Master Thesis

Population Studies

The association between physical environmental conditions and different groups of congenital anomalies in the northern Netherlands

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Abstract

Worldwide, it is estimated that 10% of under five-year-olds die as a result of congenital anomalies. Therefore, congenital anomalies are presenting a major global health problem. However, the causal and mechanistic origins of most congenital anomalies remain unknown. There is only a small number of studies that examine the association between physical environmental conditions and congenital anomalies. The purpose of this study is to use an exploratory quantitative study design with Geographic Information Systems (GIS) elements to investigate whether there is an association between physical environmental conditions and different congenital anomaly groups in the northern Netherlands. Data of the European Surveillance of Congenital Anomalies and Twins (EUROCAT) Northern Netherlands (NNL) is used as data source for the congenital anomalies. The population in this study consists of babies and foetuses born with non-chromosomal and non-monogenic congenital anomalies in the northern Netherlands. Different groups classified according to the organ system are included. Due to the absence of non-malformed children in the EUROCAT NNL database, congenital anomaly groups are compared with a chromosomal and monogenic congenital anomaly group. Multinomial logistic regressions are performed for predictors of the natural and built environment and are controlled for compositional factors. This research found significant positive associations between higher percentages of agricultural land and limb anomalies, intermediate concentrations of nitrogen oxides and anomalies of the digestive system, higher concentrations of nitrogen oxides and eye and limb anomalies, and between a high liveability situation and genital and limb anomalies.

Keywords: congenital anomalies, physical environmental conditions, natural environment, built environment, multinomial logistic regression, northern Netherlands

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List of abbreviations

BZK	Ministry of Interior and Kingdom Relations
CBS	Statistics Netherlands
CC0	Creative Commons Attribute License
EUROCAT	European Registration of Congenital Anomalies and Twins
GIS	Geographic Information System
KWB	Kerncijfers Wijken en Buurten
NNL	Northern Netherlands
PRTR	Pollutant Release and Transfer Register
TOPFA	Termination of pregnancy for foetal anomaly
UMCG	University Medical Center Groningen
WHO	World Health Organization

1. Introduction

1.1 Societal relevance

Each year, there are about 3 million babies and foetuses born with congenital anomalies worldwide (Francine et al., 2014). An estimated 10% of under-five-year-olds die as a result of these congenital anomalies (WHO, 2013). Children who survive congenital anomalies can suffer from different types of malformations such as neural tube defects, cleft palates, and heart defects. Living with these malformations may lead to aesthetic and functional impairment and long term disability (Mahboubi et al., 2015; Amedro et al., 2015; Schneurer et al., 2015).

Congenital anomalies include all functional and structural alterations in embryonic or foetal development and can be the result of different causes. The different causes of congenital anomalies can be distributed into four broad groups: 10-30% of all congenital anomalies are a result of a genetic cause, environmental factors are responsible for 5-10% of the cases, multifactorial inheritance for 20-35% of the cases, and most of the congenital anomalies, 30-45%, have an unknown cause. The possibility exists that 30-45% of unknown causes still be attributed to environmental factors (Walden et al., 2007). Based on the determinants of health of the World Health Organization (WHO), the broad concept of environmental factors can be subdivided into social and economic environmental factors and physical environmental factors (WHO, 2019). For this research, physical environmental factors are included in the data analyses. Chapter Three provides further explanation.

Congenital anomalies are, especially because of the deficiency of information on prevention, a major public health issue (Salavati et al., 2018). Often, congenital anomalies are a challenge for the individual, the family of the individual (Pedersen et al., 2011) but also for the society in terms of health care facility needs and quality of life (Santoro et al., 2017). By obtaining more insight into the possible association between physical environmental conditions and different groups of congenital anomalies, appropriate prevention, and screening policies can be developed to prevent part of the congenital anomalies in the future. Additionally, new insights can be valuable for future parents regarding family planning. Future parents can take the results into account and possibly use them when choosing a living environment.

1.2 Academic relevance

There are some studies (Salavati et al., 2018; Ren et al., 2018; Rudnai et al., 2014; Santoro et al., 2017; Vaktskjold et al., 2011; García et al., 2017; Gianicolo et al., 2014; Chashschin et al., 1994) that have explored the association between physical environment conditions and congenital anomalies but to date, only a small number of studies have taken place in the Netherlands. For example, the study of Salavati et al. (2018) about the association of air pollution with congenital anomalies in the northern Netherlands and the study of Spinder et al. (2017) about maternal occupational exposure and oral clefts in offspring. The studies of Seggers et al. (2015), Jonker et al. (2016) and Rozendaal et al. (2013) have also taken place in the Netherlands. However, these studies have not focussed on physical environmental conditions. The studies are about the offspring of sub fertile couples (Seggers et al., 2015), the prevalence of congenital heart defects and congenital anorectal malformations (Jonker et al., 2016), and the association between peri conceptional folic acid and the risk of oral clefts relative to non-folate related malformations (Rozendaal et al., 2013).

Housing conditions stand out as a factor within the physical environment because studies into the relationship between housing conditions and congenital anomalies are absent in the literature. According to Harville & Rabito (2018), the effect of housing conditions on birth outcomes has not been closely examined. There are only a few studies (Vettore et al., 2010; Grjibovski et al., 2004; Nowak & Giurgescu, 2017) that have investigated the association between housing conditions and birth outcomes, but congenital anomalies are not taken into account.

In this study, a geographic information system (GIS) will be used because of the underutilisation in public health research and planning (Parchman, 1995; Diehr et al., 1993). Spatial analysis with GIS supports better outcomes than one-size-fits-all approaches because these methods can be essential to the accurate placement of community-based interventions (Miranda et al., 2013; Pickett & Pearl, 2001).

This research will contribute to exploration and understanding of the association between physical environment conditions and different groups of congenital anomalies in the northern Netherlands using GIS and will, therefore, contribute to the literature.

1.3 Problem statement

Different studies have shown that besides lifestyle factors, physical environmental factors are considered an important risk factor for human health (Réquia Júnior et al., 2015). Most of these studies (Villanueva et al., 2013; James et al., 2014; Chum & O'Campo, 2015) initially do not focus on the impact of the physical environment on babies, more specifically, congenital anomalies. Although there are studies that investigate the impact of the physical environment on congenital anomalies, these studies are scarce in the Netherlands. Nevertheless, today, congenital anomalies continue to be an important cause of morbidity and mortality for children, babies, and foetuses (Agha et al., 2006). Therefore, congenital anomalies are presenting a major global health problem. However, the causal and mechanistic origins of most congenital anomalies remain unknown (Gianicolo et al., 2014).

Lack of studies that investigate the impact of physical environmental conditions on congenital anomalies in the Netherlands, absence of literature about the relationship between housing conditions and congenital anomalies, and underutilised use of GIS when describing disease patterns (Parchman, 1995; Diehr et al., 1993) requires research that may contribute to new insights about the causal and mechanistic origins of congenital anomalies.

1.4 Objective and research questions

The objective of this study is to use an exploratory quantitative study design with GIS elements to explore whether there is an association between physical environmental conditions and different groups of congenital anomalies in the northern Netherlands. This objective is transformed into a central question, which is divided into three sub-questions. The first sub-question is arranged to provide a general picture of the situation regarding congenital anomalies in the northern Netherlands. The second and third sub-questions split the overarching concept from the main question, the physical environment, into natural environment and built environment. The split is chosen because of collinearity between the variables of the natural and built environment (Appendix E).

Central question

What is the association between physical environmental conditions and different groups of congenital anomalies in the northern Netherlands?

Sub-questions

1. What is the prevalence and what are the characteristics of (different groups) congenital anomalies in the northern Netherlands?

2. What is the association between natural environment conditions and different groups of congenital anomalies in the northern Netherlands?

3. What is the association between built environment conditions and different groups of congenital anomalies in the northern Netherlands?

1.5 Structure of the thesis

The overall structure of the study takes the form of six chapters, including introduction (1), theoretical framework (2), data and methodology (3), results (4), discussion (5), and conclusion (6). The introduction has given an overview of background information about the research topic, the societal and academic relevance, the problem statement, and the objective including research questions. Chapter Two begins by laying out the theoretical dimensions of the research and looks at the results of previous studies within the subject. Afterward, the conceptual model provides a visual representation of the relationship between concepts within the study. Chapter Two ends with the hypotheses. The data and methodology chapter describes the study design and population, data collection, data quality and limitations, ethical considerations, operationalisation of concepts and finally the methodology. Chapter Four presents the findings of the research. A presentation of descriptive statistics is followed by the results of the analyses. Chapter Five contains a discussion of the results. The last chapter, Chapter Six, indicates the strengths and limitations, recommendations and future research, and gives the overall conclusion of this research.

2. Theoretical framework

The theoretical framework gives an overview of theories that help to interpret the results of this research. In addition to theories, the literature review discusses former studies, related to the association between physical environmental conditions and congenital anomalies. Then, the conceptual model relates the concepts used in this study. At the end of the theoretical framework, the hypotheses are formulated.

2.1 Theories

Theories that explain spatial variation in health are used since this research has a spatial component. Further, theories that provide insight into which factors influence health are needed. The following theories will be used as a foundation for this research: composition versus context (with elements of the breeder hypothesis) and the health map.

The discussed theories do not specifically focus on babies and foetuses due to the lack of these theories in the literature but since the mother is in direct contact with the unborn child, the health and exposure of the mother to certain environmental factors will affect the development of the embryo or foetus. The development of congenital anomalies is dependent on the timing of exposure. For example, exposure to a particular chemical in week five may cause a congenital anomaly but exposure in a previous week may have no effect (Dolk & Vrijheid, 2003). An example of maternal exposure is exposure to air pollutants which results in low birth weight (Wang et al., 1997). Also, the mother's exposure to arsenic in drinking water during pregnancy leads to more cases of stillbirth and perinatal death (Ahmad et al., 2001). There are also studies that have focussed on the effect of physical environmental factors on congenital anomalies. The outcomes of these studies will be discussed in the literature review.

2.1.1 Composition versus context

Shaw et al. (2002) use the key terms composition and context to discuss the causes and spreading of ill health in Western industrialised societies which is a key issue in debates of medical sociologists and medical geographers. The composition and context theory focuses on spatial variation in ill health or health inequalities, where composition refers to the individual level and context to the area level. Health inequality means that there is an unequal distribution for chances of good or bad health between groups of people. These groups can be defined by common characteristics or, for example, the area in which they live.

Compositional factors include such factors as age, sex, measures of socioeconomic position, smoking, and diet. These factors can be measured at the individual level (Shaw et al., 2002). Context refers to the area level which includes factors as urbanisation, the presence of a factory and possibly related pollution, availability of health services, and the absence of sport and leisure facilities. These factors can be measured at the area level (Shaw et al., 2002).

According to Shaw et al. (2002), researchers who study health inequalities do not believe that composition and context are mutually exclusive as an explanation for ill health. It is unlikely that composition or context gives a complete explanation for spatial variation in health or health inequalities. The possibility exists that different types of people experience different effects of the context. For example, the context may influence the health outcomes of a particular group of people but other groups do not experience the same health outcomes or experience other health outcomes (Duncan et al., 1998). Therefore, the interaction between composition and context must be taken into account (Shaw et al., 2002; Duncan et al., 1998).

Mitchell et al. (2000) gives an example of a way in which context and composition are interrelated. Mitchell et al. (2000) investigated the influence of attitude and area on health in Great Britain. The measured contextual factor is industrial decrease in the period 1980-1990. This research shows that both context and composition influence the risk of poor health for residents of the area. The attitude, which is the compositional factor, has a stronger influence on the risk of poor health. In contrast to Mitchell et al. (2002), Macintyre & Ellaway (1998) finds a stronger influence of context. Their research is about the willingness to undertake activities that would promote health and is carried out in four contrasting areas within Glasgow. Data about among other things the ability to take exercise and socialise in the neighbourhood were obtained as contextual factors. Additionally, a compositional factor was obtained: the individuals' socioeconomic status. The results show different health behaviours between the four neighbourhoods and show a stronger influence of the contextual factors. It should be noted that this research focuses on health behaviour instead of health outcomes but health behaviour does have an impact on the health of individuals (Short & Mollborn, 2015).

A comparable approach to health inequalities is the breeder hypothesis. The breeder hypothesis examines two possible mechanisms that explain spatial variation in ill health. The mechanisms can be subdivided into 'exposure' and 'behaviour'. By exposure is meant exposure to different physical environment factors. Pollution, traffic and housing quality are examples of physical environmental factors with negative effects on health. Exposure can be considered as the context. The second mechanism 'behaviour' can be considered as compositional factors and refers to illness-related behaviour (Verheij, 1996). Examples of illness-related behaviour are drug/alcohol abuse and smoking (Garretsen & Raat, 1991).

The composition versus context and breeder hypothesis mainly indicates that both the individual and the area have an impact on ill-health. To give a more categorized overview of the factors that influence health, the health map of Barton & Grand (2006) is added as a foundation for this research.

2.1.2 The health map

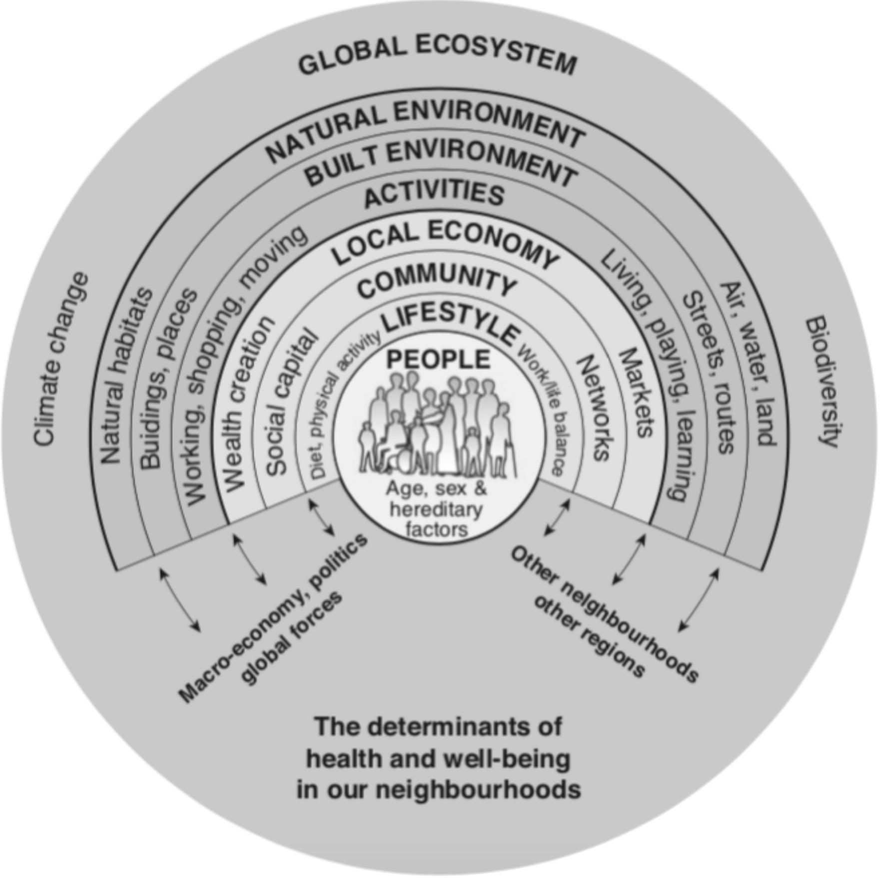
Health and well-being are largely determined by the environment in which people live but often the connexions between peoples living place and health are difficult and indirect (Barton & Grand, 2006). Therefore, the health map is created (Figure 1), which helps investigating and communicating the relationship between health and settlement. The relationship between the social, economic and physical environment and health are shown.

The health map shows many similarities with the framework of Whitehead & Dahlgren (1991). Within the framework of Whitehead & Dahlgren (1991), the different layers that have an impact on health are also shown. In addition to the Whitehead & Dahlgren (1991) framework, components based on ecosystem theories and sustainable development have also been used (Barton et al., 1995). Together this creates the health map, which displays various health determinants that could help with health impact assessments.

The model of Barton & Grand (2006) is chosen over the framework of Whitehead & Dahlgren (1991) because the model of Baron & Grand (2006) provides a better overview of the different layers that influence health and the determinants of health.

The health map shows different layers, where the inner layers are more or less fixed and can be adjusted less easily than the subsequent layers. Sex, for example, is less easy to adjust than a person's lifestyle factors (Whitehead & Dahlgren, 1991). The centre of the health map are the people, with their age, sex, and hereditary factors. The other layers which represent health determinants impact the health of these people (Baron & Grand, 2006). For instance, a different lifestyle. People have different diets, physical activities, and work. Besides, all people have a living place from which the community (social capital and networks) and the local economy (wealth creation and markets) can be diverse. The activities to be undertaken, also vary per person. People are settled in a built environment that is surrounded by a natural environment. These environments vary per settlement location and will, therefore, differ between people. This research focusses on the physical environment, in which the built and natural environment are included.

Figure 1 The health map



Source: Barton & Grand, 2006

2.2 Literature review

The literature review gives an overview of the results of previous studies within the subject. This research explores the association between physical environmental conditions and different groups of congenital anomalies in the northern Netherlands. To date, only the studies of Salavati et al. (2018) about the association of air pollution with congenital anomalies and Spinder et al. (2017) about maternal occupational exposure and oral clefts in offspring have taken place in the Netherlands. Air pollution is an example of a physical environment condition (WHO, 2019). There are more physical environmental conditions that have an impact on health. Several studies indicate an association between a specific physical environment condition and congenital anomalies. These studies will be explored to give context for this research. Although the circumstances in the northern Netherlands will deviate from the circumstances in the studies described, the results of the studies will guide the expectations of the study and the results of it.

Salavati et al. (2018) used multinomial logistic regressions to investigate the association between air pollution and the risk of congenital anomalies. In their study, 11 non-chromosomal and non-monogenic groups and one chromosomal and monogenic group are used. The non-chromosomal and non-monogenic groups are classified according to the organ system and include anomalies of the eye, respiratory tract, heart, nervous system, urinary tract, digestive system, limb, abdominal wall, genital tract, orofacial clefts, and multiple congenital anomalies. They performed analyses with the chromosomal and monogenic group as control group (control group 1), and with the non-chromosomal and non-monogenic groups (excluding the anomaly of interest subgroup) as control group (control group 2). The analyses were adjusted for sex of the child, age of the mother, area-level SES-score, level of education, folic acid use, smoking, and season of conception. Results of the analyses show a significant positive association between the pollutants $PM_{10-2.5}$[1], $PM_{2.5}$[2], and NO_2[3] and genital anomalies when using control group 2. The association between the air pollutants $PM_{10-2.5}$ $PM_{2.5}$ and NO_2 and genital anomalies were mainly driven by hypospadias since this congenital anomaly has the largest share in the subgroup genital anomalies. Eliott et al. (2001) gives a similar outcome regarding the hypospadias but in a slightly different context. They found an increased risk of hypospadias when the mother is living proximate to a landfill site during pregnancy in Great Britain. Air pollutant measurements are not included in the study of Eliot et al. (2001) but emissions from landfill sites contribute to higher local concentrations of air pollutants (Salavati et al., 2018).

Another recent study conducted by Ren et al. (2018) found an association between exposure to PM_{10} during weeks 3-8 in pregnancy and congenital heart anomalies in Beijing. The risk of congenital heart anomalies is increasing when exposed to PM_{10} during week 3-8 in pregnancy. Focus on this 3-8 week period, is chosen because this is a critical period for the development of heart anomalies (Dadvand et al., 2011; Vrijheid et al., 2011). In contrast to most of the other research into physical environmental factors and congenital anomalies who use (multinomial) logistic regressions, Ren et al. (2018) used machine learning models to investigate the effect of PM_{10} on the risks of congenital heart anomalies. They adjust the analyses for perinatal and maternal characteristics. Unlike Ren et al. (2018), Schembari et al. (2014) and Ritz et al. (2000) did not find an increased risk of congenital heart anomalies when exposed to PM_{10} in respectively Barcelona and Southern California. However, Schembari et al. (2014), did find an association between NO_2 and congenital heart anomalies. This finding is also supported by Davand et al. (2011).

Besides studies that investigate air pollution, there are also studies that investigated the relationship between other physical environmental conditions and congenital anomalies. For instance, a study on the association between arsenic in drinking water and congenital heart anomalies in Hungary carried out by Rudnai et al. (2014). The case group in this study are the anomalies of the circulatory system (heart), Down syndrome, club foot, and multiple congenital anomalies were used as controls. Data on mothers' arsenic exposure during pregnancy is estimated. Archive measurement data for each settlement where mothers lived is used for the estimation. They performed a logistic regression adjusted for sex of the child and age of the mother. The results show that pregnant women who consumed drinking water with an arsenic concentration above 10 μg/L have a higher risk of babies with congenital heart anomalies. Engel & Smith (1994) and Zierler et al. (1988) did also report significant associations between arsenic exposure and congenital heart anomalies.

Another physical environmental condition is environmental pollution caused by the long-term use of pesticides at agricultural land, analysed by García et al. (2017). Living proximate to agricultural land treated with pesticides might be a risk for human health. García et al. (2017) investigated the risk of male congenital genitourinary[4] anomalies and developing gestational disorders in areas that are exposed to pesticides in Andalusia. Outcomes are compared to areas with lower use of pesticides. Higher risks and prevalence of hypospadias, low birth weight, miscarriage, micropenis, and cryptorchidism are found in areas with higher use of pesticides compared to areas with lower use. Spinder et al. (2017) also investigated pesticides and the association with congenital anomalies but their cases were non-syndromic oral clefts instead of male genitourinary anomalies and gestational disorders. Besides pesticides, they also investigated the association between mineral and organic dust, solvents, metals, gases, and fumes and oral clefts. The difference with García et al. (2017) is the focus on occupational exposures instead of pesticides at agricultural land. Despite, the same sort of pesticides are used in both studies, which are herbicides, insecticides, and fungicides. Spinder et al. (2017) used a multinomial logistic regression adjusted for compositional factors and found increased odds ratios of maternal occupational exposure to dust and pesticides for oral clefts when using a non-chromosomal control group.

