POSITIVE HEALTH EFFECTS OF THE NATURAL OUTDOOR ENVIRONMENT IN TYPICAL POPULATIONS IN DIFFERENT REGIONS IN EUROPE (PHENOTYPE)

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Abstract

Introduction: Growing evidence suggests that close contact with nature brings benefits to human health and well-being, but the proposed mechanisms are still not well understood and the associations with health effects remain uncertain. The PHENOTYPE project investigates the interconnections between natural outdoor environments, in both rural and urban settings, and better human health and well-being in the North West, South and East of Europe. Here we provide a description of the proposed work.

Aims and methods: The PHENOTYPE project explores the proposed underlying mechanisms at work (stress reduction/restorative function, physical activity, social interaction, exposure to environmental hazards) and examines the health effects (e.g. general health and wellbeing, mental health/neural development, stress, cardiovascular, cancer and respiratory mortality and morbidity, birth outcomes and obesity) for different population groups (e.g. pregnant women and/or foetus, different age groups, socioeconomic status, ethnic groups, and patients). It implements conventional and new innovative high tech methods to characterize the natural environment in terms of quality and quantity. Preventive as well as therapeutic effects of contact with the natural environment are being covered. PHENOTYPE further addresses implications for land-use planning and green space management.

Result: The main innovative part of the study is the evaluation of possible short and long term effect of green space and the possible underlying mechanisms in 4 different countries (with quite different type of green space and use of green space) using the same methods and methodology in one research program. This type of holistic approach has not been undertaken before. Furthermore there are technological innovations such as the use of remote sensing and smartphones in the assessment of green space.

Conclusion: The project will produce a more robust evidence base on links between exposure to natural outdoor environment and human health and well-being, in addition to a better integration of human health needs into land use planning and green space management in rural as well as urban areas.

Keywords: green space, blue space, health, well being, physical activity, social contacts, restoration, stress, air pollution, remote sensing, GIS, audit, questionnaire survey, smartphones

Article summary

Strengths

The PHENOTYPE project is the largest European project on green space and health

The PHENOTYPE project examines simultaneously the possible underlying mechanisms (stress reduction/restorative function, physical activity, social interaction, exposure to environmental hazards) for the relationship between green space and health in 4 different countries in Europe

The PHENOTYPE project examines a range of possible health effects of green space using 16 different cohorts and/registries in 4 different European countries

The PHENOTYPE project uses a range of novel tools and methods to assess access and use of green space including remote sensing, smartphones, audits and interviews.

The PHENOTYPE project works closely with stakeholders and produces new information for stakeholders.

Weakness

The limited funding may not lead to the full exploitation by the wealth of data generated within the life time of the project

Introduction

Positive health effects have been observed between green space and mortality longevity (Takano et al. 2002; Mitchell and Popham 2008, Villeneuve et al. 2012), cardiovascular disease (Pereira et al. 2012), people's self reported general health (de Vries et al. 2003; Maas et al. 2006), mental health (Grahn & Stigsdotter, 2003; Hartig et al. 2003; Maas, et al. 2009b; Ottosson & Grahn, 2005, Richardson et al. 2013), sleep patterns (Astell-Burt et al. 2013a), recovery from illness (Ulrich 1994), social health aspects (Kim & Kaplan, 2004; Sullivan et al. 2004; Kweon et al 1998; Maas et al. 2009a; de Vries 2010) and birth outcomes (Donavan et al. 2012; Dadvand et al. 2012a, Dadvand et al. 2012b). Some of the associations were shown to be modified by social economic status and level of urbanity, with greater benefits for populations with lower socioeconomic class (Mitchell & Popham, 2008, Dadvand et al. 2012a) and those in more urban areas (Maas et al. 2006; Mitchell et al. 2007). Furthermore gender has been shown to modify the relationship (Richardson and Mitchell 2010b).

Increased physical activity and social contacts, psychological restoration/stress reduction, and a reduction in pollutants such as noise and air pollution, and temperature have been proposed as possible mechanisms for the health benefits of green space. Access to and/or use of green space has been associated with higher levels of physical activity (Cohen et al. 2006; Cohen et al. 2007; Coombes et al. 2010; Lachowycz and Jones 2011; Toftager et al. 2011; Rodriguez et al. 2012; Mytton et al. 2012; Annerstedt et al. 2012; Almanza et al. 2012; Astell-Burt et al. 2013b; Richardson et al. 2013) and lower levels of obesity within communities (Coombes et al. 2010; Ellaway et al. 2005; Wolch et al. 2011; Toftager et al. 2011; Pereira et al. 2013; Astell-Burt et al. 2013c; Lovasi et al 2013). Studies even suggested that 'green exercise' can have even more positive mental health benefits than other kinds of exercise (Bodin et al. 2003; Pretty et al. 2005; Bowler et al. 2010; Thompson Coon et al. 2011).

