



# THE NIJMEGEN BIOMEDICAL STUDY: AN EVERGREEN COLLECTION OF GENERAL POPULATION DATA THAT REMAINS RELEVANT

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## Insight

The Nijmegen Biomedical Study (NBS) is a valuable resource that continues to be used for research purposes. It has retained its significance even though it was established over two decades ago, much like evergreen trees that retain their leaves throughout the year. The NBS data is far from dead, it still lives on in the international research field despite no longer growing in size and being “old”. Established relationships between a risk factor and a disease typically do not change over time, meaning that just because something is “old” does not necessarily make it outdated. The author has made every effort to thoroughly analyse and synthesise the limited available information including conducting an in-depth interview with (former) project coordinators. Nevertheless, the predominant scientific source used for this article was the NBS cohort

## Introduction

The Nijmegen Biomedical Study (NBS) is a large-scale population-based cohort study conducted in the municipality of Nijmegen, the Netherlands. Its original intention was to create a general reference population (i.e., controls) for comparison with people carrying a disease of interest (i.e., cases). Cases arose from the Radboud University Medical Centre (Radboud University Medical Center) and affiliated researchers had a hard time finding control subjects from the general population, so the NBS initially intended to solve that problem. The NBS contains a large group of individuals that serves as a representative sample of the population in the Nijmegen region of the Netherlands. In addition to its original goal of creating a general reference population to be used as controls, the NBS has also proven useful for studying population characteristics and biomarkers.

The NBS is a collection of medical and lifestyle questionnaire data from 9,350 (6,468 donated a blood sample) residents aged 18-99 years of the Nijmegen municipality. NBS was founded a little over 20 years ago. Now, it is world-renowned with its data being used (as part of large meta-analyses) all over the globe. The Radboud University Medical Center is recognised for its contributions in elucidating the mechanisms underlying various diseases, including those with a hereditary or lifestyle component. One of the sources used for these contributions is the NBS, among others. There is a lot to share about this study, and through a historical review, we touch upon the scientific world before NBS was initiated, the origins of the NBS, the methodology including the follow-up phases, its success, and NBS in the present time. Note that this article may differ from most reviews, as most of the information was not publicly available and thus the author has reconstructed the information through interviews with (former) coordinators Dr ir. F. de Vegt (10/2000 – 01/2009) and dr T.E. Galesloot (09/2012 – present).

A historical view of large-scale population-based cohort studies  
The NBS was not the first large-scale population-based cohort. The first and also most famous and influential example of large-scale epidemiological studies in the world is the Framingham Heart Study (FHS).<sup>2</sup> It was initiated in 1948 in the town of Framingham,

Massachusetts, USA, and involved the recruitment of over 5,000 men and women who were followed over a long period (still ongoing!) to investigate the causes of heart disease. The study was unique in that it was one of the first large-scale population studies to focus on the identification of risk factors for chronic diseases. The participants were interviewed and underwent medical examinations every two years, and data on numerous factors, including diet, smoking, exercise, and family history, was collected. The data collected from the participants was used to identify the major risk factors for heart disease, such as high blood pressure, high cholesterol, smoking, and physical inactivity. The contemporary knowledge about the risk factors for cardiovascular disease is still based on that research. The FHS has had a significant impact on public health, and “the power of the large numbers of participants became evident. By comparing the data of people who had developed cardiovascular disease with those who did not, the researchers were able to draw relatively simple but important conclusions about risk factors.”, said Bart Kienemeny, professor of Cancer Epidemiology at Radboud University Medical Center.<sup>3</sup>

What the FHS and NBS have in common is that both remain lodestars for understanding the trends in risk factors and disease, with their respective impacts in the field of research. However, they are not comparable in the way that FHS is longitudinal, transgenerational, and aimed at understanding the epidemiology of coronary heart disease.<sup>4</sup> The NBS, like the FHS, is data-rich, and well-phenotyped, but despite having multiple phases, its design is not defined as longitudinal or transgenerational. The FHS was nevertheless a source of inspiration for the origins of NBS, perhaps just not in the design of the study.

## Initiation and follow-up

Because of the power of data in numbers, researchers all over the world followed Framingham’s design. The Radboud University Medical Center (previously UMC St Radboud), followed too, and set up the NBS in collaboration with the municipality of Nijmegen and the local public health services (GGD).

To ensure smooth operationalisation of the NBS, a pilot study was conducted from November 2001 to February 2002. Utilising the

population registers of the Nijmegen municipality, a cohort of 650 male and female residents aged 18 years or above was selected and sent a questionnaire, which included questions on lifestyle factors and health status.

