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Psychotropic-induced weight gain and telomere length: results from a one-year longitudinal study and a large population-based cohort

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Weight-inducing psychotropic treatments are risk factors for age-related diseases such as cardiovascular disorders, which are associated with both inflammation and telomere length shortening. With a longitudinal design, the present study evaluates telomere length trajectories after 1 year of weight-inducing psychotropic medication, accounting for weight changes and the inflammatory biomarker high-sensitivity C-Reactive Protein (CRP). Among 200 patients, an overall median telomere shortening of -41.2 bp was observed ($p = 0.014$), which is comparable with the general population's yearly telomere attrition. Linear regression showed on average -93.1 and -58.9 bp of further telomere shortening per five units of BMI for BMI values $< \text{or } \geq 30 \text{ kg/m}^2$, respectively ($p = 0.003$ and $p = 0.009$, respectively). Importantly, the overall telomere shortening was predicted to be increased four-fold among patients with low baseline weight (i.e., 50 kg) and with clinically relevant weight gain ($\geq 7\%$) after 1 year of treatment (interaction term between relevant weight gain and baseline weight: +6.3 bp, $p = 0.016$). Patients with relevant weight gain showed greater CRP levels (+49%; $p = 0.016$), and a telomere shortening of -36.2 bp ($p = 0.010$) was estimated whenever CRP level doubled. Mendelian randomization using UKBiobank data showed a causal effect of BMI on telomere shortening, notably stronger among patients receiving weight-inducing psychotropic treatments ($n = 9798$) than among psychiatric patients without such drugs ($n = 16228$) and non-psychiatric controls ($n = 252932$) (beta: -0.37, -0.12, -0.06, respectively; $p = 0.004$, $p < 0.001$, respectively). Ultimately, telomere trajectories were associated with 1 year weight gain and increases in CRP levels, with telomere shortening strongly enhanced by BMI increments among patients receiving weight-inducing psychotropic treatments.

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INTRODUCTION

Telomeres are the protein-DNA chromosome extremities that prevent chromosomal fusion and genome instability [1]. Cellular replications and/or biological environments such as inflammation and oxidation have been associated with telomere shortening, which decreases cellular lifespan, eventually leading to apoptosis or senescence [2]. Although telomere shortening is reversible due to the activity of the ribonucleoprotein enzyme telomerase [1], leukocyte telomere length shortening is nowadays one hallmark of aging due to its association with several age-related diseases as type 2 diabetes, dementia and cardiovascular diseases [3].

Telomere length has also been associated with psychiatric illnesses, a meta-analysis reporting shorter telomere length for

psychotic, bipolar, depression, anxiety and post-traumatic stress disorders versus the general population [4]. The psychiatric population also shows >10 years of shorter life expectancy versus the non-psychiatric population, mainly because of the development of cardiometabolic diseases such as obesity, dyslipidemia, type 2 diabetes and hypertension (i.e., several age-related diseases, as previously mentioned), which are due to several risk factors, such as unhealthy lifestyle and genetic predisposition [5–7]. Psychotropic drugs, such as antipsychotics, mood stabilizers and antidepressants are also risk factors for developing such somatic diseases, with weight gain being one of the most common adverse effects that can lead to an increase of up to +12% in baseline weight within

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6–12 months of treatment [8]. Telomere trajectories after the onset of weight-inducing psychotropic drugs are unclear. In a cross-sectional study of 256 bipolar patients and 139 controls, lithium-treated patients showed longer telomere length compared with controls, and telomere length was positively correlated with treatment duration [9]. On the other hand, another cross-sectional study including 170 patients with schizophrenia and 126 controls reported significant telomere shortening among patients receiving the atypical antipsychotic olanzapine [10].

High levels of inflammatory biomarkers such as C-reactive protein (CRP, i.e., levels >3 mg/l) have also been associated with both old age and psychiatric diseases, with evidence reporting elevated CRP (>3 mg/l) among more than one third of 950 psychiatric patients [11], and elevated CRP among non-psychiatric patients with cardiovascular diseases, metabolic syndrome and obesity [12–14]. Regarding the association between psychotropic drugs and CRP, a subclinical increase of 600% in CRP levels was reported after 8 weeks of clozapine treatment among eight patients with schizophrenia [15], and both interleukin-1Ra and CRP levels were associated with obesity in a cross-sectional study including 190 clozapine-treated patients [16]. Of note, CRP levels were previously positively associated also with psychiatric symptoms severity [17–19], the effect size of this association being attenuated when considering environmental factors such as smoking, medication use (i.e., both psychotropic and non-psychotropic) and metabolic parameters such as body mass index (BMI) [20]. Concerning the relationship between metabolic parameters, CRP and telomere length, studies including non-psychiatric individuals suggest that CRP levels partially mediate an inverse BMI-telomere length correlation [21, 22].

Although the association between telomere length or inflammation and psychiatric disorders has been established, the relationship between telomere length, inflammation, psychotropic treatment and/or the induced weight gain that might occur remains unclear. An ex-vivo study including peripheral blood mononuclear cells of six healthy individuals showed that the antipsychotics aripiprazole and haloperidol could increase telomere length by 23% and 20%, respectively, after the induction of acute oxidative stress injury [23]. Along with the latter result, the antipsychotic-induced blockage of dopamine (D₂) and serotonin (5-HT_{2A}) receptors has been suggested to increase the expression of telomerase catalytic unit, resulting in telomere lengthening [24]. Conversely, a cross-sectional study reported higher CRP levels among 41 patients with schizophrenia taking psychotropic treatments versus controls, and an inverse association between CRP and telomere length, which was independent of metabolic parameters such as BMI [25].

