RESEARCH ARTICLE

Investigating cognition in midlife

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Abstract

We here posit that measurements of midlife cognition can be instructive in understanding cognitive disorders. Even though molecular events signal possible onset of cognitive disorders decades prior to their clinical diagnoses, cognition and its possible early changes in midlife remain poorly understood. We characterize midlife cognition in a cognitively healthy population-based sample using the Cogstate Brief Battery and test for associations with cardiovascular, adiposity-related, lifestyle-associated, and psychosocial variables. Learning and working memory showed significant variability and vulnerability to psychosocial influences in midlife. Furthermore, midlife aging significantly and progressively increased prevalence of suboptimal cognitive performance. Our findings suggest that physiological changes in cognition, measured with simple tests suitable for use in everyday clinical setting, may signal already in midlife the first clinical manifestations of the presymptomatic biologically defined cognitive disorders. This pilot study calls for longitudinal studies investigating midlife cognition to identify clinical correlates of biologically defined cognitive disorders.

KEYWORDS

cognitive disorders, cognitive performance, midlife cognition, psychosocial variables, quality of life, suboptimal cognition

1 | NARRATIVE

1.1 | Cognition and cognitive disorders

Cognition refers to a complex set of brain functions ranging from attention, language, and visuospatial processes to learning, formation of memories, and executive domains.[1–4] Optimal cognitive performance is thus critical for efficient daily functioning. In fact, it is the essential prerequisite to perform most diverse tasks in response to experiences and sensory inputs in addition to influencing motor speed and coordination.[5,6] This all affects social behavior and interpersonal relationships and therefore, significantly influences quality of life. The role of cognition in the ability to live and function independently throughout the lifespan is best illustrated by aging, which over time changes

and otherwise adjusts cognitive functions.[7–10] The essential role of cognition, however, becomes often only evident in disorders that erode cognition because they all eventually interfere with independent life and functioning.

The identification of Alzheimer's disease (AD) as the major cause of dementia[11] led to an exponential growth of knowledge about cognitive disorders. As a result, cognitive disorders are today recognized to produce three major clinical phenotypes; subjective cognitive impairment (SCI), mild cognitive impairment (MCI), and dementia. While SCI consists in the subjective perception of forgetfulness, which by definition cannot be corroborated by cognitive examination,[12] MCI and dementia both elicit objectivized cognitive decline that either restricts or precludes independent life and daily activities, respectively.[13] Although still a matter of debate, these clinical phenotypes may be today at least experimentally interpreted as a continuum of progressively more severe deterioration of cognitive perception and functioning.[14–16].

Simple, clinically practical cognitive tests such as the Mini-Mental State Examination,[17] Montreal Cognitive Assessment (MoCA),[18] and Addenbrooke's Cognitive Examination[19] played an instrumental role in shaping clinical phenotypes and understanding cognitive disorders. For example, they contributed extensively to establish the incidence and prevalence,[20] discover risk factors,[21,22] and identify biomarkers[23] of cognitive disorders.

Today, cut-off values and contents of these tests assist clinicians and researchers alike in defining and monitoring progression of MCI and dementia[24,25] and in identifying deficits specific to individual cognitive disorders.[26] Recent advances in translating basic discoveries into clinical settings revealed that molecular perturbations of cognitive disorders begin decades prior to the onset of cognitive phenotypes and decline.[27] These findings led to the introduction of biological definitions of cognitive disorders[28] with the aim to further refine our understanding and evaluation of cognitive disorders including their clinical phenotypes.[29]

1.2 | Physiological cognition

The possibility to measure biomarkers provides the unprecedented opportunity to investigate diagnostics of cognitive disorders decades prior to their clinical onset. At the same time, this opportunity also uncovered the need to better understand cognition per se to clinically characterize the presymptomatic stages of cognitive disorders.[30] Studies of presymptomatic stages of cognitive disorders in familial cases[27,31,32] as well as of healthy elderly positive for biomarkers of cognitive disorders,[33,34] both documented cognitive changes that may signal the emergence of the first clinical manifestations of cognitive disorders long before the onset of currently accepted clinical phenotypes. These studies suggest that incipient pathologies underlying cognitive disorders first impair cognition within its physiological boundaries and only over time, the cumulative effect of these impairments eventually culminates in clinical phenotypes such as MCI and dementia. A better understanding of these early cognitive changes may, therefore, provide currently missing clinical correlates to the biologically defined

RESEARCH IN CONTEXT

- **Systematic review**: Although biological changes of cognitive disorders emerge in the cognitively healthy long before cognitive decline, little is known about healthy cognition and its early changes. We reviewed the literature about healthy cognition and variables influencing its physiology. Most studies of healthy cognition today focus on elderly populations, which are prone to cognitive pathologies. In midlife, however, healthy cognition remains poorly described.

- **Interpretation**: Evaluation of a cognitively healthy midlife population disclosed differences in learning and working memory, which were influenced by psychosocial and other variables. Many variables influenced learning and working memory preferentially in those performing suboptimally. Suboptimal cognitive performance became progressively more prevalent during midlife aging.

- **Future directions**: Longitudinal studies need to investigate changes in midlife cognition and test for their relationship with biomarkers of cognitive disorders. Such studies will eventually identify the earliest cognitive changes in biologically defined cognitive disorders and allow testing interventions at the therapeutically optimal time window.

HIGHLIGHTS

- Learning and working memory demonstrate significant variability.
- Suboptimal cognitive performance is common in midlife.
- Suboptimal cognitive performance becomes pervasive during midlife aging.
- Psychosocial variables influence exclusively learning and working memory.
- Poor quality of life is prevalent in those performing suboptimally.

cognitive disorders. Considering these cognitive changes likely touch the boundaries of physiological cognition, successful clinical phenotyping of presymptomatic stages of cognitive disorders requires thorough understanding of physiological cognition.

