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Research Paper

# Get up! Functional mobility and metabolic syndrome in chronic schizophrenia: Effects on cognition and quality of life

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ABSTRACT

Low mobility and poor physical health, especially metabolic syndrome, are frequently reported in patients with schizophrenia and tend to increase with age. Recent evidence suggests that metabolic syndrome may affect cognition and quality of life, while the role functional mobility is still less addressed and their interplay needs to be further explored. This study aims to analyze the effects of functional mobility on cognitive performance, symptoms and quality of life, taking into account age and also modeling it relationship with metabolic syndrome in a sample of 103 adults with chronic schizophrenia.

Data were analyzed by means of Pearson's correlations, forward stepwise regressions and mediation models.

Results showed that poorer functional mobility is associated with metabolic syndrome and related to more severe negative symptoms, worse cognitive abilities and more disrupted quality of life. Moreover, functional mobility proved to be a significant predictor of cognitive abilities and quality of life, even when other influencing factors were taken into account and independently of age. Finally, analyses showed that functional mobility mediates the effect of metabolic syndrome on both cognition and quality of life.

Taken together, these results suggest that functional mobility and metabolic syndrome may represent relevant aspects that further contribute to the evolution of cognitive deficits through all stages of the disease, with also impact on quality of life. In this perspective, the assessment of functional mobility, a non-invasive and quickly performed test may be worth to be implemented in clinical practice, with important implications for treatment and monitoring.

## 1. Introduction

The World Health Organization has identified schizophrenia as one of the 10 leading global causes of disability, with a significant disease burden worldwide (Murray et al., 2012).

People with schizophrenia display different degrees of cognitive impairment that represents one of the most critical determinants of quality of life (QoL) and daily functioning, potentially more disruptive than other symptoms (Nuechterlein et al., 2011; Penadés et al., 2019). Cognitive deficits can be detected since the onset of the disease and, according to some authors, even before the onset (Seidman et al., 2010; Jones et al., 1994). On the one hand, cognitive impairment is a core feature of psychotic disorders that provides a window into understanding developmental course and risk for psychosis; on the other, cognitive deficits represent an important determinant of disease outcome across the life span.

Cognitive deficits are indeed detectable during all stages of the disease, and there is no mystery regarding whether cognitive impairment is

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present in chronic schizophrenia, however less is known on their longitudinal trajectories. A robust and reliable cognitive impairment has been observed in up to 80% of patients (Reichenberg et al., 2009), influenced by several individual and illness related variables (Barlati et al., 2019; Bechi et al., 2021), with a negative impact on the functional outcome. However, the outcome of chronic schizophrenia is also affected by other relevant aspects, such as the poor physical health and the frequent medical comorbidities, in particular the metabolic syndrome (MetS) (Hennekens et al., 2005; Homel et al., 2002; Jin et al., 2011; McEvoy et al., 2005), defined as a clustering of at least three of interrelated cardiovascular risk-factor abnormalities, including abdominal obesity, hyperglycemia, hypertension, high triglycerides or low high-density lipoprotein (HDL) cholesterol levels (Grundy et al., 2005). Individuals with schizophrenia are at greater risk for MetS, which is in turn associated with cognitive impairment and can potentially contribute to functional decline observed in many patients throughout the course of illness.

In this regard, a recent study with a 20-year follow-up showed a significant increase in BMI in patients with schizophrenia (Strassnig et al., 2017a, 2017b). Furthermore, other studies conducted on the same cohort of patients highlighted how BMI as well as general health status and mobility limitations contribute to the long-term cognitive and functional outcome in schizophrenia (Strassnig et al., 2017a, 2017b; Strassnig et al., 2018).

In addition to this, schizophrenia often leads to unhealthy lifestyle, characterized by minimal or no exercise and marked sedentary behavior (Strassnig et al., 2006). In this view, it is interesting to note that, in older adults, the impairment in functional mobility (FM) is one of the main causes of functional disability (Lin et al., 2017). It can thus be hypothesized that a vicious cycle of cognitive deficits, poor physical health, and low activity levels may be a critical determinant of poor daily functioning and QoL in people affected by schizophrenia.

