexually-dimorphic, both genders benefit from preserving its volume for mental wellbeing.[46]

Proposed models

Using System Dynamic Modeling methodology, we wished to depict closely the relationships between brain structures, diet and mental health to propose possible gender-specific models that may better describe the results from our study and others (Figure 2). Using evidence from the literature, we constructed two gender-specific models using causal links to define the relationship between WD (as a prototype of an unhealthy diet), MD (as an architype of a healthy diet) and their potential effects on brain structures and functions (Figure 2(a,b)). Table 5 describes the specifics of the reinforcing loops. It is worth noting that these loops are virtuous when all components are in place and may turn vicious when components are absent. The brain is a complex organ; therefore, these diagrams are simplified representations of the potential associations.

WD, hippocampus volume and mental distress in men: a potential vicious cycle

Reinforcing loop 1: R1 – the effect of WD on the limbic system (LS)

The WD is deficient in essential nutrients (namely omega-3 fats and phenolic acid-rich food) crucial for optimal brain functions and mental wellbeing.[47] Therefore, regular consumption of WD with age may induce rapid brain structural changes that could potentially lead to mental distress. A cross-sectional study of 5731 mid-old age participants described that a WD-style associated with anxiety. Conversely, a healthy diet quality score was inversely linked to depression and anxiety.[48] Additionally, aging and poor diet independently induce HC atrophy.[49,50] In a longitudinal study, individuals who followed a WD-like exhibited a rapid atrophy of the left and right HC.[49] No other DP associated with atrophy of HC in that study. A review of the literature investigating the concomitant role of diet in neurogenesis and mood identified two omega-3 fats as having a major role in these processes. Docosahexaenoic acid (DHA; 22:6n-3), an omega-3 fatty acid naturally found in marine fish, promotes neurite outgrowth in HC and synaptic function.[51] DHA has gained ample attention in the scientific community for its role in the evolution of the human intelligence and higher cognitive functions.[52–54] DHA broadly controls a plethora of

