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Impact of Chronic Stress Exposure and Illness Perception on Bio-Functional Age in Overweight and Obese People on the Alteration of The Bio-Functional Age, Bio-Functional Status, And Illness Percep-tion: A Follow-Up Study

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Abstract

Objective: Self-perceived chronic stress exposure and individual illness perception have been identified as risk factors for accelerated aging. Overweight/obesity has been associated with these influencing factors, as well as an unhealthy lifestyle, which may contribute to unhealthy aging despite increasing life expectancy. This study aimed to evaluate the impact of daily perceived chronic stress exposure and individual illness perception on the bio-functional aging process in an overweight/obese population.

Methods: This research conducted a follow-up study based on the Bern Cohort Study-2014 (BeCS-14), allowing for a diachronic comparison o3f 40 subjects (bio-functional age ≥35 years) from the "nutrition" subgroup (BMI ≥25 kg/m^2). Participants underwent a standardized test battery to assess their bio-functional status, as in the previous study.

Results: The results of this follow-up study revealed a decrease in the difference between Bio-Functional Age (BFA) and Calendrical Age (CA), indicating signs of premature bio-functional aging (from 9.58 to 5.76 years, p<0.001) compared to the BeCS-14. The body functions (physical, physiological, cognitive, and emotional-social) exhibited a declining trend, while the prevalence of Non-Communicable Diseases (NCD) increased. Self-perceived chronic Stress Perception Remained Constant (SSCS, p=0.792), whereas Social Isolation (SOZI), work overload (UEBE), Excessive Demands At Work (UEFO), and Pressure to Perform (ERDR) rose irrespective of age and gender. Higher mental preoccupation with the cause of illness positively correlated with increased chronic stress perception (SSCS - PSI, rs=0.663).

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Conclusion: The findings suggest that an increase in NCD (non-communicable diseases), decline in physical and cognitive abilities, and negative changes in health behaviour contribute to accelerated bio-functional aging. Young (<45 years) overweight/obese individuals, particularly females, appear to be vulnerable to self-perceived chronic stress exposure and individual illness perception.

Introduction

Advances in medicine have increased life expectancy [1]. According to the World Health Organization(WHO), in 2020, more than a billion people worldwide were at least 60 years old, and this number is predicted to double by 2050 [2]. However, increasing life expectancy is also accompanied with a higher number of life transitions (e.g., development of co-morbidities, retirement, environmental changes, death of family and friends) which may reduce Quality Of Life (QoL) on an individual level and increase economic burden on a public level [3]. Thus, healthy aging is a major goal on both, the individual and societal level.

Aging can be operationalized in diverse ways with the most classical being the Chronological Age (CA). However, CA does not necessarily reflect aging on a functional level. Thus, the term Bio-Functional Age (BFA) was introduced reflecting an individual's bio-psycho-mental-social functioning [4,5]. The BFA can reliably be assessed by a non-invasive, validated, sex- and age-specific test battery, called the Bio-Functional Status (BFS) [6].

Several preventive and risk factors have been found to be associated with bio-functional aging. While well-preserved physical functions and good mental health are thought to be preventive [7], overweight/ obesity [8-10], related increased self-perceived chronic stress exposure [11,12,13], and individualillness perception [9,14] have been found to be risk factors for pro-aging. As the number of overweight / obese people is constantly increasing, the number of vulnerable people at risk for non-healthy aging also increases [15].

Development of overweight / obesity is multi-factorial [15,16]. Self-perceived chronic stress exposure appears to have a negative impact on health behaviors, which in turn are suggested to be risk factors for overweight/obesity [17]. Furthermore, overweight and obese individuals more often suffer from a stigma that distorts their illness perception due to different psychosocial factors, e.g., low body perception, inner satisfaction, self-esteem and sense of exclusion [18].

The Bern Cohort Study 2014 (BeCS-14) is a longitudinal observational cohort study assessing the BFS/BFA in the context of other factors (e.g., chronic stress exposure, nutrition, workplace) [6]. In a previous transversal analysis, we examined the impact of self-perceived chronic stress exposure on BFA in overweight / obese subjects [13]. In the current follow-up study after five years, we aimed to investigate whether 1) (change in) self-perceived chronic stress exposure was a predictor of premature aging, and 2) (change in) individual illness perception had an impact on BFA in overweight / obese individuals.

Material and Methods

Study design

The Bern Cohort Study 2014 (BeCS-14) is a single-centered, longitudinal, observational, non-interventional, non-randomized study, which has been described in detail before [13]. At baseline, the overweight / obese subgroup consisted of 99 subjects [6], of whom 95 were interested in continuous project participation. They were contacted for follow-up assessments, with 40 subjects (40.4%) being successfully recruited for the current study. The remaining subjects were either unavailable (n=11), deceased (n=2), declined participation (n=18), or did not respond (n=24). All study procedures were performed at the Department of Obstetrics and Gynecology, Inselspital Bern Switzerland, between 2019-12-05 and 2020-07-14. The project was approved by the Cantonal Ethics Committee Bern, Switzerland (Ref.-Nr. KEK-BE: 2019-01109) with written consent of each subject.

Assessments

Assessments at baseline [6] and at follow-up were identical. They comprised 1) a questionnaire to record the personal and family history (supplementary file 1), 2) validated questionnaires to assess self-perceived chronic stress exposure (TICS) [19,20] and illness perception (PATEF) [21], and 3) the BFS/BFA test battery [6,13], respectively. Assessments were performed by two doctoral students (LMR, TFAM).

