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results from the Danish Blood Donor Study (DBDS)**

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Kyvik, K O; Pedersen, O B

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Rigas Andreas Stribolt (Orcid ID: 0000-0002-3799-8105)

Title: The healthy donor effect impacts self-reported physical and mental health
– Results from the Danish Blood Donor Study (DBDS)

Andreas S. Rigas¹, Axel Skytthe², Christian Erikstrup³, Klaus Rostgaard⁴, Mikkel Steen Petersen³, Henrik Hjalgrim^{4,5}, Henrik Ullum¹, Kirsten Ohm Kyvik⁶, Ole Birger Pedersen⁷

Affiliations:

¹ Copenhagen University Hospital, Department of Clinical Immunology

² University of Southern Denmark, The Danish Twin Registry

³ Aarhus University Hospital, Department of Clinical Immunology

⁴ Statens Serum Institut, Department of Epidemiology Research

⁵ Copenhagen University Hospital, Department of Haematology

⁶ Department of Clinical Research, University of Southern Denmark and Odense Patient data Explorative Network (OPEN), Odense University Hospital

⁷ Næstved Hospital, Department of Clinical Immunology

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Corresponding author and reprints:

Ole B. Pedersen, MD, PhD

Department of Clinical Immunology

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Næstved Hospital

Ringstedgade 77B

4700 Næstved

Denmark

Telephone: +45 24929785

E-mail: olbp@regionsjaelland.dk

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Abstract:

Background:

The selection pressure known as the healthy donor effect should in theory result in better self-perceived health-related quality of life in donors than in non-donors.

Aims:

We aimed to quantify the healthy donor effect by comparing self-perceived mental and physical health between blood donors and non-donors.

Methods:

Short form-12 data from the Danish Twin Registry (DTR) was compared with the data from the Danish Blood Donor Study (DBDS). Data on age, sex, and smoking status were included in the analyses. The multivariable linear regression analyses were stratified by sex and age group intervals. The mental component score (MCS) and the physical component score (PCS) were outcome variables.

Results:

A total of 28,982 participants from the DTR and 36,913 participants from the DBDS were included in the study. Younger donors had higher MCS than non-donors, whereas MCS was only marginally better in older donors compared with non-donors. In contrast, PCS was almost similar between young donors and non-donors. With increasing age, non-donors had lower PCS than donors.

Summary/conclusions:

Two selection patterns were revealed. Amongst young individuals, a better self-perceived mental health was associated with being a blood donor. With increasing age, good self-perceived physical health was associated with blood donation.

Introduction

In most blood service systems, blood donors declare that they are healthy and fit at the time of donation; hence, blood donors who are not eligible for donation pause or even cease to donate blood. This selection, which gives rise to better health amongst blood donors compared with the general population, is called the healthy blood donor effect (Atsma, Veldhuizen *et al.*, 2011). The healthy donor effect has been identified and named after a similar source of bias from occupational research, namely the healthy worker effect. The healthy worker effect (*HWE*) is an observed decrease in the mortality of workers compared with the mortality of the general population (Choi, 1992). This is believed to be caused by selection at entrance (into the labour force), i.e., workers with good health are more likely to be employed and have a tendency to stop working if a disease develops (Choi, 1992). Comparable to the *HWE*, the healthy donor effect is a selection both at the entrance into the blood donor population and again at each subsequent donation where the blood donor declares that they are healthy and fit.

Self-reported, health-related quality of life (HRQL) is generally considered to be a valid measure of health status and well-being, and it has been shown to predict disease and survival in a population (Nielsen, Siersma *et al.*, 2009). To our knowledge, no prior investigation of the healthy donor effect in terms of HRQL has distinguished between physical and mental health. The Danish Blood Donor Study (DBDS) is aimed at investigating factors influencing donor health and

whether blood donation gives rise to a better health. We hypothesized that the healthy donor effect would result in better physical and mental self-perceived health scores for donors than for non-donors. In particular, we hypothesized that with increasing age, blood donors would report better physical health scores because many diseases would prevent them from donating.

