Advanced Glycation End Products in Recent-Onset Psychosis Indicate Early Onset of Cardiovascular Risk

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ABSTRACT

Objective: Profoundly increased mortality rates in schizophrenia, largely caused by a higher risk and earlier onset of cardiovascular disease, remain a major challenge. During the human lifespan, advanced glycation end products (AGEs) accumulate, and their concentration is strongly linked to cardiovascular mortality. AGE accumulation can be accelerated by several pathways, including oxidative stress.

Methods: From March 2015 through January 2016, a case-control study including 111 patients with a recent-onset psychosis, 135 controls from a validation cohort, and 286 healthy controls was performed. Patients fulfilled the *DSM-IV* criteria for schizophrenia spectrum disorders with an illness duration shorter than 5 years. Main outcome parameters were skin autofluorescence levels of AGEs, controlled for age, gender, and smoking. Correlations of AGEs with cardiovascular risk factors and clinical variables were analyzed by hierarchical linear regression analyses.

Results: An AGE measurement was possible in 77.4% of cases. AGEs were elevated by 15.1% in recent-onset psychosis compared to healthy controls ($P < .001$), corresponding to an increased accumulation of AGEs normally occurring in approximately 10 years. AGEs were not related to traditional risk factors. However, duration of illness ($P = .008$), duration of antipsychotic treatment ($P = .009$), and cumulative exposure to antipsychotics ($P = .023$) correlated with AGEs.

Conclusions: Patients with a recent onset of psychosis have increased AGE levels compared to healthy controls. These findings argue for an earlier implementation of treatment strategies aimed at preventing cardiovascular disease. Also, low-dose strategies of antipsychotics in schizophrenia could beneficially influence AGE levels.

J Clin Psychiatry 2017;78(9):1395–1401
https://doi.org/10.4088/JCP.16m10972

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Despite decades of progress in health care, a mortality gap of 20 to 25 years remains in patients suffering from severe mental illness, such as schizophrenia or bipolar disorder, compared to the general population.[1,2] Approximately 60% of these premature deaths are due to natural causes,[1,2] whereby cardiovascular disease (CVD) is a major contributor.[3] The progress in cardiovascular disease management seems to have somehow bypassed patients suffering from severe mental illness,[3] resulting in an increase in the mortality gap in the past decades.[4] It is likely that the estimated cardiovascular risk for patients with severe mental illness is underestimated by most large prospective studies of the general population, which are used to determine when (pharmacologic) treatment to prevent cardiovascular morbidity and mortality must be started.[5]

Although lifestyle factors and medication use associated with metabolic side effects are clearly related to the increased risk of cardiovascular and metabolic diseases,[6,7] the vulnerability to these diseases in schizophrenia has been implicated as an intrinsic characteristic of the disorder.[8,9] In psychotic disorders, insulin resistance seems to occur at a younger age[10] and has been shown to be already present in treatment-naive patients.[11] Apart from this, evidence for redox dysregulation with an aberrant response to oxidative stress has been shown in psychotic disorders.[12] Both metabolic dysfunctions are strongly related to cardiovascular diseases[13] and could account for this elevated risk in schizophrenia.[14–17]

The same metabolic pathways are important for formation of advanced glycation end products (AGEs).[18] AGEs are formed by nonenzymatic glycation and oxidation of proteins and lipids.[18] The extent of oxidative stress is an important factor in AGE formation.[18] Increased AGE formation has been associated with the progression of age-related diseases such as atherosclerosis,[19] diabetes,[20] and chronic renal failure.[21] Serum concentration of AGEs has been associated with vascular damage[22] and increased cardiovascular mortality in older adults.[23,24] Due to a seemingly linear relation between skin AGE concentration and age,[25,26] increased AGE concentration may serve as a marker of premature aging.

It is now possible to reliably measure the concentration of AGEs noninvasively by means of skin autofluorescence (AF).[27–30] Skin AF strongly correlates with collagen-linked fluorescence, a widely used method to determine AGE levels in skin biopsies, gas chromatography, and mass spectrometry measurements of the AGEs pentosidine, carboxymethyllysine, and carboxyethyllysine.[29,30] Skin AF has been proposed as a marker for the total skin AGE pool[29] and an indicator of oxidative stress.[27] AGE levels as measured through AF positively correlate with levels of C-reactive protein, an indicator of oxidative stress–derived inflammation,[31,32] and are inversely related to vitamin C levels, a well-known antioxidant, in vascular diseases.[31] Interestingly, an increased AGE concentration was demonstrated in 55 subjects with chronic schizophrenia compared to 55 healthy controls, matched for

age, gender, and smoking status.[33] It is, however, unknown whether AGEs are already elevated in earlier phases of the disorder.