Moreover, research pointed out that measures of FM may represent a raw index for physical health and cognitive impairment. Among these, the Timed Up Go (TUG) test is a performance-based FM test that requires an individual to perform physical activities (turning, transfers from sitting, and walking) in a clinical setting. Beside its apparent simplicity, the TUG test has the advantage of reflecting several components of FM, and thus can help predict the overall functional level of the patients (Herman et al., 2011). Studies showed that, in community-dwelling older people, the TUG performance strictly related to several factors including cognitive functioning and health status (Kwan et al., 2011). Moreover, lower FM, as measured by the TUG test, seems to predict further cognitive decline in individuals with mild cognitive impairment (McGough et al., 2011). Taken together, these findings suggest that physical tests related to lower extremity and postural control, which also emphasize velocity, such as the TUG test, might be useful in investigating the complex relationship between physical and cognitive functioning. The evaluation of FM has also been suggested as a relevant tool to be implemented in clinical practice to assess global cognitive functioning (Bramell-Risberg et al., 2012).

Despite increasing evidence in older people, according to our knowledge, there are only two studies in the literature that used the TUG test to evaluate FM in patients with schizophrenia. In one study the FM was associated with negative symptoms and neurocognition in older adults with schizophrenia (Leutwyler et al., 2014), while the other identified an association with depression (Kim et al., 2020). The topic is worth of further investigation, also in light of the disrupted FM frequently reported among patients with schizophrenia, especially in the chronic phase of the illness.

Given the increased prevalence of health issues and physical mobility impairment with age, these aspects may become more relevant in older patients and may differentially affect cognitive and functional outcome through the different stages of the illness.

Based on these premises, this study aims to analyze, through a comprehensive assessment in patients with chronic schizophrenia, the effects of functional mobility on symptoms, cognition and quality of life and, innovatively with respect to previous literature, to model the interplay with metabolic syndrome. In addition, given the relationship between age on one side and functional mobility, as well as cognition and quality of life on the other, we also explored the impact of functional mobility and metabolic syndrome on cognitive outcome and QoL in different age subgroups.

## 2. Methods

One hundred and three adults, age over 18 years, with a diagnosis of schizophrenia according to DSM-5 criteria (American Psychiatric Association, 2013), were enrolled from April to October 2021 at the Research Unit for Psychotic Disorders of IRCCS San Raffaele Hospital, Milan, Italy. Inclusion criteria were: clinical stabilization, no evidence of substance dependence or abuse, no comorbid psychiatric diagnoses, epilepsy, or any other major neurological illness or perinatal trauma, or intellectual disability. All subjects provided informed consent to a protocol approved by the local ethical committee, following the principles of the Declaration of Helsinki.

### 2.1. Assessment

All people were assessed for psychopathology, cognition, QoL, FM, and MetS. Trained psychologists evaluated cognition and QoL, while trained psychiatrists assessed the severity of psychopathology and the presence of MetS. FM was assessed by trained physiotherapists.

The severity of psychopathology was assessed with the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay et al., 1987). The PANSS evaluates different symptoms domains, specifically positive, negative, and general symptoms and also provides a total score as global index.

Neurocognitive abilities were assessed with the Italian Version of the Brief Assessment of Cognition in Schizophrenia (BACS) (Anselmetti et al., 2008). The BACS evaluated the cognitive domains that are usually impaired in schizophrenia: verbal memory, fluency, executive functions, working memory, attention, and psychomotor speed and coordination. Additionally, a measure of overall cognitive functioning (i.e., Cognitive Index, GCI) is derived from BACS subscores.

QoL was assessed with the Quality of Life Scale (QLS) (Heinrichs et al., 1984), a semi-structured interview balancing subjective questions regarding life satisfaction and objective indicators of social and occupational role functioning. This instrument includes four subscales, namely Interpersonal relations, Instrumental role, Intrapsychic foundation, and Common objects and activities and a Total score is provided as global measure.

FM was assessed with the TUG test (Herman et al., 2011). The test procedure for the TUG is relatively simple. Subjects are asked to stand up from a standard chair (seat height between 44 and 47 cm), walk a distance of 3 m (marked on the floor), turn, and walk back and sit down. Subjects are permitted to use routine walking aids and are instructed not to use their arms to stand up. No physical assistance is given. The time to complete the task is measured with a stopwatch. Timing commences on the command ‘go’ and stops when the subject's back is positioned against the back of the chair after sitting down. The task is performed three times. Shorter times indicate better performance.