Bio-Functional Status (BFS) and Bio-Functional Age (BFA)

The BFS was assessed by using a comprehensive test battery developed by Poethig et al., previously described and reported by others [4-6; 9;13; 22-24]. The test battery (22 tests, 45 variables) includes holistic characteristics from the physical (diastolic and systolic blood pressure, pulse rate at rest and during effort, vital capacity, grip strength), sensory-psychomotor (visual acuity, hearing function, psychomotor endurance), cognitive-mental (visual, auditory, verbal and cognitive reaction times, ability to concentrate, strategic thinking, memory and orientation skills) and emotional-social domain (emotional and physical well-being, exposure to stress, stress predisposition, sense of coherence), that fit into a complex theoretical model incorporating the ICF and AHA concept [6]. The test battery for BFS assessment is a validated age- and sex-specific tool (objectivity 0.96, reliability 0.93, females age validity: Total age correlation 85.2 %; total age commonality in the main factor 76.3 %) [13]. The BFA is based on a sex-specific regression and factor analysis of functional age. BFA (year-equivalents) can only be calculated for subjects with a CA of at least 35 years [6,13]. BFA < CA corresponded to slower bio-functional aging than expected, associated with normal to very well-preserved functions in one to several of the domains listed above. BFA > CA, on the other hand, reflected premature aging with a faster than expected decline in these studied functions.

Trier Inventory for the Assessment of Chronic Stress (TICS)

TICS is a standardized, validated questionnaire (Cronbach alpha 0.9) [20] and has already been described in detail before [13]. It captures nine aspects of chronic stress and indicates how often one has experienced that particular stress in the last 3 months: e.g., Work Overload (UEBE), Social Overload (SOUE), Pressure To Perform (ERDR), Job Dissatisfaction (UNZU), Job Overload (UEFO), Lack Of Social Recognition (MANG), Social Tension (SOZS), Social Isolation (SOZI) and Chronic Worry (SORG). Each of the 57 items is rated on a five-point rating scale (0 - never; to 4 - very often), where a higher score represented an increased chronic stress perception. A global score for chronic stress over the past three months can be measured using the

Screening Scale for Chronic Stress (SSCS). This is formed by five of nine aspects of chronic stress (SORG, UEBE, SOUE, UEFO, MANG). SSCS has a total score ranging from 0 to 48 points and can be divided into three subcategories of perceived chronic stress intensity based on the score: below average stress (0-11 points), above average stress (12-22 points) and extreme stress (>22 points) [25]. Reference values are only given for the three age categories and not for gender.

Illness perception (Patiententheoriefragebogen, PATEF)

PATEF is a validated German questionnaire addressing patient's illness perception [21]. And has already been described before [9]. It was composed of 46 items in total covered in eight different scales: e.g., Psychosocial Attribution (PS), consisting of Psychosocial Internal (PSI) and Psychosocial External (PSE) factors; Naturalistic Attribution (NT), consisting of Naturalistic Internal (NTI) and Naturalistic External (NTE) factors; Health Behaviour (HB) and an Overall Score (OS). The participants provided answers using a five-point rating scale (0=definitely not; to 4=very sure). The raw values were subsequently converted into stanine values (S-values (1-9)) according to age (</≥ 45 years) and sex [21]. The OS determines the intensity of mental occupation with the illness cause (S< 4 corresponds to no thoughts or theory not covered by PATEF, respectively; S=4-6 and no single scale with S> 6 correspond to mental occupation with illness cause but indecisive about the cause; S> 6 corresponds to high mental occupation). 1-3 single scales with S> 6 correspond to punched-out theory (already defined theory); 4-5 single scales with S≥ 5 correspond to diffuse theory. High S-values (> 6) in PSE (α=0.87, r=0.79) predict a high risk for helplessness and depression, whereas high S-values (> 6) in PSI (α=0.93, r= 0.73) indicate dissatisfaction and low self-esteem. High S-values (> 6) in NTE (α=0.81, r=0.74) show a highly fatalistic tendency blaming the environment, whereas high S-values (> 6) in NTI (α=0.72, r=0.74) indicate a highly possible passivity (considering their own body as "too weak"). High S-values (> 6) in HB (α=0.93, r=0.7) indicate an underlying suspicious lifestyle habit. The internal validity of the PATEF is good; correlations between PSI & PSE r=0.8, PSE & NTI r=0.7, HB & PSI=0.6. are highly significant [21].

Statistics

The statistical analysis was conducted in collaboration with the statistical institute in Leipzig using the Statistical Package for The Social Sciences (SPSS) version 27. The descriptive statistics contained the calculation of the mean, range (min-max), standard deviation and for ordinal parameters the percentages. The statistical significance was set at $p< 0.05$ applying the signed-rank Wilcoxon test, expressing the relevance with the effect size (r) (< 0.3 small effect, > 0.3 and < 0.5 as medium and values > 0.5 strong effects). Statistical correlations at baseline (same subgroup) and this follow-up study were assessed by the level of significance of 5% (two-sided) or 2.5% (one-sided) using the Spearman product-moment coefficient (r_s). There were no missing data for the BFA/BFS and PATEF, whereas 9 data sets from the anamnesis questionnaire and TICS were missing.

Results

Cohort characteristics

Table 1 presents the cohort's characteristics at baseline and follow-up after 5.4 (+3.3) years. Most participants were female. CA was 49.2 ± 11.3 years at baseline and 54.9 ± 11.4 years at follow-up. Mean BMI was within the obese range (30.4 kg/m^2) and did not significantly change across the observation period (+ 0.05 kg/m^2). However, at follow-up the standard deviation was greater than at baseline indicating a greater variation in weight gain or loss. Still, at follow-up most subjects were either overweight (42.5%), or obese (47.5%), respectively. In respect to lifestyle, there was no significant change in alcohol and tobacco consumption across the observation period while physical activity increased, e.g., the number of subjects exercising ≥ 2/week had tripled. Sleep duration remained stable, yet a deterioration in sleep quality was reported. Satisfaction with partnership and sex life was generally high. Employment level changed across the observation period with less subjects working full-time at follow-up while the number of retired participants had increased. Still, work related stress levels seemed to have increased as more subjects reported fewer sick days despite not feeling well (presenteeism). This may be due to a generally decreased health status as 17.5% of the subjects reported loss of walking ability at follow-up and 15% hospitalization up to four times during the observation period. Similarly, the prevalence of cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus) and chronic Non-Communicable Diseases (NCD) (diseases of the gastrointestinal tract, sleep disorders, depression, headache) increased from baseline to follow-up, yet no life-threatening events were registered at either time point.