Psychological restoration (Kaplan & Kaplan, 1989; van den Berg et al. 2003; van den Berg & Custers, 2011;) and reduced stress and anxiety (Ulrich et al., 1991, Grahn & Stigsdotter, 2003; Hartig et al. 2003; Maas et al. 2009; Stigsdotter et al 2010) have all been associated with access to and/or use of green and natural space. An inner city study in a deprived estate in Chicago showed the benefits of green space both to cognitive restoration (Faber Taylor 2002; Kuo & Sullivan, 2001a), self-discipline (Faber Taylor et al. 2002), reduced aggression (Kuo & Sullivan, 2001a) and reduced crime (Kuo & Sullivan, 2001b), with the latter also observed elsewhere recently (Wolfe and Mennis 2013)

Furthermore a few studies have suggested that green space is associated with more social contacts and cohesion (Kuo et al. 1998; Kweon et al. 1998; Maas et al 2009). And finally reduction of personal exposure to air pollution has been observed in areas with more green space (Dadvand et al. 2012c), while vegetation has been suggested to reduce air pollution levels, and temperature (Baldauf et al. 2009; Su et al. 2011; Park et al. 2012a, 2012b), with some suggestion that the benefits are greater for socially disadvantaged groups (Su et al. 2011). It has also been suggested that vegetation (trees, plants) and soil may have an impact on the sound level (Aylor, 1972; Fan et al. 2010; Fang & Ling, 2003, 2005; Samara & Tsitsoni, 2007; Zhang & Kang, 2007). Part of the appeal of green spaces may be related to pleasant acoustic environments (Brown, 2006 in: Health Council of the Netherlands, 2006). This may have its own, direct beneficial health effect (Health Council of the Netherlands, 2006).

While this growing evidence exists that close contact with nature brings benefits to human health and well-being, the proposed mechanisms are still not well understood and the associations with health effects remain uncertain. Furthermore, it is unclear if the possible mechanisms act in isolation or together, since with some exceptions (de Vries et al. 2013) they have been studied in isolation. A coherent conceptual framework on the proposed mechanisms is currently lacking. Also, most of the research has been conducted in the North West of Europe and USA leaving questions about the generalisability to other regions. Inconsistency and variation in indicators (eg type, size and quality) for green space have often made it difficult to compare results from different studies, and a better characterisation including that of quantity and quality of green and blue spaces is needed, not only for research but also for policymakers and spatial planners. Studies have often focused on access to green space without taking into account actual use of green space. While blue space may also have a positive effect on health, probably in combination with green space, there are only a few epidemiological studies investigating this (Völker and Kistemann 2011, Völker and Kistemann 2013, White et al. 2013)

PHENOTYPE, a collaborative research project and explores the proposed underlying mechanisms at work (stress reduction/restorative function, physical activity, social interaction, exposure to environmental hazards). PHENOTYPE is the first study designed to examine these mechanisms simultaneously in a large sample (N=4000 subjects) in various European countries using the same methodology. This allows the study of specific factors while adjusting for others, and thereby strengthening the interpretation of the results. It further examines both the long term and short term health effects (eg general health and wellbeing, mental health/neural development, stress, cardiovascular, cancer and respiratory mortality and morbidity, birth outcomes and obesity) for different population groups (e.g. pregnant women and/or foetus, different age groups, socioeconomic status, ethics groups, and patients), through analyses of existing cohort studies, observational studies and experiments. Preventive as well as therapeutic effects of contact with the natural environment are being evaluated. A coherent conceptual framework on the association between the natural environment and its effects on health and well-being is being developed, and it addresses implications for land-use planning and green space management.

The study includes both rural and urban settings, but the main focus is on the urban environment, for a number of reasons. Most of the population lives in urban areas (75%) in Europe, making these of greater relevance to public health, and rapid urbanization continues to reduce accessible natural environments for urban residents. Most people make more frequent use of the green spaces in their nearby living environment instead of travelling greater distances to rural areas, in particular people with lower socio-economic status, elderly people and children (Schwanen et al. 2002; Maas 2008). Furthermore, rural dwellers tend to have constant contact with the natural environment and it may therefore also be more difficult to assess its effects.

Lastly, the project uses an interdisciplinary and integrated approach, applying the best and most efficient methods to understand the relation between exposure to the natural environment and health. It implements conventional and new innovative high tech methods to characterize the natural environment in terms of quality and quantity. This paper provides a general overview of the research methodology of PHENOTYPE.

