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Factors associated with subjective cognitive decline in dementia-free older adults - a population based study

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Factors associated with subjective cognitive decline in dementia-free older adults – a population based study

THESE

préparée sous la direction du Professeur Julius Popp
(avec la co-direction du Professeur Armin von Gunten)

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par

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Factors associated with subjective cognitive decline in dementia-free older adults - a population based study

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Monsieur le Professeur John Prior
Vice-Directeur de l'Ecole doctorale

FACTEURS ASSOCIÉS AU DECLIN COGNITIF SUBJECTIF CHEZ LES PERSONNES ÂGÉS SANS DEMENCE – UN ÉTUDE DE POPULATION

Introduction : Le déclin cognitif subjectif est commun chez les personnes âgées, il influence la qualité de vie et peut représenter la manifestation la plus précoce d'un déclin cognitif évoluant vers une démence. À ce jour les facteurs associés au déclin cognitif subjectif sont encore peu connus.

Objectifs (1) Évaluer les associations entre le déclin cognitif subjectif et les caractéristiques démographiques, sociales, cliniques et la personnalité ainsi que la qualité de vie, avec et sans ajustement pour la performance cognitive objective. (2) Investiguer la relation entre névrosisme, qualité de vie et déclin cognitif subjectif.

Méthode : Analyse transversale d'une cohorte de 1567 sujets sans démence de l'étude CoLaus/PsyCoLaus, habitant la zone urbaine de Lausanne (Suisse) âgés de 64 ans et plus (âge moyenne 70.9 ± 4.7 ans). Le déclin cognitif subjectif a été évalué au travers d'un questionnaire validé et composé de 10 items, le Questionnaire de la Plainte Cognitive. Les traits de personnalité, la qualité de vie et le support social perçu ont été évalués avec des auto-questionnaires. Les informations sur la dépression et l'anxiété ainsi que les caractéristiques socio-économiques, activité professionnelle incluse, ont été obtenues au travers d'un entretien semi-structuré. Le fonctionnement cognitif a été évalué avec une batterie de tests neuropsychologiques complète.

Résultat : Le déclin cognitif subjectif était présent chez 18.5% de l'échantillon et était associé avec une moins bonne performance en mémoire et fluence verbale. Après avoir ajusté pour des éventuels facteurs confondants, le déclin cognitif subjectif était associé à l'activité professionnelle, le névrosisme, et la dépression. Une analyse exploratoire a révélé des associations entre le déclin cognitif subjectif et la qualité de vie, le névrosisme ainsi que leur intégration.

Conclusion : Mise à part la performance cognitive objective, le déclin cognitif subjectif est en relation avec plusieurs facteurs psychosociaux chez les personnes âgées ne souffrant pas d'une démence. Ces résultats sont importants pour le développement d'interventions pour réduire la plainte cognitive, améliorer la qualité de vie et prévenir le déclin cognitif objectif dans la population générale.

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RESEARCH ARTICLE

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Factors associated with subjective cognitive decline in dementia-free older adults—A population-based study

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Abstract

Background: Subjective cognitive decline (SCD) is common in older adults, affects quality of life (QoL), and may represent the earliest clinical manifestation of cognitive decline evolving to dementia. Still little is known about factors associated with SCD.

Objectives: (1) Assess the associations between SCD and demographic, social, clinical, and personality characteristics as well as QoL, with and without adjustment for objective cognitive performance, and (2) investigate the relations between neuroticism, QoL, and SCD.

Methods: Cross-sectional analysis of a cohort of 1567 dementia-free community-dwellers from the urban area of Lausanne, Switzerland, aged 64 years and older (mean age 70.9 ± 4.7 years), from CoLaus/PsyCoLaus. SCD was assessed using a validated 10-item questionnaire. Personality traits, QoL, and perceived social support were evaluated using self-report measures. Information on depression and anxiety status and socioeconomic characteristics including professional activity were elicited using a semi-structured interview. Cognitive functioning was assessed through a comprehensive neuropsychological test battery. Statistical analysis was based on logistic regression.

Results: SCD was present in 18.5% of the sample and it was associated with lower performance in memory and verbal fluency tasks. After controlling for possible confounders, professional activity, neuroticism, and current depression were associated with SCD. Exploratory analysis revealed associations of SCD with QoL, neuroticism, and their interaction.

Conclusion: Besides objective cognitive performance, SCD is related to several psychosocial factors in dementia-free community-dwelling older people. These findings are relevant for the development of healthcare interventions to reduce cognitive complaints, improve QoL, and prevent cognitive decline in general population.

KEYWORDS
dementia, depression, elderly, personality, quality of life, subjective cognitive decline

Key points

- This study (1) assesses the associations between subjective cognitive decline (SCD) and demographic, social, clinical, and personality characteristics, as well as quality of life (QoL),

with and without adjustment for objective cognitive performance, and (2) investigates the relationships between neuroticism, QoL and SCD.
- Besides cognitive performance, specific psychosocial factors are independently associated with SCD in dementia-free older people, namely professional activity, neuroticism, and current depression.
- Exploratory analysis revealed associations of SCD with QoL, neuroticism, and their interaction.
- Different psychological and social factors independently contribute to the risk of SCD in older adults and they need to be considered when proposing interventions to reduce cognitive complaints and prevent cognitive decline.