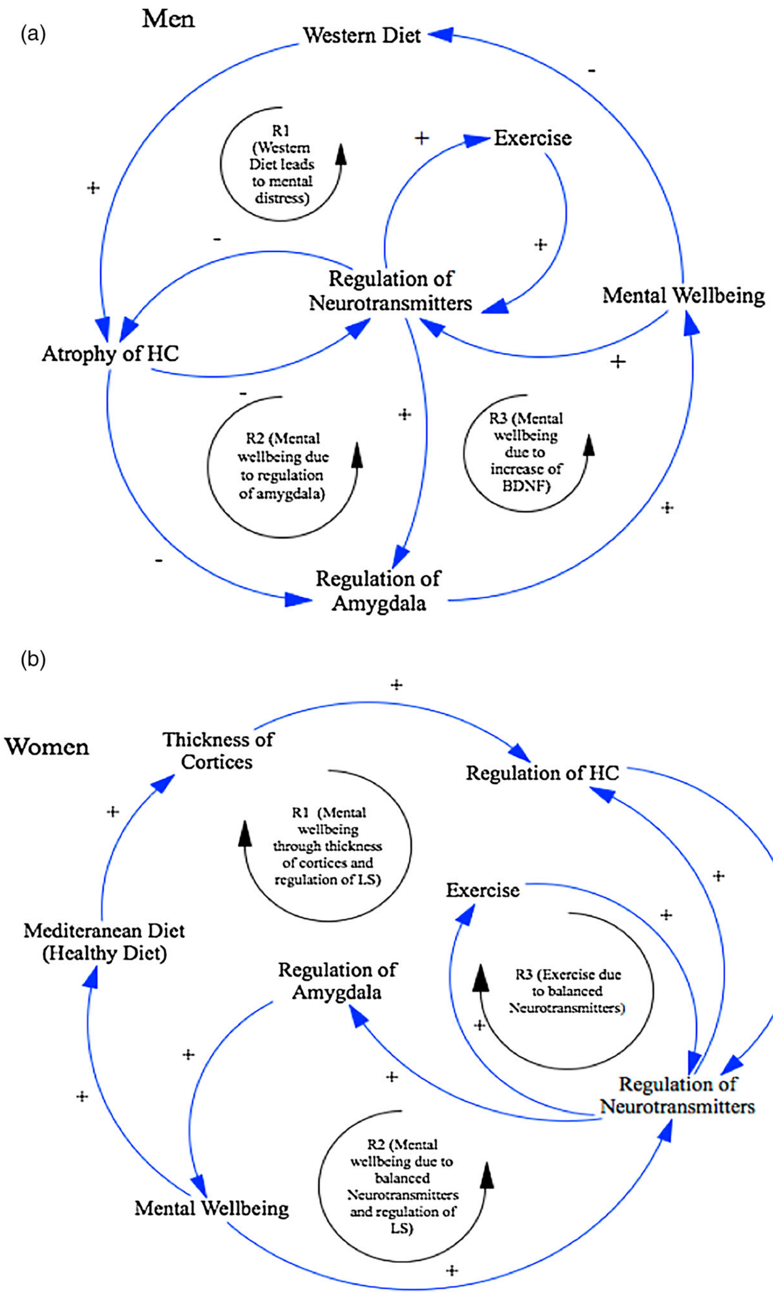

Figure 2. (a) Reinforcing loops around Western diet, dysregulation of the limbic system (LS) due to atrophy of Hippocampus (HC) and due to lack of exercise. A positive casual link explains a change in the same direction (e.g. one factor stimulating another) and a negative link refers to a change in the opposite direction (or inhibition of functions). (b) Reinforcing loops around Mediterranean diet, cortical thickness and regulation of the limbic system (LS). Another reinforcing loop describes the effect of exercise on regulation of LS through regulation of neurotransmitters. A positive casual link explains a change in the same direction (e.g. one factor stimulating another) and a negative link refers to a change in the opposite direction (or inhibition of functions).

physiological processes such as neurotransmitter release, transcription regulation, axon myelination, neuroinflammation, and neuronal differentiation.[55,56] It is concentrated in GM which contributes to subcortical volume. Particularly, DHA is localized in cellular and organelle membranes at synaptic terminals, in mitochondria and endoplasmic reticulum.[57,58] Therefore, DHA deficiency could potentially induce homeostatic disturbances by altering synaptic transmission, cellular survival and protein and lipid biosynthesis, respectively.[59–61.] *In vitro,* depletion models of DHA reported loss of neurites, reduced expression of synapsins, a family of proteins that regulates neurotransmitter release, and significantly impaired long-term potentiation (LTP), an established form of synaptic plasticity.[62] Beside DHA, marine fish provides another crucial fatty acid from the omega-3 family, eicosapentaenoic acid (EPA; 20:5n-3). Like DHA, EPA plays a significant role in maintaining functional integrities of brain structures. Additionally, EPA and DHA stimulate the production of anti-inflammatory molecules, resolvins and

Table 5. Description of the reinforcing loops between men and women.

Loop name	Components
Men	
R1 Unhealthy Diet and effect on LS	Western diet (Unhealthy diet) → Atrophy of HC → Dysregulation of amygdala → Mental distress → Western diet
R2 Distress due to Dysregulation of LS	Atrophy of HC → Dysregulation of amygdala → Mental distress → Lack of exercise → Atrophy of HC
R3 Distress due to decrease in BDNF	Atrophy of HC → Lower BDNF → Dysregulation of Amygdala → Mental distress → Lack of exercise → Atrophy of HC
Women	
R1 Mental wellbeing through thickness of cortices and regulation of LS	Mental wellbeing → Mediterranean diet (Healthy Diet) → Thickness of cortices → Regulation of HC → Regulation of neurotransmitters → Regulation of amygdala→ Mental wellbeing
R2 Mental wellbeing due to balanced neurotransmitters and regulation of LS	Mental wellbeing → Regulation of neurotransmitters → Regulation of amygdala → Mental wellbeing
R3 Mental wellbeing due to exercise	Exercise → regulation of neurotransmitters → Exercise

Note: LS: limbic system; HC: Hippocampus.