Finally, the presence of MetS was identified based on anthropometric and blood chemistry measurements according to the most commonly used criteria, the ATPIIIA criteria (Huang et al., 2009).

### 2.2. Statistical analysis

The analyses were performed with STATISTICA Software for Windows (Version 8 StatSoft Inc., Tulsa, OK, USA) and the Statistical Package for the Social Sciences (IBM-SPSS for MAC, Version 25).

The relationship between FM and cognitive performance, symptoms,

QoL, and MetS was first analyzed by means of Pearson's correlations between the TUG score and each subtest score of BACS, PANSS, QLS and each MetS criterion. Furthermore, to assess differences in functional mobility between patients with and without MetS, we performed an ANOVA with TUG score as dependent variable and the diagnosis of MetS as independent variable.

Moreover, to evaluate the predictive effect of TUG on both cognitive performance and QoL also taking into account other possible influencing factors, we performed two forward stepwise regressions. In details, we included BACS GCI and QLS total score respectively for model 1 and 2 as dependent variables and TUG score, MetS, sex, age, education, duration of illness, and chlorpromazine equivalent dosage as predictors.

Given the correlation between age and TUG score, to better explore the effect in different subgroups according to age, we performed other two forward stepwise regressions separately in patients younger vs older than 42 years (this cut-off was selected based on the median age of the sample). In particular, given the reduced size of these subsamples, we included only the TUG score and MetS as predictors, maintaining BACS CGI and QLS total score as dependent variables.

Finally to estimate the interplay between MetS and FM on both cognition and QoL, we performed two mediation models. In details, we tested whether the TUG score mediates the relationship between MetS and GCI, in the first model, and QLS total score in the second model.

Mediation models were tested using the PROCESS tool for SPSS (Hayes, 2017), performing model 4, which evaluates the effects of full mediation (i.e., the direct effect of X on Y did not remain significant once the mediators are included in the model), as well as the effects of partial mediation (i.e., the direct effect of X on Y loses significance once the mediators are included in the model). The bootstrapping procedure recommended by Preacher and Hayes (2008) was applied for testing the significance of mediating and indirect effects. We used 5000 bootstrap resamples to generate the 95% confidence percentile intervals (CI). In cases where zero did not fall within the 95% CI of the bootstrapped samples, the mediating effect was considered statistically significant. The $R^2$ was calculated as the mediation effect size measure (Fairchild et al., 2009), while to estimate the effect sizes of the indirect effects the completely standardized indirect effects were used (Preacher and Kelley, 2011).

## 3. Results

Table 1 shows demographic, clinical, cognitive, physical, and functional measures of the sample.

Correlation analysis (see Fig. 1 and Table 2) shows that TUG score is positively related to negative symptoms, age, duration of illness, and negatively related to BACS subscores (i.e., working memory, psychomotor coordination, verbal fluency, processing speed, executive functions, and GCI), and QLS scores (i.e., interpersonal relations, self-directedness, and total score).

The ANOVA ($F = 6.01$, $p = .02$) showed significantly higher TUG scores in patients with MetS ($6.17 \pm 1.41$), compared to patients without MetS ($5.49 \pm 1.07$).

The forward stepwise regression on BACS GCI was significant ($F = 5.23$, $p = .007$, adjusted $R2 = 0.10$) and showed that both TUG score ($p = .004$, $\beta = -0.34$) and MetS ($p = .04$, $\beta = 0.24$) were significant predictors of global cognitive functioning, with higher functional mobility and lower MetS being associated to better cognitive performance. No significant effects emerged for the other assessed variables, including age and duration of illness.

The forward stepwise regression on QLS Total score was also significant ($F = 6.99$, $p = .002$, adjusted $R2 = 0.14$). TUG score ($p = .003$, $\beta = -0.34$) and sex ($p = .03$, $\beta = -0.24$) were significant predictors, with higher functional mobility and female sex being associated to better QoL. Again, no significant effects were observed for the other variables, namely age, education, duration of illness, chlorpromazine equivalent, nor MetS.

