Accumulation rate of advanced glycation end products in recent onset psychosis: A longitudinal study

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ARTICLE INFO

Keywords:
Cardiovascular diseases
Metabolic syndrome
Oxidative stress
Psychotic disorders
Schizophrenia
Premature aging

ABSTRACT

Schizophrenia is associated with excessive oxidative stress. Production of advanced glycation end products (AGEs) in the skin is strongly associated with oxidative stress. Increased skin AGE-levels have been demonstrated at cross-sectional level in recent onset psychosis and chronic schizophrenia, indicating increased cardiovascular risk. We aimed to investigate factors underlying AGE-accumulation and accumulation rate of AGEs in recent onset psychosis. From December 2016 through May 2017, 66 patients and 160 (highly educated) healthy controls from a previous case-control study of AGE-levels were assessed for a follow-up measurement 12–24 months after baseline. Possible determinants of AGE-accumulation were analyzed. AGE-accumulation rates in patients and controls were compared adjusted for relevant confounders. In healthy controls, a significant association of AGE-accumulation with ethnicity and tobacco exposure was found. An indication of a markedly higher AGE-accumulation rate was found in patients suffering from recent onset psychosis compared to healthy controls, independent of ethnicity and tobacco smoking, but not independent of cannabis use (more prevalent in patients than controls), although results were not significant.

1. Introduction

Over the past decades, life expectancy in people suffering from mental illnesses has remained severely reduced (Plana-Ripoll et al., 2020), mainly due to natural causes (Erlangen et al., 2017). In schizophrenia, the contribution to premature death from cardiovascular disease (CVD) has increased over the years (Tanskanen et al., 2018). This increased vulnerability to CVD may be associated with etiological factors of psychotic disorders (Harris et al., 2013). Therefore, it is important to investigate common denominators for psychiatric illness and increased CVD risk (Bahorik et al., 2017; Baune et al., 2012; Khandaker et al., 2015; Shimbo et al., 2005). The wide variety of pathways leading to an increased vulnerability to CVD and other age-related diseases in schizophrenia has been compiled in the concept of accelerated aging (Kirkpatrick et al., 2008), a topic that has been the subject of great interest in psychosis research (Kirkpatrick and Kennedy, 2018; Nguyen et al., 2018). Inflammation and oxidative stress are thought to be important pathways driving accelerated aging (Okusaga, 2014) and are widely considered to contribute to both the development of psychiatric disorders, including schizophrenia (Assies et al., 2014; Flatoe et al., 2013; Fournier et al., 2014; Ng et al., 2008; Slavich and Irwin, 2014), and of CVD (de Almeida et al., 2020; Finkel and Holbrook, 2000; Willerson and Ridker, 2004).

Investigating oxidative stress throughout the course of schizophrenia is therefore necessary. However, measuring oxidative stress is methodologically challenging, due to the short half-life or low concentration in biological samples of several biomarkers (Marrocco et al., 2017; Strobel et al., 2011). One validated approach is measuring the concentration of advanced glycation end products (AGEs) in the skin (Mulder et al., 2006). AGEs are formed by non-enzymatic glycation and oxidation of proteins and lipids –a process strongly associated with oxidative stress (Goldin et al., 2006; Vistoli et al., 2013). Serum AGE-levels have been linked to CVD in populations with (Kiuchi et al., 2001; Nin et al., 2010) or without diabetes (Kizer et al., 2014; Semb et al., 2009) and to the progression of several age-related diseases (Miyata et al., 1997; Stitt et al., 1997; Yan et al., 2003). AGEs bind irreversibly to collagen, thereby accumulating in the skin, where their concentration is an indicator of cumulative oxidative stress (Mulder et al., 2006). In the skin, increased AGE-levels could serve as a measure of accelerated aging, knowing that skin AGE-levels show a
linear association with calendar age in healthy individuals (Koetsier et al., 2010; Na et al., 2001). Skin AGE-levels have been linked to CVD morbidity and mortality in different high risk groups (Meerwaldt et al., 2005, 2007; Mulder et al., 2009) and in the general population (van Waeringe et al., 2019).