Given the conflicting results concerning psychotropic drugs and their metabolic and/or inflammatory consequences regarding telomere length, longitudinal studies evaluating the association of both inflammation and psychotropic-induced metabolic adverse effects on telomere trajectories are needed, as well as studies inferring causality of such associations. For this reason, this study aims to elucidate whether telomere length changes after 1 year of weight-inducing psychotropic medication in a cohort of psychiatric patients in Switzerland. Of note, due to the multiple factors influencing telomere length, an aging-related telomere shortening should be expected, as well as telomere changes due to weight gain/loss, and to senolytic [26] or telomerase-enhancing treatments (e.g., antipsychotic drugs as previously suggested). Thus, if a change in telomere length is found, we aim to investigate in which direction the latter change goes (i.e., lengthening or shortening); whether the telomere change is associated with metabolic features (e.g., BMI) and inflammation; whether we could validate our results in a large population-based cohort (UKBiobank).

METHODS

Study design

From the PsyMetab cohort ongoing since 2007 at the Department of Psychiatry of Lausanne University Hospital in collaboration with a private mental health care center (Les Toises; Lausanne), 200 patients starting a psychotropic treatment and with at least two available blood samples and weight measures were selected for the telomere analysis. With the approval of the Ethics Committee of the Canton of Vaud and upon signature indicating informed consent, PsyMetab collects clinical data (e.g., weight) and blood samples as described elsewhere [27]. Informed consent was obtained for all participants included in the present study. Blood samples analyzed in the present study were collected at the beginning of the treatment (T0) and after 1 year (T12). To evaluate telomere trajectories within 1 year, additional blood samples collected at one and 3 months were analyzed for 38 and 47 patients, respectively. The included psychotropic treatments could have a high (i.e., clozapine, olanzapine and valproate), medium (i.e., lithium, mirtazapine, quetiapine, and risperidone) or low risk (i.e., amisulpride and aripiprazole) of inducing weight gain [28]. High sensitivity CRP levels (Cobas integra 400 plus Roche®, Roche Diagnostic, Rotkreuz, Switzerland) were also available for 162 patients at T12.

Telomere analysis

Telomere length was examined by quantitative polymerase chain reaction (qPCR) and telomere-to-single-copy-gene (T/S) ratios were obtained (See Supplementary Appendix). Although these qPCR results were not directly compared with another telomere length method, we used a conversion formula generated in the same lab using the same assay format to roughly estimate telomere length in base pairs (bp, i.e., base pairs = 3274 + 2413. (T/S)) [29]. Briefly, this conversion formula derived from side-by-side comparison of telomere restriction fragment (TRF) analysis and qPCR using a series of genomic DNA samples from the human fibroblast primary cell line IMR90 at different population doublings, as well as with the telomerase protein subunit gene (hTERT) transfected into a lentiviral construct [29].

Statistical analysis

Telomere lengths at T0 and T12 were compared with one another using two-sided Wilcoxon matched-pairs signed-rank test. T0- or T12-length associations with other continuous and binary variables were tested using Pearson correlation and the two-sided unpaired Wilcoxon rank-sum test, respectively. Linear regression on telomere bp difference at T12 (i.e., T12 telomere length—T0 length) and logistic regression on important telomere shortening (i.e., percentile of bp difference from 25% to the minimum value) or lengthening (i.e., percentile from 75% up to the maximum value) at T12 were applied. Both regressions were adjusted for age, sex, smoking status (i.e., smokers and ex-smokers versus non-smokers), antidepressant co-medication, also including metabolic variables such as clinically relevant weight gain (CRWG, i.e., ≥7% from baseline), baseline weight or 1 year BMI. Since we found a non-linear relationship between BMI and telomere differences, the piecewise function was applied to BMI with a knot at 30 kg/m² to analyze telomere length trajectories for obese versus non-obese subjects. Since inflammation could mediate the association between BMI and telomere length [21], additional models including CRP were performed to ascertain whether metabolic effects persist after accounting for inflammation. Moreover, since the different diagnoses did not influence our outcomes nor our results in linear and logistic regression (data not shown), this covariate was not included in the models. For further details on statistical analysis see Supplementary Appendix. R environment for statistical computing version 4.0.2 and Stata 17.0 (StataCorp; College Station, Texas) were used for the analysis, and *p*-values ≤ 0.05 were considered statistically significant.

Validation in UKBiobank

In order to validate the explored associations and to infer causality through a Mendelian randomization (MR) analysis, a psychiatric cohort was defined using a cross-sectional approach in the UKBiobank (UKBB), a large population-based British cohort previously described elsewhere [30]. Briefly, the UKBB (2006–2010) includes clinical and genetic data of >500,000 British citizens aged between 40 and 69, including blood biomarkers and demographic indicators. Among this cohort, participants were selected according to quality measures, ethnicity, and relatedness, and they were classified as cases or psychiatric controls, according to the

prescription of at least one high or low metabolic-risk medication, respectively (see Supplementary Table 1 for medication lists). Additionally, a control group within the general population was defined including participants not taking any of the medications listed in Supplementary Table 1, and not taking weight-inducing medications according to the SIDER database [31]. Associations and interactions were evaluated for BMI, educational attainment (i.e., a proxy for socio-economic status), CRP and telomere length phenotypes, considering every pairwise group combination (i.e., cases vs psychiatric controls, cases vs population-based controls, and psychiatric vs population-based controls), and the effect of BMI, educational attainment and CRP on telomere length was assessed using MR analysis in each group (See Supplementary Appendix and Supplementary Table 2 for demographics of the three groups).

RESULTS

Univariate analysis

An overall telomere shortening of 41.2 bp ($p = 0.014$) was found among the 200 patients (Table 1). A significant telomere length shortening was indicated for patients experiencing CRWG ($p = 0.040$), taking medium- or low-risk drugs ($p = 0.023$, $p = 0.029$, respectively), and for patients with CRP levels > 3 mg/l at T12 ($p = 0.006$).