The aim of the study described in the current article is to investigate the concentration of AGEs in patients suffering from recent-onset psychosis compared to healthy controls. If increased AGE accumulation can be demonstrated in patients with recent-onset psychosis, such accumulation could be an indication that cardiovascular risk is already increased in this population before the influence of treatment and chronicity factors transpire.

Clinical Points

- Cardiovascular disease is a major contributor to premature death in schizophrenia, and the current preventive treatment strategies are insufficient in this population.
- Elevated levels of advanced glycation end products in recent-onset psychosis are an early sign of increased cardiovascular risk, indicating that early introduction of preventive treatment is warranted.
- Low-dose strategies of antipsychotics might be beneficial with respect to cardiovascular risk in psychosis.

METHODS

From March 2015 through January 2016, a cross-sectional case-control study was performed in inpatient and outpatient treatment settings at the Department of Early Psychosis of the Academic Medical Centre in Amsterdam and the Early Intervention Psychosis Services of Arkin in Amsterdam, The Netherlands. Included were patients aged 18–45 years, of diverse ethnicities, diagnosed with schizophrenia, schizoaffective disorder, schizophreniform disorder, or a nonaffective psychotic disorder not otherwise specified (*DSM-IV*). Recent-onset psychosis was defined as a psychotic episode having first occurred no more than 5 years prior to inclusion. Patients suffering from a neurologic disorder or with a glomerular filtration rate below 60 mL/min/1.73 m^2 were excluded, the latter because decreased renal clearance can cause elevated AGE levels.[34]

A skin AF measurement using the AGE Reader[29] (Diagnoptics, Groningen, The Netherlands) was performed on the inner side of the subject's dominant forearm on healthy, undamaged skin without blemishes and not exposed to skin creams. The mean of 3 consecutive measurements was used for statistical analyses according to protocol, even though the test-retest reliability was very high (intraclass correlation coefficient = 0.97).

Consecutively, a conventional cardiovascular risk assessment was performed following national guidelines,[35,36] collecting the following variables: age, gender, body mass index (BMI), waist circumference, blood pressure, smoking habits and lifetime cumulative tobacco exposure[37] expressed in pack years (the product of smoking rate in cigarette packs per day and duration of tobacco use in years), level of physical activity (insufficient physical activity was defined as < 30 minutes of physical activity < 5 days per week[35]), familial risk of CVD (defined as ≥ 1 first-degree relative with CVD < 65 years[35]), family history of psychosis, comorbidities, and current medication use. When available, blood glucose levels, blood lipid spectrum levels, and (estimated) glomerular filtration rate tested within 6 months prior to or after inclusion were retrieved from the subject's medical file, as well as information on duration of illness, duration of untreated psychosis, current medication use, and time since introduction of antipsychotics. Cumulative exposure to antipsychotic treatment in patients was estimated by multiplying the time since introduction in years by the current dosage of antipsychotics in chlorpromazine equivalents.[38] Cumulative exposure was expressed in dose years, with 1 dose year corresponding to a daily intake of 300 mg chlorpromazine during 1 year. The presence of atherogenic dyslipidemia was defined as a triglyceride level ≥ 150 mg/dL and/or an HDL level < 40 mg/dL in males or < 50 mg/dL in females.[36] An impaired fasting glucose was defined as a glucose level ≥ 110 mg/dL.[36] The presence of metabolic syndrome was evaluated following the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) guidelines.[36]

Individual reference skin AF values from a healthy white population (n = 135) used for validation of the AGE Reader were provided by the manufacturer of the AGE Reader,[25] and age, gender, and smoking parameters were provided; this group will be referred to as the validation cohort. An additional, independent control group was obtained through conducting skin AF measurements and cardiovascular risk assessment in a group of healthy medical students of different ethnicities from the University of Amsterdam (n = 286); this group will be referred to as the Amsterdam control cohort.