Table 1: Characteristics of the cohort at baseline and follow-up.

Parameter		Baseline (n=31)	Follow-up (n= 40)
Sex [%]	Female	83.9 (n=26)	85 (n=34)
	Male	16.1 (n=5)	15 (n=6)
Chronological age (mean ± SD) [years]		49.2 ± 11.3	54.9 ± 11.4
BMI (mean ± SD) [kg/m^2]		30.1 ± 4.3	30.4 ± 5.0
Working field [%]	Economy/Administration/Service	25.8	22.5
	Social/Nursing/Education	38.7	37.5
	Student	3.2	0.0
	Others (Retired, Language, technical jobs)	35.5	40.0
Employment level [%]	Full time	48.4	35.0
	Part time (50-89%)	29.0	35.0
	Part time (<50%)	16.1	7.5

	Retired	0.0	22.5
	Jobless (incl. students)	6.5	0.0
Working despite feeling sick [%]	Never	45.2	17.5
	Once	16.1	20.0
	2-6 times	25.8	30.0
	>6 times	13.0	7.5
	Missing answer	0.0	25.0
Sick days (last month) [%]	None	71.0	50.0
	1 or more days	29.1	25.0
	Missing answer	0.0	25.0
Stress due to sick days [%]	Yes	12.9	22.5
	No	87.1	50.0
	Missing answer	0.0	22.5
Alcohol frequency [%]	Never	9.7	10.0
	Once a month	9.7	22.5
	2-4x/month	38.7	30.0
	2-3x/week	38.7	32.5
	≥4x/week	3.2	5.0
Smoking [%]	Never smoked	51.6	55.0
	Ex-smoker	38.7	32.5
	At least 10 cigarettes per day	9.7	12.5
Sports [%]	Rarely	9.7	15.0
	≤1/week	25.8	17.5
	1-2/week	51.6	37.5
	≥2/week	12.9	30.0
Sleep duration (h) [%]	≤5 hours	0.0	5.0
	6h	32.3	25.0
	7h	48.4	57.5
	≥8 hours	19.4	12.5
Sleep quality [%]	Rather good or better	83.9	80.0
	Rather bad or worse	16.1	20.0
Satisfaction with partnership [%]	Very low	0.0	2.5
	Low	3.2	10.0
	Medium	12.9	7.5
	High	32.3	17.5
	Very high	51.6	62.5
Satisfaction with sex life [%]	Very low	9.7	10.0
	Low	6.5	5.0
	Medium	25.8	10.0
	High	29.0	40.0
	Very high	29.0	35.0
Personal history [%]	Hypertension	25.8	37.5
	Diabetes mellitus	6.5	7.5
	Hyperlipidemia	25.8	27.5
	Disease of GIT	32.3	35.0
	Sleep disorder	35.5	45.0
	Depression	22.6	27.5
Life threating events [%]		0.0	0.0
Hearing aid [%]	Yes	Missing data	10.0
	No	Missing data	90.0

Glasses [%]	Yes	Missing data	80.0
	No	Missing data	20.0
Number of medications (mean ± SD) [n]		Missing data	1.9 ± 1.8
Most common medicaments [%]	Vitamins and supplements	Missing data	30.0
	Antihypertensives	Missing data	25.0
	Herbal preparations	Missing data	15.0
	Psychotropic drugs	Missing data	12.5

Abbreviations: Mean: Mean Value; SD: Standard Deviation; N: Number Of Probands Answering The Questionnaire; BMI: Bodi-Mass-Index. At baseline 9 data sets were missing.

Bio-Functional Status (BFS) and Bio-Functional Age (BFA)

Supplementary file 2 presents the cohort's BFS items and BFA at baseline and follow-up. Mean BFA was 44.4 ± 8.1 year-equivalents at baseline (n=34 subjects, 85%), and 53.9 ± 8.0 year-equivalents at follow-up (n=35 subjects, 87.5%), respectively. There was a significant difference when comparing baseline and follow-up BFA ranges (Δ +9.5 year-equivalents, p< 0.001, r=0.62) with BFA range being wider at baseline. At follow-up BFA range had decreased by 50% (p< 0.001, r=0.43), indicating premature aging.

When comparing single BFS items and sub domains at baseline and follow-up, a significant decrease in physical fitness was observed, e.g., performance time (p=0.012, r=-0.29), and performance time index (p=0.039, r=0.24). Furthermore, dental status deteriorated (p=0.008, r=-0.43), body height decreased (p=0.002, r=-0.49), systolic blood pressure increased (p=0.025, r=0.25), visual acuity (left eye p=0.035, r=0.43; right eye p=0.005, r=0.57) and bilateral hearing (2048 Hz: p=0.077, r=0.20; 4096 Hz p=0.005, r=0.33) deteriorated, respectively.

Similarly, in the mental-cognitive sub domain, some significant adverse changes were observed. For example, test motivation (p=0.000, r=0.62), psychomotor endurance (p=0.000, r=0.54), switching capability (p=0.000, r=0.44), strategic thinking (p=0.042, r=0.23), memory performance (p=0.004, r=0.32), and orientation capability (p=0.024, r=0.253) deteriorated during the observation period. Within the psycho-social domain, physical and emotional wellbeing decreased (p=0.464) while described stress exposition increased (p=0.111). The only BFS items that improved during the observation period were acoustic (p=0.005, r=0.31) and pursuing reaction time (p=0.000, r=0.53).