Within the physical environment, previously described studies can best be attributed to the natural environment (see Fig. 1, Barton & Grand, 2006). However, this research also focuses on the built environment and especially on the relationship between housing conditions and congenital anomalies. Studies into the relationship between housing conditions and congenital anomalies are absent in the literature. To provide context for this study, the results of three studies that investigated the association between housing conditions and birth outcomes rather than congenital anomalies will be described.

In a study investigating the association between housing conditions low birth weight and preterm low birthweight among low-income women in Rio de Janeiro, Vettore et al. (2010) reported that poor housing conditions are associated with low birth weight and preterm low birthweight. Poor housing conditions mean inadequate and highly inadequate conditions. Where either internal (quality of the house and overcrowding) or external (no sewage system or pit) housing conditions were classified as inadequate and both internal and external housing conditions were classified as highly inadequate. The cases, which are a low birthweight and a preterm low birthweight group are compared with a normal weight control group. Compositional factors are included in the analysis and include among other things risk behaviours, sociodemographic characteristics, and prenatal care. Similarly to Vettore et al. (2010), Grjibovski et al. (2004) also used housing conditions in their research as one of the determinants of foetal growth in Northwest Russia. They performed a linear regression analysis and found a positive association between the type of housing and birth weight. Living in crowded housing situations and living in a shared apartment was significantly associated with birth weight loss.

In a recent systematic review of Nowak & Giurgescu (2017) the findings of eight studies about the relationship between poor-quality built environments and negative birth outcomes were analysed. Various aspects of the built environment are measured, including housing damage, property damage, physical incivilities, physical disorder, vacancy tenure, nuisance, structural deterioration, and occupancy. Analysed negative birth outcomes are low birthweight, preterm birth, and small for gestational age. Seven of the eight studies reported a significant positive relationship between poor-quality built environments and negative birth outcomes, particularly for African American women.

Together, most of these studies indicate an association between physical environment conditions and congenital anomalies or other birth outcomes. Nevertheless, the studies described often do not focus on all groups of congenital anomalies and for housing conditions, it applies that not even a group of congenital anomalies is targeted. According to Vrijheid et al. (2011), it is important to focus on a wide range of subgroups when researching congenital anomalies. This research will focus on all available groups of congenital anomalies according to the organ system, creating a more complete picture. The same congenital anomaly groups as in Salavati et al. (2018) are used, including anomalies of the abdominal wall, digestive system, eye, genital tract, heart, limb, nervous system, orofacial clefts, respiratory tract, urinary tract, and multiple congenital anomalies. In contrast to the described studies which focus mostly on one physical environmental condition, this study will explore several physical environmental conditions to create a complete picture of the association between physical environmental conditions and congenital anomalies in the northern Netherlands.

2.3 Conceptual model

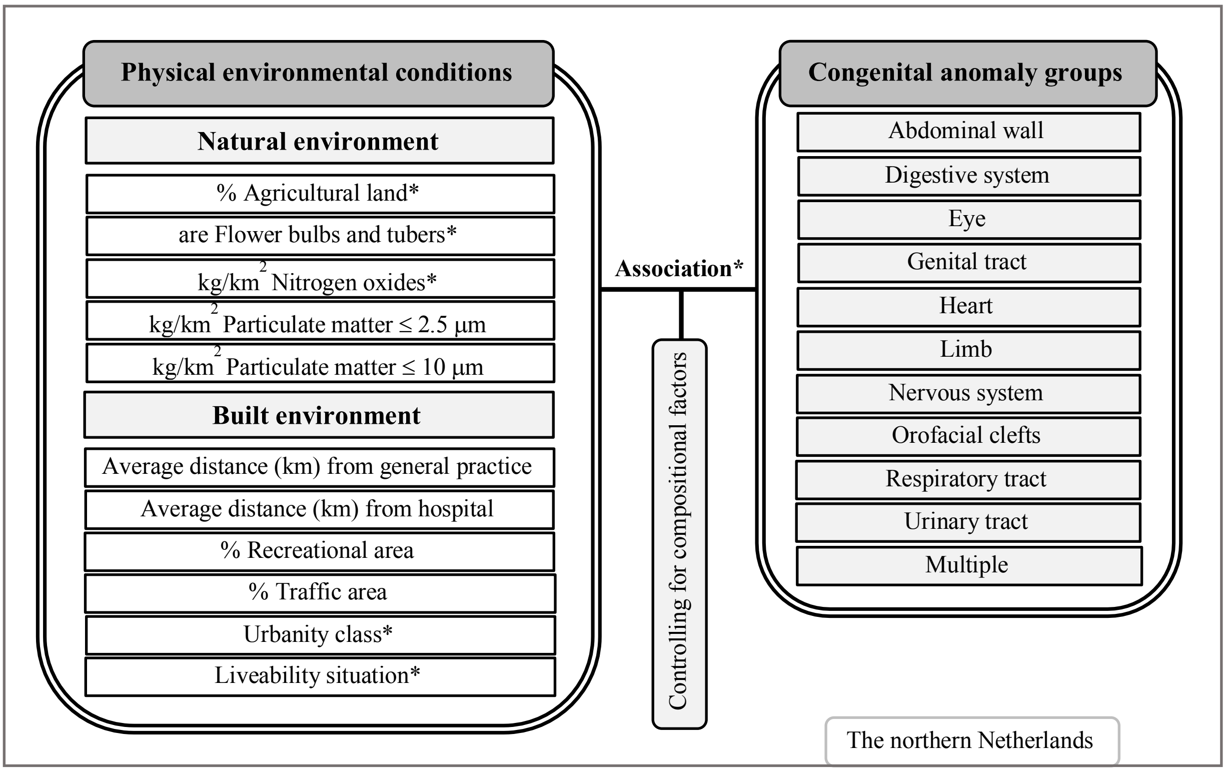
Figure 2 shows the conceptual model which provides a visual representation of the relationship between the concepts used in this study. A selection of physical environmental conditions is based on the described theories and literature. The contextual factors from the composition versus context theory described in Shaw et al. (2002) include urbanisation, the presence of a factory and possibly related air pollution, availability of health services and the absence of sport and leisure facilities. These factors are included in the research and covered by the following variables: urbanity class, kg/km^2 nitrogen oxides, kg/km^2 particulate matter ≤ 10 µm, kg/km^2 particulate matter ≤ 2.5 µm, average distance (km) from general practice, average distance (km) from hospital, and % recreational area. Emissions of nitrogen oxides, particulate matter ≤ 10 µm, and particulate matter ≤ 2.5 µm are chosen as air pollution data since particulate matter and nitrogen oxides in particular play a role in causing health effects at current concentrations in Dutch outdoor air (RIVM, 2018). Ozon also plays a particular role in causing health effects (RIVM, 2018) but data about Ozon is not available in the Pollutant Release and Transfer Register (PRTR) (2019^c). Additionally, nitrogen oxides (NO_x), particulate matter ≤ 10 µm (PM_{10}), and particulate matter ≤ 2.5 ($PM_{2.5}$) µm are chosen since the study of Salavati et al. (2018) found a significant positive association between the pollutants $PM_{10\text{-}2.5}$, $PM_{2.5}$, and NO_2 and genital anomalies.

The breeder hypothesis which is comparable with the composition versus context theory also mentions traffic and housing quality as physical environmental factors with negative effects on health (Verheij, 1996). These two factors are included in the research and covered by the following variables: % traffic area and liveability situation. The liveability situation is a score, divided into classes. The score is calculated by the Leefbaarometer and is composed of five underlaying dimensions: homes, residents, facilities, safety, and physical environment. The liveability situation is chosen as variable since housing conditions are included and because Nowak & Giurgescu (2017), Vettore et al. (2010), and Grjibovski et al. (2004) found relationships between poor quality (indoor and outdoor) built environments and negative birth outcomes (mainly low birth weight). Factors included in these researches partly correspond with the underlying dimensions of the liveability situation.

The health map (Figure 1) shows two other factors that are not described in the composition versus context theory and breeder hypothesis but are in the literature review: the factors water and land of the ‘natural environment’. Rudnai et al. (2014) conclude that pregnant women who consumed drinking water with an arsenic concentration above 10 µg/L have a higher risk of babies with congenital heart anomalies. Nevertheless, arsenic concentrations are not included in this research since the highest concentrations of arsenic-containing groundwater occur in Zeeland, South of Amsterdam and the region around the IJssel river (RIVM, 2008). These areas are not located in the northern Netherlands. In addition, concentrations of arsenic in groundwater does not have to influence drinking water since the quality check of Dutch drinking water meets the legal standards in 99.95% of the measurements (Vewin, 2017). The factor land is included in this research. This research focuses specifically on agricultural land since García et al. (2017) found higher risk and prevalence of genitourinary anomalies and gestational disorders in areas with higher use of pesticides compared to areas with lower use. Living proximate to agricultural land treated with pesticides might be a risk for human health (García et al., 2017). In the Netherlands, pesticides are on average used on 96.5% of the total agricultural land. Percentages differ per sector and crop and per pesticide type. The largest amount of pesticides is used in the flower bulbs and tubers sector compared to the other cultivation sectors (CBS, 2018). Therefore, are flower bulbs and tubers are in addition to agricultural land also included as a separate variable.

The described physical environmental conditions and the different congenital anomaly groups are included in the conceptual model. Physical environmental conditions are split into conditions of the natural environment and conditions of the built environment. Not all physical environmental conditions are tested for their association with the different congenital anomaly groups due to collinearity (Appendix E). For part of the conditions, only cross tabs are created. Conditions that are tested for associations are indicated with * in the conceptual model. The possible association will be controlled for compositional factors because the interaction between composition and context must be taken into account (Shaw et al., 2002; Duncan et al., 1998).

Figure 2 Conceptual model



2.4 Hypotheses

The first three hypotheses are formulated for the second sub-question ‘’What is the association between natural environment conditions and different groups of congenital anomalies in the northern Netherlands?’’. These hypotheses are based on the outcomes of previous studies.

H1. It is expected to find a positive association between higher percentages of agricultural land and at least genital and urinary tract anomalies.
H2. It is expected to find a positive association between higher numbers are flower bulbs and tubers and at least genital and urinary tract anomalies.
H3. It is expected to find a positive association between higher concentrations of nitrogen oxides and at least congenital heart defects and genital anomalies.

Last two hypotheses are formulated for the third sub-question ‘’What is the association between built environment conditions and different groups of congenital anomalies in the northern Netherlands?’’. Since there are no previous studies that have investigated the association between urbanity class, liveability situation and congenital anomalies, these hypotheses are based on the described theories that provide insight into which factors influence health. Due to the absence of previous studies, there is no direction for associations with (a) specific congenital anomaly group(s). Therefore, an effect is expected for one or more of the non-chromosomal or non-monogenic congenital anomaly groups. No association is expected for the chromosomal and monogenic group because there is no relationship expected between environmental factors and chromosomal and monogenic congenital anomalies (Salavati et al., 2018).

H4. It is expected to find a positive association between urban areas and non-chromosomal and non-monogenic congenital anomaly groups instead of the chromosomal and monogenic group.
H5. It is expected to find a positive association between low liveability situations and non-chromosomal and non-monogenic congenital anomaly groups instead of the chromosomal and monogenic group.

3. Data and methodology

3.1 Study design and population

The objective of this study is to use a quantitative study design with GIS elements to explore whether there is an association between physical environmental conditions and different groups of congenital anomalies in the northern Netherlands. For this exploratory qualitative study design, secondary data of the European Registration of Congenital Anomalies and Twins (EUROCAT) Northern Netherlands (NNL) will be used. EUROCAT NNL data is consistent with the subject of this research: congenital anomalies. GIS elements will be used because of the effective communication of visually presented information (Stieb et al., 2019) and because of the underutilisation of studies that analyse and describe disease patterns with GIS.

The population in this study consists of babies and foetuses born with congenital anomalies in the period 1999-2014 in the northern Netherlands, which include the provinces of Friesland, Groningen, and Drenthe. Sampling is done by selecting cases with a major congenital anomaly not associated with a known chromosomal or monogenic anomaly. The cases with a non-chromosomal or non-monogenic congenital anomaly are subdivided into groups of congenital anomalies the same way as in the study by Salavati et al. (2018). Congenital anomalies are classified according to the organ system and consist of a minimal of 30 cases, which results in the following groups of congenital anomalies: anomalies of the abdominal wall, digestive system, eye, genital tract, heart, limb, nervous system, orofacial clefts, respiratory tract, urinary tract, and multiple congenital anomalies. The last group is added for cases with multiple unrelated congenital anomalies in more than one organ system. The other ten groups include cases with single or multiple anomalies in one organ system. In this research, no emphasis is placed on congenital anomalies associated with a known chromosomal or monogenic anomaly since this research focuses on physical environment conditions and not on genetic causes. However, cases with a known chromosomal or monogenic congenital anomaly are used as control group because of the absence of non-malformed children in the EUROCAT NNL population-based registry.

3.2 Data collection

Dependent variable

For the dependent variable, different congenital anomaly groups, data of the EUROCAT NNL population-based registry will be obtained. Data about compositional factors used in this study are included in the dataset of EUROCAT NNL. Data is spread over a period of 16 years (1999-2014). The EUROCAT network focuses on monitoring major congenital anomalies among children born in defined European regions. The monitored congenital anomalies include single-gene disorders, chromosomal anomalies, and isolated or multiple anomalies (Garne et al., 2010). Northern Netherlands is one of the defined European regions and collects data for the provinces of Friesland, Groningen, and Drenthe. Collected data include general information about mother and child, socio-demographic variables, exposure of the mother, and the diagnoses of congenital anomalies (Kinsner-Ovaskainen et al., 2018). EUROCAT NNL is a research group of the University Medical Center Groningen (UMCG), via an application form on the website data can be requested for research projects.

Independent variables

For the independent variables, a selection of several physical environment conditions is made. In this study, it was decided to delineate the broad concept of environmental factors. Division of WHO is being maintained (WHO, 2019). WHO (2019) divides social and economic environmental factors and physical environmental factors. The physical environment factors were chosen in this study. The social and economic environmental factors are therefore not included. There are several reasons for this selection. First of all, various literature shows that there is a lack of studies dealing with the association between physical environmental factors and congenital anomalies in the Netherlands. Only two studies are known (Salavati et al., 2018; Spinder et al., 2017). Besides, the EUROCAT dataset to be used already contains some data on social and economic environmental factors. Without the use of physical environmental factors, little extra data is added to the dataset, which will make the research less powerful. Furthermore, there has been a lack of studies researching the relationship between housing conditions and birth outcomes. Housing conditions can be classified within the physical environment category according to WHO determinants of health (WHO, 2019). As a result, research continues to focus on environmental factors within the same category. Finally, it is not possible to identify specific social and economic environmental factors that are not yet in de dataset, since it is unusual to contact respondents when using secondary data.

Statistics Netherlands, Pollutant Release and Transfer Register (PRTR) (developed for Government of the Netherlands), and the Leefbaarometer (developed for Ministry of Interior and Kingdom Relations) are the data sources of the physical environmental variables. Statistics Netherlands is also the data source for the birth statistics, which will be used to calculate the prevalence of congenital anomalies per municipality.

From Statistics Netherlands, open data is used. Used datasets are published under the Creative Commons Attribute Licence (CC0). Data can be used freely but reference is required (CBS, 2019^{a}). The PRTR publishes data in maps, figures, and tables. PRTR also contains a database, where data can be selected for personal use (PRTR, 2019^{a}). Data from the Leefbaarometer is available as open data and is published under the CC0 (BZK, 2019^{a}). Data can be used freely and reference is not required. Table 1 shows for each data source which variables are acquired.

The acquired variables are not available for every year from the 1999-2014 period. Therefore, each independent variable gets an average value at postal code 4 or municipality level which will be applied to all annual layers from the EUROCAT NNL dataset (not applicable to the birth statistics). For an overview and explanation of available and used annual layers per variable, reference is made to Appendix A.

Table 1 Acquired variables per data source

Data source	Acquired variables
Statistics Netherlands	% agricultural land, are flower bulbs and tubers, average distance (km) from general practice, average distance (km) from hospital, % recreational area, % traffic area, urbanity class, and birth statistics
Pollutant Release and Transfer Register	kg/km^2 nitrogen oxides, kg/km^2 particulate matter ≤ 10 µm, and kg/km^2 particulate matter ≤ 2.5 µm
Leefbaarometer	Liveability situation

Sources: CBS, 2011$^{b\text{-}g}$; CBS, 2016; CBS, 2019^{b,e}; PRTR, 2019^{c}

3.3 Data quality and limitations

The database of EUROCAT NNL is a reliable and accurate source of data for the purpose of monitoring and research of congenital anomalies (Eurocat Noord-Nederland, 2019). The database consists of high quality data. Congenital anomalies are classified according to high standards and International Classification of Diseases (ICD) codes (Spinder et al., 2017). Besides information regarding the anomaly and pregnancy, additional data from a questionnaire is included in the database. A questionnaire is sent to the parents and includes questions about among other things exposure to harmful substances, chronic illness and folic acid use (Eurocat Noord-Nederland, 2019). The health-related questions are dependent on awareness of the condition (awareness bias) and may be affected by social acceptability (reporting bias) (Tijhuis et al., 2019). A limitation of the EUROCAT NNL database is the absence of non-malformed children. This ensures that a malformed group is used as control group, which increases the chance of selection bias.

Data of Statistics Netherlands meet a globally recognised standard for quality. At the beginning of 2019, the external auditor DNV GL determined that the quality management system of the entire Statistics Netherlands meets the international standard in this area: ISO 9001:2015 (CBS, 2019[d]). The Leefbaarometer uses models to estimate the liveability situation whereby the real situation may differ from the model calculations (BZK, 2019[c]). Nevertheless, the quality of data was taken into account when selecting indicators for the model calculations. Indicators must be explainable, available on a sufficiently low scale, available nationwide, available in continuous time series, and reliable (Leidelmeijer et al., 2014). A limitation of Statistics Netherlands and Leefbaarometer data is the occurrence of missing postal code values.[5]

The PRTR can contain uncertainties and inaccuracies. Factors that influence the data quality are quality and accuracy of the measurement, degree of checking errors, applicability of the used measurement method, quality and accuracy of data collection, consistency of the emission calculations, and the completeness of the emission calculation (PRTR, 2019[b]). In this research, registrations at the municipal level are used. According to the PRTR (2019[b]), additional uncertainty is added when data is used on a scale level smaller than national. The allocation of data is done generically, with the use of model calculations. However, control steps were carried out in the registration process to generate the desired quality. Emission numbers are compared with calculated numbers from previous years and with other data, for example, data from different compartments or emission sources. The use of 2019 boundaries, while data of 2010 and 2015 is obtained for calculating the average for the period 1999-2014 is a limitation of the PRTR. The use of 2019 boundaries causes that some municipalities have the same value for the variables kg/km^2 nitrogen oxides, kg/km^2 particulate matter ≤ 10 μm, and kg/km^2 particulate matter ≤ 2.5 μm (Appendix B2). It is assumed that other, different values would be assigned if the municipal boundaries correspond to the year from which data is used, which makes the data more detailed. Nevertheless, differences may be very small since discontinued municipalities are often situated next to each other and model calculations are used to calculate the emission numbers. It is not possible to make a statement about the differences in values in this study, it is only assumed there would be differences when other boundaries were used.

3.4 Ethical considerations

The anonymity of the participants is guaranteed since the data collected for the EUROCAT network is sent anonymously to the EUROCAT registries. Only a local serial number for each case is added in case extra information or further investigation is needed, which prevents a direct approach to the child or its parents (Barisic, 2009). Also, the registration of congenital anomalies of the child is voluntary and parental consent is required (Salavati et al., 2018). The full postal codes of the maternal residence at the time of birth are included in the EUROCAT NNL population-based registry, making it possible to trace the street of maternal residence at the time of birth. However, the personal data has been replaced by serial numbers (Barisic, 2009) making it impossible to find out the exact address of mother and child. Besides, this dataset is only used to investigate a complete view of the northern Netherlands and never looks in detail at the postal code level. Therefore, the investigation and sharing of the research results are done in a way that guarantees anonymity. Before the use of EUROCAT NNL data, a confidentiality agreement has to be signed, to ensure that data will be handled confidentially. Data may not be made available to others or made available for inspection for purposes other than the research purpose. Actions will be taken to protect the data. It is reported when devices with data are stolen. Data is deleted from the devices after the research has been finished.

3.5 Operationalisation of concepts

Dependent variable

The dependent variable consists of different congenital anomaly groups. Congenital anomalies include all functional and structural alterations in embryonic or foetal development (Walden et al., 2007). Groups are classified by the organ system and consist of cases with a major congenital anomaly. This results in 11 groups with non-chromosomal and non-monogenic anomalies and one group with chromosomal and monogenic anomalies. The 11 non-chromosomal and non-monogenic congenital anomaly groups are used as case groups in this research. Since the absence of non-malformed children in the EUROCAT NNL population-based registry, the chromosomal and monogenic congenital anomaly group is used as control group in this research. There is no relationship expected between environmental factors and chromosomal and monogenic congenital anomalies. Table 2 provides an overview of the represented congenital anomaly groups in this research.