protectins which confer neuroprotection.[63] Furthermore, EPA and DHA exhibit an antioxidative stress, anti-apoptotic properties with increased neurogenesis aptitude.[64] EPA promotes proliferation of progenitor neural cells while DHA stimulates their differentiation.[65] Interestingly, taking FO supplements did not associate (positively or negatively) with mental distress in men and women in our study. This finding could be explained by the lower bioavailability/ differential concentrations of EPA and DHA in pills.[66] It is worth noting that other dietary factors that contribute to neurogenesis include: caloric-restriction, phenolic-rich foods and some vitamins and minerals; however, evidence implicating their role in mood is still limited. On the other hand, folate and cobalamin, as part of the one-carbon metabolism pathway (OCMP), are involved in DNA synthesis, methylation reactions and monoamine metabolism. Disruption of the OCMP has been linked to psychiatric illness and to potentially a disruption in neurogenesis in lab animals.[67,68] Polyphenolic compounds are known for their neuroprotective effect in increasing synaptic plasticity[69] and promoting hippocampal long-term potentiation[70] with a reported effect on mood as well.[71] Collectively, in light of this information, the combination of EPA, DHA, phenolic-rich food and potentially other nutrient deficiencies in WD may have a profound effect on HC neurogenesis and neuroplasticity, and the subsequent communication with the amygdala. The inherent brain clock coupled with lack of neurogenesis culminate in a chronological atrophy of the subcortical brain regions, which eventually increases the risk of mental distress. This proposed scenario may suggest that absence of nutrient-dense food that supports the structural integrity of the GM in the limbic system may increase the risk of mental distress in men over the years.

Reinforcing loop 2: R2 – Distress due to dysregulation of LS

HC grows afferent neural circuits with emotion-related brain regions, such as PC and the amygdala. While PC rationalizes emotions, the amygdala is responsible for fear conditioning. Therefore, this cortical-limbic circuit (CLC) is critical for regulation of mood. HC houses prominent levels of glucocorticoid and glutamate receptors that control the hypothalamic–pituitary–adrenal (HPA) axis activity. Chronic stress-induced hyperactivity of HPA axis leads to structural damage in key brain regions, including HC. Consequently, HPA dysregulation leads to HC atrophy secondary to alterations in neurochemistry and neuroplasticity.[72] Moreover, mental distress negatively impacts CLC, which induces abnormal amygdala functional connectivity in areas that integrate affective processes (amygdala-associated fronto-limbic circuits, amygdala-dorsal lateral prefrontal cortex and amygdala-ventromedial PC).[73] Mental distress is usually associated with lower levels of dopamine, typically linked to lower motivation to exercise.[16,33] Subsequently, lower brain-derived neurotrophic factor (BDNF) levels contribute to HC atrophy.

Reinforcing loop 3: R3 – Distress due to a decrease in BDNF

Exercise, through BDNF, may avert some of the changes in HC synaptic plasticity and may increase dendrite complexity.[74] Consequently, neural progenitor cells in HC dentate gyrus proliferate and differentiate into functional neurons. Therefore, the absence of exercise contributes to the swift decline in HC and dysregulation of amygdala functionality.[75] Moreover, BDNF in the amygdala controls emotional learning by regulating GABAergic and glutamatergic activities and by enhancing serotonergic transmission.[76,77] Additionally, a low-quality diet is deficient in essential nutrients that bare antioxidative activities and in phenolic acid-rich food needed to fight oxidative stress (OS). Typically, OS increases with age, which reduces levels of BDNF and adds to the absence of neuroplasticity.[78] Considering all evidence together, deficiencies of key nutrients in WD and lack of exercise induce structural changes, namely in the mesolimbic system, that culminate in mental distress in men.

MDL, cortical thickness and mental wellbeing in women: a potential virtuous cycle

Reinforcing loop1: R1 Mental wellbeing through the thickness of cortices and regulation of LS

Mental wellbeing is often associated with elevated dopamine levels that increase motivation to achieve healthiness.[16] Followers of MD exhibit generally a better mood than those of the WD. Additionally, interventional studies using Mediterranean-like diet therapy reported a significant improvement in depressive symptoms.[79] Individuals with higher Mediterranean diet scores (MDS) tend to have larger frontal, parietal, occipital, and average lobar cortical thicknesses.[80] Beans (high in polyphenols) and fish (rich in omega-3 fats) intakes, specifically, associated with increased cortical thickness. Interestingly, elevated simple carbohydrate consumption, as in WD, associates with lower cortical thickness.[81] Additionally, lower adherence to MD is predictive of total brain atrophy over a 3-year period.[81] During human evolution, increased consumption of DHA correlated with a rapid growth of GM in the CC, a characteristic of the modern human brain. Additionally, DHA is an essential constituent of WM; it is the most abundant lipid in the myelin sheath and makes up over 90% of the omega-3 fatty acid in the brain.[82] Myelinated axonal tracts contribute to cortical thickness; and higher level of intra-cortical myelin associates with the complexity of a cognitive task and mental wellbeing.[83,84]