Data were analyzed using SPSS version 22.[39] Outliers were identified using a scatterplot. Within-group and between-group comparisons of characteristics were conducted using an unpaired *t* test for continuous data and a Fisher exact test for dichotomous data. Possible confounding of AGE concentration by demographic characteristics or the examined risk factors for CVD was investigated in patients and the Amsterdam control cohort using hierarchical linear regression analyses controlling for age and gender. A Bonferroni correction was applied to control for the number of variables tested.

A hierarchical multiple regression analysis was used to investigate the difference in AGE levels between patients and the provided validation cohort, controlling for age, gender, and smoking habits. A 2-sided α was used at .05. A second model was created to recalculate the difference in AGE levels between patients and the Amsterdam cohort, while correcting for age, gender, and any confounders revealed by the previous analyses. Finally, the correlation of disorder-related characteristics with AGE levels was examined in hierarchical regression analyses, controlling for age, gender, and any possible confounders that showed a trend-wise correlation ($P < .10$).

For all analyses, bootstrapping with 5,000 samples was performed to ensure a normal distribution of residuals. Outcomes were reported with a bias-corrected accelerated confidence interval,[40] adjusting for both bias and skewness in the bootstrap distribution.

Table 1. Summary of Subject Characteristics

Characteristic	Patients' AGE Measurement			Amsterdam Cohort's AGE Measurement			
	Available (n = 86)	Not Available (n = 25)	*P* Value[a,b]	Available (n = 271)	Not Available (n = 15)	*P* Value[a,b]	*P* Value[b,c]
Demographic							
Men, n (%)	66 (76.7)	19 (76.0)	1	84 (31.0)	3 (20.0)	.565	**<.001**
Age, mean (SD), y	26.0 (5.7)	26.4 (5.8)	.749	20.4 (1.6)	21.5 (2.0)	**.012**	**<.001**
Western ethnicity, n (%)	45 (52.3)	0.0 (0.0)	**<.001**	238 (87.8)	0 (0.0)	**<.001**	**<.001**
Duration of illness, mean (SD), y	2.1 (1.4)	3.1 (1.3)	**.010**	…	…	…	…
Duration of untreated psychosis, mean (SD), y	0.6 (0.9)	0.7 (0.9)	.805	…	…	…	…
Time since introduction of AP, mean (SD), y	1.5 (1.3)	2.1 (1.5)	.081	…	…	…	…
Cumulative exposure to AP, mean (SD), dose y[d]	1.7 (1.7)	2.5 (2.5)	.104	…	…	…	…
Cardiovascular risk factor							
History of smoking, n/N (%)	64/85 (75.3)	21/25 (84.0)	.428	53/271 (19.6)	3/15 (20.0)	1	**<.001**
Currently smoking, n/N (%)	52/86 (60.5)	21/25 (84.0)	.204	42/271 (15.5)	3/15 (20.0)	.728	**<.001**
Cumulative tobacco exposure, mean (SD), pack y	4.2 (5.2)	3.6 (4.1)	.598	0.2 (0.6)	0.7 (1.8)	.239	**<.001**
BMI, mean (SD), kg/m^2	24.8 (4.1)	28.4 (7.1)	**.025**	21.7 (2.4)	21.8 (2.8)	.921	**<.001**
Waist circumference, mean (SD), cm	91.9 (12.0)	95.9 (16.7)	.187	79.3 (8.1)	79.1 (13.1)	.962	**<.001**
Metabolic syndrome, n/N (%)	3/82 (3.7)	3/23 (13.0)	.118	0/264 (0.0)	0/10 (0.0)	…	**<.001**
Insufficient physical activity, n/N (%)	48/86 (55.8)	15/25 (60.0)	.820	138/251 (55.0)	10/13 (76.9)	.156	.910
Family history of psychosis, n/N (%)	23/67 (34.3)	9/22 (40.9)	.805	21/267 (7.9)	0/15 (0.0)	.318	**<.001**
Atherogenic dyslipidemia, n/N (%)	22/58 (37.9)	7/16 (43.8)	.775	…	…	…	…
Abnormal fasting glucose, n/N (%)	1/56 (1.8)	2/18 (11.1)	.133	…	…	…	…
Familial risk of CVD, n/N (%)	9/85 (10.6)	4/24 (16.7)	.477	…	…	…	…
CVD in medical history, n/N (%)	0/86 (0.0)	0/25 (0.0)	…	…	…	…	…
Diagnosis							
Schizophrenia, n (%)	49 (57.0)	18 (72.0)	.109	…	…	…	…
Schizophreniform disorder, n (%)	9 (10.5)	0 (0.0)	.451	…	…	…	…
Schizoaffective disorder, n (%)	8 (9.3)	3 (12.0)	1	…	…	…	…
Psychosis NOS, n (%)	20 (23.3)	4 (16.0)	.427	…	…	…	…