Among patients with telomere data for the four time-points, no telomere length difference was found between each time-point (Supplementary Table 3). Of note, baseline telomere length was correlated with 1 year length ($r = 0.85$, $p < 0.001$), and both lengths were correlated with age ($r = -0.52$, $p < 0.001$ for both). Telomere lengths at T0 and at T12 were not different among men and women ($p = 0.83$ and $p \approx 1$, respectively), did not correlate with BMI ($r = -0.035$ and $r = -0.064$, $p = 0.63$ and $p = 0.38$, respectively), and were not different among obese versus non-obese patients at T12 ($p = 0.64$ and $p = 0.24$, respectively). Additionally, at T12, a significant increment (1.16 versus 2.03 mg/l, $p = 0.021$) and no difference (1.26 versus 1.41 mg/l, $p = 0.67$) in CRP levels were found for patients with and without CRWG, respectively. Additional information on clinical data (intake of antihypertensive, antidiabetic and lipid-lowering drugs, and median fasting lipids and glucose levels at T0 and T12) can be found in Supplementary Table 4.

Multiple regression analysis

Multiple regression analysis showed a non-linear relationship between telomere bp difference and 1 year BMI (Fig. 1). Thus, a piecewise knot at 30 kg/m^2 was applied to 1 year BMI covariate in a linear model (Table 2, Model-1A), showing an estimated telomere attrition per five units of BMI of -93.1 bp for $\text{BMI} < 30 \text{ kg/m}^2$ ($p = 0.003$), and an estimated telomere attrition of -58.9 bp for $\text{BMI} \geq 30 \text{ kg/m}^2$ ($p = 0.009$). Similarly, when including CRWG and baseline weight in a linear model (Table 2, Model-2A), the effect of CRWG on telomere bp difference (β -estimate: -490.0 bp, $p = 0.010$), changed in function of baseline weight (interaction effect: $+6.3$ bp, $p = 0.016$, Fig. 2), suggesting that a higher baseline weight would reduce telomere shortening linked to CRWG. For example, -175 and -112 bp (i.e., four-fold and 2.5-fold the overall median shortening of 41.2 bp, respectively) were predicted for 50 kg and 60 kg patients with CRWG, respectively, according to Model-2A (i.e., $-490 + (6.3 \times 50)$ and $-490 + (6.3 \times 60)$, respectively). A non-significant three-way interaction between baseline weight, CRWG and age was also found (data not shown), excluding a moderating effect of age on the association between baseline weight-CRWG interaction and telomere bp difference.

When including both BMI and CRP values in the linear model (Table 2, Model-1B), a telomere attrition was estimated only for $\text{BMI} < 30 \text{ kg/m}^2$ (-83.4 bp per five BMI units, $p = 0.018$). Accordingly, similar results were found when including CRWG, baseline weight and CRP in a linear model (Table 2, Model-2B), with CRWG effect (β -estimate: -557.4 , $p = 0.013$) changing in function of baseline weight (interaction effect: 7.8 ; $p = 0.013$). Additionally, an

attrition of -38.0 ($p = 0.008$) and -36.2 bp ($p = 0.010$) were estimated for each CRP duplication according to Model-1B and -2B in Table 2, respectively. Similar results were found when considering only CRP levels < 10 mg/l (Supplementary Fig. 1), and when applying robust linear models to down-weight three outlying observations (Supplementary Table 5). Interestingly, the linear model with logarithm-CRP as the outcome (data not shown) showed increased CRP levels ($+49\%$) among patients with CRWG versus those with non-CRWG (β -estimate: 0.40 , $p = 0.016$).

No further associations with telomere bp difference were found for age, sex, and smoking status in these linear models, nor with a Swiss-based socioeconomic score in an additional model ($p = 0.16$). On the other hand, a mean of -114.2 bp was estimated for patients taking versus not taking antidepressant co-medications according to Model-2A ($p = 0.007$).

In logistic models (Table 3), increases of one baseline weight standard deviation (i.e., 17 kg) were associated with 3.27 and 5.40 odds of important telomere lengthening among CRWG patients when including or not including CRP in the model, respectively ($p = 0.004$ and $p = 0.001$, respectively). Moreover, when including the Swiss-based socioeconomic score, each unit increment (range: 10–85) decreased the odds of important telomere shortening by 4% ($p = 0.013$, Supplementary Table 6).

Since receptor D_2 and 5-HT_{2A} blockage have been suggested to increase telomerase activity [24], a sensitivity analysis adjusting for drugs blocking both receptors (i.e., aripiprazole, clozapine, quetiapine, risperidone and olanzapine) or only the D_2 receptor (amisulpride) versus other drugs without such blockade (lithium, mirtazapine or valproate) was performed, and no association with telomere bp difference was found (data not shown). Moreover, similar results as reported in Tables 2 and 3 were found in a sensitivity analysis (data not shown) including baseline telomere length as a covariate, and excluding the 14 samples with DNA quantity and quality below our criteria (see Supplementary Appendix—Methods).

Validation UKBB

When replicating these results using UKBB data, a significant association with telomere length was found for BMI, CRP and educational attainment when considering the three group combinations (Supplementary Table 7). Moreover, MR analysis revealed a causative effect of BMI on telomere length for cases, psychiatric and population-based controls (i.e., 9798, 16228 and 252932 included individuals, respectively), this effect being notably stronger among psychiatric cases (beta -0.37 versus -0.12 and -0.06 , respectively, see Table 4). Furthermore, a significant difference of these effects was found when meta-analyzing the two differences (-0.37 versus -0.12 and -0.12 vs -0.06) while accounting for the covariance between these estimates ($p = 0.011$). Conversely, a causative effect of CRP was found only in the non-psychiatric cohort (beta -0.04). To investigate whether CRP mediates the effect of BMI on telomere length, multivariable MR was also performed, reporting no statistical evidence of such a mechanism (beta of the indirect effect of BMI on telomere length via CRP levels: 0.005 , $p = 0.75$).