**Phases**

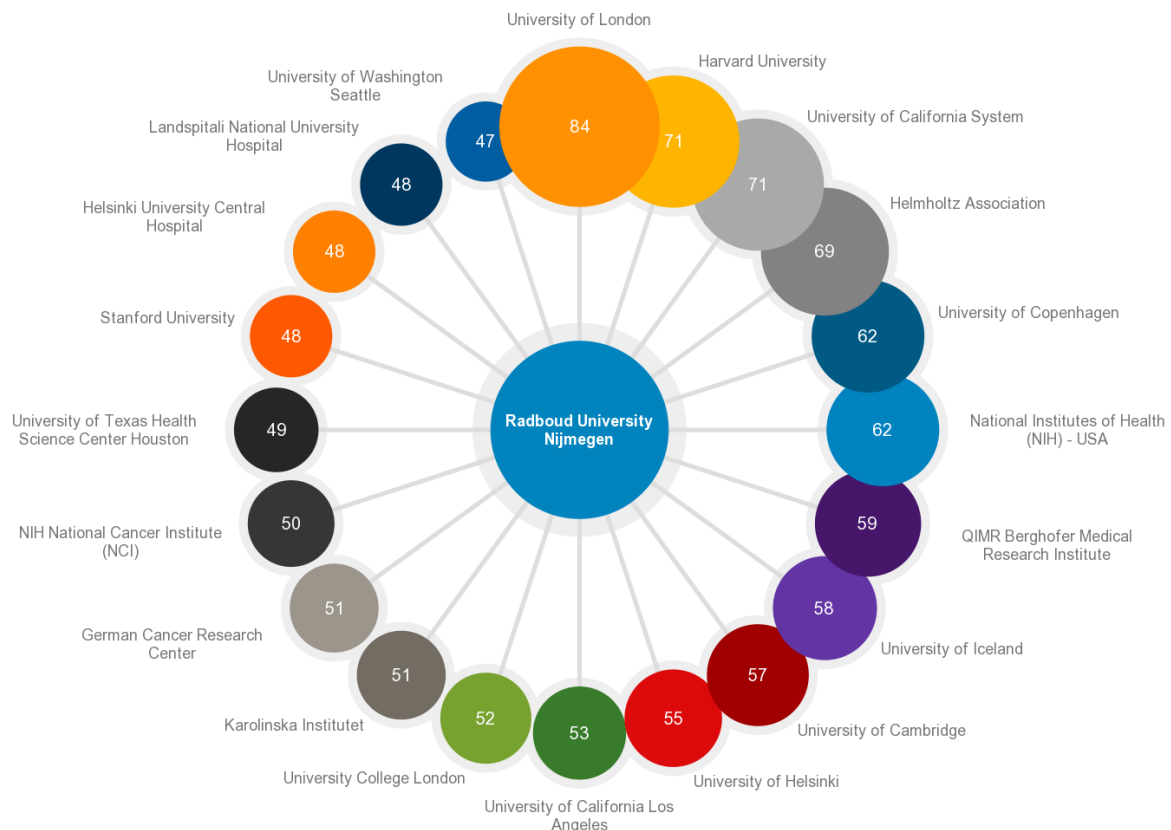
The NBS is characterized by different phases that each had their respective research objectives, mainly based on the interest and demand within the affiliated Radboud University Medical Center research groups. For example, the initial phase NBS-1 was initiated in 2002. This phase formed the basis of the collection, with a random sample drawn from the municipality registry including eligible individuals. Eligibility was based on being 18 years and above, not living in institutional care or assisted living facilities, and being able to complete a questionnaire in Dutch. In total, 22,451 individuals were invited to complete a postal questionnaire and provide a blood sample. Dutch nationality was characteristic for 96% of the invited participants. NBS-2 was initiated in 2005 and was characterized by including additional health-related questions. NBS-3 (2008) was conducted to acquire more comprehensive insights into nutritional status. A sub-phase and thus sub-study, NBS-2-NIMA, was focused on cardiovascular risk prediction using non-invasive measurements of atherosclerosis (hence the 'NIMA'). NBS-4 was also launched in 2008 to enhance the comparability and consistency of available data on risk factors between the NBS and cancer patient groups that were regularly examined as well as to gather trait data and health-related information for a more extensive range of studies. In 2012, the NBS-5 phase was carried out to gather baseline data for a research project on risk factors associated with melanoma, as well as to gather information on physical activity, pain, and dyslexia in greater detail.

**Measurements Questionnaires**

The NBS-1 questionnaire covered various topics such as demographics, medical history, health status, and lifestyle. Similarly, the NBS-2 questionnaire included questions related to pregnancy, mood, behaviour, memory, and daily activities. The NBS-2-NIMA-1, -2, and -3 questionnaires contained questions on general health, family history of cardiovascular traits, medication usage, quality of life, and medical history, with a specific focus on cardiovascular traits. The NBS-3 questionnaire was specifically designed as a food frequency questionnaire, while the NBS-4 questionnaire was geared towards collecting information on lifestyle factors, health, and disease. In addition, it also included questions related to life events, mood, behaviour, and reading problems. Finally, the NBS-5 questionnaire focused on health and disease, physical activity, sun exposure, pain, and reading problems. The NBS contains questionnaire data of 9,350 participants.