[a]Within-group comparison of characteristics of subjects with and without an available AGE measurement.
[b]Significant *P* values are shown in bold.
[c]Between-groups comparison of characteristics of patients and the Amsterdam Cohort.
[d]One dose year equals a daily intake of 300 mg chlorpromazine equivalents during 1 year.
Abbreviations: AGE = advanced glycation end product, AP = antipsychotics, BMI = body mass index, CVD = cardiovascular disease, NOS = not otherwise specified.
Symbol: … = not applicable.

The Medical Ethics Committee of the Academic Medical Centre, Amsterdam, approved this study and judged that it did not fall within the scope of the Medical Research Human Subjects Act.

RESULTS

One hundred twelve patients (76.8% male) suffering from recent-onset psychosis were eligible for inclusion. One case was identified as an outlier (skin AF > 99th percentile) and excluded from further analyses. Age varied from 18 to 43 years with a mean of 26.1 years and a median of 25 years. Mean duration of illness was 2.2 years (range, 0.1–5.0 years). Mean duration of antipsychotic treatment was 1.6 years (range, 0.0–4.9 years) with a cumulative exposure to antipsychotics of 1.9 dose years (range, 0.0–8.3 dose years). Four patients had not been exposed to antipsychotics. Of all subjects, 58.3% were of non-Western origin, with most subjects originating from Morocco (15.4%), Surinam (14.4%), or Turkey (6.7%).

There were no cases of established kidney failure, diabetes mellitus, or a history of CVD. Atherogenic dyslipidemia was present in 39.2% of the cases in which recent lipid spectrum levels were available. In 3 cases, an increased fasting glucose level was found. Demographic characteristics or cardiovascular risk factors in patients with complete blood results available did not significantly differ from those with absent or incomplete results. In 25 patients (22.5%), all of non-Western origin, an AGE measurement was not possible due to a dark skin color. BMI of these patients was significantly higher (28.4 vs 24.8 kg/m^2; $P < .05$) and duration of illness was significantly longer (3.1 vs 2.1 years; $P < .05$) than in the other cases, as shown by an independent samples *t* test.

Table 2. AGE Levels in Arbitrary Units[a]

Age Group	Patients		Validation Cohort		Amsterdam Cohort	
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n
18–21 y	1.62 (0.34)	17	1.30 (0.16)	22	1.37 (0.20)	216
22–25 y	1.69 (0.26)	32	1.51 (0.25)	22	1.50 (0.30)	51
26–29 y	1.77 (0.25)	18	1.62 (0.26)	18	1.39 (0.11)	4
30+ y	1.99 (0.37)	19	1.73 (0.34)	73	…	…

[a]Skin autofluorescence is calculated by dividing the amount of emitted light intensity (from 50 individual scans, each 200 ms) between 420 and 600 nm by the amount of excitation light intensity between 300 and 420 nm, expressed as arbitrary units in order to correct for differences in light absorption.
Abbreviation: AGE = advanced glycation end product.
Symbol: … = not applicable.

Two hundred eighty-six students were included in the Amsterdam control cohort, with mean age 20.5 years (range, 18–29 years). In 15 controls (5.2%), an AGE measurement was not possible due to a dark skin color. Characteristics of patients and controls are shown in Table 1. Results in Table 1 are presented separately for subjects in whom an AGE measurement was possible and for those in whom this was not. AGE levels per age group are shown in Table 2.