Self-perceived chronic stress exposure

Table 2 presents the cohort's baseline and follow-up TICS data also comparing them to the T 50 reference cohort (T50 C) provided by the TICS inventory. At baseline and follow-up, the mean SSCS was similar and somewhat lower than the T 50 C, suggesting a constant, lower than average self-perceived chronic stress exposure. When comparing TICS sub domains between baseline and follow-up, there was only a significant change found for "chronic worrying" (SORG), indicating that subjects at follow-up worried significantly less about problems outside their control (e.g., worrying about personal health issues, or environmental impacts on the human body). Based on the global score SSCS three stress level categories can be differentiated (below average stress, above average stress, extreme stress). These are presented in **Table 3** comparing baseline and follow-up data of the cohort. In particular, the > 31-year-olds, majority women, with a BMI class of 3 and 4, with slow aging (BFA < CA) showed below average stress levels. A higher stress level was found among younger persons and with a higher BMI class. The extreme stress level decreased tremendously across the observation period in all subgroups but the youngest.

Table 2: Self-perceived chronic stress exposure.

TICS domain	Baseline (mean (SD)) (n=40)	Follow-up (mean (SD)) (n=40)	T50C	Range	Max Score	Baseline 5^{th}–95^{th} percentile	Follow-up 5^{th}–95^{th} percentile	Statistical difference (significant p<0.05)
Screening scale (SSCS)	12.1 (6.6)	12.0 (6.6)	13.0	2.0- 29.0	48	2.1-24.9	3.0–27.7	p=0.79
Work overload (UEBE)	11.2 (5.1)	12.2 (6.6)	12.5	0.0 27.0	32	1.1–19.0	2.0-25.9	p=0.60
Social overload (SOUE)	10.1 (4.7)	9.2 (4.7)	7.0	0.0-19.0	24	2.0–17.0	1.0–15.0	p=0.17
Pressure to perform (ERDR)	11.7 (6.6)	12.3 (5.9)	17.0	0.0-23.0	36	2.0-25.9	1.1–22.0	p=0.19
Work discontent (UNZU)	8.5 (4.6)	8.0 (4.8)	9.0	1.0-22.0	32	0.1–14.0	1.0–17.0	p=0.22
Excessive demands at work (UEFO)	4.6 (2.5)	5.0 (3.3)	4.5	0.0-14.0	24	0.1–8.0	0.0–11.0	p=0.62
Lack of social recognition (MANG)	3.8 (2.6)	3.8 (2.8)	4.0	0.0-12.0	16	0.0–9.0	0.0–9.0	p=0.84
Social tensions (SOZS)	4.3 (3.5)	3.9 (2.7)	5.0	0.0-10.0	24	0.0-10.9	0.1–9.0	p=0.40
Social isolation (SOZI)	5.7 (3.7)	6.0 (5.4)	5	0.0-22.0	24	0.1-13.9	0.1–21.8	p=0.95
Chronic worrying (SORG)	38.1 (19.9)	4.0 (2.9)	14	0.0-14.0	16	2.0-57.9	0.0–11.9	p=0.00 r=0.59

n: number of probands; mean: mean value, SD: standard deviation; T50C: Reference Cohort (provided by the TICS inventory), r: effect size of a significant correlation.

Table 3: Self-perceived chronicstress exposure, assessed by global score SSCS.

Parameter	Below average stress (SSCS<11 points) [%] (n) p-value	Above-average stress (SSCS 12-22 points) [%] (n) p-value	Extreme stress (SSCS >22 points) [%] (n) p-value
Sex (correlation with stress levels: p<0.001, r=0.56)			
Females (n_1=34; n_2=26)	Follow-up: 47.1 (16) Baseline: 42.3(11)	Follow-up: 47.1 (16) p=0.01 Baseline: 50.0 (13) p=0.001	Follow-up: 5.8 (2) Baseline: 7.7 (2)
Males (n_1=6; n_2=5)	Follow-up: 33.3 (2) Baseline: 60.0 (3)	Follow-up: 66.6 (4) Baseline: 40.0 (2)	Follow-up: 0.0 (0) Baseline: 0.0 (0)
Whole Cohort (n_1=40, n_2=31)	Follow-up: 45.0 (18) Baseline: 45.1 (14)	Follow-up: 50.0 (20) Baseline: 48.4 (15)	Follow-up: 5.0 (2) Baseline: 6.5 (2)
Age categories (correlations with stress levels: p<0.001, r=0.62)			
Age category «16-30 years» (n_1=1, n_2=3)	Follow-up: 0.0(0) Baseline: 33.3 (1)	Follow-up: 0(0) Baseline: 66.6 (2)	Follow-up: 100.0 (1) Baseline: 0.0 (0)
Age category «31-59 years» (n_1=25, n_2=22)	Follow-up: 44.0 (11) p=0.01 Baseline: 45.5 (10) p=0.002	Follow-up: 52.0 (13) Baseline: 45.5 (10)	Follow-up: 4.0 (1) Baseline: 9.0 (2)
Age category «60-72 years» (n_1=14, n_2=6)	Follow-up: 50.0 (7) p=0.008 Baseline: 50.0 (3)	Follow-up: 50.0 (7) p=0.008 Baseline: 50.0 (3)	Follow-up: 0.0 (0) Baseline: 0.0 (0)
Aging groups (correlation with stress levels: p<0.001, r=0.59)			
Aging group «rapidly aged» (BFA>CA) (n_1=6, n_2=2)	Follow-up: 50.0 (3) Baseline: 0.0 (0)	Follow-up: 50.0 (3) Baseline: 100.0 (2)	Follow-up: 0.0 (0) Baseline: 0.0 (0)
Aging group «normal aging» (BFA=CA)(n_1=3, n_2=1)	Follow-up: 33.3(1) Baseline: 100.0 (1)	Follow-up: 66.6 (2) Baseline: 0.0 (0)	Follow-up: 0.0 (0) Baseline: 0.0 (0)
Aging group «slowly aged» (BFA<CA)(n_1=26, n_2=24)	Follow-up:50.0 (13) p=0.802 Baseline: 45.8(11) p=0.811	Follow-up: 46.2 (12) p=0.001 Baseline: 45.8 (11) p=0.001	Follow-up: 3.8 (1) Baseline: 8.3 (2)
BMI groups (correlation with stress levels: p<0.001, r=0.84)			
BMI group 1 (<18.5 kg/m^2) (n_1=1, n_2=0)	Follow-up: 0.0 (0) Baseline: 0.0 (0)	Follow-up: 100.0 (1) Baseline: 0.0 (0)	Follow-up: 0.0 (0) Baseline: 0.0 (0)
BMI group 2 (18.5-24.9 kg/m^2)(n_1=4, n_2=0)	Follow-up: 50.0 (2) Baseline: 0.0 (0)	Follow-up: 50.0 (2) Baseline: 0.0 (0)	Follow-up: 0.0 (0) Baseline: 0.0 (0)
BMI group 3 (25.0-29.9 kg/m^2)(n_1=16, n_2=20)	Follow-up: 62.5 (10)p=0.002 Baseline: 45.0 (9) p=0.003	Follow-up: 31.25 (5) Baseline: 45.0 (9) p=0.003	Follow-up: 6.25 (1) Baseline: 10.0 (2)
BMI group 4 (30.0-34.9 kg/m^2)(n_1=11, n_2=10)	Follow-up: 54.5 (6) p=0.014 Baseline: 50.0 (5)	Follow-up: 45.5 (5) Baseline: 50.0 (5)	Follow-up: 0.0 (0) Baseline: 0.0 (0)
BMI group 5 (35.0-39.9 kg/m^2) (n_1=7, n_2=1)	Follow-up: 0.0 (0) Baseline: 100.0 (1)	Follow-up: 100.0 (7) p=0.008 Baseline: 0.0 (0)	Follow-up: 0.0 (0) Baseline: 0.0 (0)
BMI group 6 (>40 kg/m^2)(n_1=1, n_2=0)	Follow-up: 0.0 (0) Baseline: 0.0 (0)	Follow-up: 0.0 (0) Baseline: 0.0 (0)	Follow-up: 100.0 (1) Baseline: 0.0 (0)