DISCUSSION

To our knowledge, the present longitudinal study is the first examining the associations of one-year telomere trajectories with both inflammation and psychotropic-induced weight gain, indicating a median overall telomere shortening of 41.2 bp among 200 psychiatric patients, which is in line with a systematic review reporting 32 to 45 bp attrition per year in the general population [32]. However, stronger telomere attrition was predicted among patients with low baseline weight and one-year CRWG.

Significant telomere attrition was found for patients taking low- and medium-metabolic-risk drugs, but, surprisingly, not for

Table 1. Clinical characteristics and one-year telomere differences.

	Total patients (N = 200)^a		
Age (years)	36 (26–49) ^b		
Baseline telomere length (bp)	6019.9 (5742.1–6400.5) ^{b,c}		
One-year telomere length (bp)	6008.6 (5697.3–6382.7) ^{b,c}		
Baseline weight (kg)	71 (61.5 – 81.5)		
Baseline BMI (kg/m²)	24 (21–29)		
Missing BMI	5 (2.5%)		
	N (%)	T12–T0 (bp)	p-value^d
Overall telomere shortening^e	200 (100%)	–41.2 (–217.7 – +115.1)	0.014
Age categories			
≤25 years	47 (23.5%)	–68.7 (–258.1 – +110.7)	0.12
>25 and <65 years	137 (68.5%)	–37.2 (–212.1 – +126.1)	0.10
≥65 years	16 (8%)	–11.5 (–180.3 – +37.8)	0.30
Sex			
Men	113 (56.5%)	–74.3 (–233.8 – +133.7)	0.069
Women	87 (43.5%)	–15.4 (–200.8 – +95.3)	0.11
Ethnicity^f			
Europeans	145 (72.5%)	–45 (–211.7 – +116.31)	0.038
Other	44 (22%)	–24.2 (–258.6 – +121.7)	0.28
Missing	11 (5.5%)	–50.7 (–177.1 – +48.7)	0.41
CRWG^g			
Yes	89 (44.5%)	–61.4 (–191.4 – +95.3)	0.040
No	111 (55.5%)	–18.4 (–235.5 – +127.5)	0.13
Risk level of drugs^h			
High	37 (18.5%)	+40.2 (–127.4 – +203.6)	0.35
Medium	116 (58.0%)	–53.2 (–233.8 – +113.0)	0.023
Low	47 (23.5%)	–71.6 (–235.9 – +56.1)	0.029
Diagnosesⁱ			
Schizophrenia	86 (43%)	–64.9 (–235.5 – +110.7)	0.043
Bipolar disorder	38 (19%)	–30.3 (–205.0 – +161.6)	0.62
Depression	33 (16.5%)	–88.2 (–224.6 – +89.5)	0.16
Others	26 (13%)	+3.9 (–189.1 – +113.9)	0.63
Schizoaffective disorders	16 (8%)	+18.5 (–225.3 – +148.9)	0.94
Missing	1 (0.5%)		
Smoking^j			
Smokers	111 (55.5%)	–45.2 (–200.8 – +99.9)	0.089
Ex-smokers	6 (3%)	+121.7 (22.1 – +212.0)	0.31
Non-smokers	83 (41.5%)	–61.8 (–249.6 – +112.0)	0.034
Previous psychotropic drug(s)^k			
No	50 (25%)	–76.7 (–237.6 – +43.7)	0.035
Yes	150 (75%)	–18 (–211.7 – +126.1)	0.11
Antidepressant use^l			
Yes	68 (34%)	–156.1 (–237.3 – +53.0)	<0.001
No	132 (66%)	–1.4 (–185.0 – +150.1)	0.65
CRP at T12			
High >3 mg/l	51 (25.5%)	–81.8 (–233.5 – +45.4)	0.006
Low ≤ 3 mg/l	111 (55.5%)	–17.6 (–200.8 – +180.5)	0.56
Missing	38 (19%)	–74.3 (–249.2 – +110.7)	0.17
Drug^m			
Amisulpride	16 (8%)	–89.8 (–252.9 – +33.4)	0.044
Aripiprazole	31 (15.5%)	–45.2 (–235.9 – +95.3)	0.18
Clozapine	13 (6.5%)	40.2 (–152.8 – +127.5)	0.95

Table 1. continued

	Total patients (N = 200) ^a		
Lithium	23 (11.5%)	-91.4 (-224.6 - +99.0)	0.22
Mirtazapine	11 (5.5%)	-151.6 (-260.3 - +42.4)	0.46
Olanzapine	15 (7.5%)	-37.2 (-177.1 - +212.0)	0.85
Quetiapine	57 (28.5%)	-33.5 (-212.1 - +112.0)	0.080
Risperidone	25 (12.5%)	-7.7 (-249.6 - +133.7)	0.71
Valproate	9 (4.5%)	117.3 (22.1 - +270.7)	0.098

^aProportions (%) and medians (Q1 - Q3) are reported for categorical and continuous variables, respectively.

^bSignificant Pearson correlation between both telomere lengths (i.e., baseline and 1 year) and age ($r = -0.52$, $p < 0.001$ for both). Minimum age: 12; maximum age: 91.

^cSignificant Pearson correlation between baseline and 1 year telomere length ($r = 0.85$, $p < 0.001$). Median (Q1 - Q3) of T/S ratio at T0: 1.14 (1.02-1.30). Median (Q1 - Q3) of T/S ratio at T12: 1.13 (1.00-1.29).

