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Advanced glycation end products measured by skin autofluorescence are associated with melancholic depressive symptoms – Findings from Helsinki Birth Cohort Study

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ABSTRACT

Background: Millions of people live with depression and its burden of disease. Depression has an increased comorbidity and mortality that has remained unexplained. Studies have reported connections between advanced glycation end products (AGEs) and various disease processes, including mental health. The present study evaluated associations between AGEs, depressive symptoms, and types of depressive symptoms.

Methods: From the Helsinki Birth Cohort Study, 815 participants with a mean age of 76 years were recruited for this cross-sectional study. Characteristics regarding self-reported lifestyle and medical history, as well as blood tests were obtained along with responses regarding depressive symptoms according to the Beck Depression Inventory (BDI) and Mental Health Inventory-5. Each participant had their AGE level measured non-invasively with skin autofluorescence (SAF). Statistical analyses looked at relationships between types of depressive symptoms and AGE levels by sex.

Results: Of women, 27% scored ≥10 on the BDI and 18% of men, respectively. Men had higher crude AGE levels (mean [standard deviation], arbitrary units) (2.49 [0.51]) compared to women (2.33 [0.46]) ($p < 0.001$). The highest crude AGE levels were found in those with melancholic depressive symptoms (2.61 [0.57]), followed by those with non-melancholic depressive symptoms (2.45 [0.45]) and those with no depressive symptoms (2.38 [0.49]) ($p = 0.013$). These findings remained significant in the fully adjusted model.

Conclusions: The current study shows an association between depressive symptoms and higher AGE levels. The association is likely part of a multi-factorial effect, and hence no directionality, causality, or effect can be inferred solely based on the results of this study.

Depression is a leading cause of disability, affecting over 322 million people worldwide and more years are lost to disability due to depression than any other condition in the world [42]. Depression greatly contributes to the overall burden of disease [43], and the World Health Organization has predicted that by 2030 it will be the leading cause of burden of disease in the world [24]. Furthermore, depression and

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physical health, such as cardiovascular disease, are intertwined [43].

According to Markkula and Suvisaari depression, especially in women, has been increasing in prevalence, and is associated with a two-fold risk of death compared to non-depressed individuals. However, this increased risk cannot be fully explained by behavior or physical illness [25]. It has been indicated that different underlying mechanisms may be responsible for non-melancholic and melancholic types of depression, with metabolic and inflammatory dysregulations possibly being responsible for the prior and underlying hypothalamic-pituitary-adrenal axis dysregulations for the latter [22,29].

Advanced glycation end products (AGEs) are a group of chemical modifications of proteins and lipids [17]. AGEs are formed through the Maillard reaction; a nonenzymatic glycation of sugar aldehydes into Schiff bases, Amadori products, and finally AGEs [17]. AGEs are part of the aging process [32], but have also been indicated as factors in various diseases such as diabetes mellitus, cardiovascular disease (CVD), Alzheimer's Disease, depression and schizophrenia [1,12,15,18,27,44]. They alter tissues by binding to the receptor for AGEs (RAGE), which activates signaling pathways that enhance oxidative stress, generate proinflammatory cytokines, alter glucose metabolism, and induce endothelial dysfunction [7,8,15,17].

Research has shown that AGEs in tissues are not necessarily reflected accurately by urine or blood sampling [26]. Immunochemical assays are able to measure both fluorescent and non-fluorescent AGEs, but both types have been shown to behave similarly, indicating that fluorescence could be used as a marker [26]. Traditionally biopsies have been used to measure the fluorescence in tissues, but SAF has been validated as a non-invasive tool for measurement of AGEs in skin [26]. This method has also been used in the Maastricht Study, where both SAF and plasma AGEs were measured, showing that SAF has a stronger association with depression and depressive symptoms than plasma AGEs [38].

Several non-communicable diseases including type 2 diabetes mellitus and depression are characterized by a low-grade chronic inflammation, which has been proposed as a connection between AGEs and depression [10]. Endothelial dysfunction, oxidative stress, inflammation, and arterial stiffening have also been independently associated with depression [36,39]. Tissue AGEs can be measured non-invasively with SAF, potentially making them an emerging biomarker for the aging process. Research has shown that AGE levels measured by SAF is higher in diabetic individuals than non-diabetics [40]. It has also been shown that other factors such as age and smoking are responsible for different percentages of variance in SAF in diabetics versus non-diabetics [40].