To date, understanding of human cognition evolves around cognitive decline rather than focusing on physiological cognition. Physiological cognition is, in fact, rarely addressed in clinical practice and in clinical studies typically represented by the experimental "control" group, which serves as the benchmark for comparing cognitive phenotypes and disorders. In clinical settings, therefore, knowledge of
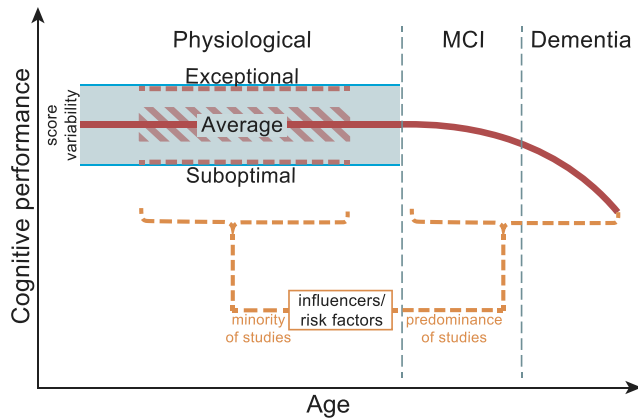
FIGURE 1 Illustration depicting midlife physiological cognitive performance. Hatching space indicates exceptional, average, and suboptimal physiological cognitive performances. Mild cognitive impairment (MCI) and dementia are included as possible pathological outcomes of cognitive aging

TABLE 1 The basic characteristics of the population-based sample

	No (%)	P^a
N	509	
Age[b]	48.3 ± 10.6	
Sex		
Females	248 (48.7%)	.564
Males	261 (51.3%)	
Age groups		
26–40 years	148 (29.1%)	.001
41–55 years	209 (41.1%)	
56–68 years	152 (29.9%)	
Education[c]		
Without GCSE	49 (9.6%)	< .001
With GCSE	198 (38.9%)	
University	262 (51.5%)	
Marital status		
Single	92 (18.1%)	< .001
Married	326 (64.0%)	
Partner	5 (1.0%)	
Divorced	73 (14.3%)	
Widow	11 (2.2%)	

Abbreviations: GCSE, General Certificate of Secondary Education; SD, standard deviation.
[a] Assessed using one sample Chi-square test.
[b] Values presented as mean ±SD.
[c] University education includes higher vocational school, bachelor, master, and doctoral degrees.

physiological cognition remains scarce (Figure 1). Furthermore, considering the prevalence of cognitive disorders increases with age, the majority of clinical studies sample older populations.[12–14] Experimental "control" groups in these studies, which represent the major source of knowledge about physiological cognition, also consists in older populations characterized by cognitive changes and incipient neurodegenerative and other brain pathologies.[9,35] These observations suggest that although older populations fit well into the experimental "control" group in cognitive disorder studies, they are not best suited for studies addressing physiological cognition. Studies addressing physiological cognition would, therefore, optimally examine participants in their midlife where there is minimal confounding effect of age and related pathologies.

1.3 | Cognition in midlife

Considering physiological cognition remains poorly studied in clinical settings, typically serves as the experimental "control" group in clinical studies commonly involving older populations, and needs to be better understood in the presymptomatic stages of cognitive disorders, we here ask whether measuring and characterizing physiological cognition in midlife with simple tests suitable for use in everyday clinical settings can be instructive in understanding cognition and its disorders. To this end, we first examine basic characteristics of selected key cognitive functions, test for their physiological spectrum of performances, and then evaluate the effects of aging and screen for variable that may influence physiological cognition in midlife.

Several reasons make this pilot study important and timely in understanding and evaluating cognitive disorders. First, characterization of physiological cognition may well uncover unique features of cognitive functions that may be either protective or a risk for developing cognitive disorders in later life. Second, considering aging represents the major risk factor for many cognitive disorders, characterizing cognitive

aging in midlife may facilitate understanding the relationship between aging and cognitive disorders. Third, identifying variables that influence physiological cognition in midlife will contribute to understanding its regulatory mechanisms and in differentiating early cognitive changes of the presymptomatic stages of cognitive disorders. Fourth, better understanding of physiological cognition will help identify select cognitive parameters that will be used in the future as the benchmark in diagnosing early cognitive changes and phenotypes of the presymptomatic stages of cognitive disorders. And fifth, eventual future therapies for cognitive disorders will need to be provided to patients at an optimal time window when damage to brain structures is minimal and cognition preserved—therefore, a long time before the onset of MCI or dementia. Characteristics of the physiological cognition will likely play an important role in defining clinically the optimal therapeutic time window for cognitive disorders.

1.4 | Investigating cognition in midlife

To investigate physiological cognition in midlife, we examined a well-characterized adult population-based sample representing randomly selected 1% of the entire community (Table 1).[36] Compared to

previously reported population-based samples,[37,38] the population examined in this pilot study showed a significant number of participants reaching advanced educational milestones. This finding may suggest a role of education in raising interest to enroll in clinical studies. Alternatively, it could also indicate that sampling exclusively an urban community results in increased recruitment of participants with advanced education. Considering that previous work showed an interaction between education and cognitive testing,[39,40] higher prevalence of advanced education in the examined sample needs to be taken into account when interpreting the results of this pilot study.

To examine physiological cognition, we selected simple tests suitable for use in everyday clinical settings. We first used MoCA to exclude possible MCI and dementia and ascertain cognitive health of the examined population-based sample. We then characterized physiological cognition using the Cogstate Brief Battery (CBB),[41,42] which measures four key cognitive functions: attention, psychomotor speed, learning, and working memory. Because attention and psychomotor speed are evaluated using response times, while learning and working memory are rated based on accuracy,[42–44] CBB allows for a simple and rapid examination of different cognitive functions using two independent and yet complementary cognitive measurement units with scores recorded and processed automatically. In contrast to many other simple tests, which focus largely on demonstrating cognitive decline phenotypes using scales with a predetermined range of scores, CBB is not scale-based and allows measuring the entire distribution of scores of cognitive functions. This is important when investigating physiological cognition, because it allows establishing and comparing characteristics of individual cognitive functions based on the patterns of their distributions.

The examined population-based sample has been extensively studied from most different research prospectives.[36,45–48] This represents a significant strength of this study as it allows us to investigate physiological cognition in relation to a wide range of clinical parameters. Based on previously reported risk factors of cognitive decline,[49] we here decided to test for associations between physiological cognition and cardiovascular, adiposity-related, lifestyle-associated, and psychosocial parameters to identify variables that may regulate or otherwise influence midlife cognition. Considering the cross-sectional design of this pilot study, the preliminary findings reported here need to be interpreted with prudence prior to their further confirmation by longitudinal studies.