Methods and results

Figure 1 summarizes the different parts of the study and the interdependencies between the different parts, namely the characterisation of the natural environment and the way it is used, examination of the underlying mechanisms in daily life settings, short and long term effects of the natural environment, and the implications for management and policy of the natural environment (see overview Figures 1 and web figure 1). In this section we will elaborate on each of these parts. A summary of the mechanisms, outcomes, populations and areas selected for investigation are given in Table 1.

Characterising the natural environment and the way it is used.

The research includes evaluation of the natural environment, which includes for the purposes of the project:

- Green spaces (e.g. roof gardens, city parks, court yards) and "greenery"; forests, nature reserves/parks, mountains, farmland, trees, landscaping
- Blue spaces; water such as canals, ponds, creeks, rivers, beaches etc.

Although many of these may actually not be ´´natural´´ since they have been man-made, for the purpose of the project we classify them as such.

One of the main aims of PHENOTYPE is to examine the importance of both quantitative (e.g. amount, type, access, use) and qualitative characteristics (e.g. acoustic quality, identity, variety, safety, rubbish) of the natural environment by collecting detailed data on these characteristics using a combination of methods. The focus lies on natural environments at different scales and distances from the home (city/town, neighbourhood, street level) and where possible also at other places where people stay (work, school, on their way to home/school, recreational). In addition, actual use of the natural environment is taken into consideration. To achieve the aim, a detailed assessment will be conducted in 4 case cities (Barcelona, Spain; Doetinchem, the Netherlands; Kaunas, Lithuania; and Stoke-on-Trent, United Kingdom), with less detailed assessment in other study areas.

PHENOTYPE uses conventional land use maps, remote sensing data from satellites and aerial photography, complemented by detailed discussions with volunteers and other stakeholder living and working in the studied areas to derive comparable classifications of the natural environment in different countries. Collected data will contribute to the characterisation of the natural environment (both quantitative and qualitative e.g. accessibility, acoustical quality, recreational activities, walkability etc). For the quantitative characterisation, PHENOTYPE makes use of available land use maps such as COordination and INformation on the Environmental programme, initiated by the European Commission (CORINE)(EAA 2005) and Urban Atlas (EAA 2010), and remote sensing and aerial photography to obtain comparable indices such as NDVI (Weier and Herring, 2011) of the natural outdoor environment in different countries. Landsat Enhanced Thematic Mapper Plus (ETM+) data are applied to a classification and regression tree (CART) model to categorise land cover types for the urban areas of interest (Su et al 2010). Early application of the NDVI in Barcelona, Spain showed good results (Web Figure 2, Dadvand et al. 2012a)

To collect additional qualitative information on the natural environment and on other physical and social features, systematic observations (audits) are conducted by trained researchers in selected neighbourhoods in the 4 case cities. The researchers walk through the neighbourhood, systematically coding characteristics such as the architectural character, maintenance of the landscape, and perceptions on how a place looks and feels. To collect comparable information in the 4 case cities, two standardized forms are used. One form is used for evaluating the streetscape, using indicators derived from the Street Typology developed by Leijdelmeijer et al. (2002), a list of evaluating the quality of green by Van Dillen (2012) and the audit tool developed by Van Lenthe et al. (2006). A second form is used for evaluating the natural spaces in the study areas of at least 1 ha. It is an adapted form of the Neighbourhood Green Space Tool developed by Gidlow et al. (2012).

To gain insight into the way people use the natural environment, a face to face questionnaire survey is conducted to collect data on 1000 people in the 30 selected neighbourhoods in each of the 4 case cities, and an in-depth study using “Calfit”, a smartphone-based monitor of time-location patterns and momentary states, on a subsample (n=100) of the participants of the questionnaire survey. The Calfit software runs on a Google Android operating system and as currently configured can collect data on physical activity using the motion sensor and geographic location though a global positioning system (GPS), to obtain information on minutes spent and physical activity levels in different natural environments (Web Figure 3). The instrument has been validated against the Actigraph accelerometer (Donaire et al. 2013), combined with other pollution measurements to assess likely inhalation (de Nazelle et al. 2013), and lab-validated using the Cosmed metabolic monitoring system.

The work will produce different indicators of natural space that can be used in the studies described below. The aim is to make a hierarchy of indicators with on the bottom simple measures such as NDVI that can be easily obtained for all the study areas and on the top detailed measures of for example green space with actually information on the quantity, quality and use that can only be obtained for only some areas after in-depth study. As part of the work, we will examine the relationship between the simple and detailed measures to better understand how detailed information on small scale can help the interpretation of health studies conducted in larger areas with only simple measures available using existing epidemiological studies and registries (see below).