1 | INTRODUCTION

Subjective cognitive decline (SCD), defined as the individual's feeling of worsening cognition, is common in older adults. Prevalence ranges between 6.1% and 73.8%, increases with advancing age, and depends, among other factors, on the sample and the SCD assessment, varying from a single question to structured questionnaires.[1,2] Evidence growing over past decades pointed out that, in older subjects with normal cognition, SCD is related to greater risk of developing cognitive decline and dementia and is associated with biomarkers of Alzheimer's disease (AD),[3] indicating a disease stage that precedes the first objective cognitive symptoms.[4–6] Hence, it may be the potentially earliest manifestation of developing dementia, and in particular AD. SCD can affect emotional and social functioning, and quality of life (QoL) not only because of its negative psychological impact, but also as one of the first signs of cognitive decline. Recently, efforts have been made to identify features of SCD associated with AD and future cognitive and functional decline, and to propose a research framework for SCD as a preclinical manifestation of AD.[4,7]

While there is growing evidence on SCD, still little was consistently reported about psychological and socioeconomic factors associated or contributing to SCD. Among previous reports, some cross-sectional studies have related SCD to depression,[8–11] personality traits,[12,13] or physical diseases.[14] Other studies reported associations between occurring SCD and lower QoL.[15–17] Overall, these reports remain inconclusive, however, with some studies describing further factors such as higher age, female gender, and low educational level associated to SCD and others reporting no association.[9,18] A better understanding of factors related or contributing to SCD would be critical for the development of preventive and early therapeutic interventions to reduce cognitive complaints, improve QoL, and prevent cognitive decline.

In the present study, we address factors putatively related to SCD in a relatively large dementia-free population-based cohort. Our main objective is to identify factors associated with SCD while considering several demographic, social, clinical, and personality characteristics along with cognitive performance. Of note, we here determined the presence of SCD as a clinical feature using a structured and validated questionnaire and considered objective performance in different cognitive domains. While in the clinical continuum of AD, from normal cognition to dementia, SCD was proposed as a preclinical stage different from the stage of mild cognitive impairment (MCI) by the cognitive performance being in the normal range,[19] we here investigate SCD, not as a delimited stage, but as a feature in the whole elder non-demented population without any further a priori exclusion.

Previous reports have highlighted the impact of personality, in particular of neuroticism on QoL[20] and possible consequences of SCD on QoL, and vice versa.[15–17] As neuroticism is related to anxious and negative thoughts and feelings, higher neuroticism score may contribute to lower perceived QoL. Hence, we further exploratorily investigated the association between SCD and QoL and tested the influence of neuroticism on this relationship.

2 | METHODS

2.1 | Subjects

Data of the present analyses stemmed from CoLaus/PsyCoLaus, a prospective population-based cohort study. CoLaus was designed to determine cardiovascular risk factors, while PsyCoLaus was subsequently added to assess relationships with personality traits and psychiatric disorders, including cognitive impairment. The data concerning the physical assessment were thus obtained from the original CoLaus survey. The other variables were obtained 1 year later when PsyCoLaus was started. The study has been previously described in detail.[21,22] A total of 6734 individuals aged 35–75 years were randomly selected from the residents of the city of Lausanne, Switzerland between 2003 and 2006 according to the civil register. The first two follow-up evaluations of the cohort were completed between 2009 and 2013 as well as 2014 and 2018. At the first follow-up cognitive assessments were introduced for all the participants aged 65 years and older.[21] Accordingly, this evaluation was used as baseline assessment for the present paper.

The sample for the cross-sectional analysis included all 1567 subjects aged 65 years and older who accepted the neuropsychological evaluation ($N = 1574$), excluding participants with a Clinical Dementia Rating (CDR) > 0.5 ($N = 7$). Two participants younger than 65 years at inclusion visit (64 and 7 months, respectively) with available cognitive and SCD evaluation were also considered. The

CoLaus/PsyCoLaus study was approved by the Institutional Ethics Committee of the University of Lausanne and informed written consent was obtained from all participants.

2.2 | Assessment methods and measures

Participants underwent the "Questionnaire de la Plainte Cognitive" (QPC), a validated 10-item yes/no questionnaire assessing the presence of subjective cognitive difficulties in the last 6 months. According to the QPC scoring system, SCD is present when the subject answers "yes" to 3 or more items; and/or to item 5, and/or to items A, 4, 5, 7, 8 (Figure 1). Information on age, living conditions, education, and professional activity as well as diagnostic criteria for major depressive (MDD) and anxiety disorders (see Table 1) were elicited using the French version of the semi-structured Diagnostic Interview for Genetic Studies.[23] Socioeconomic status (SES) of the subject's household (iSES-25) was determined using the Hollingshead Scale.[24] Personality dimensions (neuroticism and extraversion) were assessed using the NEO-FFI-R[25] and the Eysenck Personality Questionnaire.[26] Perceived social support was measured using The Multidimensional Scale of Perceived Social Support (MSPSS).[27] QoL was assessed using the Manchester Short Assessment of QoL (MANSA).[28]

The administered neuropsychological test battery included Grober and Buschke Double Memory Test (DMT) for episodic memory,[29] DO40 picture-naming test for verbal fluency (VF),[30] Stroop Test for executive processing,[31] and figures drawing from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery for constructional praxis.[32] Furthermore, the CDR[33] was performed (details are provided in the Appendix). Interviewers were psychologists, who were trained over 2 months. Each interview and cognitive test was reviewed by senior psychologists.