1.5 | Characteristics of midlife cognition

We first screened the population-based sample for cognitive decline and excluded participants with MoCA scores consistent with cognitive decline from the study (Figure 2). We next investigated characteristics of physiological cognition using CBB in a cognitively healthy population-based sample (Figure 3A). Measurements of attention, psychomotor speed, and learning all produced scores that were normally distributed with one central peak corresponding to the mean value of all the scores (Figure 3B). Working memory scores behaved differ-
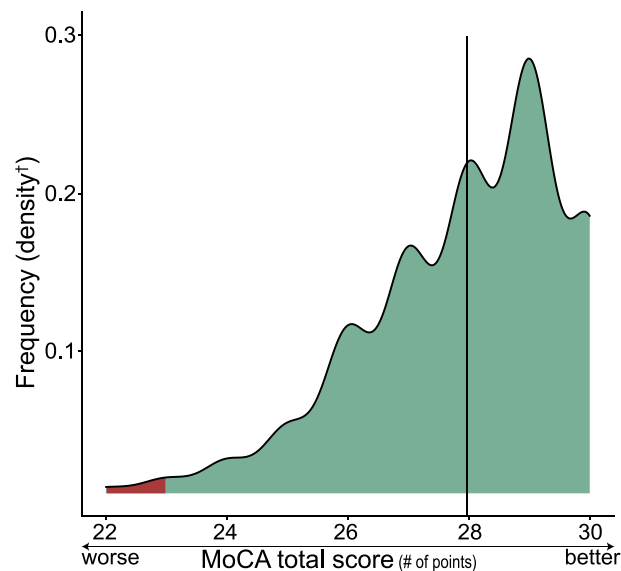

FIGURE 2 Montreal Cognitive Assessment (MoCA) total score distribution. The vertical solid line shows MoCA mean total score. Red area depicts MoCA scores consistent with mild cognitive impairment (MCI). [†]Probability density function based on kernel density estimation

ently and assumed a bimodal distribution with the second peak centered around scores of those performing better. Comparing patterns of score distributions of examined cognitive functions, we found that distributions of learning and working memory were significantly more widespread compared to the ones obtained for attention and psychomotor speed.

Because previous work showed that −1 standard deviation (SD) from the CBB-based average learning and working memory composite score discriminated MCI from physiologically healthy elderly,[43] we used the cut-off of ±1 SD to model physiological cognition as a spectrum of cognitive performances. Considering the normal distribution of most recorded cognitive function scores, segmenting cognitive function distributions by ±1 SD identified 70% of the participants performing averagely and the remaining 30% exceptionally well or suboptimally (Table 2). The exception to this finding was working memory in which approximately 38% of the participants performed exceptionally well. To examine the effects of midlife aging on physiological cognition we compared patterns of distribution of cognitive scores in the population-based sample divided into 26- to 40-, 41- to 55-, and 56- to 68-year-old age groups. We found significant age-dependent decrease in the performance of all examined cognitive functions with psychomotor speed most vulnerable to the effects of aging (Figure 3C and D). The prevalence of those performing suboptimally increased with age at the expense of those performing exceptionally well earlier in life (Table 3).

We last tested for cardiovascular, adiposity-related, lifestyle-associated, and psychosocial variables that may influence physiological cognition in midlife (Figure 4). All variables found to influence midlife cognition affected exclusively learning and working memory. Among them, the psychosocial variables were the most common and significant. In fact, apart from cholesterol levels and physical activity, we
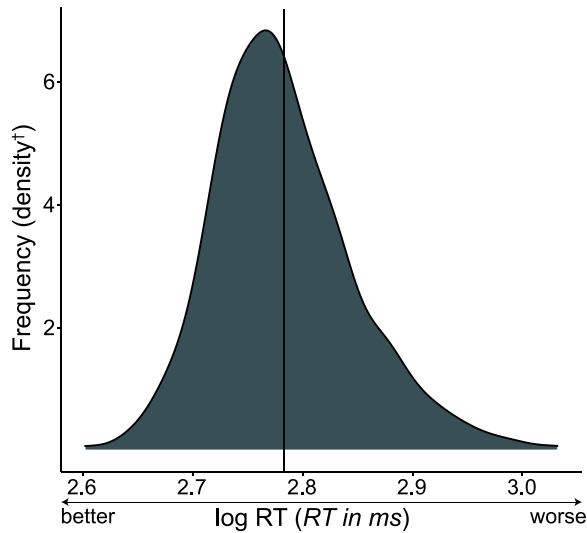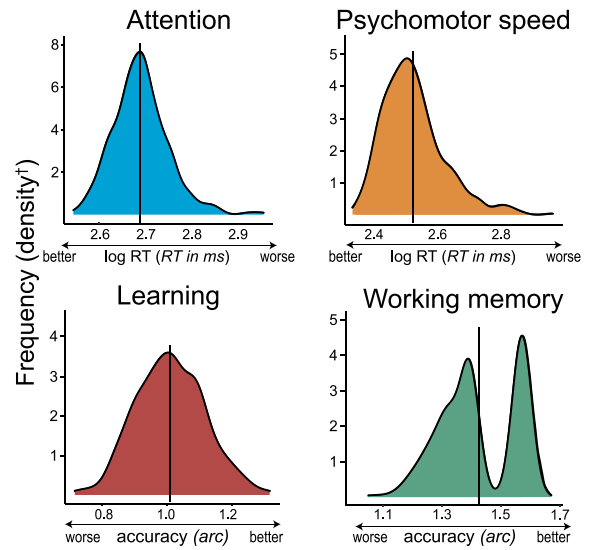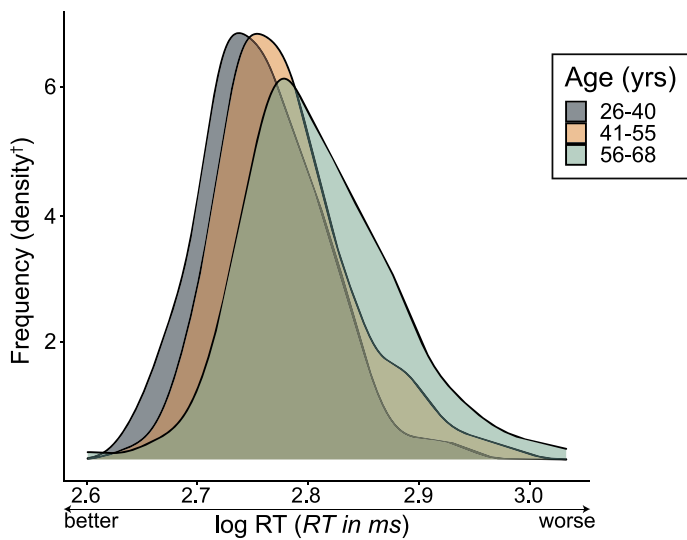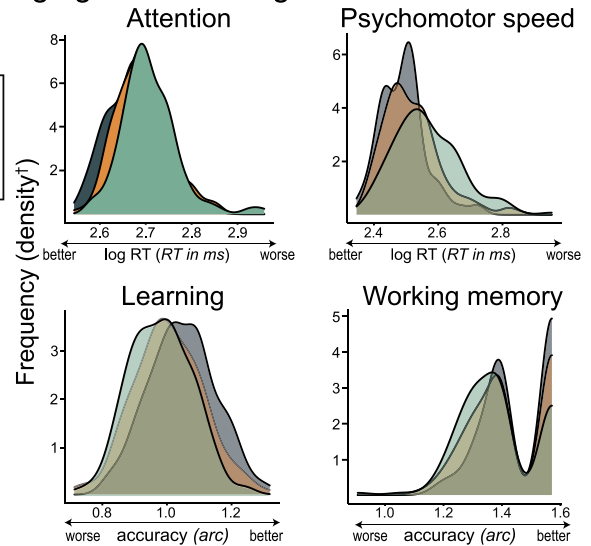
FIGURE 3 Distributions of raw Cogstate Brief Battery (CBB) scores. In (A) and (B), the vertical solid lines show mean total raw scores. The colors in (C) and (D) differentiate distributions of individual age groups. [†]Probability density function based on kernel density estimation