Examining the underlying mechanism in the daily life setting

New data will be collected to explore in detail and simultaneously the proposed mechanisms underlying the relationship between the natural environment and health and well-being, in the four case cities. In each of these cities 30 neighbourhoods varying in socio-economic status and in their distance to green space are selected. In these neighbourhoods the natural environment will be characterised, and a selection of 1000 randomly selected residents (4000 in total, 18-75 years) will participate in a questionnaire survey, a smartphone study, and in in-depth interviews (Web Figure 4). The choice of items was based on the proposed mechanisms and was achieved via an interactive process of experts within the PHENOTYPE team and others in the institutions involved. As much as possible questions were derived from existing and validated indices. The questionnaire was piloted by the four centers separately with specific attention for comprehensibility, clarity and duration and was adapted based on these pilots. The questionnaire is structured along several main clusters of questions: i) residential situation: ii) dwelling iii) wellbeing and health, and iv) personal characteristics. It includes questions on perceived quality and use of green and blue space in the residential area and in the immediate living environment, perceived environmental and social quality including aspects as noise, amenities and social cohesion, lifestyle, subjective health and questions related to personal background. The questionnaire was developed in English and translated and back translated in Dutch, Spanish and Lithuanian. More details on the frameworks and questionnaire will be described in a forthcoming paper by Van Kamp et al. (In prep). Also we will assessment cognitive fatigue in each subject as measured by CTT.

From the 1,000 volunteers in each of the 4 case cities who complete the questionnaire, 100 people are approached to take part in a smartphone study (400 in total). During 7 subsequential days the emotional state of the subject, the local environment (e.g., different quantities or qualities of natural space) and the social setting are assessed with the smartphone and the innovative Calfit technology. Besides objectivegeolocation and physical activity, subjective data on stress reduction/restoration and social contacts are collected simulataneously. The latter data are collected through interactive diaries capable of eliciting ecological momentary assessment (EMA). EMA is a novel approach to elicit responses to electronic surveys throughout the course of daily life (Shiffman et al. 2008). The participant receives prompts at random intervals to complete small surveys on the phone, which then have time and location stamp.

From the people who participate in both the questionnaire survey and the CALFIT study and who indicate they wanted to volunteer, 80 people (20 in each case city) are approached for semi structured interviews. These interviews are conducted to gain more detailed information on specific topics included in the questionnaire survey and CALFIT/EMA. Topics addressed include the motivation for travel routes, the effect of natural environment on mood, behaviour and well-being, the attitude towards and importance of (experiences with) natural environment, and reasons for using or not using the natural environment.

Epidemiological studies to examine long term effects of the natural environment

By using existing epidemiological studies and registries and linking these to the natural space indicators described earlier, the association between natural environment and a range of different long term health effects will be examined in an efficient and cost effective manner. PHENOTYPE makes use of 16 existing cohorts and registries with good health outcome data in Spain, the Netherland, Lithuania, and United Kingdom (Web Table 1), linking these to newly created natural environment indicators. Comparable estimates are produced for various regions in Europe for the effects on pregnancy outcomes, foetus development, children's health and adult population morbidity and mortality. We specifically focus on:

- the natural outdoor environment and ethnicity, socio-economic status, women´s health and pregnancy outcomes;
- the natural outdoor environment and foetus development, birth weight, and gestational age;
- the natural outdoor environment and general development, neurodevelopment, cognitive function and respiratory health in children;
- the natural outdoor environment and respiratory health in various European cities;
- the natural outdoor environment and general health, physical activity, specific morbidity and mortality.

The assessment of natural environment indicators will be mainly based on satellite data and land use maps as CORINE and Urban atlas, and sometimes local data. This will restrict to some extent the evaluation of the effect of the natural environment, but this is the only realistic and achievable approach. All studies examine the role of socio-economic status, which has been suggested as an effect modifier for the relationship between exposure to the natural environment and health benefits. The European Community Respiratory Health study (ECRHS) (Burney et al 1994) further allows for examination of exposure to the natural outdoor environment and health effects in a range of different European cities. Some cohorts such as the Born in Bradford study (Wright et al. 2012) offers a unique opportunity to investigate the role of ethnicity in the relationship between exposure to the natural outdoor environment and health benefits, in Bradford study half of the participants are from Pakistani background, with information on both the mother and baby from pregnancy to early years in life.

Experiments to examine short term effects of the natural environment

To examine short term effects of the natural environment on health and well-being, one or more experimental studies are conducted in each country in which individuals are exposed to different types of natural and urban environments (i.e., environmental conditions). The majority of data collection is field-based to maximise the ecological (as well as internal) validity of any observed effects.