**Table 1**
Demographic, clinical, cognitive, physical, and functional characteristics of the sample.

| | Mean ± SD/% |
|---|---|
| *Socio-demographical and clinical data* | |
| Age (years) | 44.95 ± 13.06 |
| Education (years) | 11.41 ± 2.96 |
| Onset (years) | 25.57 ± 8.43 |
| Duration of illness (years) | 18.87 ± 10.06 |
| Treatment – equivalent dosage | 390.52 ± 315.47 |
| *Metabolic parameters* | |
| Systolic blood pressure (mm Hg) | 122.66 ± 13.31 |
| Diastolic blood pressure (mm Hg) | 76.61 ± 11.21 |
| High-density lipoprotein (HDL, mg/dl) | 47.45 ± 13.39 |
| Fasting blood sugar (mg/dl) | 96.01 ± 35.27 |
| Triglycerides (TG, mg/dl) | 150.21 ± 72.44 |
| Diagnosis of MetS (ATP IIIA criteria) | 48% |
| *PANSS* | |
| Positive scale | 16.74 ± 5.13 |
| Negative scale | 21.73 ± 5.99 |
| General scale | 40.85 ± 9.77 |
| Total score | 79.18 ± 16.75 |
| *BACS* | |
| Verbal Memory | 41.94 ± 14.21 |
| Working Memory | 16.83 ± 4.73 |
| Psychomotor Coordination | 64.58 ± 16.87 |
| Verbal Fluency | 38.70 ± 13.64 |
| Attention and Processing Speed | 40.61 ± 12.25 |
| Executive Functions | 14.27 ± 4.63 |
| Global Cognitive Index | 1.45 ± 1.01 |
| *Quality of Life* | |
| QLS - Interpersonal relations | 20.33 ± 10.86 |
| QLS - Instrumental role | 6.77 ± 6.56 |
| QLS - Self-directedness | 27.04 ± 9.98 |
| QLS - Total | 54.54 ± 22.03 |
| *Functional mobility* | |
| TUG test (s) | 5.89 ± 1.31 |

Concerning the analysis performed in the 2 subgroups divided by age, the forward stepwise regression model on BACS GCI in the younger subgroup was significant ($F = 3.48$, $p = .04$, adjusted $R2 = 0.11$) and showed that only TUG score ($p = .02$, $\beta = -0.35$) was a significant predictor of global cognitive functioning, with poorer functional mobility being associated to worse cognitive abilities. Significantly, we did not find an effect of MetS ($p = .09$, $\beta = 0.26$). In the sample of older patients, while the model was not significant ($F = 2.62$, $p = .08$, adjusted $R2 = 0.07$), the TUG score again was a significant predictor of global cognitive functioning ($p = .03$, $\beta = -0.24$), while MetS did not resulted as a significant predictor ($p = .18$, $\beta = 0.22$).

With respect to QLS Total score, the models were significant both in the younger subgroup ($F = 4.06$, $p = .02$, adjusted $R2 = 0.13$), as well as in the older patients ($F = 4.88$, $p = .03$, adjusted $R2 = 0.10$). In both groups the TUG score was a significant predictor ($p = .05$, $\beta = -0.30$ in younger patients and $p = .03$, $\beta = -0.35$ in older patients), confirming that lower functional mobility is associated to poorer quality of life. Moreover, MetS was not a significant predictor of QoL neither in younger patients ($p = .11$, $\beta = -0.24$) nor in the older patients, where it was not included in the stepwise model.

As for mediation analyses, the first model included MetS as predictor, TUG as mediator, and GCI as outcome measure. The model was significant ($R2 = 0.143$, $F = 6.29$, $p = .003$), explaining 14% of variance (see Table 3 and Fig. 2).