Table 2 Represented congenital anomaly groups

	Case groups[a]		Control group
1	Abdominal wall defects	1	Chromosomal and monogenic anomalies
2	Anomalies of the digestive system		
3	Eye anomalies		
4	Genital anomalies		
5	Heart defects		
6	Limb anomalies		
7	Anomalies of the nervous system		
8	Oro-facial clefts		
9	Anomalies of the respiratory tract		
10	Anomalies of the urinary tracts		
11	Multiple congenital anomalies		

[a] None of the cases classified in these groups have a congenital anomaly with a chromosomal or monogenic cause

Independent variables

There are 11 physical environmental variables (five natural and six built environmental variables) included in this research, from which five are included in the analyses. Table 3 presents the summary statistics of all categorical variables, separately for the cases and controls. Several steps are taken to prepare and create these categorical variables for the multinomial logistic regressions and/or the cross tabs. After selecting and obtaining the annual data layers for each variable, data is edited. The variables % agricultural land, average distance (km) from general practice, average distance (km) from hospital, % recreational area, % traffic area, and urbanity class are obtained from ‘kerncijfers wijken en buurten (KWB)’ (CBS, 2011[b-g]; CBS, 2016) which are datasets from Statistics Netherlands. KWB datasets contain the most common postal code 4 in each neighbourhood, which are used to edit the data. Postal codes outside the northern Netherlands and needless variables were removed from the KWB. Duplicate postal codes are merged and average values are calculated for the relevant postal codes. As a result, the KWB consists of single northern Netherlands postal codes with the corresponding data for the independent variables. From all edited KWB annual data layers, one average value is calculated for each variable at postal code 4 level. The variable are flower bulbs and tubers is available at the municipality level (CBS, 2019[b]). The first available annual data layer was in 2000 but municipal boundaries have changed in the period 2000-2014. Values from discontinued municipalities have to be added to the new municipalities. For an overview of the performed actions, reference is made to Appendix B1. Once the values are added, the number are flower bulbs and tubers is available for each municipality in the northern Netherlands of the selected annual layers. From the data of all selected annual layers, average values are calculated at the municipality level. For the variables kg/km^2 nitrogen oxides, kg/km^2 particulate matter $\leq$ 10 µm, and kg/km^2 particulate matter $\leq$ 2.5 µm data is available at the municipality level

(PRTR, 2019^{c}). When obtaining the data from the PRTR, only municipalities based on the 2019 boundaries can be selected. In this research, municipal boundaries of 2014 are used since this is the most recent year in the dataset of EUROCAT NNL. Therefore, boundaries are not corresponding with the PRTR. Although a lot of municipalities used in this research were not discontinued in 2014, they are considered that way, since the PRTR use the municipal boundaries of 2019. For an overview of the unavailable municipalities in the PRTR and the municipalities whose values they have received reference is made to Appendix B2. From the data of the selected annual layers, average values at municipality level are calculated. Data from the variable liveability situation is provided at postal code 4 level. Postal codes outside the northern Netherlands were removed from the data. Afterward, an average value from the used annual data layers is calculated for each postal code. For the birth statistics at the municipality level, data for the period 1999-2014 is used (CBS, 2019^{e}). In this period, municipal boundaries have changed. The birth statistics from discontinued municipalities have to be added to the new municipalities. For an overview of the performed actions, reference is made to Appendix B3. The sum of live births per municipality is calculated for the period 1999-2014, this will be used as a denominator for calculating the prevalence of congenital anomalies.

The next step is linking the physical environmental variables to the EUROCAT NNL dataset. The EUROCAT NNL dataset contains of full postal code for each case, which can be split into numbers and letters. The variables available at postal code 4 level can be linked to these postal code numbers with vertical search in Microsoft Excel. The variables available at municipality level can be linked to the EUROCAT NNL dataset with a vertical search based on the municipality name. Prior to linking the data, municipality names have to be added to the EUROCAT NNL dataset. To each case, a municipality name is added with a vertical search in the postal code table of the Netherlands. This vertical search was based on full postal code which is already in the EUROCAT NNL dataset.

Added municipality names are also used to calculate the number of congenital anomalies per municipality. These numbers, which are the numerators in the prevalence calculations, can be linked to the birth statistics of Statistics Netherlands (CBS, 2019^{e}) with vertical search based on municipality name. To calculate the prevalence, the number of congenital anomalies per municipality is divided by the sum of live births per municipality and multiplied by 100%. Note on the calculated prevalence is the difference between the numerator and the denominator.[6] Prevalence is calculated separately for the non-chromosomal and non-monogenic congenital anomaly groups and the chromosomal and monogenic congenital anomaly group for a period of 16 years (1999-2014). Prevalence is mapped in ArcMap 10.5.1. Tables with calculated prevalence are joint with a municipal boundaries layer of 2014 of the northern Netherlands. Prevalence maps are presented in the descriptive statistics part of Chapter Four.

The expanded EUROCAT NNL dataset is edited in STATA 15.0. Continuous variables are recoded into categorical variables and labels are assigned. The classification method is Natural Breaks (Jenks), which minimize differences within classes and maximize differences between classes (Esri, 2019). Categorical variables are recoded into new categories, to create fewer classes. For variables with missing values (Table 3), an additional ‘missing’ category is added to prevent data loss. For an overview of the independent variables of the natural and built environment with a description, used categories, and associated values, reference is made to Appendix C. Cross-tabs with column percentages are generated for the independent variables of the natural and built environment in combination with the congenital anomaly groups. Cross-tabs are shown in the descriptive statistics part of Chapter Four. The association between the independent variables and the congenital anomaly groups is tested using the Pearson Chi-square test for categorical variables (Appendix F).

Table 3 Summary statistics of independent categorical variables

Independent variable		**Obs**	**(100%)**	**Missing (100%)**		**Mean**	**Min**	**Max**
Natural environment								
% Agricultural land	Cases	5,769	(99.3)	39	(0.7)	2.09	1	3
	Control	1,609	(99.5)	8	(0.5)	2.03	1	3
are Flower bulbs and tubers	Cases	5,808	(100.0)	0	(0.0)	1.24	1	3
	Control	1,617	(100.0)	0	(0.0)	1.25	1	3
kg/km^2 Nitrogen oxides	Cases	5,808	(100.0)	0	(0.0)	2.28	1	3
	Control	1,617	(100.0)	0	(0.0)	2.24	1	3
kg/km^2 Particulate matter ≤ 10 μm	Cases	5,808	(100.0)	0	(0.0)	2.22	1	3
	Control	1,617	(100.0)	0	(0.0)	2.20	1	3
kg/km^2 Particulate matter ≤ 2.5 μm	Cases	5,808	(100.0)	0	(0.0)	2.04	1	3
	Control	1,617	(100.0)	0	(0.0)	2.02	1	3
Built environment								
Average distance (km) from general practice	Cases	5,768	(99.3)	40	(0.7)	1.36	1	3
	Control	1,609	(99.5)	8	(0.5)	1.34	1	3
Average distance (km) from hospital	Cases	5,769	(99.3)	39	(0.7)	1.66	1	3
	Control	1,607	(99.4)	10	(0.6)	1.63	1	3
% Recreational area	Cases	5,769	(99.3)	39	(0.7)	1.44	1	3
	Control	1,609	(99.5)	8	(0.5)	1.47	1	3
% Traffic area	Cases	5,769	(99.3)	39	(0.7)	1.53	1	3
	Control	1,609	(99.5)	8	(0.5)	1.53	1	3
Urbanity **class**	Cases	5,768	(99.3)	40	(0.7)	1.60	1	3
	Control	1,609	(99.5)	8	(0.5)	1.63	1	3
Liveability **situation**	Cases	5,768	(99.3)	40	(0.7)	2.58	1	4
	Control	1,611	(99.6)	6	(0.4)	2.60	1	4

Note: the created missing categories are not included in these summary statistics

Compositional factors

EUROCAT NNL has obtained additional data for the compositional factors from a questionnaire that is sent to the parents, except for the area-level SES-score. There will be controlled for age at delivery, area-level SES-score, folic acid use, level of education, maternal smoking, and sex of child in the multinomial logistic regression analyses. Used compositional factors are the same as in Salavati et al. (2018) and based on the literature. Compositional factors are included because researchers who study health inequalities do not believe that composition and context are mutually exclusive as an explanation for health. Interaction between composition and context must be taken into account (Shaw et al., 2002; Duncan et al., 1998). Appendix D provides an overview of the compositional factors and associated categories. Cross-tabs with column percentages are generated for the compositional factors in combination with the congenital anomaly groups. Cross-tabs are shown in Appendix G.

3.6 Methodology

To explore whether there is an association between physical environmental conditions and different groups of congenital anomalies in the northern Netherlands, multinomial logistic regressions will be performed. The use of (multinomial) logistic regressions is common in research into physical environmental factors and congenital anomalies (Salavati et al., 2018; Spinder et al., 2017; Rudnai et al., 2014; Gianicolo et al., 2014; Landau et al., 2015; Marie et al., 2018; Vaktskjold et al., 2011). By using a multinomial logistic regression, multiple outcome categories can be included in the analysis. In this research 12 outcome categories are included in the analyses, including one reference category. The regressions will be adjusted for compositional factors shown in Appendix D. Analyses were carried out in STATA 15.0. Adjusted odds ratios (aORs), standard errors (SE), and significance are shown in the analyses part of Chapter Four.

Due to collinearity between the variables of the natural and built environment, the aORs are calculated in two separate models. The separate variables of the natural and built environment also show correlation (Appendix E). Therefore, a selection of variables is included in the analyses. Selection is based on the robustness of odds ratios (ORs) which is tested in multivariable logistic regressions.

The model for the natural environment consists of % agricultural land, are flower bulbs and tubers and kg/km^2 nitrogen oxides. Compared to the univariable analysis, ORs for this selection of variables hardly change when included in the multivariable analysis. Due to a strong correlation between the variables kg/km^2 nitrogen oxides, particulate matter ≤ 10 µm, and particulate matter ≤ 2.5 µm only kg/km^2 nitrogen oxides is included in the analysis. The model fit with kg/km^2 nitrogen oxides is slightly better and ORs are more robust compared to models with kg/km^2 particulate matter ≤ 10 µm and particulate matter ≤ 2.5 µm. Nevertheless, particulate matter ≤ 10 µm and particulate matter ≤ 2.5 µm are partly covered by nitrogen oxides since the concentration of particulate matter ≤ 10 µm and particulate matter ≤ 2.5 µm correspond with concentrations of nitrogen oxides in more than 60% of the municipalities. A high concentration of nitrogen oxides also means a high concentration of particulate matter ≤ 10 µm and particulate matter ≤ 2.5 in those municipalities. In the other municipalities, concentrations of nitrogen oxides, particulate matter ≤ 10 µm, and particulate matter ≤ 2.5 µm differ from each other. However, a high concentration of nitrogen oxides and a low concentration of particulate matter ≤ 10 µm and particulate matter ≤ 2.5 µm, for example, does not occur. There is never a whole category between concentrations of nitrogen oxides, particulate matter ≤ 10 µm, and particulate matter ≤ 2.5 µm. In the case of the example, it would be a high concentration of nitrogen oxides and intermediate concentrations of particulate matter ≤ 10 µm and particulate matter ≤ 2.5 µm.

For the built environment, urbanity class and liveability situation are included in the model. When including both variables, ORs hardly change compared to the univariate analysis. For the not included variables average distance (km) from general practice, average distance (km) from hospital, % recreational area and % traffic area it is assumed that they are covered by urbanity class (and liveability situation, since this score also includes the dimension facilities in the calculation). The number of facilities will most likely correspond to the level of urbanity. Areas with a low environmental address density do generally have a low population density. This leads to a limited support base for facilities. As a result, there are few. Areas with a high environmental address density have more facilities (SCP, 2006). There is more space in use for industrial and commercial use and infrastructure is better developed (Weng, 2007).

4. Results

Chapter Four presents the findings of the research. The descriptive statistics part, which are the findings of sub-question one, shows the prevalence of congenital anomalies per municipality, and an overview of the characteristics of the congenital anomaly groups. The analyses part which are the findings of sub-question two and three presents the results of the multinomial logistic regressions adjusted for compositional factors. Regressions are performed separately for the natural and built environment.

4.1 Descriptive statistics

4.1.1 Prevalence

Prevalence for the non-chromosomal and non-monogenic congenital anomalies and the chromosomal and monogenic congenital anomalies are calculated separately and shown in Figures 3 and 4. Prevalence is calculated for each municipality in the northern Netherlands. For the municipal boundaries, borders of 2014 are used. This results in a total of 59 municipalities.

The EUROCAT NNL database consists of 5,808 (78.2%) babies and foetuses born with non-chromosomal and non-monogenic congenital anomalies which include all congenital anomaly groups classified according to organ system. 1,617 (21.8%) babies and foetuses are born with a chromosomal or monogenic anomaly and are the control group in this research.

It can be seen from the mapped prevalence in Figure 3 that the highest prevalence of non-chromosomal and non-monogenic congenital anomalies occur in the municipality of De Marne, Winsum, Bedum, and Ten Boer. The municipality of Vlieland, Ooststellingwerf, Westerveld, Meppel, De Wolden, Emmen, Vlagtwedde, and Oldambt belong to the categories with the lowest prevalence. The mean of the prevalence presented in Figure 3 is 2.03 with a standard deviation of 0.46.

Figure 4 presents the prevalence of chromosomal and monogenic congenital anomalies, the control group. The prevalence deviates from the case groups (Figure 3). Figure 4 shows that the highest prevalence of chromosomal and monogenic congenital anomalies occur in the municipality of Heerenveen, Westerveld, Menterwolde, and Zuidhorn. The lowest prevalence occurs in the municipality of Vlieland, Marum, Stadskanaal, Pekela, and Delfzijl. The mean of the prevalence presented in Figure 4 is 0.55 with a standard deviation of 0.13.

4.1.2 Characteristics

Natural environment characteristics and built environment characteristics of babies and foetuses with (non)-chromosomal and (non)-monogenic congenital anomalies are presented in Tables 4 and 5. Table 4 shows the characteristics of variables from the natural environment, from which % agricultural land, are flower bulbs and tubers, and kg/km^2 nitrogen oxides will be used in the multinomial logistic regression of the natural environment. Table 5 shows the characteristics of the variables from the built environment, from which urbanity class and liveability situation will be used in the multinomial logistic regression of the built environment. The tables show frequencies and column percentages for the different variables. The columns consist of the congenital anomaly groups classified according to the organ system, the total for the non-chromosomal and non-monogenic congenital anomalies, and the control group: chromosomal and monogenic anomalies. From the congenital anomaly groups, the biggest group is limb anomalies 1509 (26.0%), followed by heart defects 1360 (23.4%). The smallest groups are anomalies of the respiratory tract 37 (0.6%) and abdominal wall defects 52 (0.9%).

Figure 3 Prevalence of non-chromosomal and non-monogenic congenital anomalies

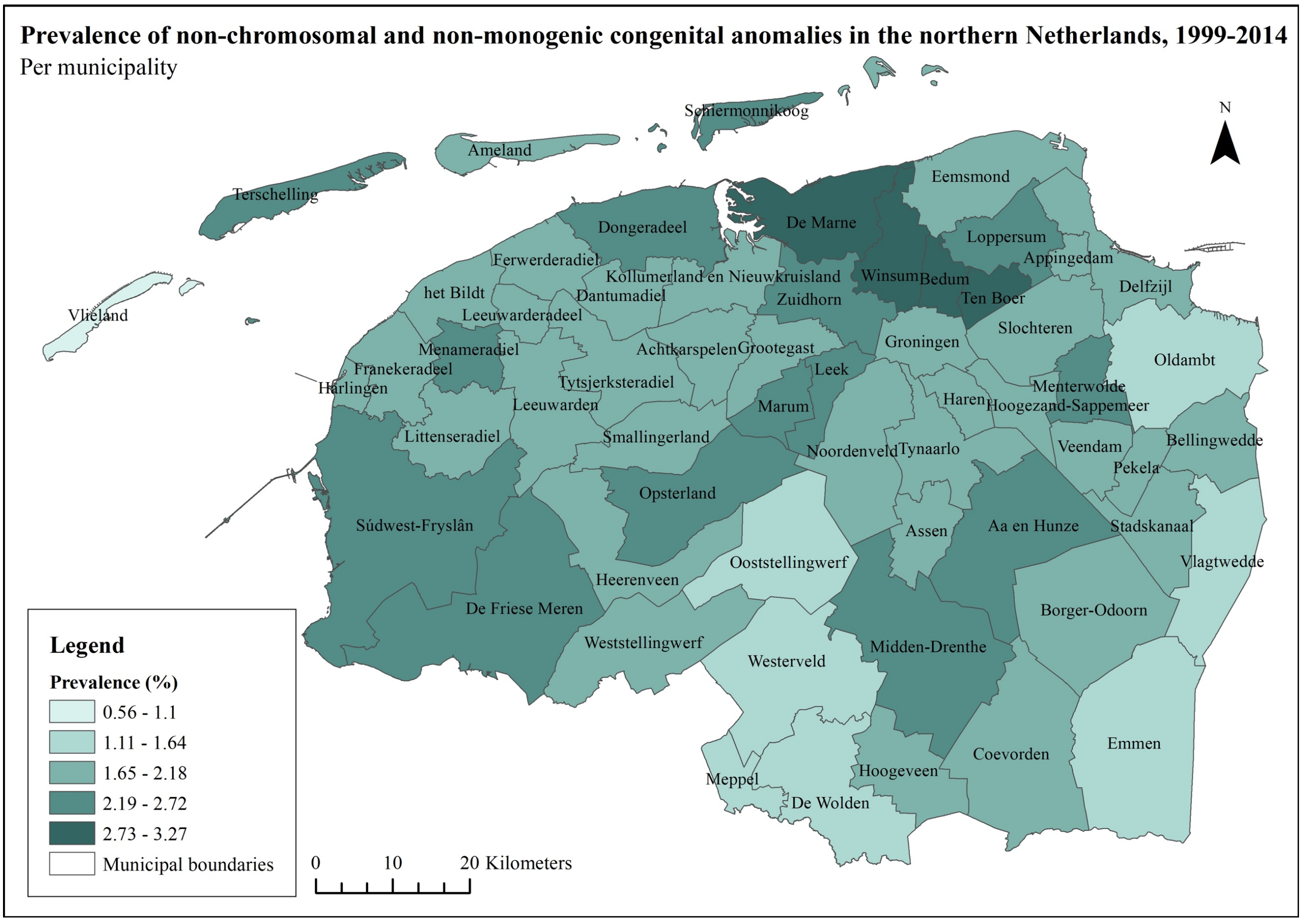
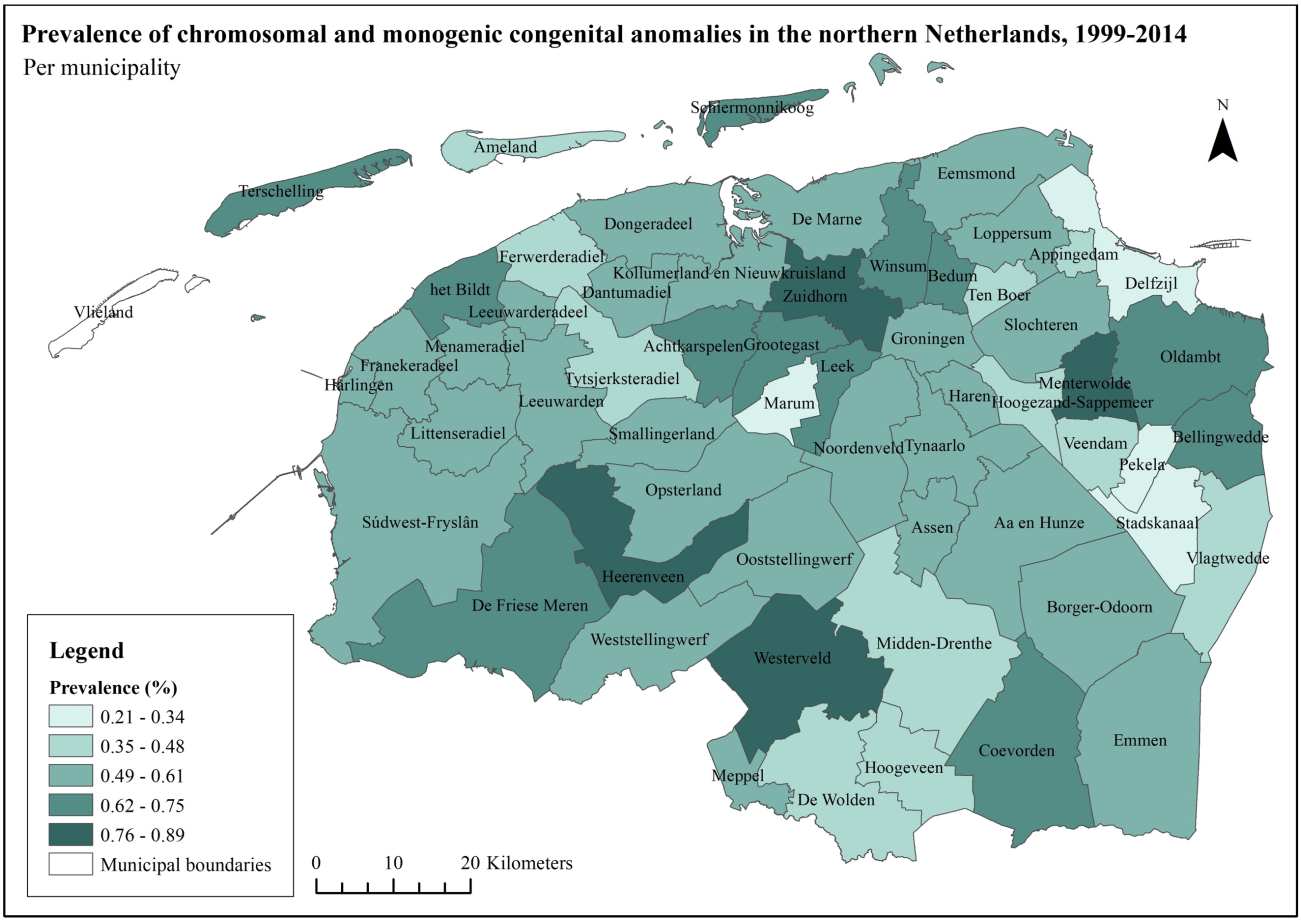


Figure 4 Prevalence of chromosomal and monogenic congenital anomalies



Note for both maps: prevalence is calculated for a period of 16 years (1999-2014) by dividing the number of congenital anomalies per municipality by the sum of live births per municipality multiplied by 100%. Due to a non-response of 20% in the EUROCAT NNL dataset, mapped prevalence per municipality may differ from the real situation.