Approximately 1 year prior to the psychiatric evaluation participants underwent a physical assessment relying on a questionnaire on cardiovascular risk factors as well as biochemical and anthropomorphic measure. The Prospective Cardiovascular Münster risk score (PROCAM 2007)[34] was derived from these measures.

2.3 | Statistical analysis

We used χ^2 and Student's *t*-tests to detect marginal associations between categorical and continuous variables and groupings, respectively. To further assess associations with SCD considering multiple variables and to identify factors independently contributing to the models, we applied binary logistic regression with SCD/no SCD as the dependent variable. We used binary logistic regression models first without (Model 1) and then including the scores in cognitive tasks (Model 2). Furthermore, we used the backward selection method to determine the best model to predict SCD identified using the Akaike Information Criterion (Model 3).

In addition, we tested the impact of interaction between neuroticism and QoL on SCD using a logistic regression model including the following independent variables: personality dimensions, QoL, age, gender, professional activity, depression, and the interaction term between neuroticism and QoL.

All analyses were performed in R environment for statistical computing.[35]

3 | RESULTS

Table 1 provides the sample description by SCD status. The two groups did not differ on demographic variables. Participants with SCD were less frequently professionally active and had more frequently current or remitted depression as well as current anxiety disorders. They also

	YES	NO
A. Have you experienced any memory change during the last six months?		
B. Do you feel like your memory is worse in comparison to your peers?		
1. Do you feel like you are getting worse in remembering recent events and/or you hear your family say more often "I have already told you"		
2. Have you forgotten about an important appointment?		
3. Do you lose things more often than in the past, or do you take longer to find them than usual?		
4. Have you experienced any difficulties with spatial orientation or failed to recognize a place you were previously familiar with?		
5. Have you completely forgotten about an event and were unable to recall it even when your close relatives/friends were talking about it or when you saw photos from the event?		
6. Do you have difficulties in finding words (this does not apply to names) and have you felt like the word was on the tip of your tongue but you could not recall it, forcing you to say "this" or "that" more frequently?		
7. Have you limited your activities (or asked for help) because of concerns that you may make a mistake) (such as filling tax declaration, paying bills, etc.)		
8. Have you noticed any changes in your personality? (such as turning inward, reducing contacts with others, or being less interested in things)		

FIGURE 1 Questionnaire de la Plainte Cognitive (QPC). SCD is present when the subject answers "yes" to three or more items; and/or to item 5; and/or to items A, 4, 5, 7, 8. SCD, subjective cognitive decline