Materials and Methods

A widely used scale for self-reported HRQL is the Short Form 36 (SF-36). For epidemiological surveys, the SF-36 has been shortened into a 12-item questionnaire (SF-12). The SF-12 measures a physical component score (PCS) and a mental component score (MCS). The SF-12 was scored giving weights to the individual items (ranging from -16.15395 to +4.61446) and adding the sum to a constant (57.65693 and 60.58847) in PCS and MCS, respectively (Bjorner, 2003; Steenstrup, Pedersen *et al.*, 2013). The SF-12 algorithm and the specific weights of each item are presented in (Steenstrup, Pedersen *et al.*, 2013). The correlation between SF-36 and SF-12 for the PCS and MCS in Denmark are 0.95 and 0.96, respectively (Gandek, Ware *et al.*, 1998). The Danish Blood Donor Study (DBDS: www.dbds.dk) is a large ongoing prospective cohort that includes repeat blood donors aged 18 to 67 years old. DBDS was initiated in 2010 (Pedersen, Erikstrup *et al.*, 2012) and has since then recruited more than 100,000 blood donors from all regions of Denmark. More than 95% of the invited blood donors chose to participate (Pedersen, Erikstrup *et*

al., 2012). Only data on age, smoking status and self-perceived health-related quality of life (HRQL) (SF-12) were available from the Danish Twin Registry (*DTR*) 2002 survey (Skytthe, Kyvik *et al.*, 2002). Likewise, data were obtained on age, smoking status, and HRQL (SF-12) in the *DBDS* group.

Statistics

Statistical analysis was performed using Stata/IC 13.0 for Mac (Stata: <http://www.stata.com/>). The characteristics of the study group were described by differences in means (95% confidence intervals) for normally distributed data and frequency statistics for binary data. The groups were compared by a two sample t-test for normally distributed data and a chi-square test for binary data. Differences in HRQL (PCS scores and MCS scores) between the *DBDS* participants and the *DTR* participants were explored with multivariable linear regression analysis, adjusting for age and smoking status. The comparable age groups in the two cohorts ranged from 20 years to 67 years. All individuals were stratified into 5 age categories: (20-24, 25-34, 35-44, 45-54, 55-67) due to an interaction between age and SF-12 scores. The analyses were further stratified by sex. A significance level of $p < 0.05$ was considered statistically significant.

Results

Data from the *DBDS* participants were collected in 2010-2012 and data from the *DTR* participants were obtained in 2002. After discarding incomplete datasets a

total of 36,913 *DBDS* participants (19,422 men and 17,491 women) and 28,982 *DTR* participants (13,474 men and 15,508 women) were available for analyses. Compared with the *DBDS* participants the *DTR* participants were older (mean difference: 2.3 years, 95%CI: 2.1-2.5 years; $p < 0.001$), and had a significantly higher proportion of current tobacco users (*DTR*: 34.0%, *DBDS*: 16.3%; $p < 0.001$). In both groups, we observed that the MCS increased with age, while PCS decreased with age, indicating that general physical health deteriorates while mental health improves over time.

The healthy donor effect on self-perceived mental health (MCS):

Donors reported better mental health than non-donors, and the difference in MCS between donors and non-donors was larger in the youngest age groups than in the oldest age groups (Table 1). In men, the mean difference in MCS between donors and non-donors decreased from 1.6 (95% CI: 1.1-2.1) to 0.35 (95%CI: 0.03-0.7) for the youngest and the oldest age groups, respectively. For women, there was a decrease in mean difference from 1.8 (95%CI: 1.3-2.3) to 0.86 (95%CI: 0.5-1.3) for those under 25 years and older than 55 years, respectively. A visual representation of the differences between donors and non-donors according to age is presented in figure 1. Across age groups, the effect of current tobacco smoking on mental health resulted in decreases of MCS that ranged from 0.55 (95%CI: 0.20-0.91) to 1.15 (95%CI: 0.76-1.54) and from 0.84 (95%CI: 0.37-1.31) to 2.24 (95%CI: 1.64-2.85) for men and women, respectively.

The healthy donor effect on self-perceived physical health (PCS):

As presented in table 1, the difference in PCS between donors and non-donors increased with increasing age.

In males older than 55 years, the mean PCS score was 2.6 (95%CI: 2.2-2.9; $p<0.001$) higher in blood donors than in non-donors. In women, the PCS difference was even higher than for men, reaching a difference of 4.3 (95%CI: 3.8 – 4.8; $p<0.001$) in the oldest age group. A visual representation of the differences between donors and non-donors according to age is presented in figure 1. Across age groups, the effect of current tobacco smoking on physical health resulted in decreases of PCS that ranged from 0.44 (95%CI: 0.06-0.81) to 1.39 (95%CI: 0.98-1.79) and 0.69 (95%CI: 0.34-1.04) to 1.55 (95%CI: 1.16-1.94) for men and women, respectively.