TABLE 2 CBB score-based spectra of cognitive performances defined by the ±1 SD cut-off

		Number of cases (%)		
	Cut-off points	Suboptimal	Average	Exceptional
Attention (log RT [in ms])	±.060	73 (14.3)	357 (70.1)	79 (15.5)
Psychomotor speed (log RT [in ms])	±.094	76 (14.9)	358 (70.3)	75 (14.7)
Learning (arc)	±.106	90 (17.7)	340 (66.8)	79 (15.5)
Working memory (arc)	±.128	79 (15.5)	238 (46.8)	192 (37.7)
Attention/psychomotor speed (log RT [in ms])	±.070	74 (14.5)	358 (70.3)	77 (15.1)
Learning/working memory (arc)	±.090	84 (16.5)	333 (65.4)	92 (18.1)
Global cognition (log RT [in ms])	±.063	74 (14.5)	365 (71.7)	70 (13.8)

Abbreviations: CBB, Cogstate Brief Battery; RT, reaction time; SD, standard deviation.

TABLE 3 CBB score-based spectra of cognitive performances defined by the ±1 SD cut-off in individual age groups

| | Number of cases (%) | | | | | | | | | |
| | 26–40 years | | | 41–55 years | | | 56–68 years | | | |
	Suboptimal	Average	Exceptional	Suboptimal	Average	Exceptional	Suboptimal	Average	Exceptional	P[a]
Attention (log RT [in ms])	13 (8.8)	97 (65.5)	38 (25.7)	31 (14.8)	147 (70.3)	31 (14.8)	29 (19.1)	113 (74.3)	10 (6.6)	<.001
Psychomotor speed (log RT [in ms])	8 (5.4)	110 (74.3)	30 (20.3)	23 (11)	155 (74.2)	31 (14.8)	45 (29.6)	93 (61.2)	14 (9.2)	<.001
Learning (arc)	15 (10.1)	98 (66.2)	35 (23.6)	39 (18.7)	139 (66.5)	31 (14.8)	36 (23.7)	103 (67.8)	13 (8.6)	.001
Working memory (arc)	10 (6.8)	68 (45.9)	70 (47.3)	34 (16.3)	93 (44.5)	82 (39.2)	35 (23)	77 (50.7)	40 (26.3)	<.001
Attention/psychomotor speed (log RT [in ms])	9 (6.1)	105 (70.9)	34 (23)	24 (11.5)	153 (73.2)	32 (15.3)	41 (27)	100 (65.8)	11 (7.2)	<.001
Learning/working memory (arc)	6 (4.1)	105 (70.9)	37 (25)	34 (16.3)	133 (63.6)	42 (20.1)	44 (28.9)	95 (62.5)	13 (8.6)	<.001
Global cognition (log RT [in ms])	7 (4.7)	105 (70.9)	36 (24.3)	27 (12.9)	156 (74.6)	26 (12.4)	40 (26.3)	104 (68.4)	8 (5.3)	<.001

Abbreviations: CBB, Cogstate Brief Battery; RT, reaction time; SD, standard deviation.

[a] Between-group differences in prevalence are based on the Chi-square test.

identified anxiety, depressive symptoms, hostility, and type D personality in addition to the quality of life all influencing physiological cognition negatively. Several variables were also found to influence specific segments of the spectrum of cognitive performances preferentially (Figure 5). For example, type D personality and hostility were underrepresented in those demonstrating exceptional cognitive performance. In contrast, cholesterol levels and poor quality of life were most prevalent in those performing suboptimally and underrepresented in those performing exceptionally well.

1.6 | Midlife cognition interpreted

The pilot experiments described in this study demonstrate unique behaviors of individual cognitive functions, find divergent cognitive performance in a significant proportion of the sampled population, show early vulnerability of cognition to aging, and identify several variables that influence physiology of cognition in midlife. Characterization of the physiological cognition in midlife with a simple cognitive test suitable for use in a clinical setting therefore was revealed to be most instructive about cognition per se and valuable for the future understanding and evaluation of cognitive disorders.

In contrast to attention and psychomotor speed, learning and working memory showed wider score distributions and significant variability in midlife. Considering both, learning and working memory, are affected early in canonical cognitive disorders such as AD,[50,51] the observed variability raises the question of whether some study participants may not present already in midlife clinical changes antedating cognitive decline in later life. This observation, together with the CBB-documented learning and working memory declines reported in healthy elderly positive for AD biomarkers,[33,34,43] supports the hypothesis that early cognitive phenotypes of the presymptomatic stages of cognitive disorders can be clinically measured and characterized in midlife. Variability in learning and working memory observed in this study, however, can also be the result of differences in the anatomic networks and physiology inherent to individual cognitive functions.[52,53] Alternatively, it may also represent differences in the measurement approach because following CBB instructions,[42–44] attention and psychomotor speed are measured as response times, while learning and working memory are recorded based on the accuracy of the responses. Future studies will likely test these hypotheses further and establish more definitively whether specific changes within boundaries of physiological cognition can be reliably measured and significant to the phenotyping of the presymptomatic stages of cognitive disorders.