TABLE 1 Clinical characteristics of the cohort

Variable	Total (1567)	No SCD (1281)	SCD (286)	Test stat. (*df*)	*p*-Value
Age [mean (*SE*)]	70.87 (0.12)	70.81 (0.13)	71.17 (0.29)	$t(399) = -1.13$	0.2586
Gender = female [% (#)]	58.65 (919)	58.86 (754)	57.69 (165)	$\chi^2(1) = 0.09$	0.7670
Living alone = yes [% (#)]	40.35 (602)	39.42 (492)	45.08 (110)	$\chi^2(1) = 2.49$	0.1149
Socioeconomic status					
iSES25 = 1 [% (#)]	4.53 (71)	4.45 (57)	4.9 (14)		
iSES25 = 2 [% (#)]	16.79 (263)	16.09 (206)	19.93 (57)		
iSES25 = 3 [% (#)]	34.29 (537)	34.77 (445)	32.17 (92)		
iSES25 = 4 [% (#)]	26.82 (420)	27.11 (347)	25.52 (73)		
iSES25 = 5 [% (#)]	17.56 (275)	17.58 (225)	17.48 (50)	$\chi^2(4) = 2.83$	0.5868
Education					
Basic = 0 [% (#)]	16.92 (265)	15.55 (199)	23.08 (66)		
Apprenticeship [% (#)]	44.44 (696)	45.78 (586)	38.46 (110)		
High school [% (#)]	22.16 (347)	22.42 (287)	20.98 (60)		
University [% (#)]	16.48 (258)	16.25 (208)	17.48 (50)	$\chi^2(3) = 11.09$	0.0113
Professionally active = yes [% (#)]	18.39 (288)	20 (256)	11.19 (32)	$\chi^2(1) = 11.51$	0.0007
MSPSS [mean (*SE*)]	2.14 (0.03)	2.11 (0.03)	2.3 (0.07)	$t(307) = -2.69$	0.0075
MANSA [mean (*SE*)]	5.52 (0.02)	5.58 (0.02)	5.23 (0.05)	$t(267) = 6.2$	0.0000
Neuroticism [mean (*SE*)]	0 (0.03)	−0.1 (0.03)	0.47 (0.07)	$t(317) = -7.87$	0.0000
Extraversion [mean (*SE*)]	0 (0.03)	0.05 (0.03)	−0.23 (0.07)	$t(312) = 3.77$	0.0002
Current MDD = yes [% (#)]	4.76 (72)	3.78 (47)	9.26 (25)	$\chi^2(1) = 13.48$	0.0002
Remitted MDD = yes [% (#)]	33.13 (501)	31.56 (392)	40.37 (109)	$\chi^2(1) = 7.37$	0.0066
Current anxiety = yes [% (#)]	2.98 (45)	2.5 (31)	5.19 (14)	$\chi^2(1) = 4.66$	0.0308
BMI [mean (*SE*)]	26.78 (0.12)	26.8 (0.13)	26.68 (0.31)	$t(374) = 0.38$	0.7030
Diabetes = yes 1 [% (#)]	16.66 (254)	15.84 (198)	20.36 (56)	$\chi^2(1) = 3$	0.0830
PROCAM 2007 [mean (*SE*)]	25.92 (0.27)	25.77 (0.29)	26.64 (0.67)	$t(341) = -1.19$	0.2354
CDR [mean (*SE*)]	0.26 (0.01)	0.25 (0.01)	0.32 (0.01)	$t(434) = -4.45$	0.0000
DMT					
Identification [mean (SE)]	15.96 (0.01)	15.97 (0.01)	15.96 (0.02)	$t(406) = 0.29$	0.7707
Immediate recall [mean (SE)]	16.45 (0.12)	16.4 (0.13)	16.64 (0.26)	$t(402) = -0.82$	0.4126
Differed free recall [mean (SE)]	11.65 (0.07)	11.8 (0.08)	10.93 (0.19)	$t(338) = 4.2$	0.0000
Differed cued recall [mean (SE)]	4.78 (0.1)	4.79 (0.11)	4.76 (0.18)	$t(470) = 0.12$	0.9076
Recognition [mean (SE)]	45.55 (0.21)	45.69 (0.23)	44.89 (0.55)	$t(357) = 1.34$	0.1800
Free recall sum of series [mean (SE)]	29.84 (0.19)	30.35 (0.19)	27.5 (0.51)	$t(343) = 5.27$	0.0000
Cued recall sum of series [mean (SE)]	17.7 (0.24)	17.76 (0.27)	17.44 (0.42)	$t(502) = 0.63$	0.5259
CERAD figures [mean (*SE*)]	10.31 (0.03)	10.34 (0.03)	10.13 (0.09)	$t(356) = 2.31$	0.0215
DO40 [mean (*SE*)]	39.7 (0.03)	39.72 (0.03)	39.59 (0.09)	$t(309) = 1.39$	0.1670
Stroop test (processing speed)					
Denomination [mean (SE)]	25.11 (2.09)	26.44 (2.48)	19.11 (2.66)	$t(839) = 2.02$	0.0440
Low interference [mean (SE)]	32.6 (2.59)	33.97 (2.98)	26.38 (4.73)	$t(526) = 1.36$	0.1754
High interference [mean (SE)]	49.39 (3.76)	51.29 (4.36)	40.85 (6.61)	$t(551) = 1.32$	0.1881

Note: *t*-Test is used to assess difference of means for continuous variables between groups with and without SCD; χ^2 test of independence is used to detect associations between categorical variables and the group.

Abbreviations: BMI, body mass index; CDR, Clinical Dementia Rating; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; DMT, Double Memory test; DO40, Dénomination Orale; iSES25, household socio-economic status; MDD, Major Depressive Disorder; MANSA, Manchester Short Assessment of Quality of life; MMSE, Mini Mental State Examination; MSPSS, Multidimensional Scale of Perceived Social Support.

score higher on the MSPSS and neuroticism scales, but lower on extroversion and the MANSA scales. There was no significant between group differences on most cognitive tests, excepting CDR, DMT free recall, CERAD figures and denomination on Stroop Test.

Table 2 depicts the results of logistic regression analyses. Model 1 confirmed associations of SCD with professional activity, current depression and neuroticism. After adjustment for measured cognitive scores only current depression and neuroticism remained significantly associated with SCD. Among the measured cognitive scores lower performance in the sum of series for free and cued recall as well as VF for animal and fruits were significantly associated with SCD. The same variables also revealed significant associations with SCD according to the backward regression analysis.

Exploratory logistic regression analysis investigating relationships between SCD and QoL selected professional activity, current depression, neuroticism, QoL and the interaction between Neuroticism and QoL as independent predictors of SCD (Table S1).

4 | DISCUSSION

In this population-based study in dementia-free people from an urban area in Switzerland, SCD was associated with both psychosocial factors and objective cognitive performance: not being professionally active, higher neuroticism, presenting current major depression, and poorer performance in memory and VF tasks.

4.1 | Demographic determinants of SCD

SCD and no-SCD groups were similar in terms of demographic factors. We confirmed the between group differences in education, with higher level of education in the SCD group. This has been reported inconsistently in previous studies.[9,36,37] Furthermore, not being professionally active, higher perceived social support, and lower QoL scores were associated with SCD.