Abbreviations: n: number of probands (n_1: number at baseline; n_2: number at follow-up); SSCS: Screening Scaleof Chronic Stress (global score); BFA: Bio-Functional Age; CA: Aalendrical Age; BMI: Body Mass Index; P-value: significance of change p<0.05 (only calculable if n>/=7); r: Effect Size of a Significant Correlation.

Impact of self-perceived chronic stress exposure on BFS/BFA

Table 4 presents the significant correlations between self-perceived chronic stress exposure and BFS/BFA, the full data set is presented in **supplementary file 3**. There was no significant correlation between the global score SSCS and BFA in general, neither at baseline (r_s=0.18, p=0.302), nor at follow-up (r_s=-0.05, p=0.797).

However, when the global score SSCS was assessed by the different aging rates (slowly aging (BFA < CA), normal aging (BFA=CA) and rapidly aging (BFA > CA)), a significant correlation was found with the category “slowly aging” (BFA< CA) (p < 0.001, r=-0.70). No significant correlation was detected between “normal aging” (BFA=CA) (p=0.109) and “premature aging” (BFA > CA) (p=0.655). When the three different stress levels (below-average, above-average and extreme) were analyzed with the aging rate itself, only a significant correlation with “below-average stress” was found (p=0.039, r=-0.37), which suggested against premature aging caused by a perceived chronic stress exposure. The analysis of the three stress levels with the three different aging rates revealed a single significant correlation between “above-average stress level” and “slow aging” (BFA< CA) (p< 0.001, r=-0.55). Thus, even a high self-perceived chronic stress exposure was not associated with “pro-aging”. These findings are presented in **Table 3.**

While there was no correlation between TICS sub domains and BFS/BFA at baseline (data not shown, (6)), there was a significant correlation between each BFS sub domain (physical, sensory-psychomotor, cognitive-mental and emotional-social) with at least one TICS sub domain. Thus, a decrease in functioning was associated with a greater self-perception of chronic stress exposure. Importantly, the strongest correlations were found between TICS subdomains and SOZI (social BFS sub domain) suggesting that subjects felt especially stressed out by

social isolation.

The only correlation that could be found at baseline and in follow-up was the association between SOZI and the pulse rate difference (r_s=-0.40, p=0.010). Based on the negative correlation, a higher pulse variation between rest and during effort indicated a lower self-perceived chronic stress, thus supporting the positive impact of physical fitness.

Illness perception

Compared to baseline, we found a significantly negative change in illness perception at follow-up represented in a higher mental preoccupation with currently occurring and potential future illnesses (**supplementary file 2**).

At follow-up, the values in the categories NTE (p=0.002, r=0.36), NT (p=0.003, r=0.34), and the number of S-values >5 (p=0.023, r=0.26) were significantly higher than at baseline [6], suggesting that subjects more often considered naturalistic factors to be responsible for their illnesses (e.g., bacteria or viruses, additional impact of the Covid-19 pandemic not specifically included).

Similar to baseline, high S-values (> 6) in the categories PSE, PSI, and HB were found at follow-up indicating that PSI (e.g., inner dissatisfaction, low self-esteem), PSE (e.g., private, and occupational stress) as well as HB (physical activity and diet) continued to play a major role in illness perception of overweight and obesity.