Modeling physiological cognition as a spectrum of cognitive performance revealed that approximately 30% of the sample exhibits exceptional or suboptimal cognitive performance in roughly equal proportions. Although the observed spectrum of cognitive performances clearly conforms with the rules of the normal distribution, where with a ±1 SD cut-off approximately 70% of the sample shows, by definition, average cognitive performance, the observed spectrum may well be informative also about changes in physiological cognition. First, a
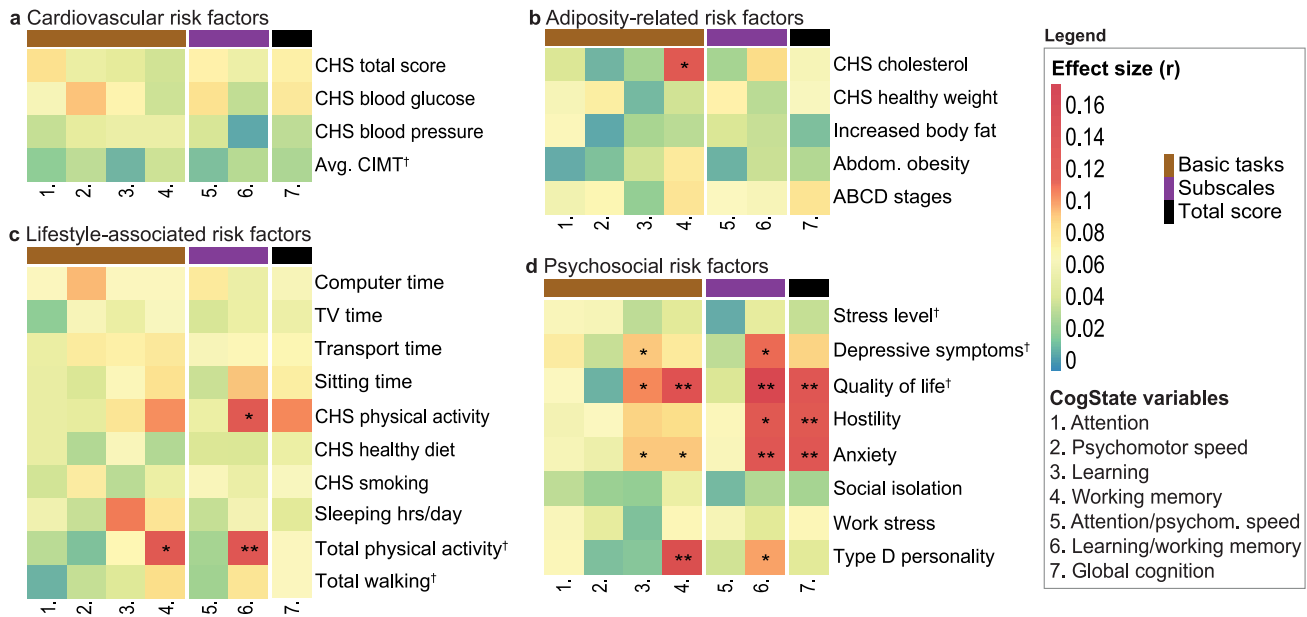
FIGURE 4 Associations between standardized physiological cognitive performances and the cardiovascular, adiposity-related, lifestyle-associated, and psychosocial variables. Heatmaps show Pearson's r effect sizes (with corresponding levels of significance) based on the analysis of variance/Pearson correlation of effect of risk factors on cognitive performance. †Pearson correlation of continuous risk factors. CHS, Cardiovascular Health Score

population-based sample exhibiting exceptional and suboptimal cognitive performances changes significantly with aging. This means that the number of participants performing suboptimally on the CBB increases hand in hand with the increase in the incidence and prevalence of cognitive disorders.[54,55] Second, several variables regulating or otherwise influencing cognition segregate those participants who are performing suboptimally. These observations, together with the reported ±1 SD cut-off defining MCI using CBB in the elderly,[43] raise the question of whether select participants showing suboptimal cognitive performance have not developed clinically measurable presymptomatic stages of cognitive disorders already in midlife. Further studies are needed to test if participants showing exceptional or suboptimal cognitive performances are either protected or prone to developing established cognitive phenotypes and decline in later life.

Although the effects of aging on physiological cognition are extensively studied,[56–58] the assessment of cognitive aging in midlife using simple tests suitable for use in a clinical setting, remains poorly investigated.[59–62] We here show that cognitive functions all undergo measurable, significant, and progressive deterioration during midlife aging with psychomotor speed most vulnerable to the effects of aging. In agreement with this observation, the prevalence of those performing suboptimally increases with midlife aging largely at the expense of those performing exceptionally well at a younger age. Considering aging is the most significant risk factor for canonical cognitive disorders such as AD,[55] these findings also raise the question of whether increased prevalence of those performing suboptimally during midlife aging does not in part reflect the earliest clinically measurable cognitive changes of presymptomatic stages of cognitive disorders. Further

longitudinal studies comparing the earliest clinically measurable cognitive changes with biomarkers of cognitive disorders will help answer this question.

This pilot study found a significant role of psychosocial variables influencing exclusively learning and working memory domains of physiological cognition in midlife. Considering impairments in learning and working memory, but not in attention or psychomotor speed, occur early in cognitive disorders,[32,33,43] this finding raises the question of whether variables influencing learning and working memory in midlife are involved in the development of cognitive disorders. In contrast, cardiovascular, adiposity-related, and lifestyle-associated variables were not found to influence physiological cognition in midlife, which is expected considering good general health of the examined sample as well as consistent with previous studies showing no major reproducible effect of any specific systemic health parameter on physiological cognition in midlife.[63] These findings, however, do not preclude a possible cumulative effect of systemic risk factors on cognitive performance or decline in later life.[64] In fact, this may be the case of the observed negative effect of increased blood cholesterol levels on midlife cognition, which based on previous studies may associate with cognitive decline in later life.[65]

