



## Letter to the Editor

**No alteration in leukocyte telomere length in schizophrenia; evidence from a meta-analysis**

Dear editor,

There are numerous studies that have evaluated the leukocyte telomere length (LTL) in schizophrenia patients and healthy controls, with controversial results (for reviews see [Russo et al., 2018](#)). Very recently, a meta-analysis concerning the LTL in schizophrenia cases has been published ([Russo et al., 2018](#)). The authors reported that LTL in schizophrenia decreased significantly compared with healthy controls. Also they found very high level of heterogeneity between studies. Here, a number of criticisms to this study are presented.

The authors of the mentioned article used study of [Vaez-Azizi et al. \(2015\)](#). Which compared the LTL between two groups of schizophrenia and probably the samples had overlapping with another report of the research group. Therefore this study should be removed from the analysis.

Very recently five studies investigating the alteration of LTL in schizophrenia have been published ([Riley et al., 2018](#); [Shivakumar et al., 2018](#); [Zhang et al., 2018](#); [Aas et al., 2019](#); [Çevik et al., 2019](#)). These studies did not include in the above-mentioned meta-analysis.

We performed a meta-analysis using 22 studies. The LTL in schizophrenia groups were normalized against the LTL of the control subjects. The pooled effect size as the standardized mean difference (SMD) and 95% confidence intervals (95% CI) was calculated. The heterogeneity between studies was evaluated with the Q and  $I^2$  statistics. We found very high level of heterogeneity between studies ( $Q = 1976.2$ ,  $df = 21$ ,  $P < 0.001$ ;  $I^2 = 98.9\%$ ).

To investigate the evidence for publication bias, the funnel plot and Egger's test were used ([Egger et al., 1997](#)). Visual inspection of the funnel plot showed an asymmetry in the distribution of studies used in the meta-analysis in standardized mean difference versus the standard errors ([Fig. 1A](#)). Statistical analysis revealed that there was significant publication bias (Egger's test,  $t = 2.73$ ,  $df = 20$ ,  $P = 0.012$ ).

Using the GPOWER software ([www.pscho.uni-duesseldorf.de/aap/projects/gpower](http://www.pscho.uni-duesseldorf.de/aap/projects/gpower)), assuming a power of 0.80,  $\alpha = 0.05$ , and an effect size of 0.4, a minimum of 100 patients and 100 controls would be necessary to detect a small to medium difference between cases and controls. There were 8 studies with >200 participants; these studies were used for reanalysis. Among studies with relatively large sample size, significant heterogeneity was observed ( $Q = 1591.3$ ,  $df = 7$ ,  $P < 0.001$ ,  $I^2 = 99.6\%$ ; [Fig. 1B](#)).

In order to investigate the possibility of involvement of ethnicity in heterogeneity, the studies were stratified to Caucasian and Asian populations. Although the heterogeneity between studies a little

bit was decreased, there was significant heterogeneity between studies from Caucasian populations ( $Q = 22.79$ ,  $df = 4$ ,  $P < 0.001$ ,  $I^2 = 82.4\%$ ). The LTL did not show significant alteration in schizophrenia patients (SMD = +0.020, 95% CI: -0.180 to +0.220,  $P = 0.845$ ; [Fig. 1C](#)). To evaluate the stability of the association, the sensitivity analysis was performed by sequential removal of each study from the analysis. Sensitivity analysis revealed the stability of the association. This means that among Caucasians the LTL in schizophrenia patients were similar to healthy controls, which it is not similar to results of [Russo et al. \(2018\)](#) study.

There were three studies from Asians. A study from Japan with very large sample size ( $n = 2283$ ) reported that schizophrenia patients had longer LTL compared with control group ([Zhang et al., 2018](#)), whereas the study of [Rao et al. \(2016\)](#) reported shorter LTL in schizophrenia. The other study did not show significant alteration in telomere length of schizophrenia patients. Therefore, significant heterogeneity among these studies was observed ( $Q = 872.6$ ,  $df = 2$ ,  $P < 0.001$ ,  $I^2 = 99.8\%$ ), and there was no significant association between LTL and schizophrenia in Asians (SMD = +0.424, 95% CI: -1.97 to +2.81,  $P = 0.729$ ). There was no evidence for publication bias in large sample studies before and after stratification by ethnicity (data not shown).