In regression analysis, professional activity was negatively associated with SCD. Possible, yet speculative, explanations may be that there is a protective effect of staying professionally active or that people with SCD may tend to abandon or avoid professional activity to avoid embarrassment and frustration. This result was not significant after the correction for the cognitive performance scores. This indicates that subtle objective cognitive difficulties may be a mediator of the association between (the absence of) professional activity and SCD. To better understand these relationships, future studies may explore whether specific professional activities are associated with SCD.

4.2 | Depression, anxiety, and personality as determinants of SCD

Current depression, current anxiety, remitted depression, higher neuroticism, and lower extroversion scores were associated with SCD. Regression analysis showed current depression, but not remitted depression, to be significantly associated with the presence of SCD. Previously, both depression[38] and subsyndromal depression[39] have been reported in association with SCD. Some studies suggested that SCD depression symptoms may be a more important determinant of SCD than objective cognitive impairment[40] as depressed subjects may report SCD more frequently than non-depressed older community residents, or dementia patients.[41] According to our findings, remission of a depressive episode might prevent the presence of SCD or contribute to its resolution. This interpretation remains speculative, however, as causality cannot be directly inferred from our results.

Current anxiety disorders were more frequent in the participants with SCD; however, the association was not significant in regression analysis. Considering its clinical relevance this relation may deserve further investigation in future studies.

While both higher neuroticism and lower extroversion were associated with SCD, in regression analysis only neuroticism remained a significant determinant of SCD. Several previous studies reported a link between SCD and personality.[12,13] Personality traits have also been linked with psychological, behavioral, and clinical risk factors for dementia and AD[42,43] and are related to educational achievements, coping skills, and the quality and quantity of interpersonal relations, which in turn, are associated with increased vulnerability to dementia.[44] A recent meta-analysis showed that higher neuroticism exposes to a greater risk of incident AD.[45]

Furthermore, subjects with cognitive impairment undergo early and specific personality changes compared to healthy controls and these may precede cognitive symptoms.[46,47] In particular, subjects with AD cerebral pathology may show marked neuroticism increase compared to pre-morbid traits[48] and neuroticism may moderate the association between SCD and brain amyloid-β deposition.[49]

In our cohort, a longitudinal analysis would help to determine if higher neuroticism associated with SCD predisposes to the development of cognitive impairment or if it reflects changes in personality due to developing cerebral AD pathology with early cognitive dysfunction, or both.

4.3 | SCD and QoL

Considering previous reports associating SCD and QoL[15–17,20] we further investigated their relationship. QoL was lower in the group with SCD. While the association was no longer significant in the regression models considering other factors, further exploratory analysis revealed QoL, neuroticism, and the interaction between QoL and neuroticism to be associated with SCD. These findings suggest that SCD may have a negative impact on QoL, and vice versa, and this in particular in older adults with higher neuroticism. The worse response to stressors, the typical tendency of higher neuroticism traits to interpret ordinary situations as threatening and minor frustrations as hopelessly difficult could in fact explain the

TABLE 2 Results of logistic regression models assessing associations of SCD with demographic, social, clinical, and neuropsychological factors

	Dependent variable: Subjective cognitive decline		
	Model 1 OR (CI)	Model 2 OR (CI)	Model 3 OR (CI)
Age	0.98 (0.94, 1.03)	0.96 (0.90, 1.01)	0.97 (0.94, 1.01)
Sex	0.74 (0.47, 1.15)	1.14 (0.67, 1.96)	
Living alone	1.31 (0.88, 1.94)	1.22 (0.78, 1.91)	
Professionally active	0.48* (0.25, 0.85)	0.58 (0.29, 1.09)	0.69 (0.41, 1.12)
Education	0.88 (0.64, 1.21)	1.01 (0.69, 1.47)	
iSES25	1.12 (0.85, 1.47)	1.16 (0.86, 1.59)	
MSPSS	0.97 (0.76, 1.22)	0.93 (0.70, 1.23)	
Current MDD	2.98** (1.29, 6.69)	2.75* (1.10, 6.70)	2.23* (1.07, 4.57)
Remitted MDD	1.40 (0.90, 2.16)	1.40 (0.85, 2.30)	1.37 (0.94, 1.98)
Current anxiety	1.00 (0.34, 2.63)	0.80 (0.26, 2.24)	
Neuroticism	1.49** (1.17, 1.89)	1.74**** (1.32, 2.31)	1.73**** (1.46, 2.06)
Extraversion	0.96 (0.77, 1.19)	0.99 (0.78, 1.26)	
Diabetes	1.17 (0.62, 2.15)	1.37 (0.66, 2.75)	
BMI	0.97 (0.92, 1.02)	0.97 (0.92, 1.02)	
MANSA	0.73 (0.50, 1.07)	0.91 (0.59, 1.41)	
PROCAM 2007	1.01 (0.99, 1.03)	1.00 (0.98, 1.03)	
CERAD		1.07 (0.86, 1.36)	
DMT			
Immediate recall		1.03 (0.99, 1.07)	
Differed free recall		1.18 (0.88, 1.60)	
Differed cued recall		1.34 (1.00, 1.80)	1.08 (0.98, 1.19)
Recognition		0.98* (0.95, 1.00)	0.99 (0.97, 1.01)
Free recall sum of series		0.90* (0.81, 0.98)	0.96** (0.92, 0.99)
Cued recall sum of series		0.90* (0.82, 0.98)	0.96* (0.92, 1.00)
Verbal fluency			
Animals		1.02 (0.98, 1.05)	
Letter P		0.99 (0.95, 1.02)	
Animals and fruits		0.88* (0.77, 0.99)	0.92* (0.84, 0.99)
Stroop test			
Denomination		0.96 (0.90, 1.01)	1.00 (0.99, 1.00)
Low interference		1.00 (0.95, 1.04)	
High interference		1.00 (0.98, 1.03)	
Observations	907	783	1049
Log likelihood	−342.08	−275.04	−438.65
Akaike Information Criterion	718.16	610.07	901.30