Results showed that the effect of MetS on GCI was mediated by the TUG score (Total indirect effect, path ab). The path showing the direct

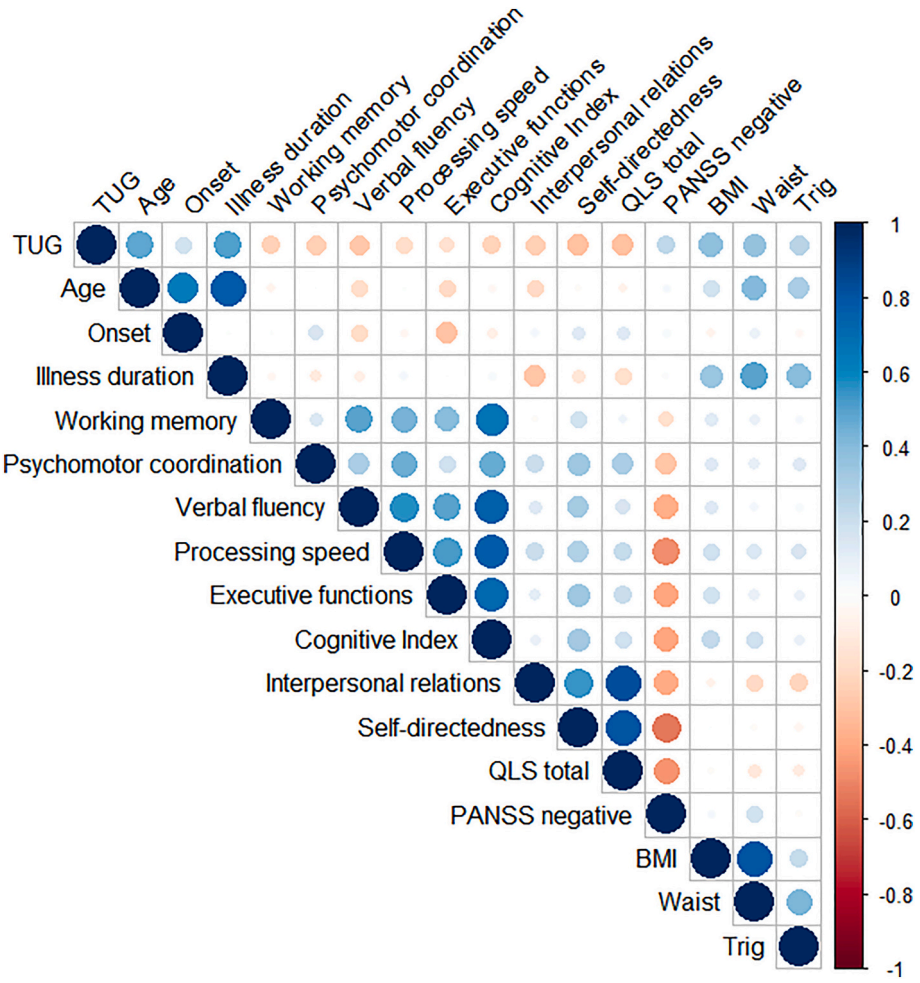



**Fig. 1.** Exploratory correlations.

relationship between MetS and the GCI was not significant (Total effect, path c); however, it became significant when the mediator was entered into the model (Direct effect, path c′). Moreover, the TUG score was significantly associated with MetS (path a) and was a significant predictor of GCI (path b). The completely standardized indirect effect was −0.20 (95% CI = −0.37 to −0.05), indicating that the relation between lower MetS and better cognitive performance is mediated by functional mobility.

The second mediation model included MetS as predictor, TUG score as mediator, and QLS Total score as outcome measure. The model was significant (R2 = 0.14, F = 5.63, p = .005), explaining 14% of variance (see Table 4 and Fig. 3).

Results showed that the effect of Mets on daily functioning was mediated by the TUG score (Total indirect effect, path ab). The path showing the direct relationship between MetS and Quality of Life was significant (Total effect, path c); however, it loses significance when the mediator was entered into the model (Direct effect, path c′). Moreover, the TUG score was significantly associated with MetS (path a) and was a significant predictor of Quality of Life (path b). The completely standardized indirect effect was −0.15 (95% CI = −0.33 to −0.002), indicating that the relation between lower MetS and higher QoL is mediated by functional mobility.

## 4. Discussion

Cognitive functioning and poor physical health status are important determinants of daily functioning and QoL in schizophrenia. A complex interplay between cognitive and physical status has been suggested and needs to be further explored also for its possible clinical implications, especially in terms of prevention and monitoring of the illness course. Moreover, disentangling the relationship between, functional mobility, metabolic syndrome, cognition and quality of life may shed new light on the evolution of cognitive impairment and functional outcomes in schizophrenia.

Our study shows a relevant role of FM in schizophrenia.