Table 3. Correlations of Possible Confounders With Skin Autofluorescence, Corrected for Age and Gender

	Patients			Amsterdam Cohort		
Variable	B	95% CI	*P* Value[a]	B	95% CI	*P* Value[a]
Ethnicity (0 = Western, 1 = mixed-descent, 2 = non-Western)	0.117	0.053 to 0.179	**<.001**	0.132	0.075 to 0.196	**<.001**
Familial risk of CVD (0 = no, 1 = yes)	0.286	0.033 to 0.568	**.034**	…	…	…
Metabolic syndrome (0 = no, 1 = yes)	0.217	−0.231 to 0.630	.338	…	…	…
Smoking habits (0 = never, 1 = ever)	−0.033	−0.172 to 0.107	.631	0.000	−0.054 to 0.008	.242
Cumulative tobacco exposure in pack years	−0.005	−0.027 to 0.019	.696	−0.031	−0.082 to 0.040	.263
Level of physical activity (0 ≥ 30 min > 5 d/wk, 1 ≤ 30 min < 5 d/wk, 2 = sedentary lifestyle)	−0.021	−0.147 to 0.105	.737	0.025	−0.029 to 0.080	.362
Family history of psychosis (0 = no, 1 = yes)	0.023	−0.131 to 0.165	.767	0.041	−0.047 to 0.136	.370
BMI in kg/m^2	0.000	−0.012 to 0.027	.850	−0.004	−0.017 to 0.008	.479

[a]Significant *P* values (at Bonferroni-corrected level) are shown in bold.
Abbreviations: BMI = body mass index, CVD = cardiovascular disease.
Symbol: … = not applicable.

Table 4. Correlations of Disease-Related Characteristics in Patients, Corrected for Age, Gender, Ethnicity, and Premature CVD in Family History

Variable	B	95% CI	*P* Value[a]
Duration of illness in years	0.084	0.036 to 0.127	.008
Duration of untreated psychosis in years	0.044	−0.041 to 0.123	.296
Time since introduction of AP in years	0.081	0.027 to 0.133	.009
Cumulative exposure to AP in dose years	0.053	0.012 to 0.095	.023

Abbreviations: AP = antipsychotics, CVD = cardiovascular disease.

Correlations of possible confounders and AGE levels, corrected for age and gender, are shown in Table 3. Ethnicity showed a significant correlation with AGE levels in both subjects and controls ($P < .001$). For the correlation of familial risk of CVD with AGE levels in patients, a trend toward statistical significance was seen. No other cardiovascular risk factors statistically correlated with AGE levels in patients or controls.

A hierarchical linear regression analysis showed that the AGE concentration in patients suffering from recent-onset psychosis was increased by 15.1% (intercept = 1.46; B = 0.222 [95% CI, 0.136–0.305]; $P < .001$) compared to the validation cohort, controlled for age, gender, and smoking habits. Smoking habits did not significantly influence AGE levels ($P = .772$), while age did (B = 0.021 [95% CI, 0.015–0.027]; $P < .001$). AGE levels in males were elevated by 6.1% compared to females (B = 0.089 [95% CI, 0.012–0.167]; $P < .05$). Repeating the regression analysis in patients compared to the Amsterdam control cohort, enabling us to correct for age, gender, and ethnicity, confirmed significantly increased AGE levels in patients compared to healthy controls (intercept = 1.51; B = 0.158 [95% CI, 0.067–0.249]; $P < .001$), rendering a difference of 10.4%.

Duration of illness, time since introduction of antipsychotics, and cumulative exposure to antipsychotics significantly correlated with AGE levels (B = 0.084 [95% CI, 0.036–0.127], $P = .008$; B = 0.081 [95% CI, 0.027–0.133], $P = .009$; and B = 0.053 [95% CI, 0.012–0.095], $P = .023$, respectively) corrected for age, gender, ethnicity, and familial risk of CVD, while duration of untreated psychosis did not ($P = .296$) (Table 4). However, significance of the correlations faded after Bonferroni correction for multiple comparisons ($P = .004$).

DISCUSSION

In our sample of patients with recent-onset psychosis, skin AGE levels were elevated by 15.1% in patients compared to the validation cohort and by 10.4% compared to healthy controls. Extrapolating these results by comparing them to the average age-dependent increase of AGEs, the impact of these results becomes apparent: the difference in AGEs between patients and both control groups corresponds to an increased accumulation of AGEs that would be expected to occur in over 10 years of aging.

