The healthy donor effect: a matter of selection bias and confounding

Femke Atsma and Femmie de Vegt

The healthy donor effect (HDE) is an important methodologic pitfall in health research among blood donors.[1] The HDE is a term applied to the phenomenon of decreased morbidity rates and a healthier lifestyle in donors when compared to the general population, but also in the comparison between donors and nondonors and between active donors and lapsed donors.[1] As a result, effect estimations obtained from studies using such comparisons may be biased.

A major topic in donor health research is the protective effect of blood donation against cardiovascular disease. This presumed beneficial effect of blood donation has often been investigated by comparing donors with nondonors.[2-5] Contrasting results were found; some studies did not find a significant effect,[2,5] while others found a decreased cardiovascular risk in blood donors and suggested that blood donation may yield a protective cardiovascular effect.[3,4] However, it is very likely that this effect was to a great deal overestimated. The beneficial cardiovascular profile was probably mainly caused by the inclusion of healthy and health conscious blood donors during the blood donation process, i.e., the HDE.

ABBREVIATION: HDE = healthy donor effect.

From the Department Donor Studies, Sanquin Research; and the Department of Epidemiology, Biostatistics and HTA, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.

Address reprint requests to: Femke Atsma, Department Donor Studies, Sanquin Research, PO Box 1013, 6501 BA Nijmegen, the Netherlands; e-mail: f.atsma@sanquin.nl.

FA is an epidemiologist in the field of donor research. Her work focuses on health outcomes, such as cardiovascular disease, in blood donors; moreover, she investigates methodologic issues encountered in this type of research. FDV is an epidemiologist in clinical epidemiology; she is involved in methodological research in the general population and in cancer patients.

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Donor health studies are very important in learning more about positive and negative effects of blood donation. To design and perform this type of research in a valid way, a thorough understanding of methodologic features of HDE is imperative. To what type of bias does the HDE belong? And how does it influence study results? A proper knowledge of the methodology of the HDE is of vital importance for a correct treatment of the bias. In this report, we present a brief overview of different biases in epidemiologic research in relation to the HDE.

THREE MAJOR TYPES OF BIAS

In research with human participants, different types of bias may occur that lead to false conclusions. Bias can be defined as any systematic error that can distort the estimation of an epidemiologic measure and may be introduced by the design or conduct of the study.[6] We will discuss the three major categories of bias as used in the field of epidemiology and relate these to the HDE, that is, selection bias, confounding bias, and information bias (Table 1).

Selection bias refers to a misrepresentation of the underlying target population resulting from procedures used to select subjects. As stated by Rothman and Greenland,[6] the crucial element of selection bias is "that the relation between exposure and disease is different for those who participate and those who should be theoretically eligible for the study population, including those who do not participate. The result is that associations observed in the study represent a mix of forces determining participation as well as forces determining disease."

Confounding appears when extraneous variables, which are not equally divided over the exposure categories, distort the association between exposure and disease. Confounding factors are associated with the exposure under study, are risk factors for the disease, and do not mediate the causal pathway between the exposure and disease (Fig. 1).[6]

Information bias originates from measurement errors of either exposure, or disease, or confounding factors. Especially, systematic measurement errors, related to specific features of study subjects (e.g., sex, presence of

TABLE 1. Three major forms of bias in research with human participants

Selection bias	Systematic differences in the exposure–disease relation between eligible subjects who do and do not participate in the study.
Confounding bias	Unfair comparison; external variables distort the association between exposure and disease.
Information bias	Inaccuracy in the measurement or classification of exposure and/or disease status.