In details, correlation analysis suggested that the deterioration of FM is associated with more severe negative symptoms and metabolic disorder, more disrupted cognitive abilities, affecting multiple domains, and a less preserved QoL, especially in social relationships and self-directedness. Moreover, FM was also related to age and duration of illness. The latter data, although not surprising because FM is typically reduced in the elderly population (Leutwyler et al., 2014), should not be underestimated as it could contribute to the progression of the impairment in patients with schizophrenia. It is interesting to note that we did not find an association between FM and positive symptoms in our sample. This may be due to the stability of patients' psychotic symptomatology. Instead, it was not surprising to find an association with the negative symptom subscale because the subscores in this scale assess some aspects of the slowed movement. According to our knowledge, there are only two studies in the literature that used the TUG test to evaluate FM in people with schizophrenia. The more recent one showed a positive correlation between higher TUG score and depression, evaluated with Beck Depression Inventory, Brief Psychiatric Rating Scale, and State and Trait Anxiety Inventory (Kim et al., 2020). This is interesting because we found a positive correlation between a higher TUG score and PANSS negative scale, which shares some traits with

**Table 2**
Correlation matrix.[a]

| | TUG test | |
|---|---|---|
| | r | p |
| Age | **0.47** | **<.001** |
| Onset | 0.19 | .06 |
| Duration of illness | **0.39** | **<.001** |
| Education | −0.15 | .14 |
| BACS - Verbal Memory | <−0.001 | .99 |
| BACS - Working Memory | **−0.24** | **.02** |
| BACS - Psychomotor Coordination | **−0.31** | **.002** |
| BACS - Verbal Fluency | **−0.30** | **.003** |
| BACS - Processing Speed | **−0.24** | **.02** |
| BACS - Executive Functions | **−0.20** | **.05** |
| BACS - Global Cognitive Index | **−0.29** | **.004** |
| QLS - Interpersonal relations | **−0.22** | **.04** |
| QLS - Instrumental role | −0.10 | .36 |
| QLS - Self-directedness | **−0.30** | **.004** |
| QLS - Total | **−0.28** | **.008** |
| PANSS - Positive scale | −0.20 | .08 |
| PANSS - Negative scale | **0.23** | **.04** |
| PANSS - General scale | −0.11 | .33 |
| PANSS - Total Score | −0.04 | .73 |
| Waist circumference | **0.35** | **<.001** |
| Systolic blood pressure | 0.17 | .10 |
| Diastolic blood pressure | 0.06 | .55 |
| HDL | −0.20 | .07 |
| Fasting blood sugar | 0.12 | .26 |
| Triglycerides | **0.24** | **.03** |
| Equivalent dosage | 0.01 | .94 |

[a] Significant results highlighted in bold (p<=.05).

**Table 3**
Mediation model through the TUG score on Global Cognitive Index: estimation of mediation effects.

| | β | SE | 95% CI |
|---|---|---|---|
| Total indirect effect (path ab) | −0.21 | 0.09 | −0.39 to −0.05* |
| MetS → TUG score → Global Cognitive Index (path $a^1d^{21}b^2$) | | | |
| Total effect (path c) | 0.30 | 0.23 | −0.16 to 0.76 |
| MetS → Global Cognitive Index | | | |
| Direct effect (path c′) | 0.51 | 0.23 | 0.06 to 0.96* |
| MetS → Global Cognitive Index | | | |
| Direct effects (paths a, b) | 0.73− 0.29 | 0.280 .09 | 0.16 to 1.30*− 0.46 to −0.11* |
| MetS → TUG score | | | |
| TUG score → Global Cognitive Index | | | |

Note: SE = standard error; 95% CI = confidence intervals at 95%. Path c refers to total direct effect; path c′ refers to direct effect after including mediators (see Fig. 2).
* Significant confidence intervals at 95% (p < .05).