We found significant heterogeneity between studies and that this heterogeneity was not related to study sample size and/or participants ethnicity. Taken together, it is suggested that factors such as age of patients, lifestyle, antipsychotic drugs, duration of disease, and hospitalization can affect the telomere length in schizophrenia patients ([Nieratschker et al., 2013](#); [Zhang et al., 2018](#)). Finally it should be noted that schizophrenia is a heterogeneous disease with several subtypes. It is obvious that each subtype may have a specific relationship with the LTL. In the studies used for current meta-analysis, patients were not categorized based on the disease subtypes, therefore, we discovered a high level of heterogeneity between studies. Future well-designed large scale studies (with information about the above-mentioned factors) are warranted to validate the present findings.

**Contributors**

FZD and NO were responsible for literature search, data extraction, data interpretation and manuscript drafting. FZD and NO had equal contributions. MS was responsible for the statistical analysis, data interpretation and manuscript drafting. All authors contributed to and approved the final version of the manuscript.

**Conflict of interest**

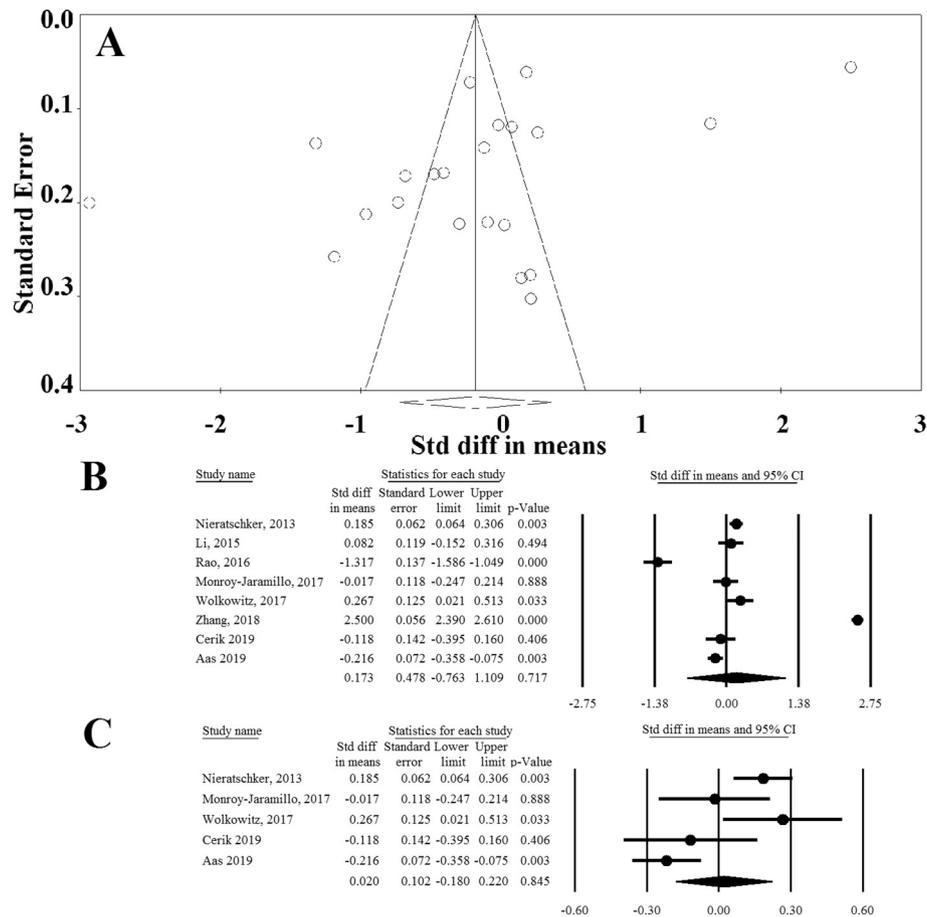
The authors declare no conflict of interest.

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**Fig. 1.** Funnel plot for association between schizophrenia and leukocyte telomere length when all studies were included in the meta-analysis (A). Forest plots for association between schizophrenia and leukocyte telomere length when studies with large sample size included in analysis (B) and studies from Caucasian populations (C).

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