Table 4 Natural environment characteristics of congenital anomaly groups and control group

	Cases												**Control group**
	Abdominal wall defects	Anomalies of the digestive system	Eye anomalies	Genital anomalies	Heart defects	Limb anomalies	Anomalies of the nervous system	Oro-facial clefts	Anomalies of the respiratory tract	Anomalies of the urinary tract	Multiple congenital anomalies	Total	Chromosomal and monogenic anomalies
N	52	535	107	482	1,360	1,509	282	427	37	550	467	5,808	1617
	0.9	9.2	1.8	8.3	23.4	26.0	4.9	7.4	0.6	9.5	8.0	100.0	100.0
% Agricultural land (postal code 4 level)													
N Low	23	161	31	180	425	481	93	131	9	175	152	1,861	557
%	44.2	30.1	29.0	37.3	31.3	31.9	33.0	30.7	24.3	31.8	32.6	32.0	34.5
N Intermediate	10	146	29	125	388	389	69	127	9	158	104	1,554	451
%	19.2	27.3	27.1	25.9	28.5	25.8	24.5	29.7	24.3	28.7	22.3	26.8	27.9
N High	19	225	47	173	539	622	118	168	19	217	207	2,354	601
%	36.5	42.1	43.9	35.9	39.6	41.2	41.8	39.3	51.4	39.5	44.3	40.5	37.2
N Missing	0	3	0	4	8	17	2	1	0	0	4	39	8
%	0.0	0.6	0.0	0.8	0.6	1.1	0.7	0.2	0.0	0.0	0.9	0.7	0.5
are Flower bulbs and tubers (per municipality)													
N Low	46	425	81	384	1,060	1,176	227	315	26	407	374	4,521	1,231
%	88.5	79.4	75.7	79.7	77.9	77.9	80.5	73.8	70.3	74.0	80.1	77.8	76.1
N Intermediate	5	96	23	83	270	304	46	103	11	132	85	1,158	362
%	9.6	17.9	21.5	17.2	19.9	20.2	16.3	24.1	29.7	24.0	18.2	19.9	22.4
N High	1	14	3	15	30	29	9	9	0	11	8	129	24
%	1.9	2.6	2.8	3.1	2.2	1.9	3.2	2.1	0.0	2.0	1.7	2.2	1.5
kg/km^2 Nitrogen oxides (per municipality)													
N Low	10	120	14	102	321	253	58	85	7	116	109	1,195	367
%	19.2	22.4	13.1	21.2	23.6	16.8	20.6	19.9	18.9	21.1	23.3	20.6	22.7
N Intermediate	18	202	35	161	438	380	86	149	13	185	134	1,801	493
%	34.6	37.8	32.7	33.4	32.2	25.2	30.5	34.9	35.1	33.6	28.7	31.0	30.5
N High	24	213	58	219	601	876	138	193	17	249	224	2,812	757
%	46.2	39.8	54.2	45.4	44.2	58.1	48.9	45.2	46.0	45.3	48.0	48.4	46.8
kg/km2 Particulate matter ≤10 µm (per municipality)													
N Low	11	119	15	98	316	269	49	85	5	104	107	1,178	338
%	21.2	22.2	14.0	20.3	23.2	17.8	17.4	19.9	13.5	18.9	22.9	20.3	20.9
N Intermediate	16	212	41	181	499	551	100	167	19	216	161	2,163	611
%	30.8	39.6	38.3	37.6	36.7	36.5	35.5	39.1	51.4	39.3	34.5	37.2	37.8

Table 4 continued

	Cases												**Control group**
	Abdominal wall defects	Anomalies of the digestive system	Eye anomalies	Genital anomalies	Heart defects	Limb anomalies	Anomalies of the nervous system	Oro-facial clefts	Anomalies of the respiratory tract	Anomalies of the urinary tract	Multiple congenital anomalies	Total	Chromosomal and monogenic anomalies
N High	25	204	51	203	545	689	133	175	13	230	199	2,467	668
%	48.1	38.1	47.7	42.1	40.1	45.7	47.2	41.0	35.1	41.8	42.6	42.5	41.3
kg/km2 Particulate matter ≤2.5 µm (per municipality)													
N Low	13	178	19	133	431	352	75	116	9	160	144	1,630	478
%	25.0	33.3	17.8	27.6	31.7	23.3	26.6	27.2	24.3	29.1	30.8	28.1	29.6
N Intermediate	17	207	51	189	531	631	108	175	18	209	166	2,302	621
%	32.7	38.7	47.7	39.2	39.0	41.8	38.3	41.0	48.7	38.0	35.6	39.6	38.4
N High	22	150	37	160	398	526	99	136	10	181	157	1,876	518
%	42.3	28.0	34.6	33.2	29.3	34.9	35.1	31.9	27.0	32.9	33.6	32.3	32.0

As shown in Table 4, a high percentage of agricultural land is most common among the cases (40.5%) and controls (37.2%). The anomalies of the respiratory tract group have the highest percentage (51.4%) in the ‘high’ category. The genital anomalies group has the lowest percentage in the ‘high’ category (35.9%). A low number of are flower bulbs and tubers are most common among both the cases (77.8%) and controls (76.1%). The anomalies of the nervous system group have, compared to the other congenital anomaly groups, the highest percentage (3.2%) in the high number are flower bulbs and tubers category but the difference with the genital anomalies group is small (0.1%). Most of the cases (48.4%) and controls (46.8%) are born in a municipality with a very high number of kg nitrogen oxides per km^2. The limb anomalies group has the highest percentage in the ‘high’ category (58.1%). The anomalies of the digestive system group have the lowest percentage in the ‘high’ category (39.8%). The ‘high’ category of the variable kg/km^2 particulate matter ≤10 µm is most common among the cases (42.5%) and controls (41.3%). For the variable kg/km^2 particulate matter ≤2.5 µm, the ‘intermediate’ category is most common for both cases and controls. The eye anomalies group and the anomalies of the respiratory tract group have the highest percentages in this ‘intermediate’ category. The percentages are respectively 47.7% and 48.7%. The highest percentage of the ‘high’ category of particulate matter ≤10 µm and ≤2.5 µm is found for the abdominal wall defects group. The highest percentages for the ‘low’ category of particulate matter ≤10 µm and ≤2.5 µm are found for the anomalies of the respiratory tract group.

Table 5 Built environment characteristics of congenital anomaly groups and control group

	Cases												**Control group**
	Abdominal wall defects	Anomalies of the digestive system	Eye anomalies	Genital anomalies	Heart defects	Limb anomalies	Anomalies of the nervous system	Oro-facial clefts	Anomalies of the respiratory tract	Anomalies of the urinary tract	Multiple congenital anomalies	Total	Chromosomal and monogenic anomalies
N	52	535	107	482	1,360	1,509	282	427	37	550	467	5,808	1617
%	0.9	9.2	1.8	8.3	23.4	26.0	4.9	7.4	0.6	9.5	8.0	100.0	100.0
Average distance (km) from general practice (postal code 4 level)													
N Low	36	356	82	360	959	1,070	202	305	22	377	326	4,095	1,159
%	69.2	66.5	76.6	74.7	70.5	70.9	71.6	71.4	59.5	68.6	69.8	70.5	71.7
N Intermediate	14	124	19	97	300	298	61	86	13	140	100	1,252	345
%	26.9	23.2	17.8	20.1	22.1	19.8	21.6	20.1	35.1	25.5	21.4	21.6	21.3
N High	2	52	6	21	93	123	17	35	2	33	37	421	105
%	3.9	9.7	5.6	4.4	6.8	8.2	6.0	8.2	5.4	6.0	7.9	7.3	6.5
N Missing	0	3	0	4	8	18	2	1	0	0	4	40	8
%	0.0	0.6	0.0	0.8	0.6	1.2	0.7	0.2	0.0	0.0	0.9	0.7	0.5
Average distance (km) from hospital (postal code 4 level)													
N Low	32	233	49	244	618	594	142	190	15	255	216	2,588	776
%	61.5	43.6	45.8	50.6	45.4	39.4	50.4	44.5	40.5	46.4	46.3	44.6	48.0
N Intermediate	17	247	44	187	614	690	113	188	17	229	191	2,537	651
%	32.7	46.2	41.1	38.8	45.2	45.7	40.1	44.0	46.0	41.6	40.9	43.7	40.3
N High	3	53	14	47	120	208	25	48	5	66	55	644	180
%	5.8	9.9	13.1	9.8	8.8	13.8	8.9	11.2	13.5	12.0	11.8	11.1	11.1
N Missing	0	2	0	4	8	17	2	1	0	0	5	39	10
%	0.0	0.4	0.0	0.8	0.6	1.1	0.7	0.2	0.0	0.0	1.1	0.7	0.6
% Recreational area (postal code 4 level)													
N Low	29	374	70	309	892	954	178	276	26	346	307	3,761	1,013
%	55.8	69.9	65.4	64.1	65.6	63.2	63.1	64.6	70.3	62.9	65.7	64.8	62.7
N Intermediate	14	115	21	121	326	417	76	114	11	156	114	1,485	433
%	26.9	21.5	19.6	25.1	24.0	27.6	27.0	26.7	29.7	28.4	24.4	25.6	26.8
N High	9	43	16	48	134	121	26	36	0	48	42	523	163
%	17.3	8.0	15.0	10.0	9.9	8.0	9.2	8.4	0.0	8.7	9.0	9.0	10.1
N Missing	0	3	0	4	8	17	2	1	0	0	4	39	8
%	0.0	0.6	0.0	0.8	0.6	1.1	0.7	0.2	0.0	0.0	0.9	0.7	0.5

Table 5 continued

	Cases												**Controls**
	Abdominal wall defects	Anomalies of the digestive system	Eye anomalies	Genital anomalies	Heart defects	Limb anomalies	Anomalies of the nervous system	Oro-facial clefts	Anomalies of the respiratory tract	Anomalies of the urinary tract	Multiple congenital anomalies	Total	Chromosomal and monogenic anomalies
% Traffic area (postal code 4 level)													
N Low	24	335	66	284	803	858	159	254	22	332	265	3,402	952
%	46.2	62.6	61.7	58.9	59.0	56.9	56.4	59.5	59.5	60.4	56.8	58.6	58.9
N Intermediate	19	146	33	135	408	433	96	119	10	153	140	1,692	459
%	36.5	27.3	30.8	28.0	30.0	28.7	34.0	27.9	27.0	27.8	30.0	29.1	28.4
N High	9	51	8	59	141	201	25	53	5	65	58	675	198
%	17.3	9.5	7.5	12.2	10.4	13.3	8.9	12.4	13.5	11.8	12.4	11.6	12.2
N Missing	0	3	0	4	8	17	2	1	0	0	4	39	8
%	0.0	0.6	0.0	0.8	0.6	1.1	0.7	0.2	0.0	0.0	0.9	0.7	0.5
Urbanity class (postal code 4 level)													
N Low	21	300	64	235	719	762	147	234	24	289	248	3,043	823
%	40.4	56.1	59.8	48.8	52.9	50.5	52.1	54.8	64.9	52.6	53.1	52.4	50.9
N Intermediate	24	165	29	158	481	524	100	136	9	194	162	1,982	563
%	46.2	30.8	27.1	32.8	35.4	34.7	35.5	31.9	24.3	35.3	34.7	34.1	34.8
N High	7	67	14	85	152	205	33	56	4	67	53	743	223
%	13.5	12.5	13.1	17.6	11.2	13.6	11.7	13.1	10.8	12.2	11.4	12.8	13.8
N Missing	0	3	0	4	8	18	2	1	0	0	4	40	8
%	0.0	0.6	0.0	0.8	0.6	1.2	0.7	0.2	0.0	0.0	0.9	0.7	0.5
Liveability situation (postal code 4 level)													
N Low	8	48	8	56	125	117	26	27	1	37	33	486	136
%	15.4	9.0	7.5	11.6	9.2	7.8	9.2	6.3	2.7	6.7	7.1	8.4	8.4
N Intermediate	18	227	38	186	536	605	109	199	14	230	180	2,342	657
%	34.6	42.4	35.5	38.6	39.4	40.1	38.7	46.6	37.8	41.8	38.5	40.3	40.6
N High	12	167	41	174	476	563	107	136	14	184	170	2,044	541
%	23.1	31.2	38.3	36.1	35.0	37.3	37.9	31.9	37.8	33.5	36.4	35.2	33.5
N Very high	14	84	19	63	216	217	39	62	8	95	79	896	277
%	26.9	15.7	17.8	13.1	15.9	14.4	13.8	14.5	21.6	17.3	16.9	15.4	17.1
N Missing	0	9	1	3	7	7	1	3	0	4	5	40	6
%	0.0	1.7	0.9	0.6	0.5	0.5	0.4	0.7	0.0	0.7	1.1	0.7	0.4

From the data in Table 5, it is apparent that most of the cases (70.5%) and controls (71.7%) have a low average distance from general practice. The eye anomalies group has the highest percentage in this ‘low’ category, but the difference with the genital anomalies group is small (1.9%). The anomalies of the digestive system group have, compared to the other congenital anomaly groups, the highest percentage (9.7%) in the ‘high’ category. Also for the independent variable ‘average distance (km) from hospital’ the ‘low’ category is most common among the cases (44.6%) and controls (48.0%). The limb anomalies group has the highest percentage (13.8%) in the ‘high’ category’. Most of the cases and controls have a low percentage recreational area in their postal code 4 level area. The percentages are respectively 64.8% and 62.7%. For the percentage traffic area variable, the low category is most common among both cases (58.6%) and controls (58.9%). The highest percentage of the ‘high’ category is found for the abdominal wall defects group. The characteristics of the urbanity class variable show that most cases (52.4%) and controls (50.9%) are born in a non-urban postal code 4 level area, which is the ‘low’ category. The anomalies of the respiratory tract group have the highest percentage (64.9%) in the ‘low’ category. The genital anomalies group has the highest percentage (17.6%) in the ‘high’ category, which means a (very) strong urban postal code 4 level area. For the final independent variable of the built environment, liveability situation, the intermediate category is most common for both cases and controls. The ‘intermediate’ category means that the liveability situation is amply sufficient. The percentages are almost equal, 40.3% for cases and 40.6% for controls. The low category is less common for both cases and controls. Percentages are equal (8.4%). The ‘low’ category means that the liveability situation is insufficient, weak, or sufficient.

The variables of the natural and built environment which are included in the multinomial logistic regressions will be adjusted for compositional factors. These compositional factors are maternal and infant characteristics. A table with frequencies and column percentages of the maternal and infant characteristics is shown in Appendix G.

4.2 Analyses

Since interaction between composition and context must be taken into account (Shaw et al., 2002; Duncan et al., 1998) and hypotheses must be tested, multinomial logistic regressions are performed for the natural and built environment to control the contextual factors for compositional factors. First, univariable and multivariable logistic regressions were performed to calculate the ORs. Afterward, multivariable logistic regression with adjustment of compositional factors is performed. Results of unadjusted univariable and multivariable and adjusted multivariable logistic regressions are combined into one table and presented in Appendix H (adjusted ORs also shown in Table 6 and 7). Adjusted OR are calculated separately for the natural and built environment due to collinearity between variables from the natural and built environment. There was also collinearity between variables from the natural environment and between variables of the built environment. Therefore, only a selection of variables is included (see Chapter Three for explanation). Although all variables were in the univariable logistic regression, only the selected variables for the multinomial logistic regressions are discussed. The results of the multinomial logistic regression for the natural environment are shown in Table 6. Results for the built environment are presented in Table 7. The outcome variable in the regressions are the different non-chromosomal and non-monogenic congenital anomaly groups. The chromosomal and monogenic congenital anomaly group is the control group. The regressions are adjusted for age at delivery, area level SES-score, folic acid use, level of education, maternal smoking and sex of child. Regressions are tested for IIA assumption, for both regressions it turns out that the unobserved portion of utility for one alternative is unrelated to the unobserved portion of utility of another alternative.

The results of the univariable logistic regression show significant positive associations between cases with digestive system and limb anomalies and a high percentage of agricultural land. Other significant positive associations are found between cases with genital anomalies and a high number are flower bulbs and tubers, between cases with eye and limb anomalies and a high number kg/km^2 nitrogen oxides, between genital anomalies and a low and high liveability situation and between limb anomalies and a high liveability situation. Univariable results indicate also significant negative associations. These associations are found between cases with abdominal wall defects, genital and nervous system anomalies and intermediate number are flower bulbs and tubers, between cases with heart defects and a high urbanity class, and between cases with abdominal wall defects and a high liveability situation.

When performing the multivariable logistic regression, ORs and significant associations remain more or less robust to the inclusion of other variables (separately for the natural and built environment). The association between cases with digestive system anomalies and a high percentage agricultural land is no longer significant and OR change from 1.30 to 1.26. Besides, the association between cases with genital anomalies and a high number are flower bulbs and tubers is no longer significant and OR change from 2.00 to 1.85. The OR of abdominal wall defects and a high liveability situation increases from 0.44 to 0.46 and is no longer significant. However, a new significant positive association has emerged between cases with multiple congenital anomalies and a high percentage of agricultural land.

Table 6 shows the results of the multinomial logistic regression for the natural environment predictors. After adjusting for compositional factors, the significant positive association between cases with limb and multiple anomalies remains. The odds of having limb or multiple anomalies compared to chromosomal and monogenic anomalies is 1.31 times higher when being born in an area with a high percentage of agricultural land than in an area with a low percentage of agricultural land. This result is significant at the $p < 0.01$ (limb) and $p < 0.05$ (multiple) level. For the predictor are flower bulbs and tubers, most congenital anomaly groups and intermediate numbers are flower bulbs and tubers are negatively associated. This means that the odds of having chromosomal and monogenic anomalies compared to all non-chromosomal and non-monogenic groups (except for anomalies of the respiratory and urinary tract) are higher in the intermediate category than the low category. This result is significant at the $p < 0.05$ level for abdominal wall defects, heart defects and genital, limb and nervous system anomalies and significant at the $p < 0.01$ level for anomalies of the digestive system. For the high category, the associations are the opposite. The odds of having non-chromosomal and non-monogenic anomalies (except for anomalies of the respiratory tract) compared to chromosomal and monogenic anomalies are higher in the high category than the low category. None of these results are statistically significant. The final predictor in the analysis of the natural environment is kg/km^2 nitrogen oxides. The odds of having limb and eye anomalies compared to chromosomal and monogenic anomalies are respectively 1.71 and 2.21 times higher when being born in an area with high concentrations kg/km^2 nitrogen oxides than in an area with low concentrations kg/km^2 nitrogen oxides. The results are significant at the $p < 0.001$ (limb) and $p < 0.05$ (eye) level. A new significant positive association emerged between cases with anomalies of the digestive system and intermediate concentrations of kg/km^2 nitrogen oxides (OR 1.33).

Looking at the results of the multinomial logistic regression for the built environment predictors (Table 7), there are only a few significant results for the predictor liveability situation. The odds of having genital and limb anomalies compared to chromosomal and monogenic anomalies are respectively 1.49 and 1.42 when being born in an area with a high liveability situation than in an area with a very high liveability situation. Results are significant at the $p < 0.05$ (genital) and $p < 0.01$ (limb) level. The other two significant results are negative associations between cases with abdominal wall defects and intermediate (OR 0.39) and high

(OR 0.40) liveability situations. This means that the odds in the control group compared to the abdominal wall defects are higher for these two categories of the liveability situation. For the intermediate liveability situation, the odds are 2.56 (1/0.39). For the high liveability situation, the odds are 2.50 (1/0.40). For the predictor urbanity class, most of the OR show a negative association and no significant results are found. Before adjusting for compositional factors, there was only one significant negative association between cases with heart defects and a high urbanity class (OR 0.73). After adjusting this OR increased to 0.79.

For a visualisation of the significant positive associations, reference is made to Appendix I. Seven maps are created. The maps show the distribution of categories from the physical environmental conditions in combination with congenital anomaly groups. The maps have to be interpreted carefully since congenital anomalies are displayed in absolute numbers and are not like the prevalence maps, relative. Higher numbers of congenital anomalies in a postal code 4 area or municipality do not necessarily mean that the congenital anomaly is more prevalent there since there is not corrected for the total births in the postal code 4 area or municipality.