**Blood samples and other biomaterials**

Blood samples (serum (separator), heparin, and EDTA tubes) were obtained from participants that gave informed consent. In addition, as part of the NBS-2-NIMA sub-study, urine and faeces samples, swabs from mouth, hand, foot and back, and adipose tissue biopsies were collected. The haematological and biochemical parameters collected from blood samples and biomaterials include groups such as lipids, iron status, metabolites, thyroid function, liver, inflammation status, and renal function. From all participants, 6,468 have donated



**Figure 1:** Overview of NBS data in collaboration with research publications outside of Radboud University Medical Center. Including publications. Latest update from 2017.

a blood sample.

## Genomics

The blood samples also created a huge reservoir for large-scale DNA research. This turned out to be a stroke of luck as new techniques for analysing DNA emerged in the years following the collection in 2002. "In 2006, a chip came onto the market that allowed you to see a person's DNA all at once. The lucky thing was that at the NBS, we were one of the few in the world who had blood samples ready from thousands of people to isolate DNA from at that time." said prof. dr. Kiemeny.<sup>3</sup> The NBS has genome-wide genotype data available for 5,363 samples.

## The success of NBS

The NBS is something the (former) project coordinators and presumably, the full project team are very proud of. NBS has its origins in Nijmegen and provides us with a glimpse into the historical logistics of data collection, such as the manual entry of data from paper questionnaires. The success of the Nijmegen Biomedical Study (NBS) is not easily comparable to the headline-grabbing discoveries and scientific advancements that come out of research within Radboud University Medical Center. It should be noted that there are headline-grabbing studies based on observational research as well, but in such cases, the focus is usually on the findings related to a particular disease or health issue, rather than the study design (i.e., NBS) itself. Additionally, one could argue that there actually are headline papers that include the NBS. However, they usually do not focus solely on the NBS but instead include NBS data in a meta-analysis or as controls in case-control studies. In figure 1, the collaboration of NBS data in other research publications including the number of publications is shown.

The fact that the data is still being used shows the relevance and impact of the study. An example of success for NBS is that it served as a reference population in the development of reference values for, for example, thyroid function<sup>5</sup> and hepcidin<sup>6</sup>, which has implications for the diagnosis and treatment of various conditions. The NBS was used as a control population in the Nijmegen bladder cancer study that led to the finding of a sequence variant (8q24) that conferred susceptibility to urinary bladder cancer.<sup>7</sup> Another important finding from the Nijmegen Biomedical Study is the reference values for kidney function that are specific to age and gender. This information was obtained by studying the NBS samples, and it can help doctors better understand their patients' kidney health.<sup>8</sup> Overall, while the NBS may not be making headlines in the same way as other research, its impact and importance should not be underestimated.

The NBS holds questionnaire data from almost 10,000 participants and genomics data for more than 5,000 participants. During its peak, the NBS played a significant role in the scientific output of Radboud University Medical Center, with approximately 240 (based on 2018 data) research publications showcasing novel findings that gained global attention. Some of these studies were featured in prestigious journals such as *Nature*, *Science*, and the *New England Journal of Medicine*. Many NBS studies were conducted in collaboration with databases from universities around the world, which helped eliminate errors by replicating the studies on multiple occasions. Researchers can avoid searching for new control subjects for subsequent studies due to the availability of this enormous well-phenotyped database (genetically, environmentally, and biochemically).

## NBS in the present time

The last convulsions of NBS date back to 2013, when the NBS-5 data collection was completed. With this much data, one might wonder what the project team's current tasks and responsibilities are, and what is being done with the data at present time.

Currently, the coordinator's tasks include data management, assessment of applications for data requests and its subsequent data transfer contracts within Radboud University Medical Center, as well as on national and international levels. To this date, there is still some demand for the NBS data, with the genome-wide chip data (GWAS) being most frequently requested.

The NBS is a data-rich collection of population data that no longer grows but is far from dead. The data still lives on as it is still being used internationally.

The NBS collected data on genetic, biochemical, and environmental factors from thousands of Nijmegen residents over two decades ago. Although the data may be considered old by some, it is still highly valuable because established relationships between risk factors and diseases or traits don't change (much) over time. For instance, if a certain genetic variant is known to be associated with an increased risk for a specific disease or trait, that association is unlikely to change in a significant way over time. Similarly, environmental factors such as smoking or diet have well-established links to various health outcomes, and these relationships are also unlikely to change substantially over time. Therefore, the data collected by NBS two decades ago can still be used to identify and study the relationships between various risk factors and diseases/traits and can provide valuable insights into the causes and prevention of various health conditions.

With the rise of the Radboud University Medical Center Biobank, all biomaterials from the NBS are stored there and are available upon request. The questionnaire data is also still available upon request and is to this date being used in various educational activities in the faculty of medical sciences at Radboud University.

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