To analyze the change in illness perception more specifically, three subgroups of "mental preoccupation with the cause of illness" were established (no mental preoccupation; mental preoccupation, but indecisive about the cause of illness; high mental preoccupation). Interestingly, at follow-up the subgroup "high mental preoccupation with the cause of illness" had almost doubled. Furthermore, a shift in the general direction of illness perception was observed. While subjects mainly focused on psychosocial reasons at baseline, they considered both, PS and NT factors, to be responsible for their current illness overweight/obesity. While sex did not have a significant impact on the category OS at follow-up (r_s=-0.01, p=0.941), age did with younger subjects (< 45 years) showing a higher OS (r_s=-0.30, p=0.065). In addition, there was a significantly positive correlation between higher BMI and OS (r_s=0.32, p=0.044) indicating that illness perception of overweight/obese individuals was more often altered and that mental preoccupation with occurring illnesses increased. At baseline, these findings could not be observed (no significant correlations).

Impact of self-perceived chronic stress exposure on illness perception

Table 5 presents the significant correlations between self-perceived chronic stress exposure and illness perception; The full data set is presented in supplementary file 3. Similar to baseline [6], most of the TICS sub domains had a significantly positive correlation with PATEF categories at follow-up. This finding indicated that a higher illness perception was related to an increased self-perceived chronic stress exposure and vice versa. Furthermore, at follow-up there were significant correlations between PSE and PSI and the TICS global score SSCS and other subdomains (ERDR, UEFO, SOZI, SORG). This finding indicated that psychosocial factors (e.g., private, and/or professional relationships, inner dissatisfaction, low self-esteem) were promoting greater self-perceived chronic stress exposure. When considering naturalistic factors of illness perception, significantly positive correlations between every TICS category and NTI were found, indicating that subjects viewed their own bodies as too "weak", which in turn sustained chronic stress perceptions in any domain. Furthermore, HB showed significant correlations with SSCS (r_s=0.60, p<0.001), UEBE (r_s=0.65, p<0.001) and ERDR (r_s=0.65, p<0.001). This indicated a specific relation between work-associated chronic stress exposure and its impact on individuals' HB (physical activity and diet).

Table 4: Significant correlations between TICS subdomains and BFS items at follow-up.

Parameter	SSCS [r_s] (p)	UEBE [r_s] (p)	SOUE [r_s] (p)	ERDR [r_s] (p)	UNZU [r_s] (p)	UEFO [r_s] (p)	SOZS [r_s] (p)	SOZI [r_s] (p)
Chronological age (CA) [years]		0.37(0.018)						
Resting heart rate (p0) [n/min]							-0.42 (0.012)	
Exercise heart rate [n/min]					-0.33 (0.047)			-0.39 (0.019)
Pulse rate difference (Δp) [n/min]								-0.38 (0.022)
Performance time [sec]							-0.36 (0.031)	
Hearing loss right 2048 Hz [%]			0.34 (0.034)					
Hearing loss left 2048 Hz [%]						-0.31 (0.049)		
Pursuing reaction time [msec]								-0.34 (0.032)
Cognitive reaction time [sec]				0.41 (<0.01)				
Ability to concentrate (time) [sec]								0.35 (0.028)
Change over capability [sec]								0.32 (0.048)
Stress predisposition [score]						0.36 (0.022)		
Social activity / duties [score]							0.32 (0.047)	

Abbreviations: [r_s]: Spearman correlation coefficient; p: p-value (significance p<0.05); SSCS: Screening Scale of Chronic Stress; UEBE: Work overload; ERDR: Pressure to perform; SOUE: Social overload; UNZU: Work. discontent, UEFO: Excessive demands at work, SOZS: Social tensions, SOZI: social isolation.

Table 5: Significant correlations between TICS subdomains and PATEF at follow-up.

Category	SSCS [r_s] (p)	UEBE [r_s] (p)	ERDR [r_s] (p)	UNZU [r_s] (p)	UEFO [r_s] (p)	SOZS [r_s] (p)	SOZI [r_s] (p)	SORG [r_s] (p)
OS [r_s]	0.70 (<0.001)	0.53 (<0.001)	0.59 (<0.001)	0.51 (<0.001)	0.58 (<0.001)	0.36 (0.024)	0.59 (<0.001)	0.59 (<0.001)
PSE [r_s]	0.59(<0.001)	0.47(<0.001)	0.55(<0.001)	0.43(<0.001)	0.33(0.038)	0.33(0.040)	0.49(<0.001)	0.53(<0.001)
PSI [r_s]	0.66(<0.001)		0.42(<0.001)	0.54(<0.001)	0.52(<0.001)	0.41(0.001)	0.61(<0.001)	0.63(<0.001)
HB [r_s]	0.60(<0.001)	0.52(<0.001)	0.65(<0.001)	0.40(0.012)	0.44(<0.001)		0.43(<0.001)	0.39(0.015)
NTE [r_s]			0.38(0.017)					0.36(0.027)
NTI [r_s]	0.56(<0.001)	0.37(0.022)	0.38(0.019)	0.48 (<0.001)	0.34(0.033)		0.51(<0.001)	0.58(<0.001)

Abbreviations: [r_s]: Spearman correlation coefficient; (p): p-value (significance p<0.05); SSCS: Screening Scale of Chronic Stress; UEBE: Work overload; ERDR: Pressure to perform; UNZU: Work discontent; UEFO: Excessive demands at work; SOZS: Social tensions; SOZI: Social isolation; SORG: Chronic worrying; OS: Overall Score (PATEF); PSE: Psychosocial External factos; PSI: Psychosocial Internal factors; HB: Health Behaviour; NTE: Naturalistic External factors; NTI: Naturalistic Internal factors.

Discussion

This follow-up study of BeCS-14 analyzed the impact of self-perceived chronic stress exposure in overweight/obese subjects on Bio-Functional Status (BFS), Bio-Functional Age (BFA), and illness perception. The key findings of this analysis were: 1) BFA was generally lower than CA but with a smaller range at follow-up indicating that some subjects had signs of functional pro-aging, 2) NCD prevalence was higher at follow-up while physical and cognitive functions declined fostering functional pro-aging, 3) self-perceived chronic stress exposure was not associated with functional pro-aging, yet significantly with 4) declining physical and cognitive functions, 5) self-perceived chronic stress exposure was especially high due to pressure to succeed, work overload, excessive demands at work, and social isolation, which was also associated with 6) an altered illness perception such as higher mental preoccupation due to currently occurring and potential future illnesses. The latter was 7) especially found in women below age 45 years as well as in overweight/obese subjects.

