Associations of environmental characteristics and lifestyle behaviours with donor blood parameters

de Groot, R.

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- CHAPTER ONE -

General Introduction

Globally, donors provide over 100 million blood donations annually. These can help save even more lives as a single donation results in more than one blood product. In the Netherlands, in 2018 340.000 blood donors made over 720.000 donations, of which 57% were whole blood donations[1]. These donations were collected at 49 fixed sites and over 80 sites were attended by mobile collection units across the country.

As the only blood service in the Netherlands, Sanquin is responsible for a stable and safe blood supply. Next to safety of recipients, the health of the voluntary non-remunerated donor must also be safeguarded. Donating blood should not impair their health. Being dependent on their donors, it is also in blood services' interest to keep donors healthy and defer them for donations only when needed. Blood components used for transfusion and those manufactured into pharmaceuticals are part of medical treatments of patients and must therefore be of high quality. While in the traditional pharmaceutical industry the origin and quality of for example all chemical commodities of paracetamol are under control, blood products originate from human blood and blood services are only to a certain extent in control of the origin[2]. For instance, variation in haemoglobin content in red cell concentrates depends on the haemoglobin level of the donor providing the donation. Blood services can set thresholds regarding haemoglobin levels to ensure a minimum content of haemoglobin in a red cell product and to safeguard the donor, but this leaves room for great variation. Although it is clear that blood services will never be able to fully control the origin of the blood itself, blood services are very interested in gaining insight and knowledge in internal and external influences of their main commodity, the blood of donors. Ultimately, insights in determinants of donor blood parameters could be used - where possible and desirable - to beneficially influence blood products.

The composition of blood is influenced by lifestyle behaviours: it reflects how active we are, how much we sit, and what we eat and drink. Unhealthy lifestyle behaviours are established risk factors for undesirable levels of blood parameters such as blood lipid levels, and this is one way how such behaviours influence non-communicable disease risk. Strategies to promote healthy lifestyle behaviours are important for public health and have been studied for decades[3-5]. Apart from individual-level benefits of having healthy blood parameter levels, blood services depend on donors who can provide blood products of sufficient quality[6], which is an additional reason why promoting health behaviour for better blood parameters is a public health priority. In order to promote healthful lifestyle behaviours, insight in the determinants of such behaviours is needed. Over the past ten to fifteen years there has been a shift from focusing primarily on individual determinants of lifestyle

behaviours (attitude, motivation, age, sex, self-efficacy, social economic status) to a more contextual or 'upstream' approach in which environmental determinants are recognized as factors that influence individuals' lifestyle behaviours[7-10], either more directly, or via or in interaction with various individual characteristics. Contextual factors include the political, social, economic, and the physical environment and are in socio-ecological models often depicted as layers of influence[11,12]. Figure 1 shows an adaptation to the commonly used layers of socio-ecological models for the present thesis. For instance, a characteristic of the physical environment is the density of fast food outlets in the neighbourhood, which has been reported to be associated with less healthy dietary behaviours[13]. The proximity to parks on the other hand could enable individuals to engage more in physical activity. As such, environmental characteristics may be important upstream determinants of lifestyle behaviours and blood parameters levels. Hence, in this thesis lifestyle behaviours potentially influencing donor blood parameters are studied.

Figure 1: Graphical representation of adapted socio-ecological model.

Blood donation eligibility and the effects of screening

To ensure both the safety and quality of blood products for patients while at the same time ensuring that blood donation does not impair donor health, prior to each donation donor eligibility is assessed and donations are screened for a selection of infectious diseases[14]. To assess eligibility to donate, donors complete a donor health questionnaire (DHQ). DHQ consists of questions on general health, medication use, risky (sexual) behaviours, recent travel history and specific diseases. Next to these self-reported questions, haemoglobin levels are measured, as well as –in some blood services, including Sanquin- blood pressure. Depending on which, if any, criterion is not met, donors are temporarily or permanently deferred from donation. The deferral of donors results in a selection of individuals who are relatively healthy[15]. Deferral is undesirable for donors and blood services as it may lead to feelings of rejection, waste of time, and confrontation with one's medical history[16,17]. Deferred donors are less likely to return, requiring blood services to recruit new donors[16,18,19].