^dWilcoxon matched-pairs signed-rank test comparison between telomere length at T0 and T12.

^eAlthough the two median lengths were 6019.9 bp at T0 and 6008.6 bp at T12, and their difference is 11.3 bp (i.e., 6008.6-6019.9 = -11.3 bp), the median difference between T12 and T0 lengths is -41.2 bp, as it depends on how many bp were lost and gained per patient.

^fGenetic ethnicities. Mixed ethnicity ($n = 36$) and African ethnicity ($n = 8$) were pooled together as "Other".

^gClinically relevant weight gain (i.e., $\geq 7\%$ from baseline weight) at T12.

^hHigh-risk drugs for inducing metabolic adverse effects: clozapine, olanzapine valproate; medium-risk drugs: lithium, mirtazapine, quetiapine, risperidone; low-risk drugs: amisulpride, aripiprazole.

ⁱInternational Classification of Diseases-10 classification: organic disorders, anxiety, personality disorder, intellectual disability, dementia, and substance use disorder were classified together as "other."

^jPatients classified as smokers at T0 and as non-smokers at T12 were classified as ex-smokers. Whether non-smokers were tobacco-naïve was unknown.

^kPatients with or without records of previous psychotropic treatments with metabolic risk in our database (i.e., see list of psychotropic drugs reported in footnote^h). Among patients with a previous psychotropic treatment, 33 had a previous low-risk drug, 87 a medium-risk and 30 a high-risk drug.

^lAntidepressant drugs among: agomelatine, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, mianserine, moclobemide, paroxetine, sertraline, trazodone, venlafaxine.

^m49 patients were prescribed with ≥ 1 additional psychotropic drug with metabolic risk at T12 (i.e., see list of psychotropic drugs reported in footnote^h).

bp base pairs, BMI body mass index, CRP C-reactive protein.

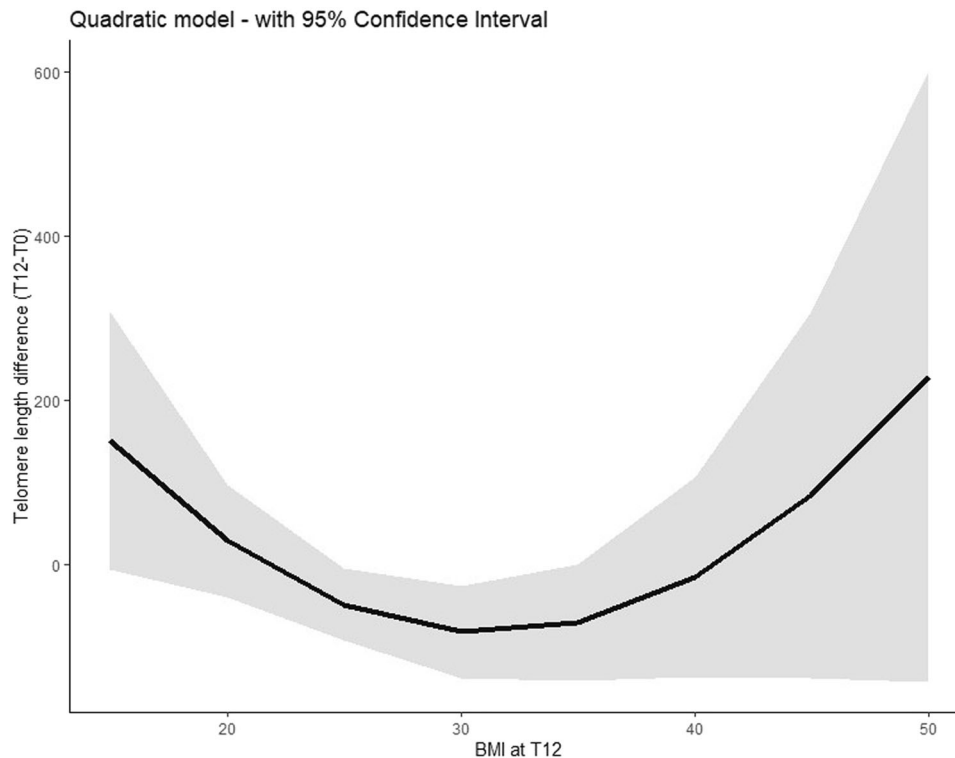


Fig. 1 Non-linear relationship between telomere base-pair differences (T12-T0) and 1-year BMI. Linear model adjusted for age, sex, smoking status, antidepressant co-medication, BMI and BMI square. BMI β -estimate: -55.3, $p = 0.026$ and BMI² β -estimate: 0.89, $p = 0.037$.

patients taking high-risk drugs. This result may be due to chance, given the low sample size, or to the potential properties of decelerating cellular aging of both mood stabilizers (i.e., valproate) and clozapine, as mentioned in previous cross-sectional studies

[33, 34]. However, unlike two previous cross-sectional studies reporting a positive correlation between telomere length and lithium treatment duration [9], and significant telomere shortening among olanzapine-treated patients versus controls [10], in

Table 2. Linear models of telomere base pair differences between T12 and T0.

Predictors	Telomere base pair differences (T12-T0) ^a					
	A			B		
	Model1 ^d					
	Estimates	CI	p	Estimates	CI	p
BMI/5 if BMI < 30 (kg/m ²) ^b	-93.1	-155.2 – -31.0	0.003	-83.4	-152.2 – -14.5	0.018
BMI/5 if BMI ≥ 30 (kg/m ²)	-58.9	-102.8 – -15.0	0.009	-47.0	-97.2 – 3.1	0.066
CRP (2 log) ^c				-38.0	-66.1 – -9.9	0.008
N	195			159		
	Model2 ^f					
CRWG [Yes] ^e	-490.0	-863.0 – -117.1	0.010	-557.4	-996.0 – -118.7	0.013
Baseline weight (kg)	-3.2	-5.9 – -0.5	0.022	-2.1	-5.1 – 0.8	0.15
Baseline weight (kg) * CRWG [Yes]	6.3	1.2 – 11.5	0.016	7.8	1.7 – 13.9	0.013
CRP (2 log) ^c				-36.2	-63.7 – -8.7	0.010
N	200			162		

^aModels below the A column do not include CRP as co-variate and vice-versa. Models were also adjusted for age, sex, smoking status (i.e., smokers and ex-smokers versus non-smokers) and antidepressant co-medication.