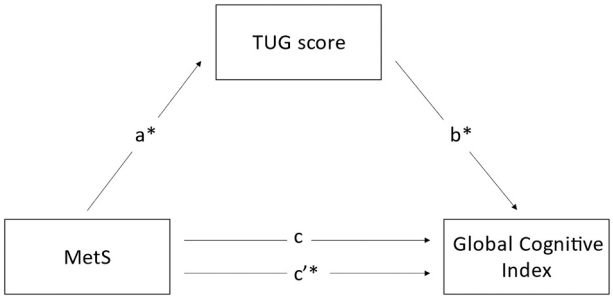



**Fig. 2.** Mediation model through TUG score on Global Cognitive Index.

depression, such as anhedonia, anergia and avolition. Moreover, Kim and colleagues found a negative correlation between better functional mobility and working memory, even though using different scales

**Table 4**
Mediation model through TUG score on Quality of Life: estimation of mediation effects.

| | β | SE | 95% CI |
|---|---|---|---|
| Total indirect effect (path ab) | −3.14 | 1.84 | −7.12 to −0.04* |
| MetS → TUG score → Quality of Life (path $a^1d^{21}b^2$) | | | |
| Total effect (path c) | −9.99 | 4.84 | −19.64 to −0.33* |
| MetS → Quality of Life | | | |
| Direct effect (path c′) | −6.85 | 4.82 | −16.46 to 2.77 |
| MetS → Quality of Life | | | |
| Direct effects (paths a, b) | 0.63 | 0.28 | 0.07 to 1.19* |
| MetS → TUG score | −5.00 | 1.93 | −8.85 to −1.15* |
| TUG score → Quality of Life | | | |

Note: SE = standard error; 95% CI = confidence intervals at 95%. Path c refers to total direct effect; path c′ refers to direct effect after including mediators (see Fig. 3).
* Significant confidence intervals at 95% (p < .05).

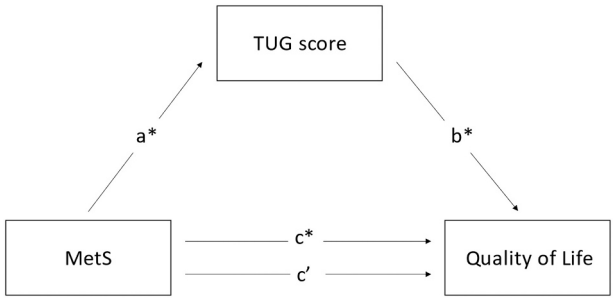



**Fig. 3.** Mediation model through the TUG score on Quality of Life.

compared to our study, which is the Sternberg Working Memory. The other study that used the TUG test to assess FM suggests that more severe negative symptoms, slower speed of processing, and being older have a negative impact on mobility (Leutwyler et al., 2014). According to previous researches, our data highlighted the association of slower speed of processing and slower TUG time. Rosano et al. (2012) provide some rationale for the association between speed of processing and mobility by suggesting that walking requires perception and interpretation of the terrain's properties and obstacles in surrounding space. A slower speed of processing could make it difficult to initiate movement, anticipate obstacles, and navigate walking in an unfamiliar environment. Future research should evaluate FM more in depth to better understand which aspects of mobility are linked to the speed of processing.

The effect of FM on cognitive outcome and QoL was also supported by regression analysis considering other known influencing factors, including especially age and duration of illness, which did not result significant. This may suggest that their role may become less relevant when functional mobility is taken into account. However, since age and functional mobility are correlated, it is also possible that functional mobility may already capture the variability related to age.

In addition, given the correlation between age and FM, to better explore the effect in different age subgroups, we divided the sample based on the median value to assess whether there was a differential effect of FM and MetS on cognitive functioning and QoL based on age. Interestingly, results highlighted the significant effect of FM in both age subgroups. More in detail, FM was a significant predictor of global cognitive functioning as well as QoL, with better FM being associated with more preserved cognitive performance and QoL. Therefore, although there was a significant relationship between age and FM, the evaluation of different age groups did not reveal a differential effect of FM based on age, suggesting the transversal applicability of the evaluation of FM in all stages of illness. Moreover, another relevant aspect taken into account was MetS. Results showed that in the whole sample

MetS was a significant predictor of cognitive functioning, however this effect was not significant when we took into account age subgroups.

Furthermore, our study innovatively modeled the effects of FM and MetS on both global cognition and QoL through mediation analyses. Indeed, these factors, fundamental in schizophrenia because they can directly influence both cognition and QoL (Bora et al., 2017; Malhotra et al., 2016; Kim et al., 2019), especially in affected elderly people (Leutwyler et al., 2014), are rarely considered together. Our findings suggest that FM has not only a direct relationship with MetS, cognition and QoL, but it also mediates the indirect relationship between MetS on one side and both cognition and QoL on the other.