Donor blood parameters

There is not just one donor blood parameter related to donor eligibility, neither can the quality of blood products be reflected by one specific parameter. This is illustrated in the guidelines blood services have to adhere to. These relate to donor eligibility and product quality and have a wide range of criteria regarding haemoglobin and ferritin levels, number of leucocytes, clear or slightly turbid appearance of plasma, and/or a haemolysis levels after a certain number of storage days. It also includes tests on transfusion transmissible infections[20]. Within this thesis, we focus on the following donor blood parameters: blood lipids, haemolysis, haemoglobin and ferritin levels as these are associated with either donor eligibility and/or blood product quality. These parameters are further detailed below.

Blood lipids - cholesterol and triglyceride levels

Cholesterol is essential for cell membrane synthesis, and cholesterol is a precursor for the synthesis of vitamin D, hormones and sex steroids[21]. Triglycerides contribute to maintaining cell membrane structures and are also a very efficient energy source[22]. Low density lipoproteins (LDL) are sometimes referred to as less healthy cholesterol while high density lipoproteins (HDL) are commonly known as the more favourable cholesterol, as HDL collects cholesterol from blood vessels and delivers this back to the liver. Although blood lipids are necessary for cell function, an excess of LDL cholesterol and triglycerides can result in the formation of plaques in arterial walls, which eventually results in atherosclerosis, one of the main drivers of cardiovascular diseases[23]. Blood lipid levels are not routinely tested in blood service practice, but there are indirect criteria that do reflect blood lipid levels in donor blood. In order for a donation to meet quality criteria, plasma must have a clear or only slightly turbid appearance. At Sanquin blood bags are visually checked during processing. If the label on the back side of the bag is not visible through the plasma, the product is discarded. Such a turbid appearance is often caused by the –predominantly male– donor having had dinner shortly before donating, by being a regular smoker, but also by already existing high triglyceride levels in the donated blood[24,25]. Next to turbidity being a reason for discarding blood products, studies have also shown positive associations of lipaemic plasma and haemolysis levels in red cell concentrates[25,26].

Haemolysis

Haemolysis is the rupture or breakdown of the red blood cell (RBC) membrane, causing the release of haemoglobin and other internal components of the cells into the surrounding fluid[27]. Haemolysis is a natural phenomenon; RBCs have a normal lifespan of approximately 120 days in healthy humans[28]. However, once donated, the natural environment of RBCs is exchanged for an artificial

blood bag. The composition of the blood bag itself, as well as additives and the way donations are processed have an influence on the storage quality of blood and consequently affect haemolysis levels. Additionally, RBCs in the bag will no longer be renewed by erythropoiesis and residues of broken-down RBCs cannot be cleared from the bag. Given that the restoration of adequate tissue oxygenation is one of the main reasons to treat patients with red cell concentrates, it is of great importance that RBCs in concentrates for transfusion remain functioning[29]. In addition, a surplus of free haemoglobin might be toxic for critically ill patients[30-32]. Because of these undesirable consequences of haemolysis, at the end of the storage period a maximum of 0.8 percent haemolysis is allowed according to European guidelines[20].