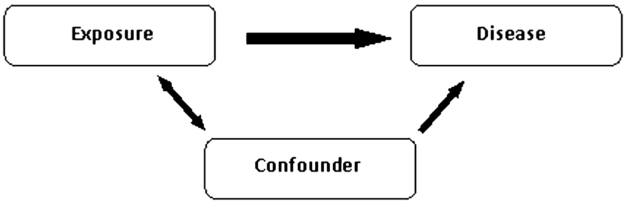

Fig. 1. Confounding of the exposure–disease association by an extraneous variable.[6]

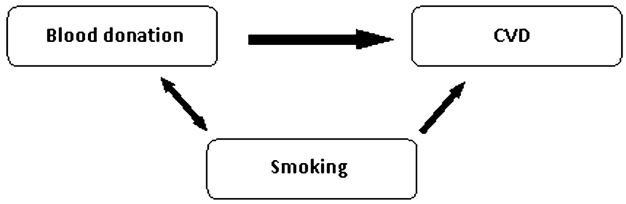

Fig. 2. Smoking as a confounder in the association between blood donation and cardiovascular disease. CVD = cardiovascular disease.

disease), are problematic. In that case, differential misclassification of subjects will occur and study results will be biased.[6]

THE HEALTHY DONOR EFFECT

When we reflect on the earlier mentioned association between blood donation and cardiovascular diseases, the question arises what type of bias is causing the HDE? We state that the HDE strongly refers to selection bias, because the observed protective effect of blood donation may not be caused by blood donation in itself, but just by the selection of healthy blood donors, who are eligible for donating blood. This phenomenon is comparable to the healthy worker effect in occupational research: selection bias occurs because subjects in the workforce are on average healthier and display lower morbidity and mortality rates compared to subjects from the general population.[7] As a consequence, health-related risk due to exposure on the work floor may be masked. Similar mechanisms may occur in cardiovascular research among blood donors. A prevalence study from our own group has shown that blood donors have a better cardiovascular health status compared to the general population.[8] However, by comparing donors with the general population or a group of nondonors, one should be cautious with drawing conclusions about causation. It is fairly impossible to disentangle whether this beneficial cardiovascular health status has been caused by giving blood or whether it is a reflection of the selection process taking place before blood donation. Therefore, the presumed protective effect of blood donation found in previous studies comparing donors and nondonors may be biased, leading to overestimations of effects. Taking these considerations into account, it may be evident that the HDE is definitely a type of selection bias, caused by the selection process before blood donation.

However, we also argue that the HDE is a type of confounding bias. External factors may disturb the association between blood donation and cardiovascular disease. These confounding effects may occur when investigating health issues within donors, but certainly also in the comparison of donors with the general population. From previous research, for instance, we know that blood donors smoke less than individuals from the general population.[8] This causes dissimilarities over the exposure categories between the two groups. Additionally, smoking is an independent risk factor for cardiovascular disease itself[9] and is certainly not an intermediate factor in the association between blood donation and cardiovascular disease. Thus, the definitions for confounding as presented in the triangle have been met (Fig. 2), which argues for confounding properties held by the HDE. As a result, estimations may be under- or overestimated.

We argue that information bias is not directly related to the HDE, but is merely a common problem in all scientific research where measurements are being done in study participants. In our example of blood donation and cardiovascular disease, the incidence of cardiovascular diseases may be measured differently in donors versus the general population and misclassification of disease status may occur. Blinding both researcher and study participant is the most recognized and widely accepted method to account for this type of bias and to prevent systematic measurement errors.

IMPLICATIONS

We state that the HDE is actually a combination of both selection bias and confounding bias. Selection bias cannot be removed from the study; it can only be recognized and described. Therefore, the HDE, as being selection bias, should be addressed beforehand, when designing the study. Donor versus nondonor comparisons should be avoided whenever possible and internal comparison groups should be used instead. One approach is to embed research within the active donor pool, since previous research has shown that the HDE is less strong within active donors.[1]

In case of confounding, the HDE can be taking into account in advance by restricting the study to specific groups (e.g., one sex category or a particular age class) or matching study subjects on important confounding factors (e.g., age and sex matching). Moreover, confounding effects can also be dealt with afterward. If confounding variables are known and measured precisely in all study participants, the confounding effect can be removed by adjusting for it in the statistical analyses.

In conclusion, health research among blood donors is very much prone to the HDE. The HDE may act as selection bias or confounding bias. When designing a study, one should carefully think through the type of bias that may be present and how the bias operates in that particular study. A clear understanding of the HDE will enable the choice of appropriate measures to address the bias, leading to more valid study results.

CONFLICT OF INTEREST

None.

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