Using a range of psychological and physiological indicators relevant to the various possible mechanisms, and inclusion of healthy and patient population groups (with mental and physical morbidities) collectively explore:

- preventive and therapeutic effects of natural environments.
- immediate and sustained changes in affective, cognitive and physiological responses indicative of well-being while engaged in a natural environment, and after leaving a natural environment
- neurobiological responses to viewing natural or urban scenes before/after experiencing stress.

Through variation in experimental design, each partner makes a novel contribution(s) to the area as (details in Web Table 2):

- UK: In healthy individuals, Study 1 compares immediate and post-exposure psycho-physiological effects of urban versus natural environments to explore whether any beneficial effects are sustained following single exposures; Study 2 uses longer-term follow-up and repeated exposure to natural environments to explore whether any effects are accumulated, sustained or attenuated.
- Netherlands: an experimental functional Magnetic Resonance Imaging (fMRI) study is conducted in healthy individuals to investigate neurobiological responses to viewing natural or urban scenes before/after experiencing stress; i.e., whether viewing natural compared to urban scenery can prevent or buffer against stress responses, and how this is represented in brain activation patterns.
- Spain: in individuals with elevated stress levels, group-based exposure and Ecological Momentary Assessment (EMA, using CALFIT technology) are used to explore the role of social interaction and the nature of physical activity, in immediate and longer term responses. Ecological validity will be enhanced through ‘free-living’ activities within environments, rather than controlling activities, again, using EMA, GPS and accelerometry to monitor the nature (and perceptions) of this activity.

- Lithuania: a clinical population with established coronary artery disease (CAD) are recruited to evaluate the therapeutic effect of the natural environment. The outcomes of this experiment may have direct clinical applications for the use of urban and different types of natural environment in cardiac rehabilitation.

Implications, policy and guidelines and involvement of stakeholders

Guidelines

PHENOTYPE will provide recommendations for policymakers and guidelines for professional practitioners involved with spatial planning and health to create natural environments that promote health and well being. For this, we focus on a human ecological perspective which allows for a better integration of human health needs into land use planning and green space management in both rural and urban areas (Lawrence 2001). Currently legal standards that have been developed with economic, technological and political priorities in mind, are leading in urban design, whereas the lifestyle, sense of community, identity, and health and well being of local populations have been largely undervalued. The guidelines will reflect the importance to consider environmental, social, economic and other components of the natural and built environments in ways that also take into account and result from the point of view of citizens. PHENOTYPE will complement the common quantitative approach by valorising the social/human functions of these environments, especially their contribution to promoting health and quality of life.

Following this broad and innovative approach, PHENOTYPE will formulate, test and validate a set of recommendations and guidelines concerning the desired characteristics of different types of natural environments in urban and rural areas, specifically their characteristic features, accessibility to them for different population groups, as well as their facilities, maintenance and services. By doing so, the work will overcome the existing applicability gap between information and knowledge accumulated by much research and policy definition and implementation.

The guidelines for professional practitioners involved with spatial planning and health will consider three core topics in relation to each of the natural environment being considered:

1. Qualitative characteristics of natural environments; recommendations concerning surface area, vegetation, water sources, ambient noise levels, views and microclimate;
2. Facilities, Maintenance and Services; recommendations about the kinds of communal facilities and services provided in each type of natural environment, as well as suggested levels of maintenance;
3. Accessibility Guidelines to Natural Environments; including requirements about access to different types of natural environments such as allotments, neighbourhood parks, children's playgrounds and nature reserves.

The baseline for the work is firstly the compilation and analysis of currently available information from existing databases and literature, and later new data collected by the project as described above. This will be complemented by the engagement with the appropriate stakeholders to assess scope for development. These insights will be combined into a conceptual framework on the underlying mechanisms of the effects of the natural environment on health and well-being.

Stakeholders and dissemination

The participation provides a forum for project assurance and benefits for PHENOTYPE are summarised as follows:

- A more robust evidence base on links between exposure to natural outdoor environment and human health/well-being for various regions in Europe. Hereby we expect to develop a better understanding of the potential mechanisms.
- A better integration of human needs into land use planning and green space management in rural as well as urban areas. Furthermore, the application of these needs in practical guidelines.

Stakeholder involvement is critical for bringing outside (policy) ideas into the research planning, to increase the usefulness of the research, and to assure a better implementation of the results of the project (Web Figure 5). In a research project, this is often limited because the lack of interest of stakeholders and the limited resources and efforts of consortia.

From the start of PHENOTYPE actively sought to establish and maintain relations and dialogues with and between key stakeholders from local, regional and national health and environment authorities, institutions and the international research community. These include policy makers, architects, urban planners, natural space managers, health professionals, and the international research community. This group is highly diverse, as we are looking at a range of professions within the subject areas of environment and health, from volunteers to scientists, community workers and policy developers. PHENOTYPE has thus far been successful in its engagement activities, providing continuous opportunities for information exchange and collaborations. These contribute to strengthening networking between researchers, policy-makers and stakeholders in order to facilitate the transfer of scientific knowledge to policy development, to exchange ideas about best practice and to help identify emerging issues on the natural outdoor environment and its mechanisms to improve health.