Iron, haemoglobin and ferritin

Iron plays a crucial role in a number of functions. The most well-known include oxygen transport via RBC haemoglobin, electron transfer and its role as cofactor for enzymes involved in many metabolic processes[33-35]. On average, humans have 2-4 grams of iron in the body, of which the majority is incorporated in the RBCs haemoglobin[33]. One to two mg of iron is lost on a daily basis, mostly through desquamation of epithelial cells, for example shedding of skin cells and in premenopausal women also via loss of blood during menstruation[33,35,36]. Iron homeostasis is tightly regulated and consists of three main mechanisms[33,35]. Firstly, recycling of aged RBCs and secondly through dietary iron absorption. The third mechanism concerns iron stores; iron losses that are not compensated for by an increased dietary iron intake can be replenished by the release of stored iron. On the other hand, if iron intake exceeds the need, it can be stored. Ferritin levels are an indicator of the size of these stores. Discrimination in iron status, that is iron overload, normal or anaemia can be determined with several biomedical indices, including haemoglobin and ferritin levels[35]. Normal haemoglobin levels differ by sex and age. With respect to ferritin, the World Health Organization (WHO) defines levels lower than 15 μg/L indicative of depleted iron stores[37]. Anaemia is defined by the WHO as haemoglobin levels lower than 7.45 mmol/L (<120 g/L) for women and 8.07 mmol/L (<130 g/L) with further categorization into mild, moderate and severe anaemia[37].

Iron deficiency is associated with an array of negative health consequences such as fatigue and restless leg syndrome, particularly when coinciding with anaemia[38-40]. Iron deficient non-anaemia (IDNA) is estimated to affect one third of the world population and high risk groups are children, adolescents and women of reproductive age[37]. Another group at risk of iron deficiency are blood donors, who lose about 250 mg of iron with a standard 500 ml whole blood donation[41]. This is a considerable amount given normal iron

levels of 2-4 gram in adults[33,41]. Minimum haemoglobin levels are set in place to prevent anaemia and iron deficiency in donors and to ascertain sufficient haemoglobin content in red cell concentrates[20]. Also maximum numbers of donations per year and the assessment of haemoglobin levels are standard practice, although criteria vary between blood services[42]. Recently some blood services also started measuring ferritin levels in donors[43]. Failing to meet minimum haemoglobin levels is the most common reason for on-site donor deferrals[18,19]. For example, in the Netherlands about 10% of the whole blood donors who attend a donation session are deferred, of which half due to low haemoglobin levels[44,45]. Donation-induced iron deficiency or lower haemoglobin levels may also negatively affect physical activity levels in donors. If donors become more tired and as a result engage less in physical activity this could increase their risk on other health-related outcomes.

Lifestyle behaviours and their measurement

Lifestyle behaviours can both contribute to the prevention of non-communicable diseases and thus a healthy life, and be part of the treatment of certain diseases such as cardiovascular diseases[3-5,46]. Physical activity for instance can beneficially affect blood lipids levels, which are known risk factors for cardiovascular diseases[3]. The following lifestyle behaviours are studied in this thesis: physical activity, sedentary behaviour and dietary behaviour.

Physical activity

Physical activity is defined by the WHO as 'any bodily movement produced by skeletal muscles that requires energy expenditure'[47]. Physical activity is thus not restricted to exercise only, but also includes various daily activities such as gardening, grocery shopping, cycling to work and household chores. The beneficial health effects of physical activity are well documented; regular physical activity reduces the risk of more than 25 chronic medical conditions such as breast cancer and type 2 diabetes[5]. Risk factors of medical conditions that are favourably influenced by physical activity include body weight and blood pressure[5]. Physical activity also induces metabolic and physiological changes, therewith improving blood lipid profiles (e.g. higher HDL cholesterol and lower total- and LDL cholesterol and triglyceride levels)[5,48,49]. Physical activity is generally categorized by its intensity and is frequently expressed in absolute terms by metabolic equivalent of tasks (MET). The MET system can be seen as a scale; 1.0 MET is equivalent to the energy expenditure in a resting state which is about 3.5 ml/kg/min in terms of oxygen consumption[50]. Three METs requires three times more energy compared to being in a resting state. Light intensity includes any activity that requires between 1.5 and 2.9 METs. All activities between 3.0 and 5.9 METs are defined as moderate intensity and

all activities that require more energy expenditure as vigorous intensity[46]. The beneficial of in particular moderate-to-vigorous physical activity on overall health and disease prevention are well-established in scientific research. The WHO guideline recommends at least 150 minutes per week of moderate physical activity or the engagement in 75 minutes of vigorous physical activity or a combination of moderate-to-vigorous physical activity that is equivalent[46].