Note: Odds ratios (OR) and their corresponding confidence intervals for each variable are presented. Significant associations are highlighted with stars. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

Abbreviations: BMI, body mass index; CDR, Clinical Dementia Rating; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CI, confidence interval; DMT, Double Memory Test; iSES25, household socioeconomic status; MANSA, Manchester Short Assessment of Quality of Life; MDD, Major Depressive Disorder; MSPSS, Multidimensional Scale of Perceived Social Support; PROCAM, Prospective Cardiovascular Münster risk score.

(subjective) evaluation of the own QoL as low. In the same way, the self-consciousness over cognitive sensations could lead to an exaggerated worry and seeking for help behavior in SCD subjects with higher neuroticism traits.

4.4 | Cognitive performance and SCD

Several cross-sectional studies have failed to find an association between SCD and cognitive performance.[50,51] This might be due, in part, to small sample sizes, small group differences in cognitive performance between complainers and non-complainers, especially if the analysis was performed in cognitively normal subjects only, and to a high impact that factors other than cognition may have. Studies in larger cohorts observed an association of SCD with cognitive performance that was independent of factors such as depression.[52,53] Another possible explanation may be the differences in the definition of SCD and the used assessment tools. Indeed, the prevalence of SCD in our population seems relatively low compared to previous studies indicating a rather selective rule of the overall QPC score, which classifies as non-SCD subjects having some complaints, but not enough to fulfill the criteria for SCD. In our study, SCD subjects had lower performance in free and cued recall tasks suggesting poorer encoding and retrieving capacities when compared with non-SCD subjects. Poorer performance in VF tasks was also associated with SCD. This is notable considering that VF has been reported as one of the earliest signs of beginning cognitive decline leading to dementia and difficulties in this domain are often present months or even years before major cognitive changes.[54,55]

Whether the origin of the diminished performance on these tests resides in the impact of psychological variables as depression and neuroticism, or it represents the very beginning clinical manifestation of cerebral pathology, or both, is unclear. The ongoing longitudinal follow-up of this cohort will help to address this question. Nevertheless, given that SCD is relatively easy to assess and it may reflect the subjective experience of subtle, but relevant, cognitive decline its assessment may be performed in the first place to select elderly subjects at risk of having or developing cognitive impairment, and that may particularly benefit from subsequent cognitive testing.

5 | LIMITATIONS

In the present study, we only considered participants at 64 years of age or older. This may be considered as a limitation as SCD may appear earlier. The relatively large sample size could have an impact on statistical power with repercussions on between group differences. The inclusion of subjects with CDR = 0.5 in both groups, often supporting the diagnosis of MCI in clinical settings, may be seen as a limitation as these subjects are at higher risk of cognitive decline than people with normal cognition. However, there is a clinical continuum between normal cognition and mild impairment, and, also considering previous evidence on the link between SCD and future cognitive decline in the presence of mild impairment at baseline, not excluding those participants allows for a more complete exploration of these complex relationships in the general population.

6 | CONCLUSION

In this study in non-demented community-dwelling older adults from the general population we identified several non-cognitive factors associated with SCD including professional activity, neuroticism, and current depression. Most of these associations remained significant after considering performance in cognitive tasks. Furthermore, we report interactions between neuroticism, QoL and SCD. We also report associations between SCD and poor performance in memory and VF tests. Together, these findings suggest that, besides objective cognitive performance, different psychological and social factors may independently contribute to the risk of older adults to experience SCD.

While SCD is relevant for the individual's QoL, whether the factors associated with SCD are related to the risk of future cognitive decline needs further studies. The ongoing longitudinal follow-up of this cohort will help to address this additional question. Interventions in subjects with SCD to improve QoL and prevent cognitive decline may consider these factors to propose tailored approaches.

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CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interests.