Several studies have tried before to estimate an individual's Bio-Functional Age (BFA) by applying multiple parameters, such as telomere length and DNA methylation [26,27]. Yet, so far, no specific parameter has been identified [28,29]. To our knowledge, the holistic validated BFS test battery applied in Be CS-14 is the best approach to determine BFA [28-31]. In our BeCS-14 follow-up analysis we found a smaller range between CA and BFA at follow-up compared to baseline indicating an above-than-average BFA in some subjects. In particular, this observation was made in overweight/obese subjects supporting previous studies [8,32]. Both, physiological aging and overweight/obesity have been shown to cause chronic inflammation leading to insulin resistance, oxidative stress, and DNA damage [8,33,34], respectively. Obviously, these factors may also accelerate aging, which in turn contribute to reduced longevity and more comorbidities [8,33,34]. Furthermore, pro-aging could also be caused by various other factors, such as mental or physical illness, psychosocial and socioeconomic stressors [36,37].

In our follow-up study, 40% of subjects reported a health deterioration across the observation period, another 17.5% difficulties in walking, both being signs of NCD. Indeed, an age associated increased NCD prevalence was also reported by others [38,39]. Similarly, a healthy lifestyle has been linked to slower functional aging [40], while risk factors like overweight/obesity, alcohol and tobacco consumption, sedentary lifestyle and sleep deficit have been linked to functional pro-aging [41], and NCD development [42]. As the participants in our follow-up study only showed minor changes in lifestyle habits, we did not observe a correlation with BFA changes.

Physical and cognitive functions declined with aging in our cohort which is in line with previous studies [42,43]. Specifically, we observed a decrease in hearing function and visual acuity with more subjects needing optical and/or acoustic aids. In particular, there was an association with increasing BMI [8,45]. Premature hearing loss may be due to impaired vascular function in overweight/obese people [45,46]. Presbycusis is the most widespread sensory impairment and affects one in three persons aged above 65 years [47]. It is accompanied by a reduced QoL due to increased social isolation and frustration of not being capable to properly absorb ambience sound [47,48]. Social isolation and anxiety due to hearing loss has been shown to significantly increase morbidity and mortality [49]. Similarly, age-related impairment of visual acuity has been described before, including a higher prevalence of presbyopia, glaucoma, macular degeneration, and age-related cataract [10,50]. As a result, orientation and mobility being decisive for a good QoL have been found to decline to impaired visual acuity [50]. In addition, we observed an increase of systolic blood pressure across the observation period. This finding is in line with previous studies reporting an age-related increased rigidity of vessel walls and calcifications [51]. Obesity/overweight is an additional risk factors for hypertension and coronary artery disease [52]. Grip hand strength is a surrogate marker of muscle mass and strength. Aging is associated with muscle mass loss [53] and thus loss of grip hand strength [10,53], which was also found in our follow-up study. This supports the parameter grip hand strength being suitable for BFA assessment [54], as enhanced grip hand strength has been found to be associated with an overall better health outcome, and with a reduced risk for cardiovascular events [55]. Likewise, cognition also deteriorated in our subject assessment. Aging causes a chronic inflammation that negatively affects the synaptic plasticity and neurogenesis of the brain. This is aggravated by age-associated diseases and leads to brain atrophy and reduced hippocampal volume [56]. Accordingly, we found that cognitive functions, especially cognitive switching capability, memory performance, strategic thinking and orientation ability decreased, which is consistent with previous findings [57]. Other studies found that cognitive function reduction was worsened by hearing loss, hypertension and diabetes mellitus [58].

In our study, we observed a shift in self-perceived chronic stress exposure towards younger (< 60 years) and heavier subjects. Indeed, greater psychosocial stress has been found to increase the risk of developing overweight/overweight (par-

ticularly by changes in HB), which may accelerate bio-functional aging through its associated comorbidities [42,59]. In addition, overweight/obesity and self-perceived stress exposition may reinforce each other, resulting in a vicious cycle [60]. Yet, in our follow-up study we did not find an association between self-perceived chronic stress exposure and premature bio-functional aging, affirmed by the correlation between SSCS and "slow aging" (BFA < CA). This contrasts our previous finding in the whole Be CS-14 baseline cohort in which we found a significantly positive correlation between SSCS and ΔBFA-CA indicating a higher self-perceived chronic stress exposure was associated with bio-functional pro-aging [13]. Therefore, in our current overweight/obese follow-up cohort, we speculate that increased self-perceived chronic stress exposure due to overweight/obesity was not the only cause for premature bio-functional aging, but that other factors (e.g., NCD and HB) may have had an impact, too. As mentioned above, we found a decrease in physical, cognitive, and emotional-social functioning across the observation period which was significantly positively correlated to self-perceived chronic stress exposure. For example, higher BFA or systolic blood pressure, and lower cognitive reaction time, cardio performance, hand grip strength or test motivation were significantly associated with an increased self-perceived chronic stress exposure, respectively. Our findings are supported by previous studies showing an association between lower heart rate variability and higher stress perception as well as stress-related disease incidence, respectively [61,62]. In addition, deterioration in sensory functions has been linked to a higher level of self-perceived stress perception, and vice versa [63].