There are multiple ways to assess levels of physical activity in humans, which can roughly be divided in two categories. The first is self-report measures through the use of questionnaires, diaries and interviews[51]. The advantages of these are the low burden for participants, ease of administration in large studies, and the relatively low costs[51]. Disadvantages include the over- and underestimation of physical activity which is partly attributable to recall and social desirability bias and thus limit the validity and reliability[52]. The second category is direct measures that include motion sensors and monitors, i.e. accelerometers, pedometers[51]. Direct (or device) measures are considered to be less prone to recall and social desirability bias and to provide more accurate estimates than self-reported measures (higher validity and reliability)[53]. Although accelerometers objectively measure physical activity, the choice of algorithms, valid wear days, and cut-off points to translate the raw data to more meaningful metrics is somewhat arbitrary and greatly influences estimates[54]. Due to the declining costs and technological improvements in recent years, the use of accelerometers is more feasible and therefore increasingly common in large epidemiological studies[55].

Sedentary behaviour

Passive behaviours such as driving a car, watching television, reading a book but also working at a desk are considered to be sedentary behaviour. More formally the definition is: 'any waking activity that has an energy expenditure of ≤1.5 METs while in a sitting or reclining position'[49]. In the past decade, sedentary behaviour, independent of physical activity, has been associated with multiple health outcomes such as all-cause mortality, cardiovascular disease and certain cancers[56,57]. Literature reviews report sedentary behaviour to be positively associated with metabolic syndrome of which high triglyceride and reduced HDL cholesterol are components[58]. As such sedentary behaviour of donors could have implications for the general health of donors which could eventually influence donor eligibility. Experimental studies have shown that uninterrupted sedentary behaviour for 2 to 7 days increases triglyceride levels[59]. Yet, to date no international sedentary behaviour recommendations exists. Although some national governments have recommendations these generally lack quantifications and merely suggest to sit less, reduce (or minimize)

sedentary time and to interrupt long periods of sedentary time[60]. Similar to physical activity sedentary behaviour can be measured using accelerometers and (self-administrated) questionnaires.

Dietary behaviours

Dietary behaviour consists of three main concepts: food choices, eating behaviour and dietary intake. This thesis focusses on the intake of dietary iron and dietary fat (cholesterol, unsaturated and sutured fats).

High dietary intakes of saturated fat, cholesterol, alcohol and salt are associated with unfavourable blood lipid levels, whereas foods high in unsaturated fat and especially omega-3 fatty acids such as fish and nuts with more favourable blood lipids[61-64]. As previously mentioned, absorption of iron is part of iron homeostasis, and iron intake is therefore also important for donor blood quality. Two types of dietary iron can be distinguished[65]. Haem-iron is mainly found in animal foods and non-haem iron in plant-based foods[65]. The former has higher bioavailability, meaning that haem-iron is better absorbed (15-35%) than non-haem iron (1-10%), this also depends upon iron status[65,66]. Chiefly non-haem iron absorption is influenced by an interplay of dietary inhibitors and enhancers. Phytate and polyphenols have an inhibitory effect and are found in grains, beans, seeds, vegetables, fruit, coffee and a selection of teas[65]. Only calcium has, next to a negative effect on non-haem iron absorption also a negative effect on haem iron absorption[65]. Another enhancer of iron absorption is vitamin C. RBCs require vitamin B12, folate and iron for their maturation, a deficiency in any of these can eventually result in anaemia[65,67]. Studies assessing the intake of dietary iron and haemoglobin levels and iron stores in donors thus far have been inconclusive[68-70]. This could potentially be explained by the fact that these studies used food item reporting rather than more detailed assessments of haem and non-haem iron intake.

