Associations of environmental characteristics and lifestyle behaviours with donor blood parameters

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Summary

Blood services have set up a multitude of selection and eligibility criteria for donors and blood products to ensure the safety of donors and the quality of blood products. However, little was known about effects of donor lifestyle behaviours - such as physical activity, sedentary behaviour and dietary behaviour, and environmental characteristics - on blood parameters. Environmental characteristics are factors that influence individuals' lifestyle behaviours, either directly or via or in interaction with various individual characteristics. The environmental characteristics of particular interest for this thesis were measures of residential density, including urban-rural differences and population density. Although blood services can only to a certain extent influence environmental characteristics and lifestyle behaviours of donors, blood services are highly interested in gaining insights and knowledge in in- and external influences of donor blood parameters. Ultimately, insights in determinants of donor blood parameters could be used - where possible and desirable - to beneficially influence blood products. The aim of this thesis was to study associations of environmental characteristics and lifestyle behaviours with donor blood parameters. This was operationalized by studying associations between 1) lifestyle behaviours and built-environmental characteristics, and blood lipid levels; 2) lifestyle behaviours and haemolysis and haemoglobin levels, including the mediating role of blood lipids and ferritin therein; 3) iron status and physical activity and physical capacity.

Study designs and populations

The studies in this thesis were performed using data from Donor InSight (DIS) and the INTERVAL trial. DIS is an observational cohort study among blood and plasma donors donating at Sanquin, the Dutch national blood service. The objectives, methods and characteristics of DIS participants during three rounds of data collection were described in **chapter 3**. In this chapter we also showed that the DIS cohort, of which data were used in the studies described in **chapters 4 – 6**, is representative of the Dutch donor population. The INTERVAL trial is a large randomized controlled trial (RCT) allocating English donors of the National Health Service Blood and Transplant to different inter-donation intervals for a period of 2 to 4 years. In **chapter 7**, a triangulation of three study designs was used to address the research aim. For the RCT study design, data of the INTERVAL trial were used from the 2- and 4-year measurement rounds.

In **chapter 2** we performed a systematic review and meta-analyses on fifty population-based studies on built-environmental characteristics and blood lipid levels in adults. In **chapter 7** we did an umbrella review with meta-analysis, i.e. a systematic review of reviews that included RCTs or prospective observational studies in humans, with iron status and/or supplementation as

exposure and any measure of physical capacity as an outcome.

We conducted a Mendelian randomization to replicate the findings of the INTERVAL trial in a sample from the general population as it could be argued that donors are a healthy selection of the population. The genetic variants associated with either haemoglobin or ferritin were obtained from data of individuals of European ancestry. We then assessed genetic associations for these variants with device-measured physical activity in participants in a subset of the UK Biobank, also of European descent (**chapter 7**).

Main findings

In our systematic review with meta-analyses in **chapter 2**, we showed that blood lipid levels of urban residents were less favourable, such that they had higher total cholesterol, lower high density lipoprotein and higher triglycerides, compared to those of rural residents. Furthermore, we noted that the majority of the eligible studies assessed differences in blood lipid levels between urban and rural residents, mainly in low- and middle-income countries. We reported our findings on whether and via which lifestyle behaviours population density was associated with blood lipid levels in the Netherlands in **chapter 4,** using data from the third round of data collection for DIS-III. No relevant or statistically significant differences were found, neither did we find evidence for mediation by objectively measured or self-reported moderate-to-vigorous physical activity (MVPA) or sedentary behaviour.

In **chapters 5** and **6** cross-sectional associations were assessed in DIS-III to examine to what extent donors' lifestyle behaviours were associated with haemolysis and haemoglobin levels and the mediating role of blood lipids and ferritin levels. We did not find any evidence that objectively measured MVPA, sedentary behaviour or selected food items were associated with haemolysis levels. Furthermore, none of the lifestyle behaviours were associated with blood lipid levels. Our results did show that blood lipid levels were positively associated with haemolysis (**chapter 5**). The dietary consumption of haem iron was positively associated, while non-haem iron was negatively associated with haemoglobin levels (**chapter 6**). Adjusting for foods preventing the absorption of non-haem iron largely diminished the negative association. Both associations were mediated by ferritin levels, indicating that the association between haem iron intake and haemoglobin can to a large extent be explained by ferritin levels.

Three study designs were used in **chapter 7** to examine to what extent iron status is associated with physical activity and physical capacity. Using INTERVAL trial data we demonstrated that there were no differences in physical activity

and sedentary behaviour outcomes between any of the inter-donation interval groups, neither did we find any indications that some groups of donors were more prone to changes in their physical activity levels. In line with these results, the Mendelian randomization study showed similar null findings. Genetically predicted haemoglobin or ferritin was not associated with time spent in device-measured MVPA. The umbrella systematic review with meta-analyses on iron status and physical capacity outcomes indicated that only in anaemic patient groups changes in iron status through supplementation beneficially influenced physical capacity outcomes. Overall, we concluded that a normal iron status was not associated with physical activity and physical capacity in the general population. Only in anaemic populations iron supplementation seemed to improve physical capacity outcomes.

Reflections on the main findings presented in this thesis, as well as methodological considerations, are provided in the General Discussion (**chapter 8**). I highlighted the need for consensus on variable definitions (i.e. physical activity levels and measures of residential density) and measurement methods to improve comparability and pooling of data. Where individual studies may lack the power to detect subgroup differences, data harmonization can contribute to answering these research questions. Moreover, comparison within or between regions/countries can shed light on the generalizability of the findings. I furthermore suggested to further study dose-response effects of population density and physical activity levels in study populations with large variation rather than dichotomizing information.

In conclusion, the findings presented in this thesis indicate that the studied environmental characteristics and lifestyle behaviours, with the exception of the positive association of haem iron consumption and haemoglobin levels, are not meaningfully associated with donor blood parameters that are relevant for blood service practicfae. Therefore, blood services are not recommended to take residential density or the studied lifestyle behaviours of donors into account for the recruitment or selection of donors. Our findings on iron status and physical activity showed that medium-to-long term lower iron status (lower ferritin levels, but still adequate haemoglobin levels) do not translate into differences in habitual physical activity levels and sedentary behaviour. This is reassuring for donors as well as for blood services as blood donation should not impair donor health.