Discussion

We compared self-reported physical and mental health between blood donors and non-donors and generally observed donors to be the healthier of the two populations, consistent with the healthy donor effect.

Noteworthy, there were two different age-related trends in self-reported blood donor health. First, it appeared that young donors had better mental health than non-donors of the same age, indicating that mental health influences entrance

into the blood donor population. However, with increasing age mental health difference between donors and non-donors diminished.

Secondly, older donors, i.e., above 50 years of age, reported better physical health than their non-donor counterparts, which was not the case in the youngest age groups. In other words, the selection process of the blood donors before each subsequent donation had a greater effect on physical health than on mental health. The most likely explanation for this change is that individuals who are not physically fit to donate will likely drop out of the donor population, while individuals with poor mental health are not as likely to drop out of the donor population. However, mental health seems to be important for becoming a blood donor in the first place. In this study, non-donors were from the Danish Twin Registry and each twin was used as a singleton in the statistical analyses. Such an approach may be feasible because the mortality in twins is similar to that in the general population(Christensen, Vaupel *et al.*, 1995). Furthermore, twins may be representative of singleton populations in epidemiological studies in regards to lifestyle variables(Andrew, Hart *et al.*, 2001).

To our knowledge, this is the first presentation of the healthy donor effect with a distinction between mental and physical health. A previous study by Atsma et al. on the healthy donor effect in regards to self-perceived health also reported that donors had better self-perceived health than non-donors. Moreover, they stated that internal comparison groups were preferable in investigations of health-

related outcomes in conjunction to blood donation (Atsma and de Vegt, 2011; Atsma, Veldhuizen *et al.*, 2011). In contrast, a recently published study by Shehu *et al.* strived to quantify the healthy donor effect, and in a rigorously adjusted model, they found that after matching donors and non-donors, the health-related differences became statistically insignificant (Shehu, Hofmann *et al.*, 2014). The health-related outcome in this study was “satisfaction with their own health”. Self-reported health and satisfaction with one’s own health are two different measures of health, although both may be of relevance in regard to future health. Moreover, neither of the two studies distinguished between physical and mental health.

Our data suggest that the blood donor selection process mainly favours better self-perceived physical health and better self-perceived mental health to a lesser extent. Additionally, while good physical health was more prominent amongst older donors, the selection based on mental health was greater amongst younger donors. These differences could be attributed to the standardized health interview performed by trained nurses or secretaries at the Danish blood banks where physical health-related questions were prioritized over mental health-related questions.

The strength in this study lies in its large numbers and minimal non-responder rate (Pedersen, Erikstrup *et al.*, 2012). A possible cause of bias was calendar year sampling bias because the *DTR* study took place in 2002, while the *DBDS* study was initiated in 2010. Moreover, this was a cross-sectional study, and any time-

related differences could also be attributed to different cohort effects. However, the Danish National Board of Health conducted a nationwide investigation of mental and physical health in 2010 and again in 2013 using the SF-12 questionnaire. They reported that the percentage of individuals with a particularly low mental health score increased approximately 0.7% points from 2010 to 2013, while there was overall no difference in physical health from 2010 to 2013(Health). Moreover, 6.8% and 5.5% of individuals in the DTR study had a MCS and PCS score below the 10 percentile from the national health investigation from the Danish National Board of Health (Health). Therefore, it appears that the general self-perceived mental and physical health may have deteriorated. This indicates that the calendar year difference between the *DTR* (2002) and the *DBDS* (2010) participants probably does not alone account for the observed difference between donors and non-donors.

In conclusion, mental health influences the entrance of younger donors into the blood donor population. On the other hand, it is the physical health that explains donor drop outs with increasing age.

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AS and KOK collected data from the DTR participants; MSP, KR, HH, HU, and OBP collected data from the DBDS participants; OBP and ASR planned the study and

performed the statistical analyses; ASR wrote the first draft of the manuscript;

All authors revised the first draft and contributed to the final.

Lastly, all authors declare that they have no conflicts of interest.

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