Increased skin AGE-levels compared to healthy controls have been demonstrated at cross-sectional level in chronic schizophrenia (Kouidrat et al., 2013) and in recent onset psychosis (Hagen et al., 2017). It is thought that these findings reflect both an increased CVD risk and chronically elevated oxidative stress in this population. In these cross-sectional studies, ethnicity, antipsychotic medication, a family history of CVD (Hagen et al., 2017), and tobacco smoking (Kouidrat et al., 2013) have been suggested to influence AGE-levels. However, the increased AGE levels in psychosis could not be fully explained by these factors. The mechanisms driving the increased AGE-formation in psychotic disorders remain to be clarified (Nguyen et al., 2018). Furthermore, it is unknown whether increased AGE-levels in psychotic disorders only originate from the premorbid phase or whether formation rate of AGEs remains elevated throughout the course of the disorder.

We performed a longitudinal cohort study, aimed to elucidate the accumulation rate of AGEs in patients suffering from recent onset psychosis versus healthy controls corrected for several possible confounders. We hypothesized that AGE-accumulation is increased in patients compared to controls. We aimed to elucidate factors associated with accumulation of AGEs, whilst distinguishing between 1) general subject characteristics, such as ethnicity, smoking behavior and metabolic parameters; and 2) disorder-specific factors, such as number or duration of psychotic episodes or exposure to antipsychotic medication. If confounders fail to entirely explain increased AGE-accumulation in recent onset psychosis, the presence of increased oxidative stress in psychotic disorders, potentially explaining its link with CVD, should be considered.

2. Methods

2.1. Participants and procedure

In a longitudinal observational study, patients and healthy controls who had previously participated in a cross-sectional study of AGE levels in recent onset psychosis (Hagen et al., 2017) were invited for a follow-up measurement 12–24 months after baseline measurement. Patients were inpatients from the Department of Early Psychiatry of the Amsterdam UMC (location AMC) and outpatients from the Early Intervention Psychiatry Services of Arkin, both situated in Amsterdam, who fulfilled DSM-5 criteria for a recent onset schizophrenia spectrum disorder or bipolar I disorder with recent onset psychotic symptoms. Recent onset was defined as occurrence of a first psychotic episode no more than 5 years prior to inclusion at baseline. Exclusion criteria were a substance-induced psychosis or a medical history of a neurologic disorder, because of expected etiological differences with primary psychotic disorders, or a glomerular filtration rate below 60 mL/min/1.73 m², because decreased renal clearance can cause elevated AGE levels (Stam et al., 2006). Medical students from the University of Amsterdam were recruited as healthy controls during class. Participation was entirely voluntary. Exclusion criteria for healthy controls were a diagnosis of any DSM-5 disorder, as reported in a self-administered questionnaire. All participants were 18 years or older at baseline and gave informed consent after the nature of the study had been fully explained. The Institutional Review Board of the Amsterdam University Medical centre approved this study and judged that it did not fall within the scope of the Medical Research Human Subjects Act (protocol numbers W15_070#16.183 and W15_305#16.184).