Table 6 Estimated adjusted odds ratios from multinomial logistic regression for the natural environment, with chromosomal and monogenic congenital anomaly group as reference (adjusted for age at delivery, area level SES-score, folic acid use, level of education, maternal smoking, and sex of child)

	Abdominal wall defects	Anomalies of the digestive system	Eye anomalies	Genital anomalies	Heart defects	Limb anomalies	Anomalies of the nervous system	Oro-facial clefts	Anomalies of the respiratory tract	Anomalies of the urinary tract	Multiple congenital anomalies
N	52	535	107	482	1,360	1,509	282	427	37	550	467
Predictor											
% Agricultural land (ref. low)											
Intermediate	0.63	1.15	1.25	0.90	1.13	1.13	0.97	1.16	1.22	1.06	0.87
	(0.25)	(0.16)	(0.35)	(0.13)	(0.11)	(0.11)	(0.18)	(0.17)	(0.61)	(0.14)	(0.13)
High	0.88	1.22	1.35	0.92	1.16	**1.31****	1.17	1.13	2.11	1.11	**1.31***
	(0.29)	(0.16)	(0.35)	(0.12)	(0.11)	**(0.12)**	(0.19)	(0.16)	(0.90)	(0.14)	**(0.17)**
Missing	0.00	1.26	0.00	1.15	1.13	2.17	1.23	0.59	0.00	0.00	1.57
	(0.00)	(0.90)	(0.00)	(0.79)	(0.59)	(0.99)	(1.02)	(0.63)	(0.00)	(0.00)	(1.01)
are Flower bulbs and tubers (ref. low)											
Intermediate	**0.35***	**0.67****	0.80	**0.69***	**0.81***	**0.81***	**0.65***	0.98	1.25	1.03	0.76
	(0.17)	**(0.09)**	(0.20)	**(0.10)**	**(0.08)**	**(0.08)**	**(0.12)**	(0.13)	(0.48)	(0.13)	(0.11)
High	1.08	1.26	1.58	1.85	1.31	1.32	1.90	1.29	0.00	1.31	1.02
	(1.16)	(0.45)	(1.03)	(0.68)	(0.38)	(0.39)	0.81	(0.53)	(0.00)	(0.51)	(0.44)
kg/km2 Nitrogen oxides (ref. low)											
Intermediate	1.52	**1.33***	1.85	1.20	1.03	1.12	1.11	1.29	1.36	1.15	0.93
	(0.63)	**(0.19)**	(0.62)	(0.19)	(0.11)	(0.13)	(0.22)	(0.21)	(0.66)	(0.17)	(0.14)
High	1.16	0.99	**2.21***	1.12	0.97	**1.71*****	1.24	1.20	1.23	1.06	1.04
	(0.46)	(0.14)	**(0.69)**	(0.16)	(0.09)	**(0.17)**	(0.22)	(0.18)	(0.58)	(0.14)	(0.14)

Note: number in parentheses are standard errors. ref. = reference category.
*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

Table 7 Estimated adjusted odds ratios from multinomial logistic regression for the built environment, with chromosomal and monogenic congenital anomaly group as reference (adjusted for age at delivery, area level SES-score, folic acid use, level of education, maternal smoking, and sex of child)

	Abdominal wall defects	Anomalies of the digestive system	Eye anomalies	Genital anomalies	Heart defects	Limb anomalies	Anomalies of the nervous system	Oro-facial clefts	Anomalies of the respiratory tract	Anomalies of the urinary tract	Multiple congenital anomalies
N	52	535	107	482	1,360	1,509	282	427	37	550	467
Predictor											
Urbanity class (ref. low)											
Intermediate	1.44	0.82	0.72	0.94	0.98	1.02	1.01	0.89	0.61	0.96	0.98
	(0.46)	(0.10)	(0.17)	(0.12)	(0.08)	(0.09)	(0.15)	(0.11)	(0.25)	(0.11)	(0.12)
High	1.03	0.86	0.94	1.25	0.79	1.08	0.83	1.02	0.79	0.94	0.88
	(0.51)	(0.15)	(0.32)	(0.22)	(0.10)	(0.13)	(0.20)	(0.19)	(0.46)	(0.16)	(0.16)
Missing	0.00	1.01	0.00	1.43	1.07	2.09	1.37	0.53	0.00	0.00	1.42
	(0.00)	(0.71)	(0.00)	(0.95)	(0.55)	(0.92)	(1.11)	(0.57)	(0.00)	(0.00)	(0.90)
Liveability situation (ref. very high)											
Low	0.75	1.11	0.87	1.59	1.21	1.15	1.50	0.79	0.16	0.76	0.78
	(0.43)	(0.28)	(0.44)	(0.43)	(0.22)	(0.22)	0.50	(0.23)	(0.18)	(0.20)	(0.21)
Intermediate	**0.39***	1.00	0.77	1.22	1.00	1.28	1.12	1.17	0.52	1.00	0.88
	(0.16)	(0.17)	(0.24)	(0.23)	(0.12)	(0.16)	(0.25)	(0.21)	(0.27)	(0.16)	(0.15)
High	**0.40***	0.95	0.97	**1.49***	1.11	**1.42****	1.35	1.01	0.81	1.00	1.08
	(0.17)	(0.15)	(0.29)	**(0.27)**	(0.13)	**(0.17)**	(0.29)	(0.18)	(0.39)	(0.16)	(0.18)
Missing	0.00	2.56	1.57	3.08	1.18	1.05	0.99	2.95	0.00	1.79	4.42
	(0.00)	(1.60)	(1.97)	(2.73)	(0.73)	(0.66)	(1.16)	(2.56)	(0.00)	(1.34)	(3.37)

Note: number in parentheses are standard errors. ref. = reference category.
*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

5. Discussion

Different studies have shown that besides lifestyle factors, physical environmental factors are considered an important risk factor for human health. Most of these studies initially do not focus on the impact of the physical environment on babies, more specifically, congenital anomalies. In this study, the association between physical environmental conditions and different groups of congenital anomalies in the northern Netherlands is explored. Compared to previous research that often focuses on one congenital anomaly group, this study focuses on all available groups of congenital anomalies according to the organ system, creating a more complete picture. Hypotheses on the association between natural and built environmental conditions and congenital anomaly groups are tested. To indicate the association, multinomial logistic regressions adjusted for compositional factors (Appendix D and G) are performed for the natural and built environment.

When using chromosomal and monogenic congenital anomalies as control group, the analysis of the natural environment shows significant positive associations between a high percentage of agricultural land (ref. low) and the limb and multiple congenital anomaly groups. The detected significant associations are not in line with Hypothesis 1 and the research of Garcia et al. (2017) who found a significantly higher risk and prevalence of genitourinary anomalies in areas with higher use of pesticides compared to areas with lower use. In this research, only a small insignificant positive association (aOR 1.11; Table 6) is found between a high percentage of agricultural land (ref. low) and the anomalies of the urinary tract group. For the genital congenital anomaly group, an insignificant negative association is found. The insignificant associations are partly in line with Hypothesis 1 since the association was positive for the anomalies of the urinary tract group. Although Garcia et al. (2017) use the predictor pesticides, it is assumed there is a link between the amount of agricultural land and the amount of pesticide use. In the Netherlands, pesticides are on average used on 96.5% of the total agricultural land (CBS, 2018).

Besides agricultural land, flower bulbs and tubers are also included as a predictor for the natural environment since the largest amount of pesticides is used in the flower bulbs and tubers sector compared to the other cultivation sectors (CBS, 2018). Both predictors are measured on a different scale level. The hypothesis for this predictor is, similar to the hypothesis of agricultural land, formulated based on the results of Garcia et al. (2017). Contrary to the research of Garcia et al. (2017), this study did not find significant positive associations between the genital and urinary tract congenital anomaly groups and high numbers are flower bulbs and tubers (ref. low). However, there is find an insignificant positive association between the genital and urinary tract anomaly group (ref. chromosomal and monogenic congenital anomaly group) and a high number are flower bulbs and tubers (ref. low) (aOR respectively 1.85 and 1.31; Table 6). These insignificant positive associations are in line with Hypothesis 2. There are also found significant associations for the predictor are flower bulbs and tubers but those were significant negative associations between intermediate numbers are flower bulbs and tubers (ref. low) and abdominal wall defects, heart defects, digestive system, genital, limb, and nervous system anomalies (ref. chromosomal and monogenic congenital anomaly group). This indicates that the chromosomal and monogenic anomaly group compared to the abdominal wall defects, heart defects, digestive system, genital, limb, and nervous system anomaly groups is positively associated with intermediate number are flower bulbs and tubers (ref. low). This finding was unexpected since there is no relationship expected between environmental factors and chromosomal and monogenic congenital anomalies. However, it could be due to the scale level (municipality) that cases with chromosomal and monogenic congenital anomalies get the classification 'intermediate' while they are not living close to agricultural land with flower bulbs and tubers (and therefore have less chance of being exposed to pesticides). Based on this research, no statement can be made about the distance to agricultural land.

A possible explanation for the different outcomes of this study and that of Garcia et al. (2017) for the predictors agricultural land and are flower bulbs and tubers are the differences between the studies. Garcia et al. (2017) use only male children for the genital and urinary tract anomalies. In this research, 99.4% of the genital anomaly group is male (which is common for these anomalies). In the anomalies of the urinary tract group, 72.7% is male. This means that females are also included in analyses of this study. Besides, in this study, all major genital and urinary tract anomalies are included. Garcia et al. (2017) only focus on specific groups of genital and urinary tract anomalies (cryptorchidism, hypospadias, micropenis). Classification of agricultural areas also differs and the amount of pesticide use could not be compared since there is no information available on the amount of pesticide use at the used scale levels (postal code 4 and municipality). The last difference is the control group. Unlike the chromosomal and monogenic congenital anomaly group used in this study, Garcia et al. (2017) use children living in the same health district, not presenting the illness under study as control group.

For the predictor nitrogen oxides, it was hypothesised to find positive associations between higher concentrations nitrogen oxides and at least congenital heart defects and genital anomalies (Hypothesis 3). This hypothesis is partly supported since positive associations are found between intermediate and high concentrations of nitrogen oxides (ref. low) and genital anomalies (ref. chromosomal and monogenic congenital anomaly group). However, this result is not significant. When using the same reference groups, this study found a significant positive association between intermediate concentrations of nitrogen oxides and the anomalies of the digestive system group. Significant positive associations are also found between high concentrations of nitrogen oxides and the eye and limb anomalies groups. The highest aOR is found for the eye anomalies group (aOR 2.21; Table 6). This differs from the findings presented in Schembari et al. (2014), Davand et al. (2011) who found positive associations between nitrogen dioxides and heart defects. Nitrogen dioxides are covered by the nitrogen oxides predictor. Results of Salavati et al. (2018) also differ from this study, they found a barely insignificant positive association between nitrogen oxides and dioxides and limb anomalies and an insignificant negative result between nitrogen oxides and dioxides and eye anomalies when using a chromosomal and monogenic congenital anomaly group as reference. When using the non-chromosomal and non-monogenic groups (excluding the anomaly of interest subgroup) as control group, they found a barely significant positive association between nitrogen dioxides and genital anomalies. For nitrogen oxides, the association is almost the same but not significant. Different air pollutant assessment methods could possibly explain the inconsistent findings. Besides, the studies, except for Salavati et al. (2018), use different criteria and classification methods for congenital anomalies.

The multinomial logistic regression of the built environment contains the predictors urbanity class and liveability situation. For the predictor urbanity class, no significant associations were found. It was expected to find a positive association between urban areas and non-chromosomal and non-monogenic congenital anomaly groups instead of the chromosomal and monogenic group (Hypothesis 4). For intermediate urban areas (ref. low) most of the associations are negative, which means that the chromosomal and monogenic group compared to all non-chromosomal and non-monogenic groups (except for abdominal wall defects, limb anomalies, and anomalies of the nervous system) is positively associated with intermediate urban areas. For high urban areas (ref. low) most of the associations are also negative, which means that the chromosomal and monogenic group is compared to all non-chromosomal and non-monogenic groups (except for abdominal wall defects, genital and limb anomalies, and oro-facial clefts) is positively associated with high urban areas. These findings are unexpected since there is no relationship expected between environmental factors and chromosomal and monogenic congenital anomalies. Besides, results are not in line with a theory about contextual factors. Shaw et al. (2002) state that urbanisation contributes to ill health. Although this theory does not specifically focus on babies and foetuses, health effects are expected since the mother is in direct contact with the unborn child. It seems possible that findings are due to the high amount of low urbanity class postal code 4 areas in the northern Netherlands, which causes that more children with anomalies are born in a low urban area. This is the case for both non-chromosomal and non-monogenic groups as for the chromosomal and monogenic group (control group). Nevertheless, on average, slightly more children with chromosomal and monogenic anomalies are born in intermediate and high urban areas. Differences with the average of the non-chromosomal and non-monogenic groups are only 0.7% for the intermediate urbanity class and 1.0% for the high urbanity class (Table 5), but could have been decisive for the results found.

The second and also last predictor of the built environment is liveability situation. It was hypothesised to find a positive association between a low liveability situation and non-chromosomal and non-monogenic congenital anomaly groups instead of the chromosomal and monogenic group (Hypothesis 5). This hypothesis is supported for the anomalies of the digestive and nervous system, genital and limb anomalies and the heart defects group. For these groups (ref. chromosomal and monogenic congenital anomaly group) positive associations are found for a low liveability situation (ref. very high). However, associations are not significant. Significant positive associations are found between a high liveability situation (ref. very high) and the genital (aOR 1.49; Table 7) and limb (aOR 1.42; Table 7) anomalies group (ref. chromosomal and monogenic congenital anomaly group). Besides, when using the same reference groups, significant negative associations are found between a high and intermediate liveability situation and abdominal wall defects. This means that the chromosomal and monogenic group compared to the abdominal wall defects group is positively associated with an intermediate and high liveability situation compared to a very high liveability situation. This unexpected association occurs more often. The results, from which most not in line with Hypothesis 5 could possibly be explained by the low number of low liveability situations in the northern Netherlands. On average only 8.4% of children with non-chromosomal and non-monogenic congenital anomalies are born in a low liveability situation. This percentage is the same for the chromosomal and monogenic group. Intermediate and high liveability situations are most common in the northern Netherlands. Due to the low number of low liveability situations and the high number of intermediate and high liveability situations, the aORs for many congenital anomaly groups increases instead of decreases as the liveability situation becomes higher. Based on the theory and literature on other birth outcomes (Shaw et al., 2000; Verheij, 1996; Vettore et al., 2010; Grijbovski et al., 2004; Nowak & Giurgescu, 2017) this is not expected but the situation in the northern Netherlands appears to be different.

6. Conclusion

6.1 Strengths and limitations

The use of a big dataset from EUROCAT NNL is a strength of this research. The EUROCAT NNL database consists of high quality data and is a complete database since it registers all birth types. Important is the registration of pregnancies which are terminated for foetal anomaly (TOPFA). Most other studies only use live births but excluding TOPFA may lead to underestimation of the association between physical environmental conditions and congenital anomalies. Another strength is the use of different congenital anomaly groups which was recommended by Vrijheid et al. (2011).

Despite the strengths of this study, there are limitations to be acknowledged. First, this study was limited by the absence of a non-malformed control group in the EUROCAT NNL database. Using malformed controls may increase the chance of selection bias. A second limitation is that physical environmental conditions are averages for the period 1999-2014 since data were not available for every year from this period. However, these averages have been calculated as well as possible (see Appendix A). A third limitation is that exposure to physical environmental conditions is estimated at settlement level instead of personal level. It is possible that the mother did not stay at the settlement location during pregnancy or is exposed to the physical environmental factors. In this study, it is assumed that moving behaviour is randomly distributed between the cases and controls and that due to the large number of cases and controls, a large number of mothers did stay at the birth address during pregnancy.

6.2 Recommendations and future research

From the findings of this research, no direct policy recommendations could be made but the findings could make policymakers aware of the contribution of physical environmental conditions on congenital anomalies which might help prevent congenital anomalies in the future. To formulate clear policy recommendations, future research is needed first. Since the congenital anomaly groups classified according to organ system consists of different types of anomalies, the groups are heterogeneous. Future research should take this heterogeneity into account to find out if the physical environmental conditions are associated with one or more isolated anomalies. If clear associations are found, the evidence about the association between physical environmental conditions and congenital anomalies becomes clearer and after extensive research prevention policy could be formulated. It is also recommended that future research use natural environment data measured at a lower scale level if available because of heterogeneity within a municipality. In this study, data was collected at the lowest scale level accessible for this study but other studies may have access to other sources or collect data on a lower scale level themselves.

6.3 Conclusion

The objective of this study was to use an exploratory quantitative study design with GIS elements to explore whether there is an association between physical environmental conditions and different groups of congenital anomalies. Multinomial logistic regressions adjusted for compositional factors are performed for the natural and built environment and the prevalence of congenital anomalies is mapped. The highest prevalence of non-chromosomal and non-monogenic congenital anomalies occur in the municipality of De Marne, Winsum, Bedum, and Ten Boer. The highest prevalence of chromosomal and monogenic congenital anomalies occur in the municipality of Heerenveen, Westerveld, Menterwolde, and Zuidhorn. Prevalence in municipalities with the highest prevalence does not differ much from the prevalence in other municipalities. For the natural environment, significant positive associations are found between higher percentages of agricultural land and limb anomalies, intermediate concentrations of nitrogen oxides and anomalies of the digestive system, and between higher concentrations of nitrogen oxides and eye and limb anomalies. For the built environment, significant positive associations are found between a high liveability situation and genital and limb anomalies. All non-chromosomal and non-monogenic congenital anomaly groups are compared with the control group, chromosomal and monogenic congenital anomalies. These findings broaden the evidence about the association between physical environmental conditions and congenital anomalies and contributes to the literature in this field.

Endnotes

[1] Particulate matter with aerodynamic diameter 2.5-10 μm.

[2] Particulate matter with aerodynamic diameter ≤ 2.5 μm.

[3] Nitrogen dioxide.

[4] Congenital anomalies of the genital and urinary tract.

[5] A value is classified as missing when postal code values are missing for all used annual data layers. A value is not classified as missing when postal codes values are missing for part of the annual data layers. In that case, the values of other available years are used to calculate the average postal code value of the variable.

[6] The numerator consists of all births types, which include live birth, still birth, spontaneous abortion, and termination of pregnancy for foetal anomaly (TOPFA). The denominator consists only of live births, since the unavailability of other birth types at Statistics Netherlands (CBS, 2019[e]). However, the number of still birth and spontaneous abortion is low in the EUROCAT NNL dataset. The prevalence will not show remarkable differences when the still birth and spontaneous abortion cases are not included in the calculation. The number of cases with termination of pregnancy for foetal anomaly is higher but they were probably born alive when termination had not taken place. Therefore, these cases will be considered as live birth in the numerator. Ultimately, this results in the occurrence of 5,715 (98.4%) live births, 63 (1.1%) stillbirths, and 30 (0.5%) spontaneous abortions of a total of 5,808 births in the non-chromosomal and non-monogenic congenital anomaly groups. The chromosomal and monogenic congenital anomaly group consists of 1,491 (92.2%) live births, 67 (4.1%) stillbirths, and 59 (3.6%) spontaneous abortions of a total 1,617 births.

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Appendix A Availability of variables and used annual layers per variable

Year	**99**	**00**	**01**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**14**	**15**
Dependent variable and compositional factors																	
Source: EUROCAT NNL																	
Congenital anomaly groups	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	■
Age at delivery; area-level SES-score; folic acid use; level of education; maternal smoking; sex of child	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	■
Independent variables																	
Source: Statistics Netherlands																	
% Agricultural land[a]			x		🟦 x			x		🟦 x							■
are Flower bulbs and tubers[b]		🟩 x	▒ x	▒ x	▒ x	🟩 x	▒ x	▒ x	▒ x	▒ x	🟩 x	▒ x	▒ x	▒ x	▒ x	🟩 x	■
Average distance (km) from general practice[a]									x	🟦 x		x	x	x	x	🟩 x	■
Average distance (km) from hospital[a]									🟦 x	x	x	x	x	🟦 x			■
% Recreational area[a]			x		🟦 x			x		🟦 x							■
% Traffic area[a]			x		🟦 x			x		🟦 x							■
Urbanity **class**[a]	🟦 x		x		x	🟦 x	x	x	x	x	🟩 x	x	x	x	x	🟩 x	■
Source: Pollutant Release and Transfer Register (Government of the Netherlands)																	
kg/km^2 Nitrogen oxides[b]												🟦 x					🟦 x
kg/km^2 Particulate matter ≤ 10 µm[b]												🟦 x					🟦 x
kg/km^2 Particulate matter ≤ 2.5 µm[b]												🟦 x					🟦 x
Source: Leefbaarometer (Ministry of the Interior and Kingdom Relations)																	
Liveability **situation**[a]				🟦 x						🟦 x				x		🟩 x	■

[a] Scale level: postal code 4

[b] Scale level: municipality

Explanation

In the first instance, an interval of five years is assumed when selecting annual data layers for calculating the average values. This results in the use of four annual layers in the period of 1999-2014. It concerns the following annual layers: 1999, 2004, 2009 and 2014. However, an interval period of five years is not available for each independent variable. This results in a varied number of used annual layers per independent variable. In all cases, an attempt is made to choose an annual layer that is as close as possible to the interval period but also to use an equal number of years between the deviating intervals. Variation in used annual layers also occurs when strong fluctuations in values occur between the chosen annual layers. If possible, additional annual layers are added for the respective variable to arrive at a more accurate average. For the final selection of annual layers per independent variable, reference is made to the above table. For a clarification of the symbols used in the table, reference is made to the table below.

Clarification of symbols and colours

Dependent variable and compositional factors	
X	Data is available for this annual layer
Independent variables	
X	Data is available for this annual layer and the chosen scale level
	No data is available for this annual layers and the chosen scale level
🟩	Annual layer used for calculating average – equal to chosen interval period
🟦	Annual layer used for calculating average – deviating from chosen interval period
▒	Extra added annual layers for a more accurate calculation of the average

Appendix B Performed actions for missing or changed municipalities

Appendix B1 Independent variable: are Flower bulbs and Tubers

	Discontinued municipalities or name changes *Period 2000-2014*	**New municipality (name) and performed actions** *Period 2000-2014*
1	Boarnsterhim (disc. on 01-01-2014)	De Friese Meren: 531 hectare (3.5%) Heerenveen: 4561 hectare (30.2%) Leeuwarden: 7567 hectare (50%) Súdwest-Fryslân: 2467 hectare (16.3%) *All values 2000-2013 calculated and added**
2	Bolsward (disc. on 01-01-2011)	Súdwest-Fryslân *All values zero, no actions performed*
3	Dantumadeel	Dantumadiel *Name change, values to new name*
4	De Fryske Marren	De Friese Meren *Name change, values to new name*
5	Gaasterlân-Sleat (disc. on 01-01-2014)	De Friese Meren *All values 2000-2013 added*
6	Lemsterland (disc. on 01-01-2014)	De Friese Meren *All values 2000-2013 added*
7	Menaldumadeel	Menameradiel *Name change, values to new name*
8	Nijefurd (disc. on 01-01-2011)	Súdwest-Fryslân *All values 2000-2010 added*
9	Reinderland (disc. on 01-01-2010)	Oldambt *All values 2000-2009 added*
10	Scheemda (disc. on 01-01-2010)	Oldambt *All values 2000-2009 added*
11	Skarsterlân (disc. on 01-01-2014)	De Friese Meren *All values 2000-2013 added*
12	Sneek (disc. on 01-01-2011)	Súdwest-Fryslân *All values zero, no actions performed*
13	Winschoten (disc. on 01-01-2010)	Oldambt All values zero, no actions performed
14	Wûnseradiel (disc. on 01-01-2011)	Súdwest-Fryslân *All values 2000-2010 added*
15	Wymbritseradiel	Súdwest-Fryslân *All values zero, no actions performed*

* For each municipality, it is calculated which part of the value goes to the municipality. Values for each year in the period 2000-2013 are calculated separately, by multiplying the value of each year by the stated percentage per municipality. The result is added to the new municipality.