The finding that AGE levels are increased in patients suffering from recent-onset psychosis is consistent with previous reports on skin AGE levels in chronic schizophrenic patients[33] and plasma pentosidine measurements in schizophrenia patients compared to healthy controls.[15,41,42] An elevation of AGEs has been shown to predict cardiovascular morbidity in diabetes independent of known risk factors such as HbA_{1c}, a measure of glycemic control.[43] As alongside glycation, oxidation has been shown to be a key contributor to AGE accumulation,[18] oxidative stress seems to be an important factor contributing to AGE accumulation and thereby increased cardiovascular risk. Oxidative stress has been implicated as a causative factor not only in increased cardiovascular risk,[14] but also in disturbance of brain development and neurotransmission in schizophrenia.[15,44] Although to our knowledge no studies have yet examined an association of AGE accumulation and brain structure or functioning in patients with psychiatric disorders, increased AGEs were found to be associated with decreased gray matter volumes and cognitive decline in type 2 diabetes.[45]

In an earlier study in older patients with schizophrenia (N = 55, mean age = 43.07 years), the AGE concentration was found to be 29.5% higher compared to that in 55 healthy, age- and gender-matched controls.[33] When the same extrapolation

as mentioned previously was applied, this finding corresponds to an increased accumulation of AGEs that would normally build up over approximately 25 years. This estimation is strikingly consistent with the decrease in life expectancy seen in severe mental illness compared to the general population.[1,2] This increasing divergence of AGE levels between patients and healthy controls in chronic schizophrenia compared to recent-onset psychosis could imply that, in addition to the elevated concentration of AGEs in the first phase of the disorder, the accumulation rate of AGEs further increases over the course of the disorder.

In accordance with international guidelines,[35,46] no patients in our cohort were eligible for preventive treatment due to their young age. Although, according to international prospective studies, subjects below the age of 50 years are considered to have a low absolute cardiovascular risk,[46] increased AGE accumulation in young patients suffering from psychosis might indicate a relatively high risk for this specific population. The current results underline the need for an adjusted preventive treatment strategy in patients with psychotic disorder,[13] aiming to address an increased cardiovascular risk in this vulnerable population at an earlier age.

Confounders

The elevated AGE levels seemed to be uninfluenced by traditional cardiovascular risk factors. Even though in literature tobacco smoking has been recognized as an exogenous source of AGEs[47] and a confounder for skin AGE concentration in chronic schizophrenia,[33] current results show no correlation of AGE levels with tobacco smoking. Possibly, this is due to the young age of our cohort and the relatively short time of exposure to tobacco smoking. A previously described association of lipid values and AGE levels[48] is also absent in this sample.

The current results do however imply that AGE accumulation in recent-onset psychosis could be affected by cumulative exposure to antipsychotic treatment. Fading of the correlation of duration of illness and AGE concentration after correction for exposure to antipsychotics also points in this direction, although it is hard to distinguish between these 2 factors. In recent literature, antipsychotic medication has been identified as a possible confounder for oxidative stress in schizophrenia.[15] Antipsychotic treatment has been linked to increased oxidative stress in animal studies,[49–52] although literature is still inconclusive.[53–55] Also, antipsychotics are known to negatively influence cardiometabolic risk factors, such as insulin sensitivity.[56,57]

Kouidrat et al[33] report no effect of current antipsychotic treatment dose on skin AGE concentrations in chronic schizophrenia; neither does a post hoc analysis of current dosage in our cohort show any effect ($P = .813$). However, we have evaluated cumulative antipsychotic exposure, rendering a more reliable estimate of its effect over the years. Cumulative exposure to antipsychotics has previously been shown to have stronger correlations to deleterious effects on brain volume.[58–60] The current results are in line with other findings that antipsychotics could be a double-edged sword in treating psychosis.[61] However, the fact that increased serum markers of oxidative stress have been found in treated as well as treatment-naive patients with schizophrenia,[62] together with findings of gene variants in schizophrenia that increase oxidative stress response,[63] suggests that oxidative stress is not solely mediated by the use of antipsychotics.[49] Nevertheless, low-dose strategies of antipsychotics might be beneficial in the cardiovascular risk profile of individuals with schizophrenia.

Because increased cardiovascular risk is even more prevalent in ethnic minorities,[64–67] we included not only white but also non-Western subjects. AGE concentration in non-Western subjects was significantly increased compared to that in Western subjects, a finding that is supported by literature on racial differences in inflammation susceptibility.[68,69] The patient group had more subjects of non-Western ethnicity compared to the independent control group. After correction for ethnicity was made, significantly increased AGE levels in patients suffering from early psychosis remained.