The PHENOTYPE website www.phenotype.eu provides an overview of the project, progress, actualities, surveys and publications. The site has a sign up form for periodic newsletters through which all stakeholders are regularly informed. It guarantees continuous visibility, and provides a means for interested parties to respond to activities, or to contact us with invitations to attend workshops, etc. PHENOTYPE is also found on social media twitter (@greenhealth4eu) and LinkedIn. The PHENOTYPE databases and overall results will be exploitable by policy makers at national and international level in areas including urban planning and health.

Conclusion

The PHENOTYPE project is an FP7 collaborative action, funded by the EC to explore the mechanisms underlying positive short term and long term health effects for different population groups. PHENOTYPE applies conventional and new innovative high tech methods to characterize the natural environment in terms of quality and quantity. Preventive as well as therapeutic effects of contact with the natural environment will be covered. The proposed work aims to address the limitations of some of the studies that have been published so far (Table 2). Furthermore it addresses implications for land-use planning and green space management. The project will produce a more robust evidence base on links between exposure to natural outdoor environment and human health and well-being. This in turn will contribute to improved integration of human health needs into land use planning and green space management in rural and urban areas.

"No additional data available yet".

Author statement

Mark J Nieuwenhuijsen, Hanneke Kruize, Christopher Gidlow, Michael Jerrett, Jolanda Maas, Edmund Seto, Peter Jan van den Hazel, Roderick Lawrence, and Regina Grazuleviciene and wrote the original grant proposal on which the study design and paper is based. Mark J Nieuwenhuijsen drafted the version of the paper and received input from all the authors. All authors read and commented on the paper and agree with the final version.

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Ethics approval was obtained for all aspects of the study by the local ethics committees in the countries where the work was conducted, and sent to the European Commission before advancement of the study.

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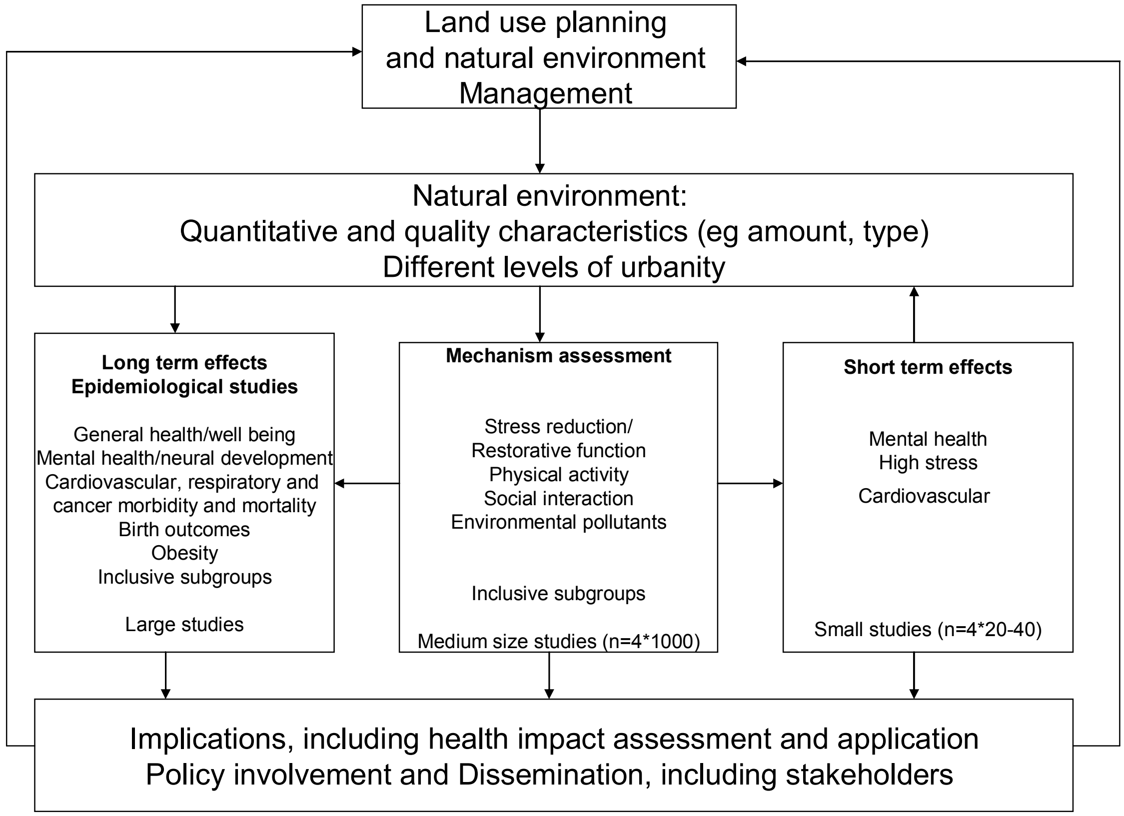