MD is rich in a variety of phenolic bioactive compounds that exhibit a broad control over gene expression ranging from transcription regulation and mRNA stability, to protein translation and post-translational modifications.[85] These different cellular and molecular processes support synaptogenesis precisely in CC.[86] Specifically, beans and nuts contain a complex assortment of polyphenolic antioxidants that confer protection against OS.[87] Consequently, enhanced synaptic plasticity culminates in improvement in cognitive, motor, and emotional behaviors.[88] A meta-analysis of 12 prospective studies with a collective sample size of over 1.5 million subjects reported that strong adherence to MD reduces significantly incidences of neurodegenerative diseases suggestive of brain volume preservation.[89] In a cross-sectional study of the elderly population without dementia, participants who adhered to MD exhibited larger brain volumes, both in GM and WM of key regions. The study also reports that consumption of a near serving of fish at least once a week or reduction of meat to 100 g or less a day, may also provide a substantial protection against brain atrophy.[90]

Reinforcing loop 2: R2 – Mental wellbeing due to balanced neurotransmitters and regulation of LS

As mentioned above, cortical thickness improves metal wellbeing. Dense GM and WM potentiate the neural circuit between PC, HC and amygdala to rationalize emotions. This CLC cross-talk is mediated by the two major neurotransmitters in the brain; glutamate, an excitatory brain chemical, and gamma-aminobutyric acid (GABA), an inhibitory brain chemical. A balance of both neurotransmitters is needed for proper regulation of other neurotransmitter release. Explicitly, the amygdala is highly innervated with 5-hydroxytryptamine and dopaminergic fibers,[91,92] which support regulation of aversive emotions such as fear and anxiety.[93] Increasing evidence suggests that adherence to MD may be inducing epigenetic modifications protective against mental disease with a trans-generational effect.[94] Epigenetic modifications in key genes may confer protection against day to day and seasonal alterations in dietary patterns making individuals more resilient to mental distress. MD is also rich in folate, a B-vitamin, which is an integral part of the OCMP. In the OCMP, 5-methyl tetrahydrofolate assists with the generation of S-adenosylmethionine (SAM), the universal methyl donor for DNA and histone methylation reactions as well as for dopamine biosynthesis.

Epigenetic modifications are heritable and may explain causality of complex diseases when genome-wide association studies (GWASs) fail to identify specific culprit genes. In fact, GWASs have not identified specific genes that significantly associate with anxiety and depression; hence, the current line of thinking is consideration of the epigenome as a potential contributor.[95] Therefore, an efficient OCMP has the potential to boost dopamine levels as well as induce favorable epigenetics marks that support mental wellbeing.

Reinforcing loop 3: R3 – mental wellbeing due to exercise

Mental wellbeing promotes motivation to exercise.[16] Elevated BDNF and its receptor-tyrosine kinase B levels stimulate neurogenesis and synaptogenesis.[75] Consequently, a regulation of GABAergic and glutamatergic transmission supports an effective emotional learning in the amygdala which promotes mental wellbeing.[96,97]

Collectively, women's mental wellbeing may be sensitive to a threshold of nutrients such as polyphenols, omega-3 fats and potentially components of the OCMP, which MD is an excellent source of. This conclusion is further potentiated by the fact that taking a multivitamin (which is expected to contain folic acid) and FO supplements did not associate with mental wellbeing in our results. These supplements lack the spectrum of polyphenols archetypally provided by MD; in addition, micronutrients from pills present a bioavailability issue that limits their effectiveness.

Therefore, women with an optimal cortical thickness are more likely to retain a higher level of cognitive functions and mental wellbeing. An interesting observation from our results, women who consume an MD style and exercise regularly are more likely to have a graduate degree. One cannot but pose the question: Does cortical thickness play a role in the pursuit of higher education in women? There could be a common factor driving both the dietary pattern and the graduate degree status of these women. A graduate degree in women may induce a feeling of accomplishment and empowerment to live a healthier lifestyle. In fact, education has been associated with a healthier lifestyle.[98] However, this finding was generalized to both genders. Higher education may also mean 'brain exercise' which may increase BDNF levels. The fact that higher education did not associate did not associate with mental distress in men may also support this proposition.