Appendix B2 Independent variables: kg/km^2 Nitrogen oxides; kg/km^2 Particulate matter $\leq 10\ \mu m$; kg/km^2 Particulate matter $\leq 2.5\ \mu m$

	Annual layers 2010 and 2015 **Missing municipalities:** ***Based on municipal boundaries of 2014***	**Annual layers 2010 and 2015** **Have received values from:** ***Based on municipal boundaries of 2019***
1	Bedum	Het Hogeland
2	Bellingwedde	Westerwolde
3	De Marne	Het Hogeland
4	Dongeradeel	Noardeast-Fryslân
5	Eemsmond	Het Hogeland
6	Ferwerderadiel	Noardeast-Fryslân
7	Franekeradeel	Waadhoek
8	Grootegast	Westerkwartier
9	Haren	Groningen
10	het Bildt	Waadhoeke
11	Hoogezand-Sappemeer	Midden-Groningen
12	Kollumerland en Nieuwkruisland	Noardeast-Fryslân

13	Leek	Westerkwartier
14	Leeuwarderadeel	Leeuwarden
15	Littenseradiel	Leeuwarden: 43.30 km^2 (33.1%)* Sûdwest-Fryslân: 67.38 km^2 (51.6%)* Waadhoeke: 19.99 km^2 (15.3%)*
16	Marum	Westerkwartier
17	Menameradiel	Waadhoeke
18	Menterwolde	Midden-Groningen
19	Slochteren	Midden-Groningen
20	Ten Boer	Groningen
21	Vlagtwedde	Westerwolde
22	Winsum	Het Hogeland
23	Zuidhorn	Westerkwartier

* The value kg/km^2 nitrogen oxides, particulate matter ≤ 10 µm, and particulate matter ≤ 2.5 associated with the municipality is multiplied by this percentage. This has been done for all three municipalities who receive km^2 from Littenseradiel. Results of the multiplications are added, to arrive at the value for Littenseradiel.

Appendix B3 Live births per municipality

	Discontinued municipalities or name changes ***Period 1999-2014***	**New municipality (name) and performed actions** ***Period 1999-2014***
1	Boarnsterhim (disc. on 01-01-2014)	De Friese Meren: 531 hectare (3.5%) Heerenveen: 4561 hectare (30.2%) Leeuwarden: 7567 hectare (50%) Súdwest-Fryslân: 2467 hectare (16.3%) *All values 2000-2013 calculated and added**
2	Bolsward (disc. on 01-01-2011)	Súdwest-Fryslân *All values zero, no actions performed*
3	Dantumadeel	Dantumadiel *Name change, values to new name*
4	De Fryske Marren	De Friese Meren *Name change, values to new name*
5	Gaasterlân-Sleat (disc. on 01-01-2014)	De Friese Meren *All values 2000-2013 added*
6	Lemsterland (disc. on 01-01-2014)	De Friese Meren *All values 2000-2013 added*
7	Menaldumadeel	Menameradiel *Name change, values to new name*
8	Middenveld (disc. on 01-01-2000)	Midden-Drenthe *Value of 1999 added*
9	Nijefurd (disc. on 01-01-2011)	Súdwest-Fryslân *All values 2000-2010 added*
10	Reinderland (disc. on 01-01-2010)	Oldambt *All values 2000-2009 added*
11	Scheemda (disc. on 01-01-2010)	Oldambt *All values 2000-2009 added*
12	Skarsterlân (disc. on 01-01-2014)	De Friese Meren *All values 2000-2013 added*
13	Sneek (disc. on 01-01-2011)	Súdwest-Fryslân *All values zero, no actions performed*
14	Winschoten (disc. on 01-01-2010)	Oldambt All values zero, no actions performed
15	Wûnseradiel (disc. on 01-01-2011)	Súdwest-Fryslân *All values 2000-2010 added*
16	Wymbritseradiel	Súdwest-Fryslân *All values zero, no actions performed*
17	Zuidlaren (disc. on 01-12-1999)	Tynaarlo *Value of 1999 added*

* For each municipality, it is calculated which part of the value goes to the municipality. Values for each year in the period 2000-2013 are calculated separately, by multiplying the value of each year by the stated percentage per municipality. The result is added to the new municipality.

Appendix C Independent variables

Variable	Description	Categories	Values
Natural environment			
% Agricultural land (postal code 4 level)	Percentage land in use for agriculture and horticulture, including greenhouse horticulture (CBS, 2011[a]).	Low	0 - 24
		Intermediate	25 - 59
		High	60 - 99
		Missing	-
are Flower bulbs and tubers (per municipality)	Are land with horticultural crops grown in open area (CBS, 2019[b]).	Low	0 - 3384
		Intermediate	3385 - 19457
		High	19458 – 56517
kg/km^2 Nitrogen oxides (per municipality)	Nitrogen oxides are generated during combustion processes by oxidation of nitrogen from the air (RIVM, 2018).	Low	21287 - 577054
		Intermediate	577055 - 1171320
		High	1171321 – 3738160
kg/km^2 Particulate matter ≤ 10 µm (per municipality)	Air pollution small enough to be inhaled (≤ 10 µm). Naturally generated or during combustion processes (RIVM, 2018).	Low	810 - 63784
		Intermediate	63785 - 132176
		High	132177 – 200738
kg/km^2 Particulate matter ≤ 2.5 µm (per municipality)	Air pollution small enough to be inhaled (≤ 2.5 µm). Naturally generated or during combustion processes (RIVM, 2018).	Low	710 - 40021
		Intermediate	40022 - 81926
		High	81927 - 133939
Built environment			
Average distance (km) from general practice (postal code 4 level)	Average distance in kilometres to a property or space in which one or more general practitioners work together (CBS, 2011[a]).	Low	0 - 1.8
		Intermediate	1.9 - 3.7
		High	3.8 - 9.3
		Missing	-
Average distance (km) from hospital (postal code 4 level)	Average distance in kilometres to a hospital: an institution for the examination, treatment and nursing of the patient (CBS, 2011[a]).	Low	0 - 8.1
		Intermediate	8.2 - 16.9
		High	17.0 - 55.8
		Missing	-
% Recreational area (postal code 4 level)	Percentage land in use for recreational use, including: parks and gardens, sport fields, allotment garden, day recreational area, and site recreational area (CBS, 2011[a]).	Low	0 - 6
		Intermediate	7 - 16
		High	17 - 65
		Missing	-
% Traffic area (postal code 4 level)	Percentage land in use for rail, road, and air traffic (CBS, 2011[a]).	Low	0 - 4
		Intermediate	5 - 7
		High	8 - 18
		Missing	-
Urbanity class (postal code 4 level)	The concentration of human activities based on the average environmental address density. Categories are distinguished from very strong urban to non-urban (CBS, 2019[c]).	Low	< 500[a]
		Intermediate	500 – 1500[b]
		High	1500 - ≥ 2500[c]
		Missing	-
Liveability situation (postal code 4 level)	Liveability situation in a postal code 4 level area, composed of five underlying dimensions: homes, residents, facilities, safety and physical environment (BZK, 2019[b]).	Low	Insufficient, weak, sufficient
		Intermediate	Amply sufficient
		High	Good
		Very high	Very good, excellent
		Missing	-

[a] Addresses per km^2, category non-urban (CBS, 2019[c]).

[b] Addresses per km^2, categories little urban and moderately urban (CBS, 2019[c]).

[c] Addresses per km^2, categories strong urban and very strong urban (CBS, 2019[c]).

Appendix D Compositional factors included in the analyses

Compositional factor	**Categories**
Age at delivery	15 – 19 20 – 24 25 – 29 30 – 34 35 – 39 40 – 44 > 44 Missing
Area-level SES-score[a]	Low Intermediate High Missing
Folic acid use	No use or incorrect use Used somewhere in peri conceptual period Missing
Level of education	Low Medium High Missing
Maternal smoking	No Yes Missing
Sex of child	Male Female Missing

[a] EUROCAT NNL has obtained these data from the Netherlands Institute of Social Research and not from a questionnaire like the other five compositional factors. Area level SES-score is determined at postal code 4 level and is based on income and labour market position and educational level of the residents in the area (Salavati et al., 2018).

Appendix E Associations between independent variables

Pearson chi-square test statistics for associations between independent categorical variables

	% Agricultural land[a]	are Flower bulbs and tubers	kg/km2 Nitrogen oxides	kg/km2 Particulate matter ≤10 µm	kg/km2 Particulate matter ≤2.5 µm	Average distance (km) from general practice[a]	Average distance (km) from hospital[a]	% Recreational area[a]	% Traffic area[a]	Urbanity class[a]	Liveability situation[a]
% Agricultural land[a]	1.000										
are Flower bulbs and tubers	370.5696 (4) 0.000***	1.000									
kg/km2 Nitrogen oxides	269.5301 (4) 0.000***	576.4185 (4) 0.000***	1.000								
kg/km2 Particulate matter ≤10 µm	462.0258 (4) 0.000***	801.0026 (4) 0.000***	7100.00 (4) 0.000***	1.000							
kg/km2 Particulate matter ≤2.5 µm	925.0446 (4) 0.000***	593.3478 (4) 0.000***	7900.00 (4) 0.000***	8800.00 (4) 0.000***	1.000						
Average distance (km) from general practice[a]	1900.00 (4) 0.000***	440.2687 (4) 0.000***	144.3468 (4) 0.000***	33.6033 (4) 0.000***	110.1420 (4) 0.000***	1.000					
Average distance (km) from hospital[a]	2400.00 (4) 0.000***	369.3140 (4) 0.000***	189.1316 (4) 0.000***	315.6323 (4) 0.000***	1100.00 (4) 0.000***	645.1751 (4) 0.000***	1.000				
% Recreational area[a]	3200.00 (4) 0.000***	97.0883 (4) 0.000***	239.6629 (4) 0.000***	187.5585 (4) 0.000***	538.5862 (4) 0.000***	741.8636 (4) 0.000***	935.5828 (4) 0.000***	1.000			
% Traffic area[a]	1000.00 (4) 0.000***	122.4898 (4) 0.000***	242.0533 (4) 0.000***	332.4387 (4) 0.000***	460.0096 (4) 0.000***	85.2538 (4) 0.000***	561.5646 (4) 0.000***	758.7005 (4) 0.000***	1.000		
Urbanity class[a]	5400.00 (4) 0.000***	300.6095 (4) 0.000***	526.9598 (4) 0.000***	729.2482 (4) 0.000***	1300.00 (4) 0.000***	1500.00 (4) 0.000***	2900.00 (4) 0.000***	2700.00 (4) 0.000***	1100.00 (4) 0.000***	1.000	
Liveability situation[a]	1200.00 (4) 0.000***	306.4827 (6) 0.000***	466.2417 (6) 0.000***	539.7808 (6) 0.000***	654.4087 (6) 0.000***	464.8191 (6) 0.000***	915.6278 (4) 0.000***	910.8982 (6) 0.000***	118.5778 (6) 0.000***	587.7960 (6) 0.000***	1.000

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

[a] Category ‘missing’ is deleted for this variable

Appendix F Associations between independent variables and congenital anomaly groups

To indicate the association between the independent variables and the (non)-chromosomal and (non)-monogenic congenital anomaly groups, Pearson's Chi-square test was used. The results of the Chi-square test are presented below. The Chi-square test shows a significant association between the variables are flower bulbs and tubers, kg/km^2 nitrogen oxides, kg/km^2 particulate matter ≤10 µm, kg/km^2 particulate matter ≤2.5 µm, average distance (km) from general practice, average distance (km) from hospital, liveability situation, and the congenital anomaly groups. No significant association was found between the variables % agricultural land, % recreational area, % traffic area, urbanity class, and the congenital anomaly groups.

	Pearson Chi-squared test		
Independent variables	value	df	p-value
% Agricultural land (postal code 4 level)[a]	31.9218	22	0.079
are Flower bulbs and tubers (per municipality)[b]	32.9500	20	0.034*
kg/km2 Nitrogen oxides (per municipality)	102.5081	22	0.000***
kg/km2 Particulate matter ≤10 µm (per municipality)	35.3316	22	0.036*
kg/km2 Particulate matter ≤2.5 µm (per municipality)	52.1904	22	0.000***
Average distance (km) from general practice (postal code 4 level)[a]	34.0902	22	0.048*
Average distance (km) from hospital (postal code 4 level)[a]	57.1400	22	0.000***
% Recreational area (postal code 4 level)[a,b]	29.8631	20	0.072
% Traffic area (postal code 4 level)[a]	23.8484	22	0.355
Urbanity class (postal code 4 level)[a]	31.5098	22	0.086
Liveability situation (postal code 4 level)[a]	49.2461	33	0.034*

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

[a] Category 'missing' is deleted for this variable

[b] The anomalies of the respiratory tract group is not included in the Pearson Chi-squared test for this variable because of the occurrence of 0 values in cells.

Appendix G Maternal and infant characteristics (compositional factors)

Maternal and infant characteristics of congenital anomaly groups and control group

	Cases												**Control group**
	Abdominal wall defects	Anomalies of the digestive system	Eye anomalies	Genital anomalies	Heart defects	Limb anomalies	Anomalies of the nervous system	Oro-facial clefts	Anomalies of the respiratory tract	Anomalies of the urinary tract	Multiple congenital anomalies	Total	Chromosomal and monogenic anomalies
N	52	535	107	482	1360	1509	282	427	37	550	467	5808	1617
%	0.9	9.2	1.8	8.3	23.4	26.0	4.9	7.4	0.6	9.5	8.0	100.0	100.0
Age at delivery													
N 15 - 19	3	1	0	5	12	12	2	5	1	9	8	58	14
%	5.8	0.2	0.0	1.0	0.9	0.8	0.7	1.2	2.7	1.6	1.7	1.0	0.9
N 20 - 24	5	56	2	48	146	141	28	34	4	51	48	563	102
%	9.6	10.5	1.9	10.0	10.7	9.3	9.9	8.0	10.8	9.3	10.3	9.7	6.3
N 25 - 29	10	196	36	149	402	469	107	136	12	157	135	1,809	396
%	19.2	36.6	33.6	30.9	29.6	31.1	37.9	31.9	32.4	28.6	28.9	31.2	24.5
N 30 - 34	21	176	52	181	513	602	95	168	11	219	182	2,220	539
%	40.4	32.9	48.6	37.6	37.7	39.9	33.7	39.3	29.7	39.8	39.0	38.2	33.3
N 35 - 39	13	85	14	72	234	225	40	70	8	99	80	940	406
%	25.0	15.9	13.1	14.9	17.2	14.9	14.2	16.4	21.6	18.0	17.1	16.2	25.1
N 40 - 44	0	14	3	10	37	29	10	7	1	13	11	135	141
%	0.0	2.6	2.8	2.1	2.7	1.9	3.6	1.6	2.7	2.4	2.4	2.3	8.7
N > 44	0	1	0	0	3	1	0	0	0	0	1	6	10
%	0.0	0.2	0.0	0.0	0.2	0.1	0.0	0.0	0.0	0.0	0.2	0.1	0.6
N Missing	0	6	0	17	13	30	0	7	0	2	2	77	9
%	0.0	1.1	0.0	3.5	1.0	2.0	0.0	1.6	0.0	0.4	0.4	1.3	0.6
Area-level SES-score													
N Low	16	146	26	143	356	376	68	111	12	140	120	1,514	418
%	30.8	27.3	24.3	29.7	26.2	24.9	24.1	26.0	32.4	25.5	25.7	26.1	25.9
N Intermediate	33	350	75	307	910	1,002	194	297	22	367	313	3,870	1097
%	63.5	65.4	70.1	63.7	66.9	66.4	68.8	69.6	59.5	66.7	67.0	66.6	67.8
N High	3	13	2	24	56	85	12	11	2	28	23	259	66
%	5.8	2.4	1.9	5.0	4.1	5.6	4.3	2.6	5.4	5.1	4.9	4.5	4.1
N Missing	0	26	4	8	38	46	8	8	1	15	11	165	36
%	0.0	4.9	3.7	1.7	2.8	3.1	2.8	1.9	2.7	2.7	2.4	2.8	2.2

Table Appendix G continued

	Cases												**Control Group**
	Abdominal wall defects	Anomalies of the digestive system	Eye anomalies	Genital anomalies	Heart defects	Limb anomalies	Anomalies of the nervous system	Oro-facial clefts	Anomalies of the respiratory tract	Anomalies of the urinary tract	Multiple congenital anomalies	Total	Chromosomal and monogenic anomalies
Folic acid use													
N No use	4	75	21	72	227	205	55	75	4	87	76	901	266
%	7.7	14.0	19.6	14.9	16.7	13.6	19.5	17.6	10.8	15.8	16.3	15.5	16.5
N Use	34	331	65	313	835	937	175	297	26	327	313	3,653	994
%	65.4	61.9	60.8	64.9	61.4	62.1	62.1	69.6	70.3	59.5	67.0	62.9	61.5
N Missing	14	129	21	97	298	367	52	55	7	136	78	1,254	357
%	26.9	24.1	19.6	20.1	21.9	24.3	18.4	12.9	18.9	24.7	16.7	21.6	22.1
Level of education													
N Low	6	81	17	51	165	124	35	64	8	55	72	678	192
%	11.5	15.1	15.9	10.6	12.1	8.2	12.4	15.0	21.6	10.0	15.4	11.7	11.9
N Medium	24	208	36	184	546	606	111	187	13	214	173	2,302	605
%	46.2	38.9	33.6	38.2	40.2	40.2	39.4	43.8	35.1	38.9	37.0	39.6	37.4
N High	10	136	36	149	398	470	79	112	10	170	145	1,715	508
%	19.2	25.4	33.6	30.9	29.3	31.2	28.0	26.2	27.0	30.9	31.1	29.5	31.4
N Missing	12	110	18	98	251	309	57	64	6	111	77	1,113	312
%	23.1	20.6	16.8	20.3	18.5	20.5	20.2	15.0	16.2	20.2	16.5	19.2	19.3
Maternal smoking													
N No	27	336	70	318	894	970	193	282	23	366	317	3,796	1107
%	51.9	62.8	65.4	66.0	65.7	64.3	68.4	66.0	62.2	66.6	67.9	65.4	68.5
N Yes	20	105	20	82	265	273	55	94	9	99	101	1,123	274
%	38.5	19.6	18.7	17.0	19.5	18.1	19.5	22.0	24.3	18.0	21.6	19.3	16.9
N Missing	5	94	17	82	201	266	34	51	5	85	49	889	236
%	9.6	17.6	15.9	17.0	14.8	17.6	12.1	11.9	13.5	15.5	10.5	15.3	14.6
Sex of child													
N Male	29	396	63	479	717	477	133	257	21	400	240	3,212	802
%	55.8	74.0	58.9	99.4	52.7	31.6	47.2	60.2	56.8	72.7	51.4	55.3	49.6
N Female	23	139	44	3	643	1,032	140	170	16	150	227	2,587	815
%	44.2	26.0	41.1	0.6	47.3	68.4	49.7	39.8	43.2	27.3	48.6	44.5	50.4
N Missing	0	0	0	0	0	0	9	0	0	0	0	9	0
%	0.0	0.0	0.0	0.0	0.0	0.0	3.2	0.0	0.0	0.0	0.0	0.2	0.0

It can be seen from the data in the table that most of the mothers of the cases and controls were 30 – 34 years old at the time of delivery. The percentages are respectively 38.2% and 33.3%. For the control group, a higher percentage of mothers is older than 40 years at the time of delivery. The intermediate area-level SES-score is most common among both the case group (66.6%) and the control group (67.8%). The lowest area-level SES-score is most common among the anomalies of the respiratory tract group, the highest area-level SES-score among the abdominal wall defects group. Most of the mothers used folic acid somewhere in the peri conceptional period (62.9%) cases, (61.5%) controls. The group of eye anomalies has the highest percentage of no use or incorrect use of folic acid use (19.6%). A medium level of education is most common for both cases (39.6%) and controls (37.4%). The anomalies of the respiratory tract group have the highest percentage of low educated mothers. The abdominal wall defects group has the highest percentage of mothers who smoked during pregnancy (38.5%). The anomalies of the nervous system group have the highest percentage of mothers who did not smoke during pregnancy (68.4%), but differences between all congenital anomaly groups are small. From the cases, 3212 (55.3%) of the babies and foetuses are male, 2587 (44.5%) are female. From the control group, 802 (49.6%) of the babies and foetuses are male, 815 (50.4%) are female. Most of the genital anomalies group are male (99.4%), most of the limb anomalies group are female (68.4%).