The association between anxiety and depressive symptoms and cognitive decline[66,67] in the healthy elderly[68–70] and presymptomatic stages of cognitive disorders[71–73] is well documented. We here extend these observations by showing that anxiety and depressive symptoms influence physiological cognition already in midlife and by identifying personality traits such as hostility and type D personality in addition to quality of life as variables negatively influencing physiological
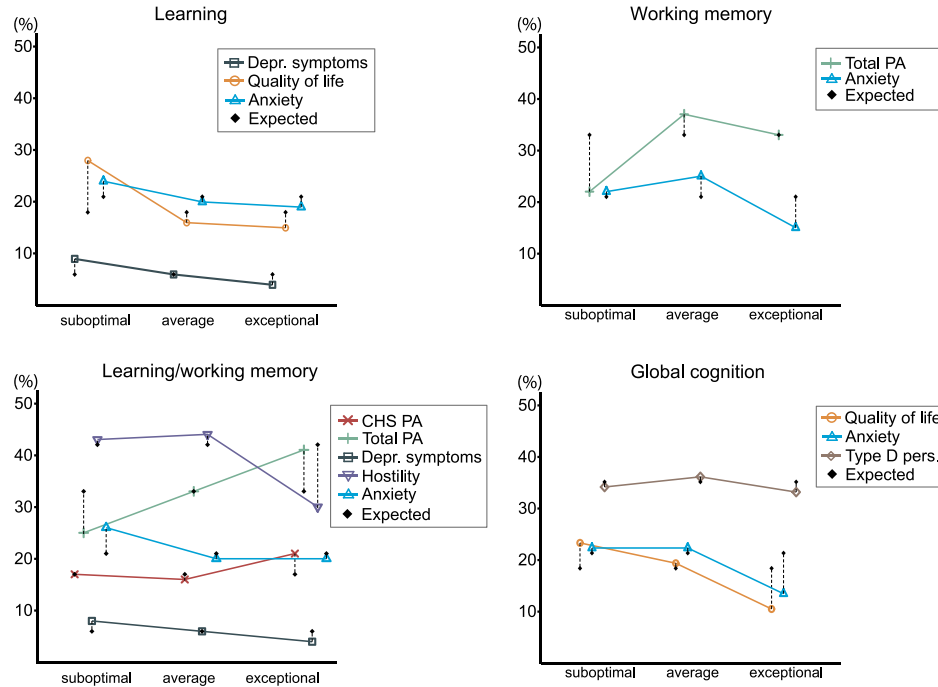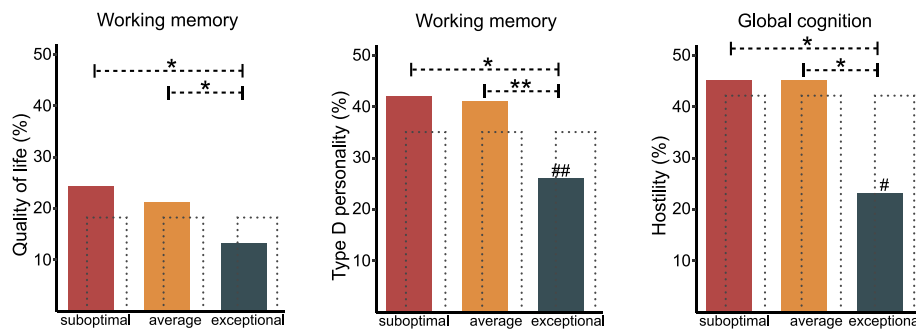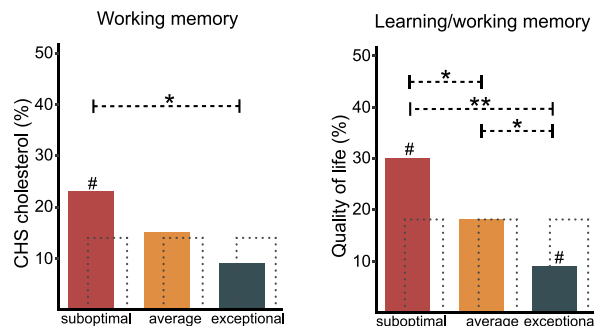
FIGURE 5 Prevalence of variables influencing physiological cognition in different segments of the spectrum of the physiological cognitive performance. Lowest categories of individual variables influencing physiological cognition were compared to the exceptional, average, and suboptimal segment of the spectrum of physiological cognitive performance. Lowest categories were defined as follows: poor (Cardiovascular Health Score [CHS] physical activity and cholesterol), present (dichotomic psychosocial factors), lowest (quality of life), low (total physical activity), and moderate/severe (depressive symptoms). In (A), points show observed and expected prevalence. Solid lines indicate changes in the prevalence different physiological cognitive performances. Dashed lines depict distances between observed and expected values. In (B) to (C), color bars show observed prevalence in individual cognitive performances, doted bars indicate expected prevalence. Horizontal upper lines depict significant differences in distribution between pairs of cognitive performances, above-plot hashtags indicate significant deviations (#: $P < .05$, ##: $P < .01$) of observed values from expected values in individual cognitive performances

cognition. These preliminary findings are novel considering the role of personality traits and quality of life in cognition remain in general poorly investigated.[74–76] Observation of significantly reduced prevalence of hostility, type D personality, and quality of life among those performing cognitively exceptionally well documents further their negative influence on physiological cognition.

1.7 | Conclusions about midlife cognition

This pilot study demonstrates that measurements of physiological cognition using simple tests suitable for use in everyday clinical settings prove to be most instructive in understanding cognition and its disorders already in midlife. Learning and working memory showed significant variability, which was further influenced by psychosocial and other variables. Intriguingly, learning and working memory were both reported to be affected early in cognitive disorders,[33,43] while psychosocial variables were found to increase the risk and commonly precede or otherwise associate with biomarkers and cognitive disorders.[71,72] These observations, together with the observed pervasive effect of suboptimal cognitive performance in midlife, raise the question of whether subtle changes within physiological boundaries do not signal already in midlife the very first clinical manifestations of presymptomatic stages of cognitive disorders. Future longitudinal studies will eventually identify the earliest robustly measurable clinical correlates of biologically defined cognitive disorders. These studies will also establish whether exceptional cognitive performance in midlife protects against cognitive decline in later life and allow for interventions ranging from targeting variables influencing suboptimal cognition to testing novel therapeutics at the clinically most opportune time window.

2 | CONSOLIDATED RESULTS AND STUDY DESIGN

Cross-sectional examination of physiological cognition in midlife was performed on a well-characterized midlife population-based sample.[36] Cognitive health of the sample was secured using the MoCA. Physiological cognition was then investigated using the CBB and tested for associations with cardiovascular, adiposity-related, lifestyle-associated, and psychosocial variables.

2.1 | Demographic characteristics of the population-based sample

The sample consisted of 509 participants with a median age of 49 years (range, 26–68; interquartile range, 40—57; Table 1). University degrees (262, 51.5%) followed by completion of the General Certificates of Secondary Education (198, 38.9%) were the most frequently achieved educational milestones. Medical conditions self-reporting questionnaire indicated that the population-based sample was overall in good health (Table SA.1 in supporting information).

2.2 | Physiological cognitive performance in midlife

The population-based sample exhibited mean CBB-derived raw global cognition score of 2.78 (SD ±0.64) (Figure 3A). Mean raw attention and psychomotor speed scores amounted to 2.69 (SD ±0.06) and 2.52 (SD ±0.09) log reaction time (RT; in milliseconds), respectively. Mean raw learning and working memory scores amounted to 1.01 (SD ±0.11) and 1.42 (SD ±0.13) arcsin of accuracy (arc), respectively (Figure 3B). Attention/psychomotor speed and learning/working memory composite scores amounted to 2.61 (SD ±0.07) log RT (RT in milliseconds) and 1.22 (SD ±0.09) arc, respectively. Distribution of the raw cognitive scores produced Gaussian curves except for raw working memory scores, which generated a bimodal curve (Table SA.2 in supporting information).