Similar to the baseline measurement (Hagen et al., 2017), for the follow-up measurement, all participants were subjected to three consecutive skin autofluorescence measurements (intraclass correlation coefficient for absolute agreement was 0.906) using a calibrated AGE-reader (Meerwaldt et al., 2004) (Diagnoptics, Groningen, the Netherlands) and a CVD risk assessment including an interviewer-assisted questionnaire, compiling the evaluation of body mass index (BMI), waist circumference, blood pressure, cumulative tobacco exposure since first assessment, level of physical activity, and familial risk of CVD (defined as ≥1 first-degree relative with CVD, onset before the age of 65). Family history of psychosis, and comorbidities were also evaluated. Autofluorescence measurements were conducted from the volar side of the dominant forearm. If an AGE-measurement could not be conducted accurately due to a low UV-reflectance of the skin, this was indicated by the AGE-reader and no measurement was provided. AGE-accumulation rate was calculated as the mean increase in skin AGE-level in arbitrary units (AU) divided by the duration of follow-up in months. In patients, glucose and lipid spectrum levels measured up to 6 months prior to or after follow-up measurement were retrieved from the medical file if available. Criteria for metabolic syndrome were evaluated following the National Cholesterol Education Program Adult Treatment Panel III guidelines (NCEP-ATP-III, 2002). Exposure to antipsychotic medication was calculated as the product of the prescribed dosage and duration of use according to the medical file and issued prescriptions by the patient's pharmacy. Exposure per month was expressed in a factor of a mean daily dosage of 100 mg chlorpromazine equivalents (Gardner et al., 2010). Information regarding number of psychotic episodes, remission in between episodes and admission to a psychiatric ward between baseline and follow-up was obtained from the patients' medical file and verified with the patient's physician. Course of the disease was categorized as “single episode, followed by complete remission”, “≥1 episodes, with complete remission between episodes”, “≥1 episodes, followed by partial remission” and “chronically ill”, based on descriptions by Ram and by Wiersma (Ram et al., 1992; Wiersma et al., 1998).

2.2. Statistical analyses

Statistical analysis was performed using SPSS 22 (IBM, 2013). Within group differences of characteristics in patients and healthy controls were analyzed using a paired t-test and between group differences using an unpaired t-test for continuous data and a Pearson’s chi-squared or Fisher exact test for dichotomous data.

In order to identify any possible determinants of AGE-accumulation rate, the association of AGE-accumulation rate with general subject characteristics (ethnicity, criteria for metabolic syndrome, familial risk of CVD, exposure to tobacco smoking, cannabis use, weight gain) was investigated in patients and controls through hierarchical multiple regression analyses, corrected for sex. Second, in patients, factors that are related to the disorder or variation in phenotype, i.e., course of disease, duration of admission and exposure to antipsychotic medication, were investigated separately. A Bonferroni-correction was applied. Semi-partial correlation coefficients (sr) were reported.

The relation of AGE-accumulation rate and diagnostic status was investigated through a hierarchical regression analysis, corrected for sex and any significant confounders as identified in the analyses mentioned above. Semi-partial correlation for diagnostic status was reported to indicate the unique contribution of diagnostic status to the AGE-accumulation rate. Finally, it was investigated whether adding variables to the analysis that significantly differed between patients and controls improved the accuracy of the model (adjusted R²). A two-sided alpha was set at 0.05.

For all analyses, bootstrapping with 5000 samples was performed in order to ensure a normal distribution of residuals. Outcomes were reported with a bias-corrected accelerated confidence interval (Efron, 1987), adjusting for both bias and skewness in the bootstrap distribution.
3. Results

3.1. Characteristics of patients and controls

Of 111 patients included at baseline, 78 could be retrieved and invited for a follow-up measurement. Sixty-six patients (78.8% male) agreed to participate in this follow-up measurement. Patients who did not participate in the follow-up study were more often of non-Western ethnicity, more often smokers, and had a higher BMI compared to patients who participated in the follow-up measurement.

At first assessment, mean age of patients was 26.6 years (median = 25, range = 18 - 41). Mean duration of follow-up was 20.1 months (range = 12 - 24). Among patients of non-Western ethnicity, most originated from Morocco (n = 10), Turkey (n = 3), and the Republic of Suriname (n = 3). Of 66 patients, 49 were using antipsychotic medication at follow-up. In 5 patients, antipsychotic medication was started during follow-up, while 7 patients had stopped using medication. Eighteen patients had been admitted during follow-up, in 7 cases involuntarily. Four patients met the criteria of metabolic syndrome at follow-up, all of whom did not at baseline; one patient met those criteria at baseline, but not anymore at follow-up. One patient had commenced smoking during follow-up and none had quit, leading to a prevalence of tobacco smoking of 53.0%. Forty-three patients (65.2%) had a history of regular cannabis use and 27.3% used cannabis to a prevalence of tobacco smoking of 53.0%. Forty-three patients (65.2%) had a history of regular cannabis use and 27.3% used cannabis in the week before the follow-up measurement.