The aim of this study was to evaluate whether there is an association between AGEs and depressive symptoms, and whether there is a difference in association between non-melancholic and melancholic types of depressive symptoms in regards to AGEs.

1. Methods

1.1. Subjects

The Helsinki Birth Cohort Study (HBCS) is a cohort of 13,345 men and women born between 1934 and 1944 at the Helsinki University Hospital or Helsinki City Maternity Hospital in Helsinki, Finland. All subjects attended child welfare clinics in Helsinki, with the majority also attending school in Helsinki. Details of the records attained regarding birth, child welfare, and school health have previously been published [3,14].

By 1971 each member of the Finnish population was given a unique identification number. From the original cohort 8760 individuals (4630 men and 4130 women) born at Helsinki University Hospital were identified. In 2001–2004 2902 subjects who were alive and living in Finland were selected from this pool using random-number tables. Of the participants that were invited to participate in the study 2003 individuals took part. In 2011 1404 subjects from this group of 2003 people, still alive and living within 100 km of the study clinic in Helsinki, were invited for another clinical study; 1094 subjects participated. Using the same criteria in 2017–2018 we invited subjects to participate in a clinical follow-up, and 815 individuals participated in the study at hand.

1.2. Ethics

The study protocol was approved by the Coordinating Ethical Committee of the Hospital District of Helsinki and Uusimaa. Prior to participation each subject gave written informed consent. All study procedures followed the ethics outlined by the declaration of Helsinki.

1.3. AGE

Tissue AGE was measured by SAF using an AGE-reader (AGE Reader, Type 214B00102, DiagnOptics BV. Groningen, The Netherlands), with participants in a seated position, from the volar side of each participant's dominant forearm. Only healthy skin, excluding dermatological diseases and normal skin variations (such as birthmarks or tattoos), was eligible for SAF measurements. The skin was cleaned in preparation for the reading. Any subject having used lotion or topical solutions on this part of the skin had a minimum 2 h-period before a SAF reading was performed. All subjects had non-pigmented skin as recommended for reliable SAF results [26]. SAF is expressed as arbitrary units (AU), which is the ratio of emitted light intensity from the AGE reader (420–600 nm wavelength range) and the reflected excitation light intensity from the skin (300–420 nm wavelength range), multiplied by 100. The measurement procedure has been described in more detail by Meerwaldt et al. [26] and van Dooren et al. [38].

1.4. Depression

The BDI, a self-reported 21-category questionnaire of behavioral manifestations of attitudes and symptoms specific to depression [4], was used to assess depressive symptoms among the subjects. A cut-off of $\geq$10 total points, of a possible 0–63 point range [5], was utilized. This screening tool has been validated to screen for subjects with clinical depression [5]. The $\geq$10-point cut-off is used to identify any individual showing depressive symptoms, ranging from mild to severe depression, with anyone scoring below this not showing symptoms significant enough to warrant a diagnosis of depression [5].

A total of 185 subjects (22.7% of study population) scoring $\geq$10 of the BDI were identified. These subjects were classified as having either melancholic depressive symptoms (30 subjects) or non-melancholic depressive symptoms (155 subjects) using melancholic symptoms (sadness, past failure, loss of pleasure, guilty feelings, punishment feelings, loss of interest, irritability, change of sleeping and appetite) according to the DSM-IV in a similar way as in prior publications [33,34,41]. Subjects were classified as melancholic if the melancholic symptom score outnumbered the non-melancholic ones [33,34,41].

The five-item Mental Health Inventory (MHI-5), a 5-question form, was also used to screen for mood disorders in the subjects [6,31]. The questions addressed feelings of nervousness, calmness, happiness, feeling down, and inability to cheer up [31]. The questions were scored on a Likert scale and through linear transformation standardized to a 0–100 range scale with an inverse correlation to mood disorders [31]. These results were recorded and compared with the BDI results for validity of measurement of depressive symptoms.