While food diaries and 24 hour recall methods are valid measurement tools to capture detailed actual food intake, they are time consuming and multiple days need to be assessed to estimate habitual dietary intake[71]. Long-term habitual intake was of most interest for this thesis, because average intake was expected to be associated with haemoglobin levels. Only a limited amount of dietary iron can be absorbed per day[65,66], which makes habitual intake more relevant than information on dietary iron intake of a couple of recent days. This can be achieved using food frequency questionnaires (FFQ). These questionnaires cover a range of food items and inquire about the frequency, size and number of portions from which nutritional intake can be estimated[71]. FFQs are commonly used in large epidemiological studies due to their easy administration, low costs and thus feasability[71]. A FFQ specifically designed

to capture haem and non-haem iron intake was used in our study on lifestyle behaviours and haemoglobin to address gap in the literature. This FFQ was also used to assess dietary intake of food items high in saturated fat and cholesterol and foods high in unsaturated fat.

Environmental determinants of lifestyle behaviours

Socio-ecological models of health are often used to explain health behaviour and assume multiple interrelated levels that influence health behaviour (Figure 1)[8,11]. As previously described these levels include the social, physical, economic, and policy environment. The physical environment includes everything that is available in the environment[10]. A major component is the built environment which consists of among others parks, recreational facilities, density measures, urban or rural residence, and walkability, but also the interconnectivity of streets[8]. The following example illustrates how various environmental characteristics are related to physical activity. Some neighbourhoods have more leisure time physical activity facilities than others which may enable inhabitants to engage in physical activity[72]. Depending on entrance fees, it may be that some facilities may not be affordable to certain groups (economic environment). The policy environment includes the policies and allocation of funds by politicians which can influence the availability and accessibility of the previously mentioned leisure time physical activity facilities. Social-environmental determinants can explain that –while parks could promote physical activity– if safety concerns related to for example litter or insufficient lighting exist, visits to parks may be limited.

The built environment

In this thesis several built-environmental characteristics are studied. A wide range of built-environmental determinants and lifestyle behaviours and various health outcomes have been investigated in the past[73-75]. For instance, residents of urban areas have higher risk/incidence of type II diabetes and higher body mass index[73,76]. Appraising the current knowledge is challenging with the ever-rising number of publications and inconsistencies in results of individual studies. Systematic reviews (with meta-analysis) offer a solution for these challenges, can identify gaps, and also offer research directions. Nonetheless, based on all available evidence it can be concluded that the results are inconsistent. Whilst several reviews are published on built-environmental characteristics and health outcomes, none concern associations between built-environmental characteristics and blood lipid levels.

Research aim and objectives

This chapter began by describing blood parameters and their relevance for general health and blood services. Subsequently arguing that, next to lifestyle behaviours, also determinants of lifestyle behaviours, such as built-environmental characteristics, should be studied because they may be upstream determinants of lifestyle behaviours, and subsequently of blood parameters. Although a variety of associations of built-environmental characteristics and blood lipid levels have been studied, there is yet no overview of the current state of the knowledge concerning this topic. Additionally, underlying pathways between built-environmental characteristics and blood parameters have been hypothesized but have not been disentangled using more sophisticated statistical analyses such as mediation analyses. The interest in haemoglobin levels by blood services was also explained in the introduction, as not meeting the haemoglobin level eligibility criteria is the most common reason for on-site donor deferral in blood bank practice. However, knowledge of associations between lifestyle behaviours and blood parameters in donors is limited and contradictory. In particular, research on physical activity in blood donors is scarce and relied on self-reported data only. Laboratory studies on donor blood parameters, having relatively low sample sizes, did take donor characteristics into account but to study lifestyle behaviours, larger sample sizes and more elaborate information of donors are required. Another topic is the potential effect of blood donation on donor health. In particular, the loss of iron with whole blood donations could lead to lower physical activity levels in donors which may affect general health of donors. Furthermore, blood donation – and the associated iron loss – allows for studying the effect of iron loss on physical activity. Up to now, the effect of iron status has primarily been studied in either a diseased or in an athletic population, not in healthy subjects, such as blood donors.