Of the 286 healthy controls that had previously participated, 160 were successfully approached for a follow-up measurement. Mean age of the control group was 20.9 years (median = 20, range = 18 - 26) at inclusion. Mean duration of follow-up for controls was 14.7 months (range = 14 - 16). Non-Western healthy controls mostly originated from Turkey (n = 3), Indonesia (n = 2) and Afghanistan (n = 2). In all patients and controls included in the follow-up measurement, a successful AGE-measurement was conducted.

On average, patients were older, more often male and of non-Western ethnicity, and had been exposed to tobacco and cannabis more often than healthy controls. More detailed characteristics of subjects are shown in Tables 1a and 1b.

3.2. Association of general characteristics with AGE-accumulation rate

In healthy controls, a positive association of AGE-accumulation rate and tobacco exposure was found ($B = 291.7 \times 10^{-3}$ [95% CI = 65.7 to 430.4 $\times 10^{-3}$]; sr = 0.17; $p < .001$). In patients, no significant association between AGE-accumulation and tobacco exposure was found ($B = -28.0 \times 10^{-3}$ [95% CI = -132.2 to 81.7 $\times 10^{-3}$]; sr = -0.08; $p = .63$). AGE-accumulation rate was associated with ethnicity ($B = -4.5 \times 10^{-3}$ [95% CI = -7.5 to -1.4 $\times 10^{-3}$]; sr = -0.19; $p = .003$) in healthy controls (higher accumulation rate in subjects of Western origin compared to non-Western subjects), but not in patients ($B = -1.8 \times 10^{-3}$ [95% CI = -5.3 to 1.9 $\times 10^{-3}$]; sr = -0.13; $p = .36$). In patients, no significant associations of AGE-accumulation rate with any of the other investigated variables were found (table 2).

3.3. Association of disorder-specific factors with AGE-accumulation rate

We found no significant associations of AGE-accumulation rate with exposure to antipsychotic medication, course of disease or duration of admission (Table 2).

3.4. Relation of AGE-accumulation rate and diagnostic status

After correcting for sex and the identified confounders (ethnicity and tobacco exposure), a hierarchical linear regression analysis showed an AGE-accumulation rate in patients of $8.7 \times 10^{-3}$ AU per month, compared to $4.8 \times 10^{-3}$ AU per month in healthy controls (adjusted $R^2 = 0.021$; intercept = $4.8 \times 10^{-3}$; $B = 3.9 \times 10^{-3}$ [95% CI = -0.3 to 8.1 $\times 10^{-3}$]; sr = 0.11; $p = .07$). Distribution of AGE-levels at baseline and follow-up are shown in Fig. 1.

Although no association with AGE-accumulation rate was found for cannabis use, calendar age and time between baseline and follow-up measurement, these variables did significantly differ between patients and controls and were therefore added to the primary model. The addition of cannabis use slightly improved the accuracy of the model (adjusted $R^2 = 0.036$), yielding an AGE-accumulation rate of $7.4 \times 10^{-3}$ AU per month in patients compared to $4.4 \times 10^{-3}$ AU per month in healthy controls (intercept = $4.4 \times 10^{-3}$; $B = 2.9 \times 10^{-3}$ [95% CI = -1.7 to 7.5 $\times 10^{-3}$]; sr = 0.08; $p = .20$). Adding calendar age or time in between baseline and follow-up measurement to the model did not improve the accuracy and these variables were omitted from the model.

4. Discussion

To the best of our knowledge, accumulation rate of AGEs in the skin as measured by autofluorescence and its determinants have not been previously investigated longitudinally in any population. The current study showed a significant association of exposure to tobacco smoking and ethnicity with AGE-accumulation rate in healthy controls. An indication of an increased AGE-accumulation rate was shown in patients suffering from recent onset psychosis compared to healthy controls, independent of ethnicity and tobacco smoking but not independent of cannabis use.