Raw attention (1.474), psychomotor speed (1.427), and global cognition (.714) scores gave rise to leptokurtic and raw working memory (−.744) scores to platykurtic distribution of curve shapes. Raw learning (−.136) scores were the closest to the mesokurtic curve shape. Signed-likelihood ratio tests showed significant differences in coefficients of variation between all pairs of CBB measured cognitive functions (learning vs. working memory, $P = .002$; all other pairs, $P < .001$). These measurements of variation are consistent with the above analysis of kurtosis in showing higher coefficients of variation for learning (10.46%) and working memory (8.98%) compared to attention (2.22%) and psychomotor speed (3.72%). Raw cognitive scores were significantly worse in older age group compared to the young and middle-aged group ($P < .001$, Figure 3C and 3D). Psychomotor speed ($P < .001$), but not attention ($P = .50$), learning ($P = .43$), or working memory ($P = .10$), exhibited significant age-related changes in the coefficient of variation.

To model physiological cognition, we generated spectra of cognitive performances by segmenting distributions of standardized cognitive scores for each cognitive function by ±1 SD cut-off. Segmentation divided distributions of the raw cognitive scores into a central region comprising scores within ±1 SD, representing average cognitive performance, and into two "tails" encompassing scores either above or below one SD, representing exceptional or suboptimal cognitive performance, respectively. Analysis of the spectra showed 71.7%, 13.8%, and 14.5% of the raw cognitive scores corresponding to average, exceptional, and suboptimal physiological performances, respectively (Table 2). All cognitive functions showed similar 70:15:15 ratio in the distribution of their raw cognition scores apart from working memory in which almost 38% of the sample performed exceptionally. When we divided the sample into 26- to 40-, 41- to 55-, and 56- to 68-year-old age groups, we observed progressive and significant increase in the prevalence of suboptimal cognitive performance and at the same time, a decrease in those performing exceptionally well (Table 3).

2.3 | Variables influencing physiological cognitive performance

Cardiovascular variables, including the Cardiovascular Health Score (CHS) framework-derived total score, arterial blood pressure, and

blood glucose, as well as the average carotid intima media thickness showed no associations with physiological cognition (Figure 4A).

Examination of adiposity-related variables found significant association between adiposity-related CHS score of blood cholesterol levels and the working memory task ($P = .046$) with higher cholesterol levels associated with poorer physiological cognitive performance (Figure 4B). Other adiposity-related parameters, including the CHS framework-derived body weight, Adiposity-Based Chronic Disease (ABCD)-based abdominal obesity, and body fat scores, showed no associations with the physiological cognition.

Lifestyle-associated variables identified significant association between the CHS-derived physical activity and learning ($P = .037$) and the total physical activity and learning ($P = .008$) and the learning/working memory composite ($P = .011$; Figure 4C). Intermediate physical activity was associated with the best cognitive performance (Figure SA.3 in supporting information). Other lifestyle parameters, including sedentarism, length of sleep, the coronary heart disease (CHD) framework-derived healthy diet, and smoking scores showed no associations with the physiological cognition.

Assessment of psychosocial variables found several significant associations with cognitive performance (Figure 4D, Tables SA.4 and SA.5 in supporting information). Anxiety associated with poorer learning ($P = .045$) and working memory ($P = .047$) and influenced the learning/working memory ($P = .008$) and the global cognition composite scores ($P = .008$). Depressive symptoms negatively influenced learning ($P = .048$) and the learning/working memory composite score ($P = .016$). Hostility was inversely associated with the learning/working memory ($P = .012$) and the global cognition composite scores ($P = .009$). Type D personality was associated with poorer working memory ($P = .002$) and the learning/working memory composite score ($P = .030$). Lower quality of life was associated with poorer learning ($P = .023$) and working memory ($P = .005$) and influenced negatively learning/working memory ($P = .001$) and the global cognition composite scores ($P = .006$).

2.4 | Variables influencing the spectrum of cognitive performances

We found that adiposity-related, lifestyle-associated, and psychosocial variables influenced either the entire spectrum or preferentially select segments of the spectrum of cognitive performances in midlife. Anxiety, depressive symptoms, hostility, type D personality, CHS-derived, and total physical activity and quality of life influenced individual or composite cognitive scores throughout their entire spectrum of cognitive performances (Figure 5A). Increased hostility (global cognition, $P = .034$), type D personality (working memory, $P = .016$) and poorer quality of life (working memory, $P = .048$) were significantly underrepresented in the segment corresponding to those performing exceptionally well (Figure 5B). Increased cholesterol levels (working memory, $P = .015$) and poorer quality of life (learning/working memory, $P = .003$), on the other hand, were underrepresented among those performing exceptionally well

and significantly more prevalent in those performing suboptimally (Figure 5C).

3 | DETAILED METHODS AND RESULTS

3.1 | Design and study population

The research sample consisted of the participants of the Kardiovize study, a longitudinal epidemiological cohort based on a randomly selected 1% of the population of the residents of the city of Brno, Czech Republic.[36] Six hundred eight out of a total of 2160 participants enrolled in the Kardiovize study underwent cognitive testing. Ninety-seven of them were excluded due to missing more than 10% of the demographic data or incomplete cognitive testing results. Five hundred eleven participants with complete demographic data and cognitive testing results were then screened for cognitive decline. The final sample consisted of 509 cognitively healthy participants. Participants were separated into young (26–40 years), middle-aged (41–55 years), and older (56–68 years) age groups to test for age-related cognitive changes in midlife. The baseline assessment consisted of a face-to-face interview that included a comprehensive questionnaire administered by trained nurses and physicians of the International Clinical Research Centre of St. Anne's University Hospital in Brno, Czech Republic. The questionnaire included demographic data, medical history, cardiovascular and metabolic risk behaviors, lifestyle characteristics, and a mental health survey. Laboratory measures included blood analyses of glucose, total cholesterol, and triglycerides. All participants underwent blood pressure measurements, anthropometric assessment, and characterization of body composition. Data were collected into a validated web-based research electronic data capture (REDCap) database. The research protocols of the study were approved by the institutional review board and by the ethics committee of St. Anne's University Hospital. All participants of the Kardiovize study signed informed consent.