Appendix H Results of unadjusted univariable and multivariable and adjusted multivariable logistic regressions

Results for the natural environment (% Agricultural land, are Flower bulbs and tubers and kg/km^2 Nitrogen oxides included in multivariable analysis)

		Abdominal wall defects	Anomalies of the digestive system	Eye anomalies	Genital anomalies	Heart defects	Limb anomalies	Anomalies of the nervous system	Oro-facial clefts	Anomalies of the respiratory tract	Anomalies of the urinary tract	Multiple congenital anomalies
N		52	535	107	482	1,360	1,509	282	427	37	550	467
Predictor												
% Agricultural land (ref. low)												
Intermediate	OR univ.	0.54	1.12	1.16	0.86	1.13	1.00	0.92	1.20	1.23	1.12	0.85
		(0.21)	(0.15)	(0.31)	(0.11)	(0.11)	(0.09)	(0.16)	(0.17)	(0.59)	(0.14)	(0.12)
	OR multiv.	0.63	1.15	1.31	0.90	1.15	1.14	1.01	1.19	1.18	1.10	0.89
		(0.25)	(0.16)	(0.36)	(0.12)	(0.11)	(0.11)	(0.18)	(0.17)	(0.58)	(0.14)	(0.13)
	aOR multiv.	0.63	1.15	1.25	0.90	1.13	1.13	0.97	1.16	1.22	1.06	0.87
		(0.25)	(0.16)	(0.35)	(0.13)	(0.11)	(0.11)	(0.18)	(0.17)	(0.61)	(0.14)	(0.13)
High	OR univ.	0.77	**1.30***	1.41	0.89	1.18	**1.20***	1.18	1.19	1.96	1.15	1.26
		(0.24)	**(0.15)**	(0.34)	(0.11)	(0.10)	**(0.10)**	(0.18)	(0.16)	(0.80)	(0.13)	(0.15)
	OR multiv.	0.80	1.26	1.47	0.88	1.17	**1.31****	1.21	1.16	1.94	1.12	**1.31***
		(0.26)	(0.15)	(0.36)	(0.11)	(0.10)	**(0.11)**	(0.19)	(0.16)	(0.81)	(0.13)	**(0.16)**
	aOR multiv.	0.88	1.22	1.35	0.92	1.16	**1.31****	1.17	1.13	2.11	1.11	**1.31***
		(0.29)	(0.16)	(0.35)	(0.12)	(0.11)	**(0.12)**	(0.19)	(0.16)	(0.90)	(0.14)	**(0.17)**
Missing	OR univ.	0.00	1.30	0.00	1.55	1.31	**2.46***	1.50	0.53	0.00	0.00	1.83
		(0.00)	(0.89)	(0.00)	(0.96)	(0.66)	**(1.07)**	(1.20)	(0.57)	(0.00)	(0.00)	(1.13)
	OR multiv.	0.00	1.18	0.00	1.28	1.21	**2.48***	1.27	0.51	0.00	0.00	1.81
		(0.00)	(0.82)	(0.00)	(0.81)	(0.62)	**(1.09)**	(1.03)	(0.54)	(0.00)	(0.00)	(1.13)
	aOR multiv.	0.00	1.26	0.00	1.15	1.13	2.17	1.23	0.59	0.00	0.00	1.57
		(0.00)	(0.90)	(0.00)	(0.79)	(0.59)	(0.99)	(1.02)	(0.63)	(0.00)	(0.00)	(1.01)

are Flower bulbs and tubers (ref. low)												
Intermediate	OR univ.	**0.37***	**0.77***	0.97	**0.73***	0.87	0.88	**0.69***	1.11	1.44	1.10	0.77
		(0.18)	**(0.10)**	(0.24)	**(0.10)**	(0.08)	(0.08)	**(0.12)**	(0.14)	(0.52)	(0.13)	(0.10)
	OR multiv.	**0.38***	**0.71***	0.85	**0.73***	0.84	0.84	**0.67***	1.03	1.33	1.05	0.79
		(0.18)	**(0.09)**	(0.21)	**(0.10)**	(0.08)	(0.08)	**(0.12)**	(0.14)	(0.50)	(0.13)	(0.11)
	aOR multiv.	**0.35***	**0.67****	0.80	**0.69***	**0.81***	**0.81***	**0.65***	0.98	1.25	1.03	0.76
		(0.17)	**(0.09)**	(0.20)	**(0.10)**	**(0.08)**	**(0.08)**	**(0.12)**	(0.13)	(0.48)	(0.13)	(0.11)
High	OR univ.	1.12	1.69	1.90	**2.00***	1.45	1.27	2.03	1.47	0.00	1.39	1.10
		(1.15)	(0.58)	(1.18)	**(0.67)**	(0.40)	(0.35)	(0.81)	(0.58)	(0.00)	(0.51)	(0.45)
	OR multiv.	1.05	1.23	1.67	1.85	1.30	1.33	1.89	1.27	0.00	1.30	1.01
		(1.11)	(0.44)	(1.08)	(0.65)	(0.37)	(0.39)	(0.79)	(0.52)	(0.00)	(0.49)	(0.43)
	aOR multiv.	1.08	1.26	1.58	1.85	1.31	1.32	1.90	1.29	0.00	1.31	1.02
		(1.16)	(0.45)	(1.03)	(0.68)	(0.38)	(0.39)	0.81	(0.53)	(0.00)	(0.51)	(0.44)
kg/km2 Nitrogen oxides (ref. low)												
Intermediate	OR univ.	1.34	1.25	1.86	1.18	1.02	1.12	1.10	1.30	1.38	1.19	0.92
		(0.54)	(0.17)	(0.60)	(0.17)	(0.10)	(0.12)	(0.20)	(0.20)	(0.66)	(0.16)	(0.13)
	OR multiv.	1.51	1.31	1.84	1.20	1.03	1.13	1.11	1.28	1.32	1.15	0.93
		(0.62)	(0.18)	(0.61)	(0.18)	(0.11)	(0.12)	(0.21)	(0.20)	(0.64)	(0.16)	(0.14)
	aOR multiv.	1.52	**1.33***	1.85	1.20	1.03	1.12	1.11	1.29	1.36	1.15	0.93
		(0.63)	**(0.19)**	(0.62)	(0.19)	(0.11)	(0.13)	(0.22)	(0.21)	(0.66)	(0.17)	(0.14)
High	OR univ.	1.16	0.86	**2.01***	1.04	0.91	**1.68*****	1.15	1.10	1.18	1.04	1.00
		(0.44)	(0.11)	**(0.61)**	(0.14)	(0.09)	**(0.16)**	(0.19)	(0.16)	(0.53)	(0.13)	(0.13)
	OR multiv.	1.18	0.92	**2.14***	1.06	0.95	**1.76*****	1.21	1.13	1.17	1.05	1.02
		(0.46)	(0.12)	**(0.66)**	(0.15)	(0.09)	**(0.17)**	(0.21)	(0.17)	(0.54)	(0.14)	(0.14)
	aOR multiv.	1.16	0.99	**2.21***	1.12	0.97	**1.71*****	1.24	1.20	1.23	1.06	1.04
		(0.46)	(0.14)	**(0.69)**	(0.16)	(0.09)	**(0.17)**	(0.22)	(0.18)	(0.58)	(0.14)	(0.14)

kg/km2 Particulate matter ≤10 µm (ref. low)												
Intermediate	OR univ.	0.80	0.99	1.51	1.02	0.87	1.13	1.13	1.09	2.10	1.15	0.83
		(0.32)	(0.13)	(0.47)	(0.15)	(0.09)	(0.11)	(0.21)	(0.16)	(1.07)	(0.16)	(0.12)
High	OR univ.	1.15	0.87	1.72	1.05	0.87	**1.30****	1.37	1.04	1.32	1.12	0.94
		(0.42)	(0.12)	(0.52)	(0.15)	(0.08)	**(0.13)**	(0.25)	(0.15)	(0.70)	(0.15)	(0.13)
kg/km2 Particulate matter ≤2.5 µm (ref. low)												
Intermediate	OR univ.	1.01	0.90	**2.07****	1.09	0.95	**1.38*****	1.11	1.16	1.54	1.01	0.89
		(0.38)	(0.11)	**(0.57)**	(0.14)	(0.08)	**(0.12)**	(0.18)	(0.16)	(0.64)	(0.12)	(0.11)
High	OR univ.	1.56	**0.78***	**1.80***	1.11	0.85	**1.38*****	1.22	1.08	1.03	1.04	1.01
		(0.56)	**(0.10)**	**(0.52)**	(0.15)	(0.08)	**(0.13)**	(0.20)	(0.15)	(0.48)	(0.13)	(0.13)

Note: number in parentheses are standard errors. ref. = reference category.
*** p < 0.001; ** p < 0.01; * p < 0.05

Results for the built environment (urbanity class and liveability situation included in multivariable analysis)

		Abdominal wall defects	Anomalies of the digestive system	Eye anomalies	Genital anomalies	Heart defects	Limb anomalies	Anomalies of the nervous system	Oro-facial clefts	Anomalies of the respiratory tract	Anomalies of the urinary tract	Multiple congenital anomalies
N		52	535	107	482	1,360	1,509	282	427	37	550	467
Predictor												
Average distance (km) from general practice (ref. low)												
Intermediate	OR univ.	1.31	1.17	0.78	0.91	1.05	0.94	1.01	0.95	1.99	1.25	1.03
		(0.42)	(0.14)	(0.20)	(0.12)	(0.09)	(0.08)	(0.16)	(0.13)	(0.71)	(0.15)	(0.13)
High	OR univ.	0.61	**1.61****	0.81	0.64	1.07	1.27	0.93	1.27	1.00	0.97	1.25
		(0.45)	**(0.29)**	(0.35)	(0.16)	(0.16)	(0.18)	(0.25)	(0.26)	(0.75)	(0.20)	(0.25)
Missing	OR univ.	0.00	1.22	0.00	1.61	1.21	**2.44***	1.43	0.48	0.00	0.00	1.78
		(0.00)	(0.83)	(0.00)	(0.99)	(0.61)	**(1.04)**	(1.14)	(0.50)	(0.00)	(0.00)	(1.09)
Average distance (km) from hospital (ref. low)												
Intermediate	OR univ.	0.63	**1.26***	1.07	0.91	**1.18***	**1.38*****	0.95	1.18	1.35	1.07	1.05
		(0.19)	**(0.13)**	(0.23)	(0.10)	**(0.09)**	**(0.11)**	(0.13)	(0.14)	(0.48)	(0.11)	(0.12)

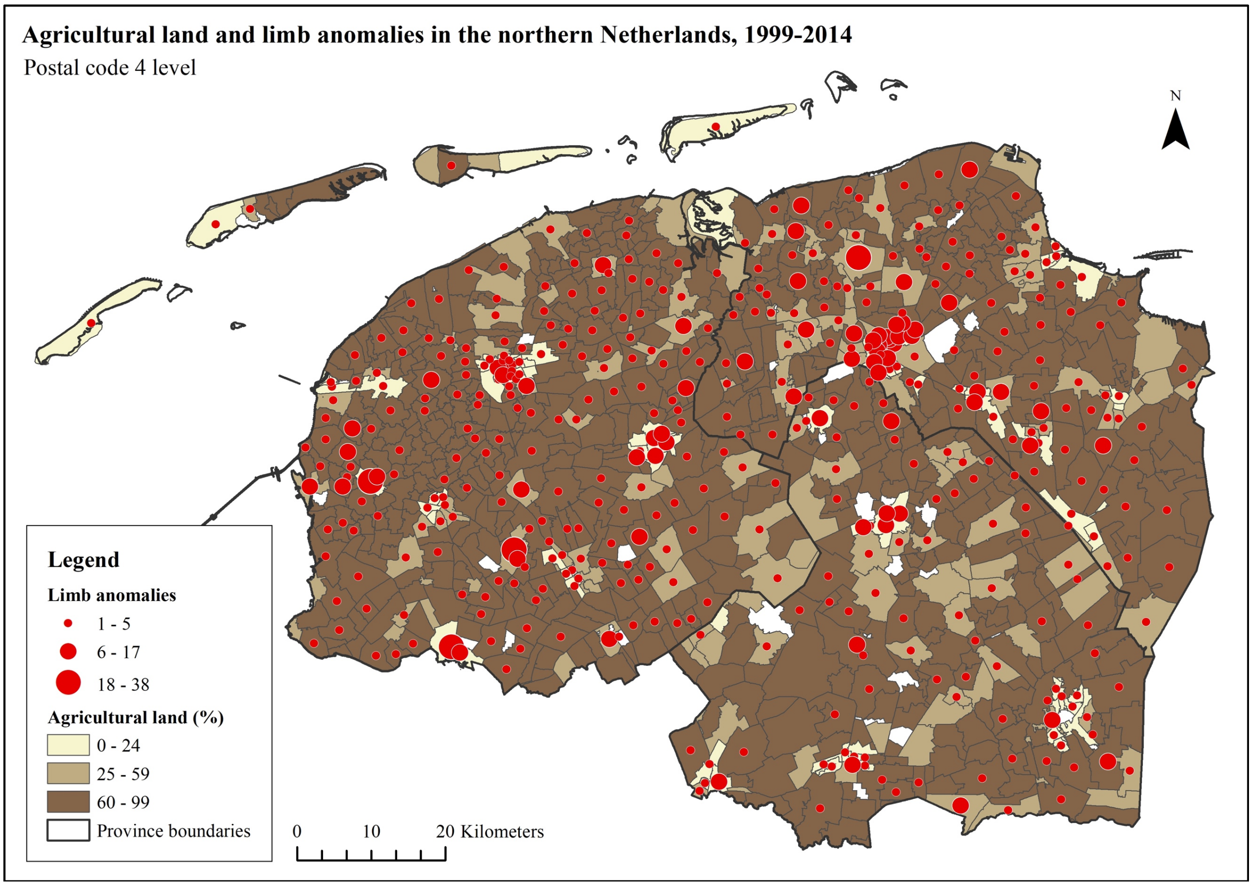
High	OR univ.	0.40	0.98	1.23	0.83	0.84	**1.51*****	0.76	1.09	1.44	1.12	1.10
		(0.25)	(0.17)	(0.39)	(0.15)	(0.11)	**(0.17)**	(0.18)	(0.20)	(0.75)	(0.18)	(0.19
Missing	OR univ.	0.00	0.67	0.00	1.27	1.00	**2.22***	1.09	0.41	0.00	0.00	1.80
		(0.00)	(0.52)	(0.00)	(0.76)	(0.48)	**(0.89)**	(0.85)	(0.43)	(0.00)	(0.00)	(0.99)
% Recreational area (ref. low)												
Intermediate	OR univ.	1.13	**0.72****	0.70	0.92	0.86	1.02	1.00	0.97	0.99	1.05	0.87
		(0.37)	**(0.09)**	(0.18)	(0.11)	(0.07)	(0.08)	(0.15)	(0.12)	(0.36)	(0.12)	(0.11)
High	OR univ.	1.93	0.71	1.42	0.97	0.93	0.79	0.91	0.81	0.00	0.86	0.85
		(0.75)	(0.13)	(0.41)	(0.17)	(0.12)	(0.10)	(0.21)	(0.16)	(0.00)	(0.15)	(0.16)
Missing	OR univ.	0.00	1.02	0.00	1.64	1.14	2.26	1.42	0.46	0.00	0.00	1.65
		(0.00)	(0.69)	(0.00)	(1.01)	(0.57)	(0.97)	1.13)	(0.49)	(0.00)	(0.00)	(1.02)
% Traffic area (ref. low)												
Intermediate	OR univ.	1.64	0.90	1.04	0.99	1.05	1.05	1.25	0.97	0.94	0.96	1.10
		(0.51)	(0.10)	(0.23)	(0.12)	(0.09)	(0.09)	(0.18)	(0.12)	(0.36)	(0.11)	(0.13)
High	OR univ.	1.80	0.73	0.58	1.00	0.84	1.13	0.76	1.00	1.09	0.94	1.05
		(0.72)	(0.12)	(0.22)	(0.16)	(0.10)	(0.12)	(0.17)	(0.17)	(0.55)	(0.15)	(0.17)
Missing	OR univ.	0.00	1.07	0.00	1.68	1.19	**2.36***	1.50	0.47	0.00	0.00	1.80
		(0.00)	(0.72)	(0.00)	(1.03)	(0.60)	**(1.02)**	(1.19)	(0.50)	(0.00)	(0.00)	(1.11)
Urbanity class (ref. low)												
Intermediate	OR univ.	1.67	0.80	0.66	0.98	0.98	1.01	0.99	0.85	0.55	0.98	0.95
		(0.51)	(0.09)	(0.15)	(0.11)	(0.08)	(0.08)	(0.14)	(0.10)	(0.22)	(0.11)	(0.11)
	OR multiv.	1.48	0.80	0.68	0.98	0.97	1.03	1.00	0.86	0.58	1.00	0.99
		(0.46)	(0.09)	(0.16)	(0.12)	(0.08)	(0.08)	(0.14)	(0.11)	(0.23)	(0.11)	(0.12)
	aOR multiv.	1.44	0.82	0.72	0.94	0.98	1.02	1.01	0.89	0.61	0.96	0.98
		(0.46)	(0.10)	(0.17)	(0.12)	(0.08)	(0.09)	(0.15)	(0.11)	(0.25)	(0.11)	(0.12)
High	OR univ.	1.23	0.82	0.81	1.33	**0.78***	0.99	0.83	0.88	0.62	0.86	0.79
		(0.54)	(0.13)	(0.25)	(0.20)	**(0.09)**	(0.11)	(0.17)	(0.15)	(0.34)	(0.13)	(0.13)
	OR multiv.	1.00	0.77	0.85	1.23	**0.73***	1.02	0.78	0.91	0.79	0.91	0.83
		(0.48)	(0.13)	(0.28)	(0.20)	**(0.09)**	(0.12)	(0.17)	(0.16)	(0.45)	(0.15)	(0.15)

	aOR multiv.	1.03 (0.51)	0.86 (0.15)	0.94 (0.32)	1.25 (0.22)	0.79 (0.10)	1.08 (0.13)	0.83 (0.20)	1.02 (0.19)	0.79 (0.46)	0.94 (0.16)	0.88 (0.16)
Missing	OR univ.	0.00 (0.00)	1.03 (0.70)	0.00 (0.00)	1.75 (1.08)	1.14 (0.58)	**2.43*** **(1.04)**	1.40 (1.11)	0.44 (0.47)	0.00 (0.00)	0.00 (0.00)	1.66 (1.02)
	OR multiv.	0.00 (0.00)	0.97 (0.67)	0.00 (0.00)	1.80 (1.12)	1.15 (0.58)	**2.56*** **(1.10)**	1.48 (1.18)	0.48 (0.51)	0.00 (0.00)	0.00 (0.00)	1.56 (0.97)
	aOR multiv.	0.00 (0.00)	1.01 (0.71)	0.00 (0.00)	1.43 (0.95)	1.07 (0.55)	2.09 (0.92)	1.37 (1.11)	0.53 (0.57)	0.00 (0.00)	0.00 (0.00)	1.42 (0.90)
Liveability situation (ref. very high)												
Low	OR univ.	1.16 (0.53)	1.16 (0.24)	0.86 (0.37)	**1.81**** **(0.38)**	1.18 (0.18)	1.10 (0.17)	1.36 (0.37)	0.89 (0.22)	0.25 (0.27)	0.79 (0.17)	0.85 (0.20)
	OR multiv.	1.14 (0.56)	1.32 (0.29)	0.93 (0.43)	**1.66*** **(0.37)**	1.35 (0.22)	1.11 (0.18)	1.52 (0.44)	0.92 (0.25)	0.29 (0.32)	0.82 (0.19)	0.93 (0.23)
	aOR multiv.	0.75 (0.43)	1.11 (0.28)	0.87 (0.44)	1.59 (0.43)	1.21 (0.22)	1.15 (0.22)	1.50 0.50	0.79 (0.23)	0.16 (0.18)	0.76 (0.20)	0.78 (0.21)
Intermediate	OR univ.	0.54 (0.20)	1.14 (0.17)	0.84 (0.24)	1.24 (0.20)	1.05 (0.11)	1.18 (0.13)	1.18 (0.24)	1.35 (0.22)	0.74 (0.33)	1.02 (0.14)	0.96 (0.15)
	OR multiv.	0.54 (0.20)	1.16 (0.17)	0.84 (0.24)	1.23 (0.20)	1.08 (0.12)	1.20 (0.13)	1.21 (0.24)	1.35 (0.22)	0.73 (0.33)	1.01 (0.14)	0.98 (0.15)
	aOR multiv.	**0.39*** **(0.16)**	1.00 (0.17)	0.77 (0.24)	1.22 (0.23)	1.00 (0.12)	1.28 (0.16)	1.12 (0.25)	1.17 (0.21)	0.52 (0.27)	1.00 (0.16)	0.88 (0.15)
High	OR univ.	**0.44*** **(0.18)**	1.02 (0.16)	1.10 (0.32)	**1.41*** **(0.23)**	1.13 (0.12)	**1.33**** **(0.14)**	1.40 (0.28)	1.12 (0.19)	0.90 (0.40)	0.99 (0.15)	1.10 (0.17)
	OR multiv.	0.46 (0.18)	1.00 (0.15)	1.05 (0.30)	**1.41*** **(0.23)**	1.14 (0.13)	**1.35**** **(0.15)**	1.42 (0.29)	1.10 (0.19)	0.84 (0.38)	0.99 (0.15)	1.11 (0.17)
	aOR multiv.	**0.40*** **(0.17)**	0.95 (0.15)	0.97 (0.29)	**1.49*** **(0.27)**	1.11 (0.13)	**1.42**** **(0.17)**	1.35 (0.29)	1.01 (0.18)	0.81 (0.39)	1.00 (0.16)	1.08 (0.18)
Missing	OR univ.	0.00 (0.01)	**4.95**** **(2.68)**	2.43 (2.69)	2.20 (1.59)	1.50 (0.84)	1.49 (0.84)	1.18 (1.29)	2.24 (1.61)	0.00 (0.01)	1.94 (1.28)	2.92 (1.81)

OR multiv.	0.00	**4.49****	2.19	2.14	1.45	1.42	1.15	2.14	0.00	2.02	2.82
	(0.00)	**(2.44)**	(2.43)	(1.55)	(0.82)	(0.81)	(1.26)	(1.55)	(0.00)	(1.33)	(1.76)
aOR multiv.	0.00	2.56	1.57	3.08	1.18	1.05	0.99	2.95	0.00	1.79	4.42
	(0.00)	(1.60)	(1.97)	(2.73)	(0.73)	(0.66)	(1.16)	(2.56)	(0.00)	(1.34)	(3.37)