The aim of this thesis is to study associations of environmental characteristics and lifestyle behaviours with donor blood parameters. This general aim is further specified into the following objectives:

◊ Examine to what extent and via which lifestyle behaviours built-environmental characteristics are associated with blood lipid levels,

◊ Examine to what extent lifestyle behaviours of donors are associated with haemolysis and haemoglobin levels and study the mediating role of blood lipid and ferritin levels,

◊ Examine to what extent iron status is associated with physical activity and physical capacity.

Outline

The objectives of this thesis are addressed in six chapters (Figure 2). To address the first objective, we describe in **chapter 2** a systematic review with meta-analysis focussing on associations between built-environmental characteristics and blood lipid levels in adults. The objectives and methods of the Donor InSight cohort together with a comparison with the Dutch donor population are described in **chapter 3**. We further investigate the first objective by studying associations between population density and blood lipid levels in the Netherlands in **chapter 4**. The potential mediating role of moderate-to-vigorous physical activity and sedentary behaviour was assessed, using both accelerometer-derived and self-reported data. In **chapters 5** and **6** we investigated the second research objective on associations of lifestyle behaviours and blood parameters. More specifically, in **chapter 5** the hypothesis that healthy lifestyle behaviours are inversely associated with haemolysis was tested. The aim of **chapter 6** was to study associations between dietary intake of iron and physical activity levels with haemoglobin levels and to what extent these were mediated by ferritin levels. To investigate the third objective, we assessed whether iron stores affect physical activity levels and physical capacity in adults using three complementary methods –a randomised controlled trial, Mendelian randomisation and an umbrella systematic review with meta-analysis– in **chapter 7**. The main findings of all studies and gained insights are summarised in **chapter 8**, the general discussion. Here a reflection upon the results in light of the strengths and limitations of the included studies can be found, together with suggestions for future research and practical implications.

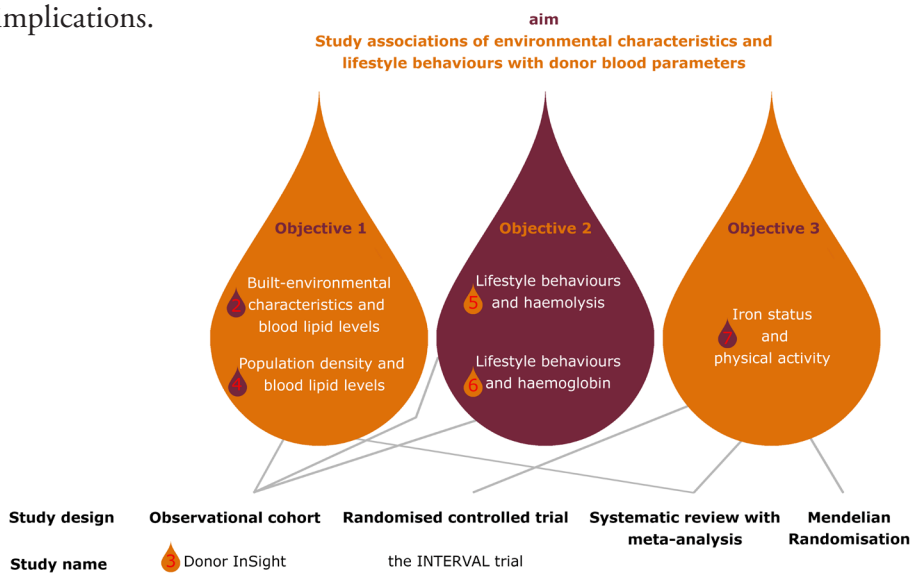

Figure 2: Overview of data sources and study designs used in the present thesis. Red numbers indicate chapter number, grey lines the study designed used per chapter.

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