1.5. Other measurements

After an overnight fast blood samples were drawn for laboratory assessment, including plasma glucose and blood lipids. Plasma glucose concentrations were measured according to a hexokinase method. Serum total cholesterol and triglyceride concentrations were measured

with the use of standard enzymatic methods [16,23]. Height was measured using a Kawi stadiometer. Weight was measured with a Seca Alpha 770 scale. Blood pressure was measured from the right arm with the subject in a seated position and was recorded as the mean of two successive readings from a standard sphygmomanometer.

Leisure-time physical activity (LTPA) was assessed by using a validated Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study 12-month LTPA history questionnaire [21]. The subjects were asked to fill in frequency (occasions per month), average duration, and intensity of each type of activity performed during the previous 12 months. For each type of activity we assigned a metabolic equivalent of task (MET) -value based on available databases (1 MET = 3.5 ml O_2/kg/min). To calculate the total amount of LTPA in MET-hours (METh), MET values were multiplied with the average duration and frequency of activities per week.

Information on health status, smoking habits, alcohol consumption and socioeconomic variables (economic status, years of education, and cohabitation) as well as medication used was obtained through questionnaires.

The Charlson Comorbidity Index (CCI) was calculated to obtain information regarding comorbid conditions and calculated according to published data [9]. Age was not accounted for as a factor of CCI in this study as all participants were similar in age, and our interest was in comorbid disease without the effect of age.

1.6. Statistical analysis

The descriptive statistics are presented as means with standard deviations (SD), or as counts (n) with percentages. Statistical comparisons between the sexes were made using the *t*-test or chi-square test. Statistical comparisons between categories of depressive symptoms were used to identify the relationship between depressive symptoms (predictor) as continuous variables and the AGE (outcome) with standardized regression coefficient beta (β). β is a measure of how strongly the predictor variable influences the criterion variable. β was measured in units of SD. Models included age, smoking status, education, socioeconomic status, relationship status, diabetes mellitus, body mass index (BMI), LTPA, and glycated hemoglobin (HbA_{1c}) as covariates; model I: crude model; model II: adjusted for age, smoking status, education, economic status, and cohabitation status; model III (fully adjusted): adjusted for age, smoking status, education, economic status, cohabitation status, HbA_{1c}, BMI, diabetes mellitus and LTPA. Cohen's standard for β values above 0.10, 0.30 and 0.50 represents small, moderate and large relationships, respectively [11]. The relationship between, for covariates adjusted, AGE levels and type of depressive symptoms in women and men was investigated through a series of two-way analysis of variances. The main effects included depressive symptoms, sex, and depressive symptoms × sex interactions. The bootstrap method was used when the theoretical distribution of the test statistics was unknown, or in the case of violation of the assumptions (e.g. non-normality). Correlation coefficients were calculated by the Pearson method. Normal distributions were evaluated graphically and with the Shapiro–Wilk W test. Stata 16.1 (StataCorp LP, College Station, TX, USA) was used for the analysis.

2. Results

Table 1 shows characteristics of the 815 study participants separated by sex. 458 women with a mean age of 76 years (SD 3), and 357 men with a mean age of 76 years (SD 3) participated in this study. There was no significant difference in HbA_{1c}, BMI or blood pressure between the sexes. Men, however, had a higher prevalence of diabetes mellitus (21%) than women (16%) (p = 0.033); they also had significantly higher LTPA (33.2 METh/ week, SD 26.4) than women (25.3 METh/ week, SD 22.9) (p < 0.001), and were more likely to have a history of smoking (62%) than women (29%). Use of antidepressant medication was more common among women (10%) than in men (4%) (p = 0.001). No differences were found between the groups in regards to use of anxiolytics, antipsychotics, or sleeping medications. Among the women 123 (27%) scored ≥10 on the BDI, with 106 (23%) being classified as having non-melancholic depressive symptoms and 17 (4%) having melancholic depressive symptoms. For men the corresponding numbers were 62 (18%), 49 (14%) and 13 (4%), respectively. The difference in this distribution between the sexes was significant (p = 0.003). The mean BDI scores were significantly higher (p < 0.001) for women (7.4, SD 5.8) than for men (5.6, SD 5.0). Likewise, on the MHI-5 the women had a significantly lower (p < 0.001) mean score (79, SD 16), than the men (84, SD 15) indicating higher depressive symptoms. On the CCI women scored lower (1.0, SD 1.6) than men (1.4, SD 1.8, p = 0.004), and AGE levels were likewise lower for women (2.33, SD 0.46) than for men (2.49, SD 0.51, p < 0.001). There was a correlation between AGE levels and HbA_{1c} (r = 0.17; 95% CI: 0.10 to 0.23; p < 0.001), and between BDI and MHI-5 scores (r = −0.71; 95% CI: −0.74 to −0.67; p < 0.001) in the participants.