Summary of main findings

Our data was generated using multivariate analyses which are considered powerful tools for data mining. The literature confirms many of our findings; however, many reports are generalized to both genders. The significance of our results is that they identified sex-specific-diet-mental health patterns which are currently lacking in the literature. The fact that mental distress level was comparable between genders supports the validity of our results. Another noteworthy finding is that our results are based on a comparison between men and women of similar mean age, which provides a better depiction of the gender-based effect of diet on mental health.

According to our results, mental wellbeing in women associates with following a healthy diet and lifestyle; whereas in men it ensues from the consumption of unhealthy food. This inference suggests that men are more likely to experience mental wellbeing until nutritional deficiencies arise. However, women are less likely to experience mental wellbeing until a balanced diet and a healthy lifestyle are followed. In men, we propose that dietary deficiencies may have a more pronounced effect on the limbic system (hippocampal-amygdala) regulation whereas dietary sufficiency in women may potentiate the mesocortical regulation of the limbic system (prefrontal cortex-hippocampal-amygdala system). Based on the compelling evidence from the literature, we are hypothesizing that the amalgamation of deficiencies in EPA, DHA, phenol-rich food and exercise precipitates subcortical atrophy and subsequently induces mental distress in men. On the other hand, the combination of a spectrum of polyphenols and other non-phenolic antioxidants, folate (as components of the one-carbon metabolism), EPA and DHA may be needed to maximize mental wellbeing in women with a resilience effect. The fact that partial intake of this dietary component did not associate with mental distress in men or with mental wellbeing in women supports these hypotheses. These findings may not be applicable to the whole population, but this evidence bares some important relevance. Factors that may affect these models should be considered in light of genetic variations, environmental stressors, age, sleep, exercise frequency and others. This overall conclusion may confirm many reports in the literature that describe women having the increased risk of psychological distress when compared to men.[1–3]

Strengths and limitations of the study

This study has many strengths and limitations. Powerful methods for analysis and prediction were used at multiple levels for data mining. Accordingly, the results provide compelling evidence that mental health in men and women in this cohort associates differentially with dietary patterns. Moreover, the study substantiates many reports in the literature that describe the differential pattern of mental disease in men and women. Therefore, it also adds to the literature by describing the potential implication of dietary factors on mental distress and wellbeing in men and women. Nevertheless, the limitations of this study include its cross-sectional design and the non-random sampling which may not represent the population at large. The study was based on a web-survey and survey research comes with a margin of error; therefore these results should be considered with this flaw in mind. Additionally, it does not take into consideration the developmental variation, genetic factors and other environmental stressors that may have affected the anatomical structures of the brain. There are limitations to the results as well. The mean age of twenty-six with a standard deviation of about eight for both genders reflects that our data represent mostly young and matured adults but not necessarily the older population. Our study does not include menopausal women and andropausal men. These two stages of life involve significant changes in brain structures due to hormonal decline. Therefore, the results of this study should not be generalized to all men and women since this important age category was not well represented.

Future direction

Imaging studies with dietary assessments are needed to confirm the hypothetical models suggested in this study. Additionally, longitudinal studies focusing on gender-based targeted dietary interventions may be necessary. If such interventions positively stimulate changes in key brain volumes, then the diet as the first line of defense against mental distress may need to be considered. Interventional studies on the effect of MD on mood and cortical thickness in post-menopausal women requires some consideration as well.

Conclusion

Dietary patterns and mental health associate differently in men and women in our study. In addition, our findings suggest that mental health in men may ensue for nutritional deficiencies subsequent to consumption of an unhealthy diet. In women, mental wellbeing may be achieved with following a Mediterranean-like diet style and lifestyle. This differential response may be linked to differences in brain morphology between men and women. Furthermore, our results suggest that men's mood may be more likely dependent on food that potentiates the limbic system. Exercise may also contribute to hippocampal density. Dietary antioxidants are necessary to decrease OS and subsequently preserve existing GM structures. Women's mood may be influenced by food that contains high levels of polyphenols (such as nuts, beans, leafy green vegetables), EPA, DHA (found in marine fish) and folate (such as in nuts, beans, leafy green vegetables). Exercise is also beneficial to women to support cerebral flow that may potentiate neural plasticity, dendritic arborization and reinforcement of the cortico-limbic circuit. Since our study is cross-sectional, we cannot conclude that is generalizable to all men and women. However, these findings act as a catalyst for further investigations in this field.

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