Immune age, but not chronological age, together with obesity and independently from sex predicts low physical working capacity

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Abstract: Cardiorespiratory fitness (CRF), a.k.a. physical working capacity, is crucial for sustained work ability in good health, but declines with aging as does the functionality of the immune system. Here, we adopted a novel metric of immune age to a cross-sectional sample of 333 females and 215 males aged 20–70 years from the 'Dortmund Vital Study' and compared its predictive capacity for low CRF to chronological age adjusting our analysis to the influence of sex and obesity. While obesity, chronological and immune age all correlated positively with low CRF in univariate analyses, multiple logistic regression revealed that obesity together with immune age, but not chronological age, were statistically significant predictors of low CRF outcome. These results indicate a potential role for the immune age in explaining the inter-individual variability of the age-related decline in physical working capacity.

Keywords: ageing, work ability, cardiorespiratory fitness, immune system

1. Introduction

Cardiorespiratory fitness (*CRF*) and physical work capacity are crucial prerequisites for sustained work ability in good health (Burdorf & Robroek 2019; Kenny et al. 2008; Smolander et al. 2000; Tengland 2011) in both physically (Ezzatvar et al. 2021; Mänttäri et al. 2021) and cognitively demanding occupations (Grabara et al. 2018). CRF is intertwined to physical activity and the immune system (Duggal et al. 2019; Smolander et al. 2000) and declines with ageing, but to a variable degree in different groups defined by sex, body composition, health status or other modifiers.

Recently, metrics of 'biological age' have gained attention or even outperformed chronological age (Wood & Jóhannsson 2020) as predictors for mortality, health and disease (Ahadi et al. 2020; Levine 2012; Levine et al. 2018), the success of vaccination in the elderly population (Goudsmit et al. 2021) or declining brain function (Higgins-Chen et al. 2021). Likewise, the concept of 'immune age' aims at quantifying, preferably by a one-dimensional marker, the decay in functions of the immune system with individually varying progression in the elderly (Pawelec 2018), which does not necessarily parallel chronological age (Alpert et al. 2019).

The present analysis aimed to compare the capacity of immune age with chronological age for predicting low CRF when adjusting for sex and obesity.

We analyzed data of the 'Dortmund Vital Study' (*DVS*), a long-term, combined cross-sectional and longitudinal interdisciplinary study on the relationship of ageing, working conditions, genetic makeup, stress, metabolic functions, cardiovascular system, immune system, and mental performance over the lifespan with a focus on healthy working adults (Gajewski et al. 2021).

2. Methods

CRF was operationalized by the outcome of the physical working capacity test *PWC130* (Finger et al. 2013), which was analyzed in a cross-sectional sample of 333 females and 215 males aged 20–70 years from the DVS baseline examinations (Gajewski et al. 2021). By dichotomization, *low CRF* was scored, if the participant could not complete the PWC130 test on the bicycle ergometer due to medical reasons, or if the power output standardized for body weight obtained for a heart rate of 130 bpm was below a sex-specific reference value of 1.25 W/kg for females and 1.5 W/kg for males, respectively (Platen 2001); otherwise, *high CRF* was scored.

Body composition (*obesity*) was assessed by the body-mass index (*BMI*) and scored as normal for BMI < P85, as overweight for P85 ≤ BMI ≤ P95 and as obese for BMI > P95, with the limiting BMI percentiles set to P85 = 25 and P95 = 30 kg/m^2, respectively (WHO 1995).

We quantified immune age based on blood samples taken from the participants. More specifically, we approximated the recently proposed score *IMM-AGE* (Alpert et al. 2019), which had been developed employing a range of 'omics' technologies. From relative frequencies of a reduced set of peripheral blood mononuclear cells (NK-cells, T-cells, total and memory/naïve sub-populations of $CD4^+$ and $CD8^+$ T-cells, $CD8^+CD28^-$ T-cells) determined by flow cytometry (Claus et al. 2016), we derived an approximate score *IMM.AGE.pcr* by principal component regression calculated by the package *pls* (Mevik et al. 2020) using R version 4.1.0 (R Core Team 2021).

Finally, we analyzed the predictive capacity of sex, obesity, chronological and immune age for the probability of low CRF in the DVS sample applying univariate and multiple logistic regression computed by the R function *glm* (Venables & Ripley 2002).

Table 1: *Results from univariate and multiple logistic regression analyses predicting the probability of low CRF by immune age (IMM.AGE.pcr), chronological age in decades (Age.decades), obesity (BMI.category) and sex.*

		Univariate logistic regression				**Multiple logistic regression**		
Predictor	N	OR[1]	95% CI[1]	p-value	q-value[2]	OR[1]	95% CI[1]	p-value
IMM.AGE.pcr	548	24.8	5.46–117	**<0.001**	**<0.001**	16.8	2.57–114	**0.003**
Age.decades	548	1.18	1.04–1.34	**0.009**	**0.012**	0.99	0.85–1.16	0.90
BMI.category	548			**<0.001**	**<0.001**			**<0.001**
normal		—	—			—	—	
overweight		2.08	1.40–3.11			2.08	1.37–3.16	
obese		6.26	3.69–10.9			5.86	3.41–10.3	
Sex	548			0.37	0.37			0.29
female		—	—			—	—	
male		1.18	0.82–1.67			0.81	0.54–1.20	

[1]OR = Odds Ratio, CI = Confidence Interval for OR
[2]False discovery rate correction for multiple testing

3. Results

For the sample from the primary *IMM-AGE* study (Alpert et al. 2019), the derivative score *IMM.AGE.pcr* approximated the original values with acceptable accuracy (Pearson correlation r>0.8, normalized root-mean-square error rmse=10%).

In the DVS sample, obesity status, chronological and immune age correlated positively with low CRF in univariate analyses corrected for multiple testing (Table 1). However, multiple logistic regression revealed that obesity together with immune age, but not chronological age, were statistically significant predictors of low CRF. Sex was non-significant, as one might have expected due to the applied sex-specific reference values (Table 1).

4. Discussion

While detrimental effects of obesity on CRF are well established (Matsuo et al. 2020; Zeiher et al. 2020), our findings on the predictive capacity of immune age for the age-related decline in CRF are in line with previous reports on markers of 'biological age' superseding chronological age as predictor for morbidity and mortality in aging populations (Alpert et al. 2019; Levine 2012; Wood & Jóhannsson 2020).

However, with the intertwined relationships between cardiorespiratory fitness, physical activity and the immune system advocating for longitudinal studies (Ahadi et al. 2020; Duggal et al. 2019; Smolander et al. 2000), our cross-sectional results will have to be verified by future longitudinal examinations within the DVS cohort.

5. Conclusion

In summary, our results indicate a potential role for the immune age in explaining the inter-individual variability of the age-related decline in cardiorespiratory fitness.

6. Literature

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