Table 1a

Subject characteristics - within group differences.

|                         | Patients n = 66 | Controls n = 160 |
|-------------------------|-----------------|-----------------|
|                         | T0       | T1       | p-valuea | T0       | T1       | p-valuea |
| AGE-level in AU (mean, SD) | 1.74 (0.34) | 1.87 (0.38) | <0.001  | 1.39 (0.19) | 1.47 (0.20) | <0.001 |
| Weight in kg (mean, SD) | 80.0 (15.0) | 82.0 (16.2) | .03  | 67.0 (10.6) | 68.7 (11.9) | <0.001 |
| Body mass index in kg/m² (mean, SD) | 24.7 (3.7) | 25.4 (4.3) | .01  | 21.5 (2.3) | 22.0 (2.5) | <0.001 |
| Waist circumference in cm (mean, SD) | 91.0 (11.5) | 95.3 (12.6) | <0.001  | 79.3 (7.9) | 79.9 (12.4) | .41  |
| Cumulative tobacco exposure in pack years (mean, SD) | 4.1 (5.8) | 4.8 (6.3) | <0.001  | 0.14 (0.5) | 0.16 (0.6) | .003  |
| Plasma LDL in mmol/L (mean, SD) | 2.8 (0.9) | 3.1 (0.9) | .07  |
| Plasma HDL in mmol/L (mean, SD) | 1.2 (0.3) | 1.1 (0.2) | .15  |
| Plasma triglycerides in mmol/L (mean, SD) | 1.2 (0.5) | 1.5 (0.9) | .12  |
| Plasma glucose in mmol/L (mean, SD) | 4.9 (0.5) | 5.1 (0.9) | .37  |
| AP dosage in CPZ-equivalents (mean, SD) | 281 (211) | 226 (187) | .20  |

Abbreviations: AGE = advanced glycation end product, AP = antipsychotics, AU = arbitrary units, CPZ = chlorpromazine, HDL = high density lipoproteins, LDL = low density lipoproteins.

* Significant p-values (at Bonferroni-corrected level) are shown in bold.
Healthy controls of non-Western ethnicity showed a significantly decreased AGE-accumulation rate compared to controls of Western descent. This finding is not in line with previous literature reports of ethnic differences in oxidative stress (Fearheller et al., 2011; Morris et al., 2012). Notably, absolute AGE-levels were higher in non-Western compared to Western controls throughout follow-up. The small number of controls of non-Western descent (n = 9) increases the probability of an incidental false-positive finding. Although autofluorescence measurements have been validated in subjects with various skin colors (Koetsier et al., 2010), another possible explanation is that the autofluorescence measurement was affected by a low skin reflectance in subjects of non-Western ethnicity. The AGE Reader in subjects of non-Western origin (Koetsier et al., 2010) shows that the reflectance measurement was affected by a low skin reflectance in subjects of non-Western descent. This finding is not in line with previous literature reports of ethnic differences in oxidative stress (Feairheller et al., 2011; Morris et al., 2012). Notably, absolute AGE-levels were higher in non-Western compared to Western controls throughout follow-up. The small number of controls of non-Western descent (n = 9) increases the probability of an incidental false-positive finding. Although autofluorescence measurements have been validated in subjects with various skin colors (Koetsier et al., 2010), another possible explanation is that the autofluorescence measurement was affected by a low skin reflectance in subjects of non-Western ethnicity. The AGE Reader indicates when a reliable measurement cannot be conducted due to a low skin reflectance, but deviations caused by a borderline-low skin reflectance might have influenced our measurements. Observations of
declining AGE-levels in patients with a non-Western ethnicity, which contradicts the widely-accepted theory that AGEs remain linked to collagen in the skin (Gkogkolou and Bohm, 2012), implies a possible inaccuracy of the measurements. When post-hoc only Western patients ($n = 39$) and healthy controls ($n = 143$) were included in the analyses, AGE-accumulation rate remains increased in patients compared to controls, although, probably by loss of power, not significantly ($B = 1.1 \cdot 10^{-3}$ [95% CI $= −3.8$ to $6.1 \cdot 10^{-3}$]; $p = .66$).