3.2 | Assessment of cognitive performance

Screening for MCI and dementia was performed using the MoCA test. MoCA total score was calculated as the sum score of individual items. Physiological cognitive performance was assessed using the CBB. CBB is a short version of the computer-administered cognitive test battery requiring roughly 10 minutes for administration. It uses playing cards to examine four basic cognitive domains: visual attention, psychomotor speed, visual learning, and working memory. Performance in the examined cognitive domains is measured by recording the response time and the accuracy. According to the instructions,[42–44] attention and psychomotor speed were assessed by measuring the response time needed to correctly identify the red playing cards (identification) or to detect all new playing cards (detection), respectively. Primary outcome measures of attention and psychomotor speed were the $\log_{10}$ transformed reaction time of correct responses in milliseconds (log RT

in milliseconds). Mean log RT (in milliseconds) of these two cognitive domains was calculated to obtain the attention/psychomotor speed composite raw score. Learning and working memory were assessed by measuring accuracy in recognizing a card previously seen in the deck (one card learning) or establishing whether the current card is the same as the previous one (one back test), respectively. Primary outcome measure was the arcsine of the square root of the correct responses (arc). The mean arc of these two cognitive domains was calculated to obtain the learning/working memory composite raw score. Mean log RT (in milliseconds) of all four cognitive domains was used to calculate global cognition raw score.

To establish the spectra of physiological cognitive performances we used previously reported cut-off value of ± 1.0 SD to segment the distribution of raw scores of individual cognitive functions and their composites.[43] The same mean and segmentation of the whole population-based sample was also used to examine the spectrum of physiological cognitive performances in the individual age groups.

To examine the influence of cardiovascular, adiposity-related, lifestyle-associated, and psychosocial variables on healthy cognition, individual cognition scores were standardized by transforming raw scores into z-scores normalized for age decades and sex as previously reported.[43] Attention and psychomotor speed standardized scores were inverted to allow calculating the standardized global cognition score as well as for simpler interpretation of the results, with higher values of all scores reflecting better performance. Composite and global cognition scores were then calculated as means of respective cognitive domains scores.

3.3 | Assessment of cardiovascular health

We used the novel framework of the CHS, as defined by the American Heart Association, to probe associations between cardiovascular health and the cognitive performance.[77] The CHS evaluates three risk factors—arterial blood pressure, blood glucose, and total cholesterol, and four behavior—smoking, body mass index (BMI), physical activity, and diet. Each variable was categorized as ideal, intermediate, or poor (Tables SA.3 and A.6 in supporting information). Arterial blood pressure was measured using a routine protocol as previously described (ABPM 90207-17Q; Spacelabs Healthcare).[36] Vascular health was further examined using ultrasound measurements of the carotid intima-media thickness (CIMT; MyLabClass-C; ESAOTE SpA).[78]

3.4 | Assessment of adiposity-related variables

Two sets of variables were used to assess associations between adiposity-related parameters and cognitive performance. First, we measured healthy weight and total cholesterol levels according to the CHS framework. Second, we measured abdominal obesity and increased body fat. We then calculated the ABCD index, developed by the American Association of Clinical Endocrinologists, to assesses adiposity-related risk factors based on the amount, distri-

bution, and function of the adipose tissue (Table SA.7 in supporting information).[79,80]

3.5 | Assessment of lifestyle-associated variables

Examined lifestyle-associated variables included total physical activity levels measured by the corresponding CHS values, intensity of physical activity measured by the International Physical Activity Questionnaire long version (iPAQ-L)[81] and sedentarism calculated as the score of the time spent on various sedentary behaviors. We also measured the length of sleep. Physical activity and sleep duration were assessed as continuous as well as categorized variables (Table SA.8 in supporting information).

3.6 | Assessment of psychosocial variables

Stress levels were measured using the 10-item Perceived Stress Scale (PSS).[82] PSS score ranges from 0 to 40 points. Anxiety, hostility, social isolation, work stress, and type D personality were examined using the European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (EGCDP).[83] All variables examined were binary (present/absent). Depressive symptoms were assessed using the 9-item Patient Health Questionnaire-9 (PHQ-9).[84] PHQ-9 score ranges from 0 to 27 points. Quality of life was assessed using a self-reported questionnaire ranging from 1 to 100 points.[85] Continuous variables were categorized according to questionnaire's guidelines (Table SA.8).

3.7 | Statistical analysis

Using a random forest machine learning paradigm 0.34% of the values were imputed to correct for less than 10% of the missing values. One sample Chi-square test was used to assess the demographic characteristics of the population-based sample. Distributions and group differences in demographic variables and differences in mean scores for binary variables were calculated using the t-test and the Chi-square test, respectively. Kurtosis value and Pearson's coefficient of variation were used to assess distribution of cognition. Differences between CBB raw scores dispersion were examined using signed likelihood ratio test. Categorical variables were evaluated using analysis of variance with the Tukey post hoc test and continuous variables using the Pearson's correlation. Calculated effect sizes were transformed to Pearson's r.

To test whether cardiovascular, adiposity-related, lifestyle-associated, and psychosocial variables found to associate with physiological cognitive performance influence exceptional, average, and suboptimal cognition, or cognition globally, we used one-sample Chi-square test to assess differences between observed and expected prevalence of the worst category of all variables. Expected values were calculated as distribution of participants in exceptional, average, and suboptimal cognitive performance categories and multiplied by

the prevalence of predictor's worst category in decimal form for each cognitive variable. One proportion Z-test was used as the post hoc test to identify specific performance groups with significantly different prevalence with Bonferroni's correction of *P*-values.

Missing values were imputed in R v.3.6.3 (https://www.r-project.org/) with the missForest (v.1.4) package. Data were analyzed using SPSS v.21. Significance was evaluated at the α level of 0.5 and all testing two-sided. Figures were plotted using ggplot2 (v.1.0.12), reshape2 (v.1.6.4), and pheatmap (v.2.3.3.0) packages; the cvequality package (v.0.1.3)[36] was used to test for significant differences in dispersion of raw cognitive tasks.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

Gorazd B. Stokin devised the study. Jan S. Novotný analyzed the data. Jan S. Novotný and Gorazd B. Stokin drafted the manuscript. All authors contributed to the analysis and interpretation of the data and reviewed the manuscript.

DATA AVAILABILTY STATEMENT

The data used in this study are available upon request immediately after the publication to anyone who submits the online request that will be approved by the St. Anne's University Hospital International Clinical Research Centre internal board. The researchers must provide their research intentions and goals, and specify and justify requested variables. The data will be provided for a limited and well-defined time via cloud service or e-mail in csv format. After defined period the data should be returned, and all csv copies destroyed.

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