Even though the SSCS did not significantly change across the observation period, we observed that subjects were particularly stressed by work. More specifically, we found a significant correlation between work overload, pressure to succeed and HB with premature bio-functional aging. Our findings support previous studies showing that missing time for oneself due to work overload could significantly impact HB and increase NCD risk [19,64,65]. Due to the Covid-19 pandemic we had to postpone the start of our follow-up study. Still, as many participants worked in the health care sector they may have been affected directly or indirectly by it. Indeed, previous studies reported that health care workers in particular were physically, mentally, emotionally and socially challenged by the pandemic increasing their work load and stress [66,67] having a negative impact on individual HB [68]. Based on these and our findings, we assume that the Covid-19 pandemic increased self-perceived chronic stress exposure and bio-functional aging, especially in overweight/obese subjects.

In our follow-up study, most correlations between BFS and TICS were found within the category SOZI. Social isolation, that is the subjective perception of being alone, representing a discrepancy between desired and existing social contacts, has a negative impact on physical and mental health and results in a higher self-perceived chronic stress exposure [69,70]. For example, in vulnerable age groups (≤ 25 / ≥ 65 years), functional limitations, lower income, relationship status, and working conditions are playing a significant role in the perception of social isolation [71]. Loneliness has been found to be a risk factor for digestive problems [72], physical limitations [73], cognitive decline [74], insomnia [75], loss of libido, infertility [76], compromised immune system, and depression [77]. Furthermore, lonely people tend to be less physically active, which in turn may increase their cardiovascular risk [78,79], and are more likely to be overweight/obese and addicted to alcohol [80]. Our findings support those studies as we found social isolation to be a determining factor for the development and conservation of self-perceived chronic stress exposure, overweight/obesity, and premature bio-functional aging.

Finally, we found an association between self-perceived chronic stress exposure and illness perception in our overweight/obese cohort. The greater the mental preoccupation with the cause of the occurring illness (overweight/obesity), the greater the level of self-perceived chronic stress exposure, and vice versa. The dominating categories of illness perception found were PSI (e.g., inner dissatisfaction, low self-confidence), PSE (e.g., private and occupational stress), HB (physical activity and diet), and NTE (e.g., global warming, harmful pathogens), respectively. The most vulnerable groups in our cohort were women < 45 years with a BMI ≥ 25 kg/m^2. These findings support more general observations that overweight/obese individuals showed an increased illness perception (e.g., stigma), which was a key determinant for HB [14,18]. As the individual perception of illness duration and symptoms have been found to have a significant impact on illness outcomes and control [81], patient medical education is crucial [82]. For example, a negative illness perception promotes self-perceived chronic stress exposure and lowers an individual's health status and quality of life [83]. In contrast, individuals with a positive attitude towards the respective illness have been shown to be more resistant to chronic stressors, to better cope with tensions, and to more likely find solutions for daily life tasks [82,84].

Obviously, our BeCS-14 cohort study has strengths and limitations. The main strength is its prospective observational design allowing for holistically assessing bio-functional aging in a heterogenous cohort across a 5.4-years (+ max. 3.3) period. Limitations are a non-representative cohort (e.g., no equal sex, age, or job distribution), some loss to follow-up which may be at least to some degree due to the Covid-19 pandemic, application of TICS for chronic stress exposure which primarily focuses on external stress factors, and the observational design thus not only allowing for discovering causal relationships.

Conclusion

This study did not show a direct association between self-perceived chronic stress exposure and premature aging. However, the increase in the prevalence of NCD, decrease in physical and cognitive abilities and negative changes in health behaviour resulted in fostering bio-functional aging. Young (< 45 years) female overweight/obese individuals were shown to be vulnerable in self perceived chronic stress exposure and individual illness perception. Risk factors were social isolation, excessive demands at work, work overload, and pressure to succeed.

In the future, especially in this vulnerable population, a multimodal therapy concept with patient medical education should be established, so that risk factors for accelerated bio-functional aging can be identified and treated early, improving quality of life at any age.

Competing interests: LM Roggo, T Marti, P Stute, M von Wolff, N Bitterlich declare to have no conflict of interest in context of this manuscript.

Authors contributions:

LM Roggo: Conducting of assessment, statistical analysis with support of Dr. Bitterlich, writing the manuscript.

T Marti: Conducting of assessment.

N Bitterlich: Statistical analysis.

M von Wolff: Discussion of results, advise of manuscript.

D Poethig: Discussion of results.

P Stute: Principal investigator, responsible for study idea, design, finances, supervision of doctoral student and finalizing the manuscript.

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Abbreviations: AHA: Active and Healthy Aging; BFA: Bio-Functional Age; BFS: Bio-Functional Status; Becs-14: Berner Cohort Study (Conducted In 2014); BMI: Body Mass Index; CA: Chronological Age; DNA: Desoxyribonucleic Acid; GIT: Gastrointestinal Tract; ICF: International Classification Of Functioning, Disability And Health; NCD: Chronic Non-Communicable Disease; Qol: Quality Of Life; S-values: Stanine Values (PATEF); WHO: World Health Organization; TICS: Trier Inventar Zum Chronischen Stress; ERDR: Pressure to Perform (Part Of TICS); MANG: Lack of Social Recognition (Part Of TICS); SOUE: Social Overload (Part of TICS); SORG: Chronic Worrying (Part of TICS); SSCS: Screening Scale of Chronic Stress (Part Of TICS); SOZI: Social Isolation (Part of TICS); SOZS: Social Tensions (Part of TICS); UEBE: Work Overload (Part of TICS); UEFO: Excessive Demands at Work (Part Of TICS); UNZU: Work Discontent (Part of TICS); PATEF: Patiententheoriefragebogen; HB: Health Behavior (Part of PATEF); NT: Naturalistic Factors (Part of PATEF); NTE: Naturalistic External Factors (Physical-Biochemical) (Part Of PATEF); NTI: Naturalistic Internal Factors (Physical-Biochemical) (Part Of PATEF); OS: Overall Score (Part Of PATEF); PS: Psychosocial Factors (Part Of PATEF); PSE: Psychosocial External Factors (Part Of PATEF); PSI: Psychosocial Internal Factors (Part Of PATEF).

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