Table 2 shows that there was a significant association between

Table 1
Characteristics of subjects as separated by sex.

	Women	Men	P-value
	N = 458	N = 357	
Age (years), mean (SD)	76 (3)	76 (3)	0.26
Years of education, mean (SD)	12.5 (3.4)	13.4 (3.8)	<0.001
Cohabiting, n (%)	243 (53)	303 (85)	<0.001
Economic status, n (%)			<0.001
Very good	40 (9)	52 (15)	
Good	193 (42)	172 (48)	
Adequate	197 (43)	121 (34)	
Poor or very poor	28 (6)	12 (3)	
Smoking, n (%)			<0.001
Never	292 (64)	113 (32)	
History of smoking	132 (29)	219 (62)	
Current smoker	32 (7)	24 (7)	
Alcohol use, n (%)			<0.001
3–7 times/week	63 (14)	65 (18)	
1–2 times/week	102 (22)	142 (40)	
1–2 times/month	117 (26)	71 (20)	
<1 time/month	124 (27)	39 (11)	
None	52 (11)	40 (11)	
BMI (kg/m^2), mean (SD)	27.2 (4.8)	26.6 (3.9)	0.059
BP (mmHg), mean (SD)			
Systolic	145 (21)	143 (30)	0.17
Diastolic	78 (10)	79 (27)	0.75
Cholesterol (mmol/l)	5.39 (1.08)	4.71 (1.05)	<0.001
HDL (mmol/l)	1.72 (0.37)	1.42 (0.34)	<0.001
LDL (mmol/l)	3.07 (0.95)	2.71 (0.91)	<0.001
Triglycerides (mmol/l)	1.32 (0.62)	1.25 (0.63)	<0.001
Plasma glucose (mmol/l)	6.08 (1.01)	6.32 (0.98)	<0.001
HbA_{1c} (%), mean (SD) (%)	5.61 (0.47)	5.60 (0.49)	0.72
CCI, mean (SD)	1.0 (1.6)	1.4 (1.8)	0.004
Diabetes Mellitus, n (%)	71 (16)	76 (21)	0.033
Use of antidepressants, n (%)	47 (10)	15 (4)	0.001
Use of antipsychotics, n (%)	4 (1)	2 (1)	0.70
Use of anxiolytics, n (%)	3 (1)	3 (1)	0.99
Use of sleeping medicine, n (%)	14 (3)	4 (1)	0.090
LTPA (METh/week), mean (SD)	25.3 (22.9)	33.2 (26.4)	<0.001
BDI, mean (SD)	7.4 (5.8)	5.6 (5.0)	<0.001
Type of depressive symptoms, n (%)			0.003
<10 No depressive symptoms	335 (73)	295 (83)	
≥10 Non-melancholic	106 (23)	49 (14)	
≥10 Melancholic	17 (4)	13 (4)	
MHI-5, mean (SD)	79 (16)	84 (15)	<0.001
AGE (AU), mean (SD)	2.33 (0.46)	2.49 (0.51)	<0.001

Note. Economic status is a subjective assessment where the study participants identified themselves in an ordinal category. BMI = body mass index, BP = blood pressure, HDL = high density lipoprotein cholesterol, LDL = low density lipoprotein cholesterol, HbA_{1c} = glycated hemoglobin, CCI = Charlson comorbidity index, LTPA = leisure-time physical activity, BDI = Beck Depression Inventory, MET = metabolic equivalent of task, MHI-5 = Mental Health Inventory-5, AGE = advanced glycation end products, AU = Arbitrary Units.