AUTHOR CONTRIBUTIONS

Leonardo Zullo, Christopher Clark, and Julius Popp have substantially contributed to the conception and design of the work. Leonardo Zullo, Christopher Clark, Julius Popp, Mehdi Gholam, and Martin Preisig substantial contributed to the analysis and interpretation of data. Leonardo Zullo, Christopher Clark, Mehdi Gholam, and Julius Popp drafted the manuscript. All the authors provided final approval of the version published and they are responsible for the entire manuscript

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Röhr S, Pabst A, Riedel-Heller SG, et al. Estimating prevalence of subjective cognitive decline in and across international cohort

studies of aging: a COSMIC study. *Alzheimers Res Ther.* 2020; 12(1):167.
2. van Harten AC, Mielke MM, Swenson-Dravis DM, et al. Subjective cognitive decline and risk of MCI. *Neurology.* 2018;91(4): e300-e312.
3. Slot RER, Sikkes SAM, Berkhof J, et al. Subjective cognitive decline and rates of incident Alzheimer's disease and non-Alzheimer's disease dementia. *Alzheimers Dement.* 2019;15(3):465-476.
4. Jessen F, Amariglio RE, van Boxtel M, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers Demen.* 2014;10(6):844-852.
5. Lista S, Molinuevo JL, Cavedo E, et al. Evolving evidence for the value of neuroimaging methods and biological markers in subjects categorized with subjective cognitive decline. *J Alzheimers Dis.* 2015;48(suppl 1):S171-S191.
6. Visser PJ, Verhey F, Knol DL, et al. Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study. *Lancet Neurol* 2009;8(7):619-627.
7. Molinuevo JL, Rabin LA, Amariglio R, et al Implementation of subjective cognitive decline criteria in research studies. *Alzheimers Dement.* 2017;13(3):296-311.
8. Jessen F, Wiese B, Cvetanovska G, et al. Patterns of subjective memory impairment in the elderly: association with memory performance. *Psychol Med.* 2007;37(12):1753-1762.
9. Minett TS, Da Silva RV, Ortiz KZ, et al. Subjective memory complaints in an elderly sample: a cross-sectional study. *Int J Geriatr Psychiatry.* 2008;23(1):49-54.
10. Mendes T, Gino S, Ribeiro F, et al. Memory complaints in healthy young and elderly adults: reliability of memory reporting. *Aging Ment Health.* 2008;12(2):177-182.
11. Hill NL, Mogle J, Wion R, et al. Subjective cognitive impairment and affective symptoms: a systematic review. *Gerontologist.* 2016;56(6): e109-e127.
12. Studer J, Donati A, Popp J, et al. Subjective cognitive decline in patients with mild cognitive impairment and healthy older adults: association with personality traits. *Geriatr Gerontol Int.* 2014;14(3): 589-595.
13. Pearman A, Storandt M. Self-discipline and self-consciousness predict subjective memory in older adults. *J Gerontol B Psychol Sci Soc Sci.* 2005;60(3):153-157.
14. Jorm AF, Butterworth P, Anstey KJ, et al. Memory complaints in a community sample aged 60-64 years: associations with cognitive functioning, psychiatric symptoms, medical conditions, APOE genotype, hippocampus and amygdala volumes, and white-matter hyperintensities. *Psychol Med.* 2004;34(8):1495-1506.
15. Maki Y, Yamaguchi T, Yamagami T, et al. The impact of subjective memory complaints on quality of life in community-dwelling older adults. *Psychogeriatrics.* 2014;14(3):175-181.
16. Mol M, Carpay M, Ramakers I, et al. The effect of perceived forgetfulness on quality of life in older adults; a qualitative review. *Int J Geriatr Psychiatry.* 2007;22(5):393-400.
17. Montejo P, Montenegro M, Fernandez MA, et al. Memory complaints in the elderly: quality of life and daily living activities. A population based study. *Arch Gerontol Geriatr.* 2012;54(2):298-304.
18. Caramelli P, Beato RG. Subjective memory complaints and cognitive performance in a sample of healthy elderly. *Dement Neuropsychol.* 2008;2(1):42-45.
19. Jessen F, Amariglio RE, Buckley RF, et al. The characterization of subjective cognitive decline. *Lancet Neurol* 2020;19(3):271-278.
20. Pocnet C, Antonietti JP, Strippoli MF, et al. Individuals' quality of life linked to major life events, perceived social support, and personality traits. *Qual Life Res.* 2016;25(11):2897-2908.
21. Firmann M, Mayor V, Vidal PM, et al. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovasc Disord.* 2008;8:6.
22. Preisig M, Waeber G, Vollenweider P, et al. The PsyCoLaus study: methodology and characteristics of the sample of a population-based survey on psychiatric disorders and their association with genetic and cardiovascular risk factors. *BMC Psychiatry.* 2009;9:9.
23. Nurnberger JI , Jr, Blehar MC, Kaufmann CA, et al. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. *Arch Gen Psych.* 1994;51:849-859.
24. Hollingshead A. *Four-factor Index of Social Status.* New Haven, CT: Yale University; 1975.
25. Costa PT, McCrae RR. *Revised NEO Personality Inventory (NEO-PI-R) and NEO Five-Factor Inventory (NEO-FFI) Professional Manual.* Odessa, FL: Psychological Assessment Resources; 1992.
26. Eysenck HJ, Eysenck SBG. *Manual of the Eysenck Personality Scale (Adults).* London, UK: Hodder and Stoughton; 1991.
27. Zimet GD, Dahlem NW, Zimet SG, et al. The multidimensional scale of perceived social support. *J Personality Assess.* 1988;52(1):30-41.
28. Priebe S, Huxley P, Knight S, et al. Application and results of the Manchester Short assessment of quality of life (MANSA). *Int J Soc Psychiatry.* 1999;45(1):7-12.
29. Buschke H, Sliwinski MJ, Kuslansky G, et al. Diagnosis of early dementia by the Double Memory Test: encoding specificity improves diagnostic sensitivity and specificity. *Neurology.* 1997;48(4): 989-997.
30. Deloche G, Hannequin D. *Test de dénomination orale d'images: DO 80.* Paris: Éd. du Centre de psychologie appliquée; 1997.
31. Stroop JR. Studies of interference in serial verbal reaction. *J Exp Psychol.* 1935;18:643-662.
32. Morris JC, Mohs RC, Rogers H, et al. Consortium to establish a registry for Alzheimer's disease (CERAD) clinical and neuropsychological assessment of Alzheimer's disease. *Psychopharmacol Bull.* 1988;24(4):641-652.
33. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology.* 1993;43(11):2412-2414.
34. Assmann G, Schulte H, Cullen P, et al. Assessing risk of myocardial infarction and stroke: new data from the Prospective Cardiovascular Munster (PROCAM) study. *Eur J Clin Invest.* 2007;37(12):925-932.
35. R Core Team. *R. A Language and Environment for Statistical Computing.* Vienna, Austria: R Foundation for Statistical Computing; 2020. https://www.R-project.org/.
36. Montejo CP, Montenegro-Pena M, Lopez-Higes R, et al. Subjective memory complaints in healthy older adults: fewer complaints associated with depression and perceived health, more complaints also associated with lower memory performance. *Arch Gerontol Geriatr.* 2017;70:28-37.
37. Montejo P, Montenegro M, Fernandez-Blazquez MA, et al. Association of perceived health and depression with older adults' subjective memory complaints: contrasting a specific questionnaire with general complaint questions. *Eur J Ageing.* 2014;11:77-87.
38. Reid LM, Maclullich AM. Subjective memory complaints and cognitive impairment in older people. *Dement Geriatr Cogn Disord.* 2006;22(5-6):471-485.
39. Balash Y, Mordechovich M, Shabtai H, et al. Subjective memory complaints in elders: depression, anxiety, or cognitive decline?. *Acta Neurol Scand.* 2013;127(5):344-350.
40. Bolla KI, Lindgren KN, Bonaccorsy C, et al. Memory complaints in older adults. Fact or fiction? *Arch Neurol.* 1991;48(1):61-64.
41. O'Connor DW, Pollitt PA, Roth M, et al. Memory complaints and impairment in normal, depressed, and demented elderly persons identified in a community survey. *Arch Gen Psychiatry.* 1990;47(3):224-227.