Figure 1: Interdependencies of different parts of the PHENOTYPE project

Table 1 PHENOTYPE study mechanisms, outcomes, populations and regions

It will explore underlying mechanisms related to:

- stress reduction/restorative function
- physical activity
- social interaction/social cohesion

exposure to environmental hazards (e.g. noise/acoustic quality, air pollution)

Both preventative and therapeutic effects (patients) will be considered. Outcomes of interest that are evaluated are:

- general health and well-being (including medically unexplained symptoms
- (MUPS))
- mental health/neural development
- stress
- cardiovascular, cancer and respiratory mortality and morbidity
- birth outcomes
- obesity

It will examine the effects for different population groups, including more vulnerable populations:

- pregnant women and/or foetus
- age groups (children, elderly)
- (lower) socio-economic status
- ethnic minorities
- patients/people with specific health complaints

It will conduct comparative studies in different regions of Europe to examine any underlying regional, social and/or cultural differences related to the meanings, uses, mechanisms and health effects of the natural environment and we will include the:

- North west (Netherlands, England)
- South (Spain)
- East (Lithuania)

Table 2 Limitations of current green space work and work undertaking by PHENOTYPE to address these

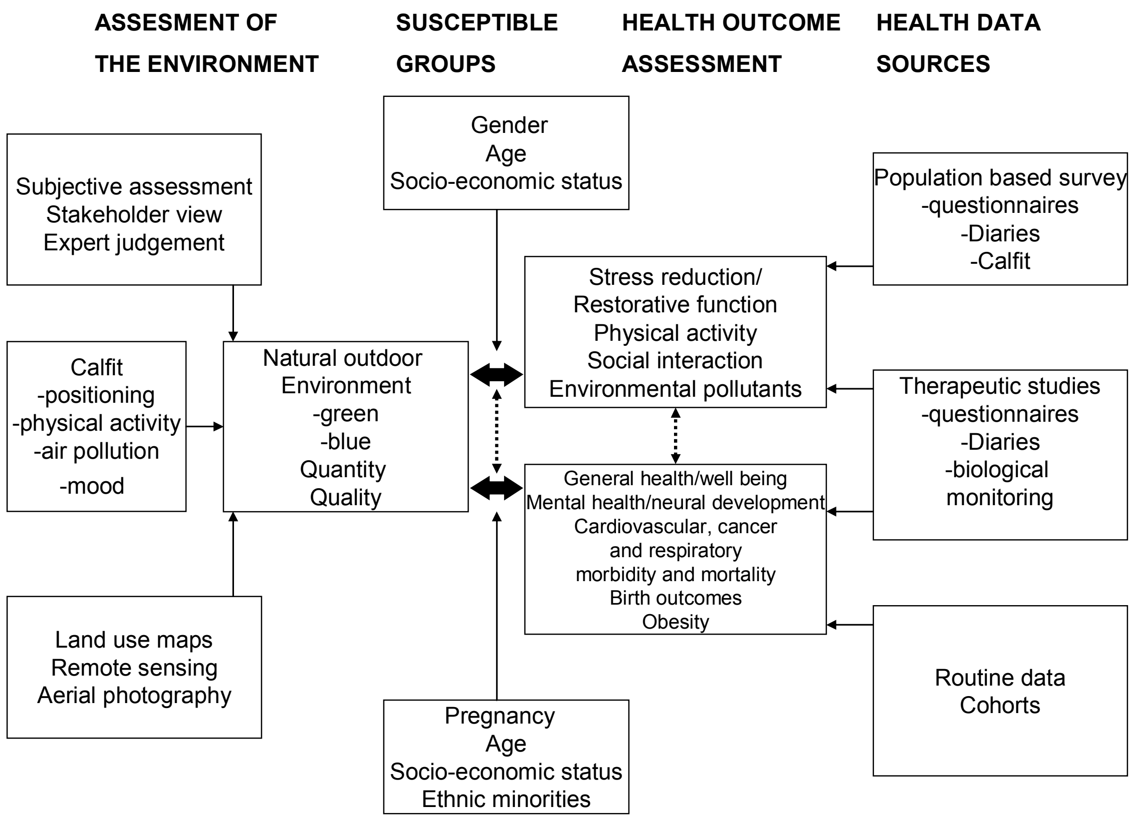
Limitations of current available work	What PHENOTYPE will do
▪ Inconsistency and variation in indicators for green or natural space have often made it difficult to compare results from different studies.	▪ Minimize the potential differences due to classification of natural space, by combining the use of conventional maps and data sources with remote sensing data and aerial photography, gather individual-level data through detailed discussions with subjects living in the areas, and use considerable stakeholder engagement to develop comparable classifications of the natural environment in different countries. ▪ Produce a more robust and comparable evidence base on links between exposure to natural outdoor environment and human health and well-being.
▪ A number of disease outcomes have been studied, but besides the routinely collected data (which use ICD coding), not always in a standardized and comparable manner in different countries	▪ Produce a more robust and comparable evidence base on links between exposure to natural outdoor environment and human health and well-being, using well studied and new outcomes with standardization between countries.
▪ Potentially very sensitive groups such as pregnant women/fetus have not been studied at all.	▪ Extend the evidence base to new outcomes and vulnerable populations e.g. pregnant women and their foetus, chronic respiratory and cardiovascular patients, ethnic minorities and