More in detail, FM seems to play an important role in the well-known relationship between MetS and cognitive and functional outcomes in schizophrenia. Indeed, FM showing a significant synergistic effect in this relationship contributes to determining the outcomes, and, therefore, can help explain the variance.

This appears particularly relevant in light of the chronic course of the disease, in which over time there is a greater prevalence of both Mets and FM, as a consequence of the physiological increase in age-related risk as well as of the increased risk related specifically to the disease (i.e., lifestyle, pharmacological treatment). Therefore, FM, as well as MetS, may represent a factor that can help explain the heterogeneity of the longitudinal trajectories of cognitive deficit in schizophrenia (Carruthers et al., 2019; Bechi et al., 2020; Spangaro et al., 2021).

Our study has some limitations. First, although the TUG test used in this study has been used to assess FM in various clinical populations, it has not yet been standardized for people with schizophrenia. Second, the sample is relatively small which hampers a deeper analysis of pharmacological treatment's effects. Further studies on a larger sample are needed to confirm our findings and to better investigate the role of FM in schizophrenia.

Despite the limitations, our results are relevant and encouraging, suggesting that FM is not only strongly related to negative symptoms as well as to several cognitive and functional domains, but it also mediates the effect of MetS on both global cognition and QoL.

Given the multidimensional deficits of schizophrenia and the necessity of lifelong treatment for patients, an integrated multidisciplinary approach is of the utmost importance to treat all aspects of the disease, from cognition to health status and independent living. This need is also supported by recent research. In particular, the Suffolk County Mental health project did a full physical performance assessment on their participants affected by psychotic disorders at the 20 year follow-up. Overall, three reports of this project showed that two thirds of the participants with schizophrenia were obese 20 years after first hospitalization for psychosis (Strassnig et al., 2017a, 2017b) and that physical health limitations have a differential effect on important areas of daily outcomes (Strassnig et al., 2017a, 2017b; Strassnig et al., 2018). Moreover, Strassnig and colleagues highlighted that, with the predictive influence of diagnosis controlled, FM, followed by negative symptoms, was the most significant predictor of employment (Strassnig et al., 2017a, 2017b).Thus, poor physical health status reduces real-world performance further in areas already undermined by the intrinsic limitations of schizophrenia, such as symptoms and cognition. In this view, health status limitations should be considered in the overall prediction of real-world functioning and interventions designed to reduce disability that target health status may be needed to address both obesity and metabolic disorders, as well as to improve physical functioning.

In this perspective, the TUG test, being a non-invasive, and quickly performed measure may represent a promising tool used as an additional index to evaluate cognitive deficits in schizophrenia, with important implications for monitoring the course of illness across the life span. Its relevance may also extend to rehabilitative settings, as FM may represent a treatment target, as well as a monitoring tool and a predictor of interventions outcome.

## CRediT authorship contribution statement

Federica Cuoco: Conceptualization; Methodology; Data interpretation; Writing - Original draft; Writing – Review & editing.
Giulia Agostoni: Methodology; Data interpretation; Formal analysis; Writing – Review & editing.
Silvia Lesmo: Clinical data acquisition; Data curation; Writing – Original draft.
Jacopo Sapienza: Patients enrollment; Clinical data acquisition.
Mariachiara Buonocore: Clinical data acquisition; Data curation.
Margherita Bechi: Clinical data acquisition; Data curation.
Francesca Martini: Patients enrollment; Clinical data acquisition.
Ilaria Ferri: Patients enrollment; Clinical data acquisition.
Marco Spangaro: Patients enrollment; Clinical data acquisition.
Giorgia Bigai: Clinical data acquisition.
Federico Seghi: Clinical data acquisition.
Carmelo Guglielmino: Patients enrollment; Clinical data acquisition.
Federica Cocchi: Patients enrollment; Clinical data acquisition.
Roberto Cavallaro: Resources; Supervision of project administration.
Marta Bosia: Conceptualization; Methodology; Data interpretation; Writing – Review & editing; Project administration.

## Declaration of competing interest

The authors declare that there is no conflict of interest.

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