Table 2
Associations between depressive symptoms in men and women (measured by Beck Depression Inventory [BDI] and Mental Health Inventory 5 [MHI-5]) and Advanced Glycation End Products (AGE) measured by Skin Autofluorescence.

		AGE		
		Model I β (95% CI)	Model II β (95% CI)	Model III β (95% CI)
Depression	BDI			
	Women	0.11 (0.03 to 0.19) p = 0.006	0.11 (0.03 to 0.19) p = 0.008	0.11 (0.01 to 0.20) p = 0.026
	Men	0.21 (0.11 to 0.30) p < 0.001	0.14 (0.06 to 0.23) p < 0.001	0.13 (0.03 to 0.23) p = 0.014
	MHI-5			
	Women	−0.13 (−0.22 to −0.04) p = 0.004	−0.13 (−0.21 to −0.05) p = 0.002	−0.11 (−0.21 to −0.02) p = 0.017
	Men	−0.15 (−0.26 to −0.04) p = 0.009	−0.10 (−0.19 to −0.01) p = 0.038	−0.10 (−0.21 to −0.01) p = 0.044

Note. Model I: Crude data. Model II: Adjusted for age, smoking status, education, economic status, and cohabitation status. Model III: Adjusted for age, smoking status, education, economic status, cohabitation status, body mass index, diabetes mellitus, glycated hemoglobin and leisure-time physical activity.
The β values express the change in depressive measurements (BDI/ MHI-5) per 1-SD unit change in AGE (artificial units). Cohen's standard for β values above 0.10, 0.30 and 0.50 represents small, moderate and large relationships, respectively.

depressive symptoms, as measured by either BDI or MHI-5, and AGE levels for both women and men (Model I). This association remained virtually the same for women when adjusting for age, smoking, economic status, education, and cohabitation (Model II). In men, when adjusting for these, the association became slightly weaker but still remained significant. When additional adjustments for BMI, LTPA, and HbA_{1c} were made the associations for both men and women still remained significant (Model III).

There was a sex-difference of 0.16 AU between men and women in crude AGE levels ($p < 0.001$; 95% CI: 0.10–0.24). The highest crude AGE levels were found in the group with melancholic depressive symptoms (2.61 AU [SD 0.57]), followed by the group with non-melancholic depressive symptoms (2.45 AU [SD 0.45]) and the group with no depressive symptoms (2.38 AU [SD 0.49]) ($p = 0.013$). There was no interaction between sex and types of depressive symptoms in regards to crude AGEs ($p = 0.33$).

The comparison of fully-adjusted mean AGE levels between the groups with no depressive symptoms, non-melancholic depressive symptoms and melancholic depressive symptoms are described in Fig. 1. The main effects (sex and depressive symptoms) were significant but their interaction was not ($p = 0.23$). There was also a difference when comparing depressive groups ($p = 0.041$). For these calculations age, smoking status, education, economic status, BMI, cohabitation status, diabetes mellitus, and HbA_{1c}, were controlled for. Participants with melancholic depressive symptoms were found to have significantly higher AGE levels than those with BDI < 10 after a post hoc comparison ($p = 0.023$).

3. Discussion

In this study we assessed how AGEs, measured by SAF, is related to depressive symptoms and type of depressive symptoms. As hypothesized, we detected an association between AGE levels and depressive symptoms both in men and women. In addition, those with melancholic depressive symptoms had higher AGE levels than those with BDI < 10. Interestingly, we also found that men had both higher AGE levels and comorbidity indexes than women, but lower rates of depressive symptoms. Furthermore, we showed that these findings were consistent when