^bBMI is expressed as five BMI units. At T12, 45 patients had a BMI ≥ 30 kg/m².

^cCRP values are expressed as base-two logarithm values.

^dFor BMI < 30 kg/m², each increase of five BMI units (e.g., from 20 to 25 or from 22 to 27 kg/m²) would lead to -93.1 (Model1-A) or -83.4 base pairs (Model1-B) on average. For BMI ≥ 30 kg/m², each increase of five BMI units (e.g., from 30 to 35 or from 33 to 38 kg/m²) would lead to -58.9 base pairs according to Model1-A. According to Model1-B, each time CRP levels doubled, a loss of -38.0 base pair was predicted.

^eClinically relevant weight gain (i.e., ≥7% from baseline weight).

^fPatients reaching CRWG at T12 showed a mean of -490.0 or -557.4 base pairs less than patients not reaching this threshold according to Model2-A and Model2-B, respectively. According to Model2-A, for each additional kg of baseline weight among patients not reaching CRWG, -3.2 base pairs were predicted, whereas for patients reaching CRWG, +3.2 base pairs were predicted for each additional baseline kg (i.e., -3.2 + 6.3). Thus, the telomere base pair difference for two fictive patients with CRWG of 50 and 80 kg would be -167.4 and 66.6 base pairs, respectively [i.e., -557.4 + (7.8*50) and -557.4 + (7.8*80), respectively], according to Model2-B.

BMI body mass index, CI 95% confidence interval, CRP C-reactive protein, N number of included patients, p p-value.

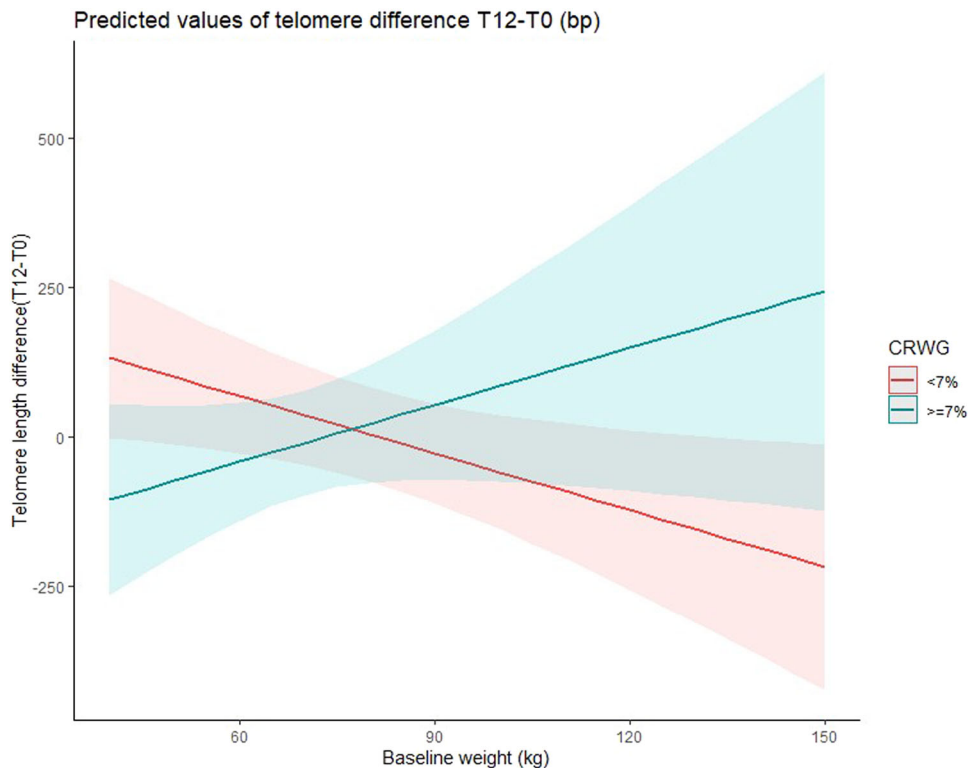


Fig. 2 Predicted values for telomere base-pair differences (T12-T0) versus baseline weight. Prediction of telomere base-pair difference versus baseline weight for patients experiencing clinically relevant weight gain (CRWG, i.e., ≥7%) or not (i.e., <7%) with 95% confidence interval according to Model-2A, Table 2.

Table 3. Logistic regression for important telomere lengthening or shortening.

Predictors	Important telomere lengthening ^a				Important telomere shortening ^b			
	A ^c	B ^c	C	D	A ^c	B ^c	C	D
CRWG [Yes]	OR 0.95 CI 0.48 – 1.87 p 0.89	OR 1.51 CI 0.69 – 3.36 p 0.31	OR 0.56 CI 0.26 – 1.17 p 0.13	OR 0.47 CI 0.18 – 1.12 p 0.10	OR 0.65 CI 0.40 – 1.01 p 0.068	OR 0.61 CI 0.34 – 1.03 p 0.085	OR 1.09 CI 0.73 – 1.61 p 0.68	OR 0.89 CI 0.56 – 1.38 p 0.62
Baseline weight (standard deviation)	3.27	1.48 – 7.64	0.004	5.40	2.02 – 16.57	0.001	0.57	0.21 – 1.82
Baseline weight (standard deviation) * CRWG [Yes]				0.84	0.64 – 1.08	0.19	1.28	1.00–1.64
CRP (2 log) ^d				200			200	162
N				162			200	162

^aImportant telomere lengthening included values for telomere base pair differences from 75th percentile up to the maximum value (i.e., from +115.1 to +1220.2 base pairs). Models below the A column do not include CRP as co-variate and vice-versa.