42. Chapman BP, Roberts B, Duberstein P. Personality and longevity: knowns, unknowns, and implications for public health and personalized medicine. *J Aging Res.* 2011;2011:759170.
43. Hampson SE. Personality processes: mechanisms by which personality traits "get outside the skin. *Annu Rev Psychol.* 2012;63:315-339.
44. Beydoun MA, Beydoun HA, Gamaldo AA, et al. Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. *BMC Public Health.* 2014;14:643.
45. Terracciano A, Sutin AR, An Y, et al. Personality and risk of Alzheimer's disease: new data and meta-analysis. *Alzheimers Dement.* 2014;10(2):179-186.
46. Donati A, Studer J, Petrillo S, et al. The evolution of personality in patients with mild cognitive impairment. *Dement Geriatr Cogn Disord.* 2013;36(5-6):329-339.
47. Pocnet C, Rossier J, Antonietti JP, et al. Personality changes in patients with beginning Alzheimer disease. *Can J Psychiatry.* 2011; 56(7):408-417.
48. Tautvydaite D, Antonietti JP, Henry H, et al. Relations between personality changes and cerebrospinal fluid biomarkers of Alzheimer's disease pathology. *J Psychiatr Res.* 2017;90:12-20.
49. Snitz BE, Weissfeld LA, Cohen AD, et al. Subjective cognitive complaints, personality and brain amyloid-beta in cognitively normal older adults. *Am J Geriatr Psychiatry.* 2015;23(9):985-993.
50. Jungwirth S, Fischer P, Weissgram S, et al. Subjective memory complaints and objective memory impairment in the Vienna-Transdanube aging community. *J Am Geriatr Soc.* 2004;52(2): 263-268.
51. Tandetnik C, Hergueta T, Bonnet P, et al. Influence of early maladaptive schemas, depression, and anxiety on the intensity of self-reported cognitive complaint in older adults with subjective cognitive decline. *Int Psychogeriatr.* 2017;29(10):1657-1667.
52. Gagnon M, Dartigues JF, Mazaux JM, et al. Self-reported memory complaints and memory performance in elderly French community residents: results of the PAQUID Research Program. *Neuroepidemiology.* 1994;13(4):145-154.
53. Jonker C, Launer LJ, Hooijer C, et al. Memory complaints and memory impairment in older individuals. *J Am Geriatr Soc.* 1996;44(1):44-49.
54. Rapp MA, Reischies FM. Attention and executive control predict Alzheimer disease in late life: results from the Berlin Aging Study (BASE). *Am J Geriatr Psychiatry.* 2005;13(2):134-141.
55. Blacker D, Lee H, Muzikansky A, et al. Neuropsychological measures in normal individuals that predict subsequent cognitive decline. *Arch Neurol.* 2007;64(6):862-871.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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