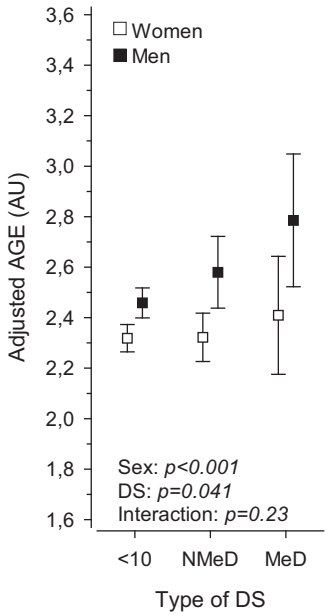

Fig. 1. Advanced Glycation End Products (AGE) in women and men based on type of depressive symptoms (DS) (measured by Beck Depression Inventory [BDI]); no depressive symptoms, non-melancholic depressive symptoms, or melancholic depressive symptoms.
Note. AGE readings are adjusted for age, smoking status, education, economic status, cohabitation status, diabetes mellitus, glycated hemoglobin, body mass index, and leisure-time physical activity. AU = Arbitrary Units. BDI < 10 = no depressive symptoms; NMeD = BDI ≥ 10, non-melancholic depressive symptoms; MeD = BDI ≥ 10, melancholic depressive symptoms. P-values were derived from a two-way analysis of variance of sex and DS in relation to AGEs. Sex = comparison of AGEs by sex; DS (depressive symptoms) = comparison of AGEs by depressive symptoms; Interaction = the interaction term of sex and DS in relation to AGEs.

using either BDI or MHI-5, and that these two measurements of depressive symptoms have a very strong correlation to each other. We also observed a correlation between HbA_{1c} and AGE levels. Overall our SAF readings seem to be comparatively lower than in the Maastricht Study [38]. When comparing our SAF levels to manufacturer reports our values are lower again, but no validation has been made for this specific age group [20]. These results indicate that the type of depression may play a role, but we are still unsure of the etiology of this connection. This leads us to think there may possibly be some confounding factors that still need to be addressed.

The Maastricht Study reported that SAF levels were independently associated with depression, and that SAF levels were associated with both cognitive and somatic depressive symptoms whereas plasma AGEs showed no such association [38]. Our study used an AGE reader by the same manufacturer as in the Maastricht Study [38]. It is known that AGEs can accumulate in a variety of tissues, including the brain and cause neurodegeneration. Research indicates that SAF, rather than plasma AGEs, may better represent AGE accumulation in brain tissue [35], which is the method we have chosen to use for comparison with depressive symptom levels.

We included everything from mild to severe depressive symptoms without distinguishing between degree of severity of these symptoms. With the cut-off for inclusion into the depressive group at ≥10 on the BDI we may have a heterogenous group in regards to severity of symptoms. Symptoms were also self-reported rather than questionnaires being administered by professionals, which may have an effect on reporting of symptoms.

Women were more likely to use antidepressant medication than men in this study. This could possibly have an effect on the current findings.

On the other hand, antidepressant use could also affect the BDI and MHI-5 scores by decreasing the severity of depressive symptoms. It is feasible to speculate whether an association between AGE levels and depressive symptoms could have been seen in women if the effects of antidepressant medications were eliminated.

A Dutch study reported that AGE levels were inversely correlated with memory, but the findings were normalized when controlling for vascular factors and depression [35], implying that these factors influence AGE levels. In the process of AGE formation, collagen and elastin in the arterial walls are targeted for non-enzymatic reactions that cause vascular stiffening [32]. Arterial stiffening in turn has been shown to be associated with depression and depressive symptoms [28].

Considering that AGE formation is accelerated by prolonged hyperglycemia [44], it is surprising that the association we found between HbA_{1c} and AGE levels was not stronger. This may possibly be due to the fact that most of the subjects had normal or fairly well controlled glucose values. Prior research has shown diabetics to have higher SAF levels than those without diabetes mellitus [40]. In the current study men were more likely to have diabetes mellitus, which could possibly contribute to them having higher AGE levels and acting as a confounding factor in this study.

Depression has been associated with higher risk of autoimmune diseases such as lupus, and higher markers of systemic inflammation [30]. Furthermore, melancholic depressive symptoms are associated with low vitamin B12 levels [45]. Vitamin B12 has been shown to have anti-oxidative effects and to potentially reduce the effects of AGEs [37].

AGEs also accumulate as a function of the aging process [15]. Over time as mitochondrial AGEs accumulate they cause increasing damage, leading to a self-perpetuating cycle of more AGE formation and further damage [15]. It has been shown that AGEs, as a reliable prognostic measure for comorbidities, is more notable in younger patients [13]. This raises the question of how age affects reliability of AGE readings in the setting of comorbidities. It may be possible that some effects on AGEs related to depression may be masked by the effect of age on AGE levels. This suggests that there may be differing processes between younger and older subjects in regards to AGEs.