^bImportant telomere shortening included values for telomere base pair differences from 25th percentile to the minimum value (i.e., from –217.7 to –1212.4 base pairs). Models below the C column do not include CRP as co-variate and vice-versa.

^cModels were also adjusted for age, sex, smoking status (i.e., smokers and ex-smokers versus non-smokers) and antidepressant co-medication. Continuous variables (i.e., age and baseline weight) were scaled according to the variable mean and standard deviation.

^dAccording to Model-A and -B, the increment of one standard deviation of baseline weight among patients with CRWG is associated with 3.27 and 5.40 odds of experiencing important telomere lengthening, respectively.

^eCRP values are expressed as base-two logarithm values.

CRWG Clinically relevant weight gain, CI 95% confidence interval, CRP C-reactive protein, N number of included patients, OR odds ratio, p p-value.

the present study no significant telomere changes were found for patients taking these two drugs. This discrepancy is possibly explained by the different study designs, with the present longitudinal study standing in contrast with a cross-sectional design comparing two different cohorts at one time-point, or by the different sample sizes (e.g., 256 bipolar patients included in the previously mentioned study [9] versus 23 patients taking lithium in the present study).

BMI was associated with telomere shortening, with BMI increases up to 30 kg/m² resulting in greater telomere attrition than increases from 30 kg/m², suggesting that increasing BMI up to becoming obese has a stronger impact on telomere attrition than increasing BMI once this threshold is reached. This result is in contrast with a previous one-year longitudinal study reporting greater telomere attrition with increased baseline obesity, possibly explained by the inclusion of non-psychiatric women experiencing chronic obesity [35]. Moreover, an approximately four-fold predicted increase in overall telomere attrition was found among patients with low baseline weight (e.g., 50 kg) and one-year CRWG, which is in agreement with a previous cross-sectional analysis reporting an inverse association between telomere length and self-reported weight gain in the general population [36]. Conversely, higher baseline weights were associated with less telomere shortening (e.g., 2.5-fold the overall shortening for 60 kg patients versus four-fold for 50 kg patients) or even telomere lengthening (+ 77 bp for 90 kg patients) among CRWG patients, with a large confidence interval predicted for the latter case. Altogether, both CRWG and BMI results suggest that gaining weight or becoming obese with weight-inducing psychotropic treatments could induce dysregulation of inflammatory biomarkers [37], which could upregulate telomere shortening. On the other hand, when already obese, telomere shortening would not be further upregulated, given the chronic inflammation state. Thus, telomere lengthening could be explained by secondary biological/pharmacological mechanisms prevailing once a chronic inflammation state is reached (e.g., psychotropic drugs' telomerase-induction properties). Of note, this result could also be explained by other uncontrolled factors, such as changes in dietary intake and physical activity experienced by overweight and obese patients. Hence, the mechanisms linking psychotropic-induced weight gain, BMI, telomere length and inflammation cannot be reflected by examining these variables alone, as other secondary factors may be involved.

Patients with CRWG had a significant increase in CRP levels, on average +49% greater than among patients with non-CRWG, suggesting that metabolic changes rather than the psychotropic treatment itself could increase inflammatory biomarkers. This agrees with a previous cross-sectional study including clozapine-treated patients showing that BMI is associated with elevated CRP levels [16]. However, these results might also be explained by other uncontrolled factors, as CRP is also associated with several environmental (e.g., poverty [38]) and medical factors (e.g., psychiatric symptoms severity [17–19]). In the present study, CRP increases were also associated with telomere attrition, which agrees with a previous cross-sectional study reporting an inverse correlation between CRP values and telomere length among patients treated with psychotropic drugs [25]. Furthermore, when adjusting our linear model for CRP values (i.e., Table 2. Model 1-B), a significant effect on telomere attrition was observed only for BMI < 30 kg/m². This could be explained by a smaller sample size (i.e., 159/195 patients with CRP values), and/or by chronic inflammation associated with obesity, which could mediate the association between obesity status and telomere shortening as suggested in a previous cross-sectional study including 5451 non-psychiatric adults [21]. Altogether, the present results indicate that both weight gain and CRP increases are associated with telomere shortening on average, and that inflammation increases are found among patients with relevant weight gain after one year of psychotropic treatment.

Table 4. Mendelian randomization results using UKBiobank data.

Beta ^a	SE	P-value	N SNPs	Q stat ^b	Q p-value ^b	Exposure	Outcome	Group ^{c,d}
-0.37	0.13	0.00417352	613	532.87	0.990563143	BMI	Telomere	Cases
-0.12	0.03	5.07E-06	633	613.19	0.696970429	BMI	Telomere	Psychiatric controls
-0.06	0.01	1.11E-08	633	1522.60	3.01E-75	BMI	Telomere	Population-based controls
0.00	0.12	0.984541935	448	364.12	0.99836974	CRP	Telomere	Cases
-0.04	0.02	0.070093414	462	543.72	0.00468493	CRP	Telomere	Psychiatric controls
-0.04	0.01	6.71E-06	464	1158.18	2.92E-61	CRP	Telomere	Population-based controls
2.35	1.75	0.17872795	43	45.37	0.33340906	EA	Telomere	Cases
0.02	0.11	0.865740958	45	57.06	0.0895339	EA	Telomere	Psychiatric controls
0.08	0.05	0.132819814	45	215.56	1.82E-24	EA	Telomere	Population-based controls

^aMendelian randomization beta coefficient.