Adding cannabis use as a covariate to our analysis considerably improved the accuracy of the model. This observation could imply that cannabis use is a determinant of AGE-accumulation. Although some components of cannabis are thought to have anti-inflammatory effects, increased levels of pro-inflammatory cytokines have been demonstrated in 34 cannabis-dependent individuals (Bayazit et al., 2017). Also, a toxic effect on mitochondria and increased oxidative stress induced by tetrahydrocannabinol has been demonstrated in vitro in mice (Wolff et al., 2015). However, it cannot be excluded that cannabis use confounds the relation of diagnostic status and AGE-accumulation, caused by a larger prevalence of cannabis use within the patient group compared to healthy controls.

Some factors that could have been expected to confound the relation between psychotic disorders and AGE-accumulation were not confirmed as confounders in our study. Several metabolic determinants have been linked to cross-sectional AGE-levels in a large cohort study (van Waateringe et al., 2016), but no association with AGE-accumulation was found with criteria for metabolic syndrome or familial risk of CVD in our cohort. Findings concerning a negative association between weight gain and AGE-accumulation did not withstand the Bonferroni correction. A protective effect of weight gain on AGE-production and accumulation does not correspond to the previously described absence of an association between BMI and cross-sectional AGE-levels (van Waateringe et al., 2016) and seems counterintuitive. Possibly, the negative association reflects a false-positive finding. Adding weight gain as a coefficient to the model did not markedly increase the accuracy of the model.

No associations between AGE-accumulation and any disorder specific factors were detected. This is in contrast to our previous findings of an association of exposure to antipsychotics and cross-sectional skin AGE-levels (Hagen et al., 2017), which was investigated using crude estimations of life-time exposure. Estimations of exposure to antipsychotic medication (or substances such as tobacco) can be difficult due to non-compliance and reporting bias. In this study, exposure to antipsychotic medication during follow-up was calculated from information on prescriptions as issued by the patient’s pharmacy and reports on dosage and compliancy in the patient’s medical file. In the cohort of older patients suffering from schizophrenia, also no association of cross-sectional AGE-levels and current antipsychotic treatment dose was observed (Koudrat et al., 2013). Literature on the effect of antipsychotic medication on oxidative stress and inflammation is contradictory (Bai et al., 2018; Berger et al., 2018; Kriisa et al., 2016). The limited exposure to antipsychotic medication in our cohort might be too small to reveal a detectable effect on AGE-accumulation within the follow-up period.

4.2. AGE-accumulation rate in recent onset psychosis compared to healthy individuals

Although the finding of an increased AGE-accumulation rate in patients compared to controls was not significant and attenuated after adjustment for cannabis use, the direction and magnitude of the association of diagnostic status and AGE-accumulation (AGE-accumulation rate was 68% higher in patients compared to healthy controls) are in line with previous findings of further increased AGE-levels in a sample of older patients suffering from schizophrenia (30% higher concentration (Koudrat et al., 2013)) compared to our recent onset psychosis cohort (10–15% higher concentration (Hagen et al., 2017)). When applying the concept of AGE-accumulation as a measure of accelerated aging (and thus applying the above mentioned increased rate of 68%),
our results indicate that over the course of 15 calendar years a patient suffering from recent onset psychosis biologically ages more than 25 years. This difference accurately corresponds with the decreased life expectancy that is reported in severe mental illness (Tiilikainen et al., 2009).

AGE-concentration in the skin is thought to indicate the cumulative level of oxidative and glycemic stress in the internal environment (Mulder et al., 2006).