We found that men have higher AGE levels than women, but that women have higher levels of depressive symptoms and antidepressant use. It has been reported that for non-smokers there is no sex difference in SAF levels, but women seem to have more changes in SAF levels in response to factors like smoking [20]. This may indicate that different scales of measurement or different controls should be used for men and women.

One explanation for our findings could be that AGE levels is affected by a variety of other comorbidities than depression alone. SAF levels have shown to be associated with lifestyle factors such as exercise, smoking, sleep, stress, and dietary intake [19,40]. In this study, men were more likely to have a history of smoking compared to women. Such a difference may influence the AGE levels recorded in the current study. This opens up the question whether these differences the present study has found, compared to other research, is related to age, lifestyle or a combination of both. Another possibility is that the Nordic genetics may have some effect on AGE levels.

A potential future direction of study could be to focus on both AGEs, vitamin B12, and systemic inflammatory markers together in relation to depression. Other further research into how, for example, exercise and sleep affects this correlation between AGEs and depression may be warranted, as sleep among other things is one major factor in separating between melancholic and non-melancholic depression. Further information regarding the diet of the subjects may also be of value as this can potentially affect AGEs. Looking at these same factors in a population without diabetics or smokers may be of great value to eliminate confounders. Further research focusing on subjects with more severe types of depressive symptoms, or studies separating the depressive group into further sub-groups of mild, moderate, or severe depressive symptoms may be warranted. Future longitudinal studies focusing on depressive symptoms and AGE levels could be of benefit in determining a causal relationship between the two.

A strength of this study is that, to our best knowledge, there are no other studies looking at AGE levels and depressive symptoms in this age population, giving us a unique insight into how age might affect how we study AGEs. Furthermore, there are limited studies utilizing SAF in the Nordic population. The overall sample size of a group of extensively phenotyped participants is a strength of the current study.

This study has some limitations. Due to the homogenous age-group of subjects the applicability of our findings to subjects of different ages is limited and studies including a wider age range of subjects would be recommended. It is also possible, that due to the advanced age of the participants, we have a biased sample in regard to survival. Individuals of this cohort with severe illnesses may have already died, or been too frail to participate, possibly leaving us with a healthier than average sample of people this age. Furthermore, the study participants were all of European descent and the results may therefore not be generalizable to other populations. The nature of the cross-sectional study with a community sample can be seen as a limitation. The community sample may not be representative of a larger population due to the sample being chosen by convenience and survival from an existing population-based cohort. The very nature of the cross-sectional study makes any interpretation of causality impossible. We are only able to observe relationships and associations at a single point in time, rendering any further interpretations purely speculative. The small size of each group after separating into different types of depressive symptoms could also be a limiting factor not allowing enough power for results to be generalizable to the overall population. Other limitations include the possible confounders previously discussed such as diabetes mellitus, smoking, antidepressant use, and dietary factors.

An increase in AGE levels of 0.024 AU is equivalent to one year of aging [2]. Based on this, we can estimate that the difference in AGE levels between men and women was equal to approximately 6.7 years of aging. Participants with melancholic depressive symptoms had AGE levels that were equivalent to 9.6 years of additional aging compared to those with BDI < 10, the corresponding number for those with non-melancholic depressive symptoms was 2.9 years compared to those with BDI < 10.

Our results indicate that there is a significant correlation between depressive symptoms and AGEs as assessed by SAF, but this connection alone is insufficient as evidence for drawing any conclusions regarding depression based solely on AGE levels. Even though this study shows a significant correlation between AGEs and depressive symptoms it is impossible to infer directionality, causality, or effect. Our findings suggest that AGEs are part of a multifactorial process that has correlations with many diseases and we have barely scratched the surface of understanding these complex connections.

4. Conclusion

Higher AGE levels were found in men as well as in individuals with melancholic depressive symptoms. Furthermore, there is in fact a significant association between AGEs and depressive symptoms, but no directionality, causality, or effect can be inferred solely based on the results of this study.

Disclosures

Nothing to disclose.

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