^bHeterogeneity Q-statistic and its p-value.

^c9798, 16228 and 252932 individuals were included in cases, psychiatric controls and population-based controls.

^dA sensitivity analysis excluding individuals receiving psychotropic drugs known to decrease weight in some cases (see Supplementary Table 1) was performed, and similar results were found (data not shown).

SE Standard Error, N number, Q Q-statistic, BMI body mass index, CRP C-Reactive Protein, EA Educational attainment.

Antidepressant co-medication was associated with greater telomere attrition. This result is in contrast with a previous 24 week longitudinal study reporting telomere lengthening after antidepressant treatment onset, with the small number ($n = 12$) of depressed patients and the included antidepressant treatments (i.e., selective serotonin reuptake inhibitors only [39] versus diverse antidepressant medications in the present study) possibly explaining the difference. Moreover, inter-individual one-unit increases in socioeconomic status were associated with decreased odds of important telomere shortening. This finding supports previous studies indicating that telomere shortening is a multifactorial biological process, which is influenced by many environmental factors [32]. Of note, the socioeconomic status examined in the present study includes income, education, occupation, and housing conditions.

MR analysis on telomere shortening in the UKBB psychiatric cohort showed a causal effect only for BMI. Indeed, MR results indicated that BMI increases strongly enhance telomere attrition when weight-inducing psychotropic drugs are prescribed, regardless of the CRP level. However, a causal effect of inflammation on telomere shortening cannot be excluded. Indeed, MR indicated that CRP levels enhance telomere attrition among non-psychiatric controls, suggesting that other unaccounted variables among the psychiatric population may have prevented the detection of this causal relationship. Moreover, several other inflammatory biomarkers (e.g., cytokines) were not considered. In addition, in UKBB, given the cross-sectional design, CRP levels were possibly measured after different treatment durations among individuals who experienced variable weight changes, whereas in our longitudinal PsyMetab study, we considered weight gain and inflammation at one year, both variables being associated one with the other. Therefore, considering inflammation cross-sectionally and independently of metabolic changes might have contributed to a non-significant effect of CRP on telomere attrition in psychiatric subjects.

Interestingly, a recent study investigated the consequences of having longer and shorter telomere length versus the general population's mean length, suggesting that 40 years-old individuals with shorter telomere length of 1 standard deviation had 2.5 years of lower life expectancy versus individuals with longer telomere length of 1 standard deviation [40]. Thus, among psychiatric patients taking weight-inducing psychotropic drugs, important BMI increases might lead to a further lowering in life expectancy than among psychiatric patients with weight-neutral treatments or among the general population.

Several limitations of the present study must be mentioned. Many environmental factors previously associated with telomere length (e.g., perceived stress levels, paternal age, marital status, etc.) or with both telomere length and weight gain separately (e.g., physical activity, alcohol consumption, diet, etc.) could not be controlled for [32], and only the inflammatory biomarker CRP was available to investigate the association between inflammation and telomere trajectories. Adherence to treatment could not be ascertained, and no data was available on the duration of psychiatric illness at baseline, nor on psychiatric symptoms severity at the time of sample collection. Moreover, although our results showed that the potential telomerase-enhancing property of antipsychotics was not associated with our outcome, the prescription of other telomerase-enhancing or senolytic drugs could not be controlled for. The effect of each psychotropic drug alone on telomere trajectories, as well as the speed of telomere changes over one year considering samples collected at one and 3 months of treatment could also not be ascertained using a multivariate analysis given the limited sample size. Moreover, given the reduced sample size in the UKBB with available longitudinal data, only a cross-sectional approach could be used to validate our associations. On the other hand, our longitudinal study, taking each patient as his/her own control, could investigate the association of psychotropic drugs, induced weight gain and inflammation with telomere dynamics, considering weight change over time and CRP levels. Finally, the UKBB statistical power allowed validation of the associations and demonstrated a causal effect of BMI on telomere shortening, which was stronger among patients receiving weight-inducing psychotropic treatments. Further longitudinal studies should evaluate the long-term metabolic impact of early weight gain on telomere length to better understand the associations between psychotropic-induced weight gain and telomere biology.

CONCLUSION

To our knowledge, this is the first study showing that one-year weight gain and increases in CRP levels are associated with telomere shortening, and that BMI increments strongly enhance telomere attrition among patients receiving weight-inducing psychotropic treatments.

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DATA SHARING STATEMENT

Data from PsyMetab cannot be publicly deposited due to participant confidentiality purposes. Data from PsyMetab can be accessed after formal application and ethical review by the Ethics Committee of the Canton of Vaud. For further details: <http://www.chuv.ch/cnp-psymetab>.

AUTHOR CONTRIBUTIONS

CBE had full access to the data in the study and takes responsibility for its integrity and accuracy. Study concept and design was provided by CBE. Acquisition of data was provided by MP, NL, CG and by MPr, FG, KJP, AvG, PC, and by JL. MP, SR, MCS and ZK provided statistical analyses and interpretation. Drafting of the manuscript was provided by MP. Each author provided critical revision of the manuscript. CBE, PC and KJP obtained funding for the study. FG, AvG, PC, and CBE provided administrative, technical, or material support.

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COMPETING INTERESTS

CBE received honoraria for conferences from Forum pour la formation médicale, Janssen-Cilag, Lundbeck, Otsuka, Sandoz, Servier, Sunovion, Sysmex Suisse AG, Takeda, Vifor-Pharma, and Zeller in the past 3 years. The authors declare no competing interests.

ETHICS

This study was carried out in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Vaud (CER-VD).

ADDITIONAL INFORMATION

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