Increased levels of oxidative stress in recent onset psychotic disorders have been demonstrated in cross-sectional case-control studies (Fraguas et al., 2018). In our model of AGE-accumulation and diagnostic status, a sizeable proportion of the variance in AGE-accumulation remains unexplained, as indicated by an adjusted R² of 0.036. In addition to ethnicity, tobacco smoking and cannabis use, AGE-accumulation might be affected by factors that were not investigated in our study. This observation supports the theory of increased levels of oxidative stress being present in patients as an intrinsic factor to psychotic disorders (Ng et al., 2008), possibly explaining the vulnerability to CVD that is associated with psychotic disorders or, more speculatively, acting as causative factor in the vulnerability to both psychosis and CVD (Camps and Garcia-Heredia, 2014), However, it is also possible that oxidative stress is associated with the disease but independent from a causal pathway.

4.3. Clinical implications

Although replication of current findings is warranted, the suggestion of increased AGE-accumulation implicates a time-dependent increase in CVD risk in psychotic disorders. Of possible determinants identified in the current study, tobacco smoking and cannabis use are modifiable factors that could serve as targets for preventive treatment.

4.4. Limitations

There are some limitations to our study. Although we succeeded to detect, motivate and include a reasonably large part of patients who had been included in the baseline measurement for a follow-up measurement, a substantial part of the patients dropped out. In our analyses, we controlled for variables that differed between included patients and drop outs, i.e., ethnicity and exposure to tobacco smoking, as confounders. Therefore, it is unlikely that our results were importantly affected by selective drop-out.

The observed power of our model of AGE-accumulation rate and diagnostic status, calculated post-hoc (Soper, 2006 - 2018), was 22%. This could be attributed to the spread of accumulation rates being wider than anticipated. Studies with a larger sample size or a longer follow-up period might allow for more definite statements on AGE-accumulation rate in psychotic disorders and detect additional determinants that have now remained unnoticed due to insufficient power.

Patients differed from healthy controls on several levels. We tried to minimize the effect of group differences by correcting our model of AGE-accumulation rate and diagnostic status for any possible confounders, as suspected from analyses of associations of individual variables with AGE-accumulation rate, or any variables that significantly differed in patients compared to healthy controls if it improved the accuracy of the model. Differences in duration of follow-up between patients and controls were caused by practical limitations of the control group (the students were only available for a follow-up measurement during specific classes). This difference was adjusted for by using the monthly AGE-accumulation rate as outcome measure. Nonetheless, a risk of residual confounding due to undetected or unmeasured determinants remains. This is an important limitation of our study, because healthy medical students are not an ideal control group since they probably do not precisely represent the population from which the cases arose and because confounding effects of investigated characteristics might have been underestimated due to insufficient power. Finally, a family history of psychosis was not an exclusion criterion for controls. Unaffected relatives of persons with psychotic disorders have been shown to present biological alterations (Pietrowksi et al., 2019) and their inclusion might have affected our results. Therefore, the analysis of AGE-accumulation rate in patients versus controls was repeated after exclusion of controls with first- or second-degree relatives with a medical history of a psychotic disorder. This post-hoc analysis also showed results similar to our primary analysis (data available upon request).

4.5. Conclusion

In conclusion, tobacco smoking and ethnicity were found to affect AGE-accumulation rate in healthy controls. An indication of a markedly, although not-significant higher AGE-accumulation rate was found in patients suffering from recent onset psychosis compared to highly educated healthy controls, independent of tobacco smoking and ethnicity but not of cannabis use. The role of cannabis as a possible determinant of AGE-accumulation should be further investigated. When replicated, our findings imply that AGE-accumulation in patients suffering from recent onset psychosis occurs at a higher pace and reflects a time-dependent increase in CVD risk and possible psychiatric chronicity. Therefore, effective interventions to decrease such risks are needed.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

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Declaration of Competing Interest

The authors have no competing interests to report.

Acknowledgement

We would like to express our gratitude to all patients and healthy controls for taking the time to participate in this project.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2020.113192.

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