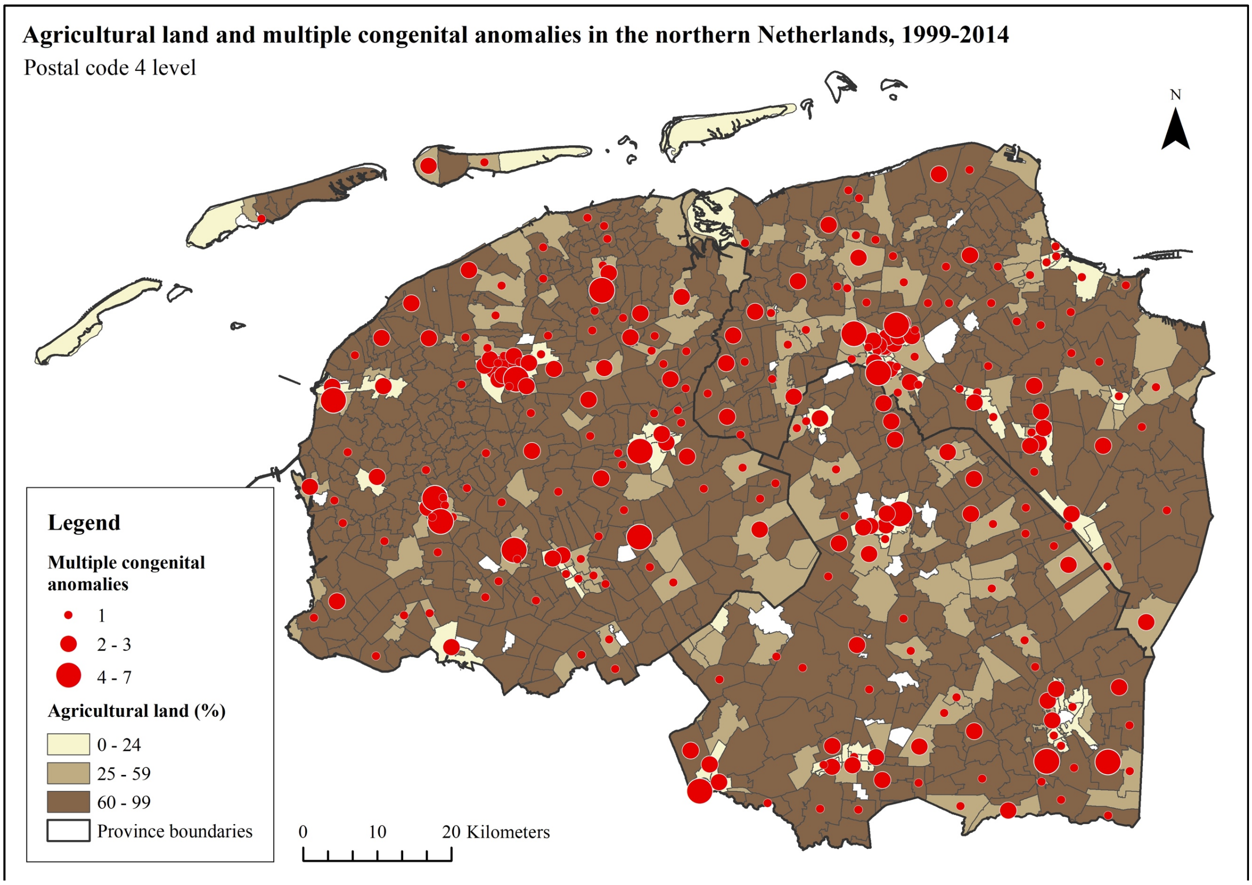
Note: number in parentheses are standard errors. ref. = reference category.
*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

Appendix I Maps for congenital anomalies with significant positive associations



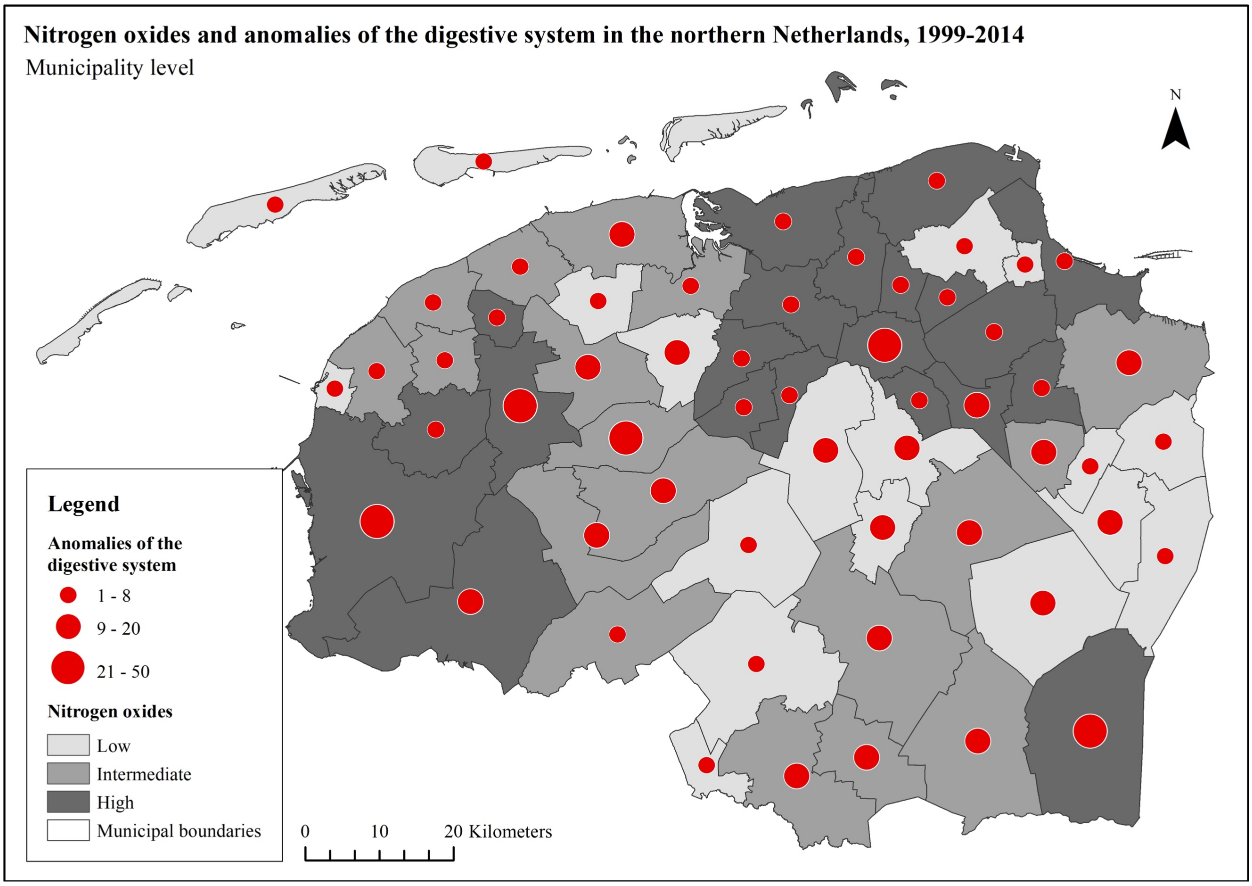
Agricultural land and limb anomalies in the northern Netherlands, 1999-2014

Postal code 4 level



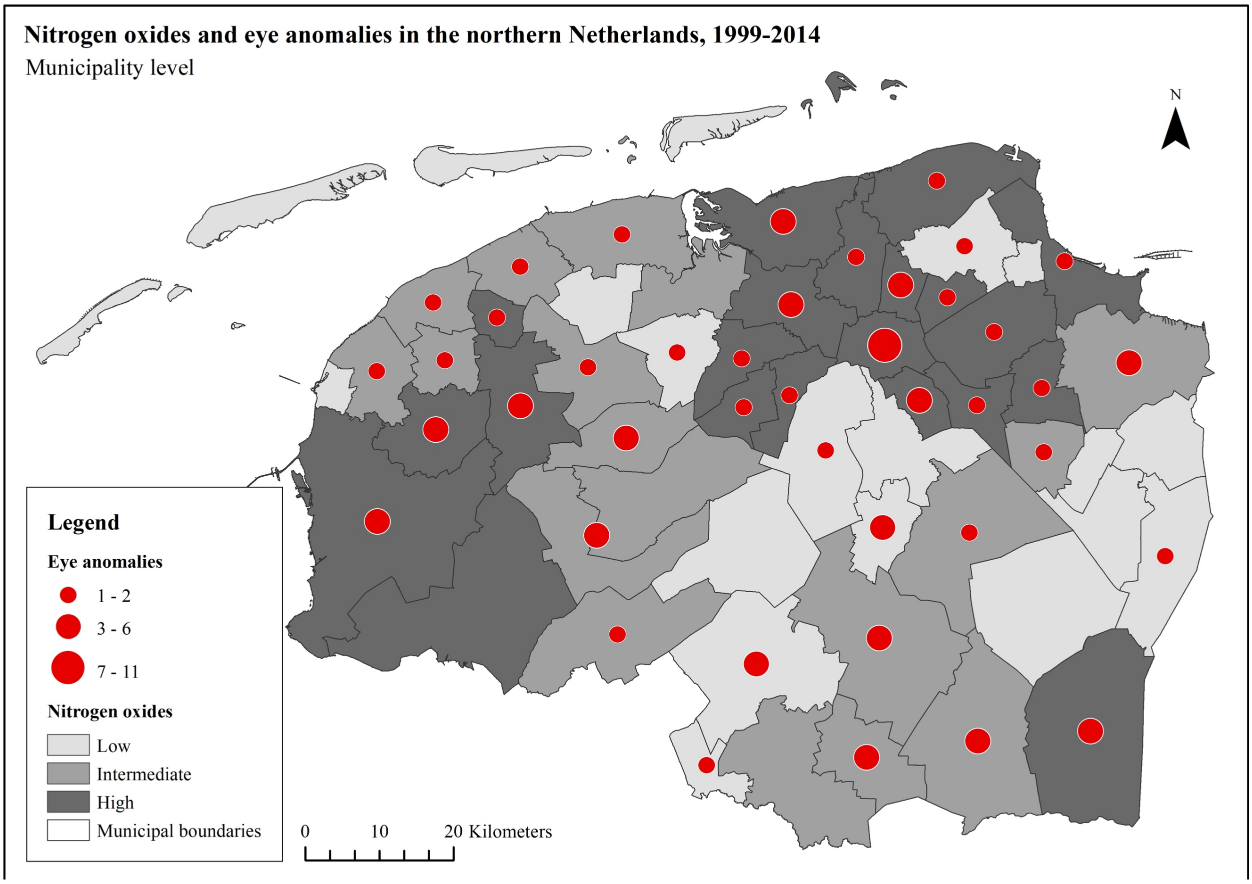
Agricultural land and multiple congenital anomalies in the northern Netherlands, 1999-2014

Postal code 4 level



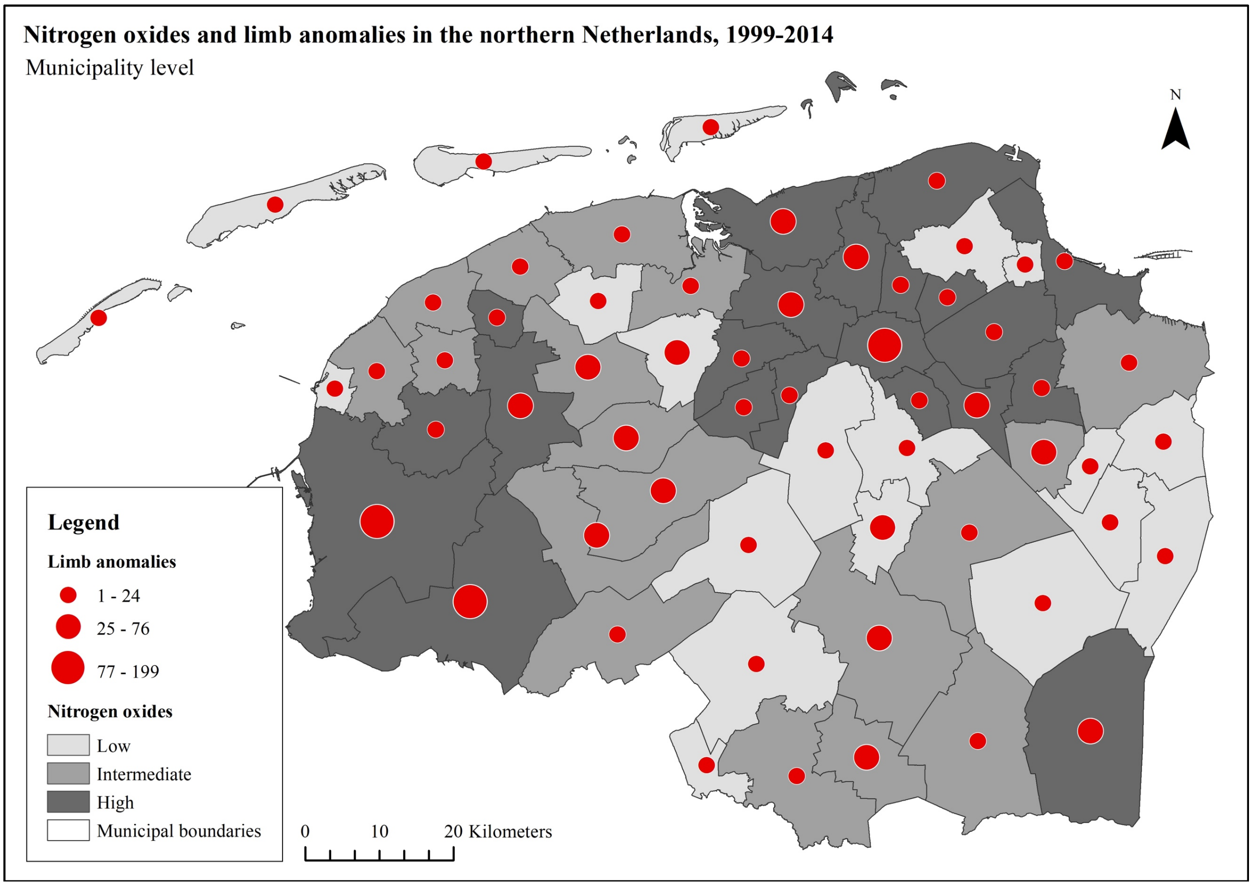
Nitrogen oxides and anomalies of the digestive system in the northern Netherlands, 1999-2014

Municipality level



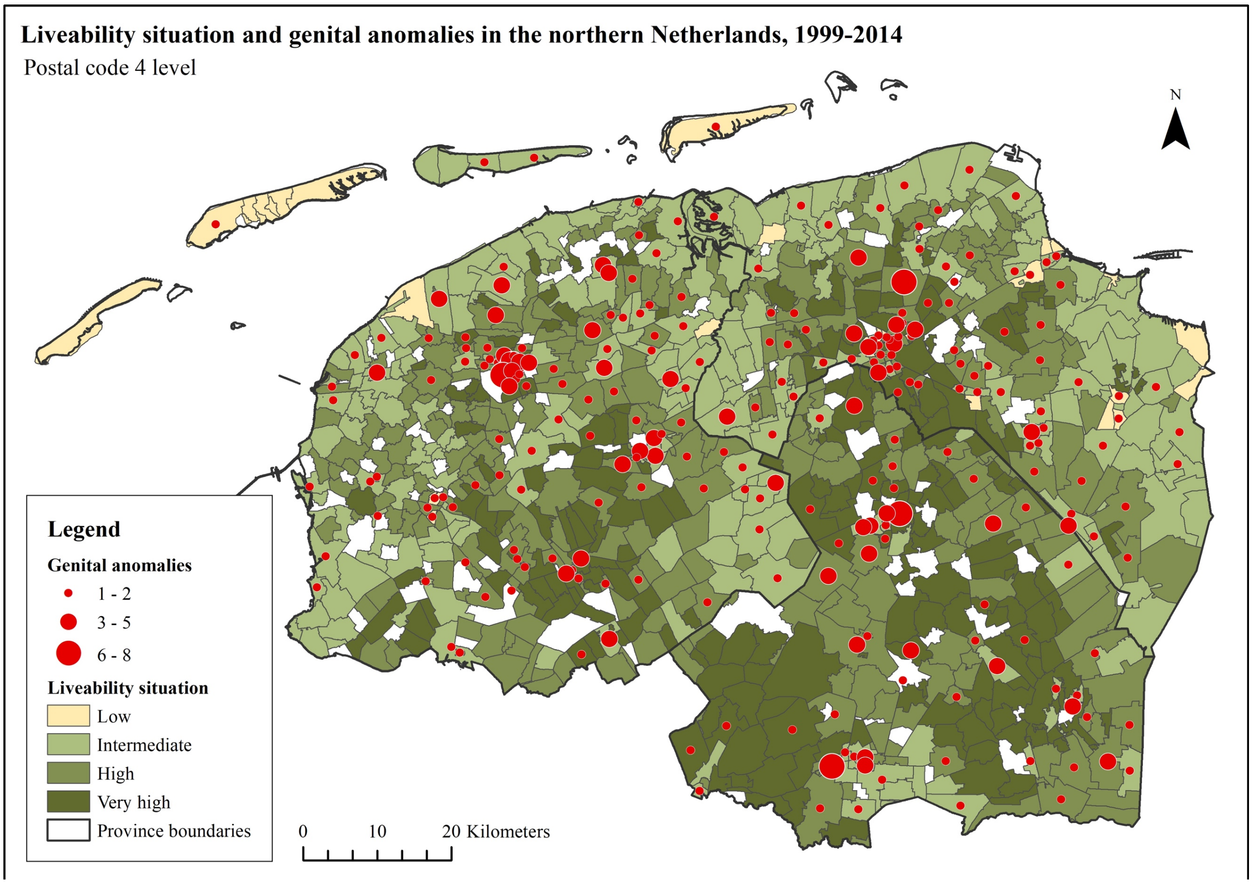
Nitrogen oxides and eye anomalies in the northern Netherlands, 1999-2014

Municipality level



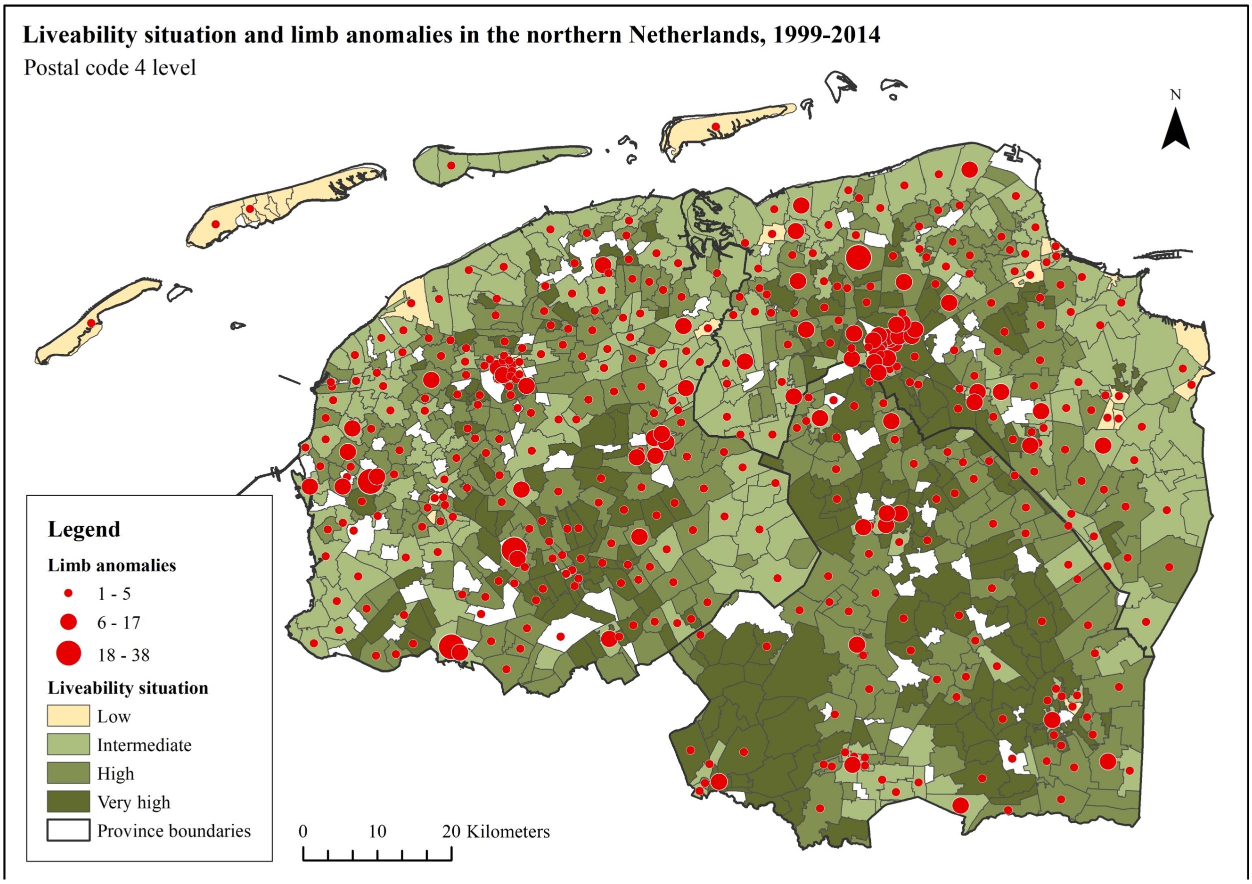
Nitrogen oxides and limb anomalies in the northern Netherlands, 1999-2014

Municipality level



Liveability situation and genital anomalies in the northern Netherlands, 1999-2014

Postal code 4 level



Liveability situation and limb anomalies in the northern Netherlands, 1999-2014

Postal code 4 level