To our knowledge, a correlation between AGE levels and a familial risk of CVD as suggested by the current study results has not previously been described. Recent findings do suggest the possibility of overlapping genetic contributors to cardiometabolic disorders and psychosis.[70,71] Two cross-sectional studies have shown an association of increased oxidative stress and a family history of psychosis,[72,73] although AGEs were not related to family history of psychosis in our cohort.

Limitations

Even though skin AGE measurements have been validated on subjects of various skin color,[74] the provided validation skin AF values were conducted from an all-white population.[29] Even though ethnicity was controlled for in the final analysis, the inclusion of subjects with darker skin tones could in theory have affected our results. However, when the analysis was repeated with white patients only, significantly increased AGE levels compared to the reference values remained ($P = .013$). Furthermore, the AGE Reader indicates when a reliable measurement cannot be conducted due to a dark skin color. This occurred in 22.5% of the subjects. These subjects differed from the remaining group in BMI and duration of illness. BMI did not significantly influence AGE levels. For duration of illness, a trend-wise, positive correlation with AGE concentration was shown, suggesting that AGE concentrations might be even further elevated in this group. Hopefully, in the future, the inability to measure AGE levels in subjects with a dark skin color can be overcome by advances in skin AF techniques.

Secondly, the Amsterdam control cohort differed from the patients in demographic characteristics and the prevalence of cardiovascular risk factors. According to our analyses, the latter does not influence AGE levels, and, therefore, it is unlikely that our results were confounded by such differences. However, age and gender are known to affect AGE concentration,[25] and ethnicity was recognized

as a confounder. Even though these factors were corrected for in our analysis of AGE levels in patients compared to healthy controls, it cannot be excluded that differences between groups could have influenced our results. However, the similarities in magnitude and significance of increase of AGE levels in cases compared with both control cohorts together with findings in previous studies[15] support the validity of our findings.

Finally, although we studied a moderate-sized sample, the strength of some analyses was compromised due to missing data. Recent blood laboratory results were not available in all cases. Cumulative exposure to antipsychotics as calculated in this study remains an estimate. Ideally, consideration of any (temporary) cessation or dosage alterations of antipsychotic treatment would give even more insight into the effect of antipsychotic treatment on AGE levels. Furthermore, the correlations found of AGEs with duration of medication use or psychosis should be interpreted with caution since they did not survive the Bonferroni correction for multiple comparisons and because of the cross-sectional nature of this study.

Autofluorescence Measurements in Clinical Practice

Conversely, being able to assess cardiovascular risk through AF while bypassing a venipuncture could be an advantage in the studied population, in which routine blood tests are not always easy to realize. Moreover, an AGE measurement might serve as a tool to help determine the need for more invasive screening methods. With several studies indicating that serum AGE and skin AGE concentrations are predictive of vascular damage and cardiovascular mortality in (diabetic and nondiabetic) populations,[22,32,75] a favorable AGE level could validate a more lenient approach, while an elevated AGE level might advocate a stricter blood-testing scheme.

CONCLUSIONS

In patients suffering from recent-onset psychosis, elevated AGE concentrations based on skin AF measurements were found, corresponding to an increase of AGE levels normally occurring in 10 years of physiological aging. Future research is needed to further investigate the processes that underlie increased accumulation of AGEs in schizophrenia in order to unveil possible targets for clinical intervention.

The results of this study emphasize the urgency to address increased cardiovascular risk through introduction of preventive treatment in this vulnerable population at an earlier age.

Submitted: May 24, 2016; accepted September 1, 2016.

Online first: April 25, 2017.

Potential conflicts of interest: All authors declare no conflict of interest.

Funding/support: None.

Previous presentation: Poster presented at the 5th Biennial Schizophrenia International Research Society conference; April 2–6, 2016; Florence, Italy.

Acknowledgments: We thank Michiel Kregel, PhD, for providing reference skin autofluorescence values, which enabled a thorough comparison between patients and a healthy population. Dr Kregel serves as operations manager at Diagnoptics B.V. Also, we express our gratitude to all patients and controls for taking the time to participate in this project.

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