	low social economic class.
▪ Most studies focused on green space; the evidence base for the effects of blue space is very limited.	▪ Not only examine the effects of green space, but also of blue space.
▪ Most of the green space studies have been conducted in the US or the North West of Europe.	▪ Conduct comparable studies across Europe and produce evidence for North Western, Eastern and Southern Europe. This will deliver insights into regional, social and/or cultural differences in relation to natural space.
▪ Most studies do not include actual use of the natural environment.	▪ Consider actual use of the natural environment, an often neglected but fundamental indicator in relation to exposure to natural environments.
▪ There appeared to be differences by social group, with some apparently benefiting more than others from natural space, but the evidence is sparse.	▪ Produce a more robust and comparable evidence base on links between exposure to natural outdoor environment and human health and well-being, with special attention for effect modification by social groups
▪ A number of potential mechanisms have been suggested, including increased physical activity and social contacts for those living near natural space, natural environments exerting	▪ Examine the proposed mechanisms (physical activity, stress, social contacts, and environmental risk factors) simultaneously in a large sample in various countries (WP2). This will enable

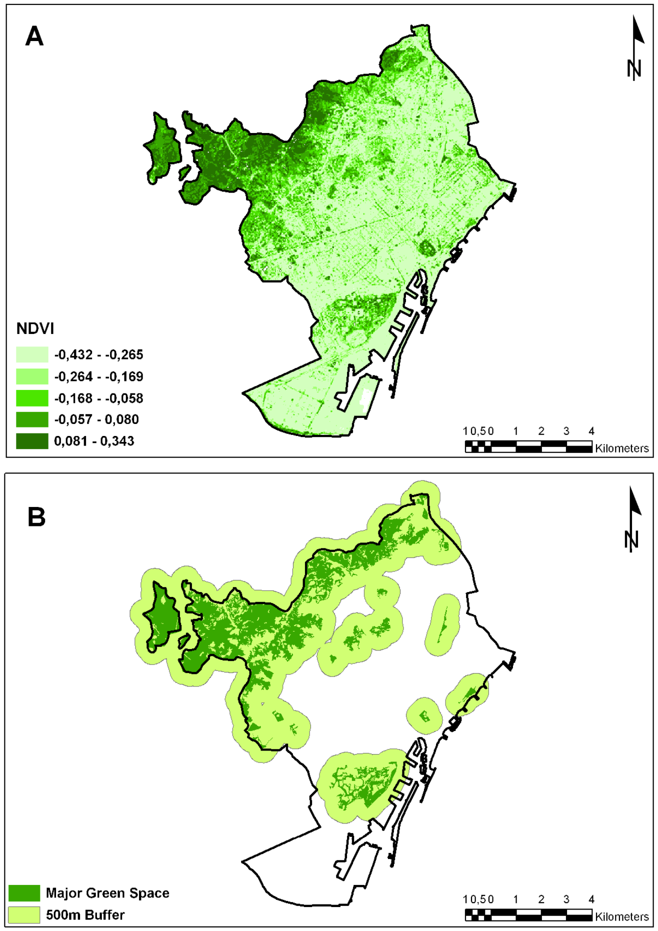
stress lowering or attention restoring effects, and reducing environmental hazards (e.g. air pollution, high temperatures). However, the studies of potential mechanisms have often been limited to assessing one mechanism at the time, which increases the likelihood of unmeasured confounding effects and misses the opportunity to study these potentially interrelated mechanisms in coherence. ▪ to study the mechanisms in coherence even though they may be interrelated	us to study specific factors while adjusting for others, and thereby strengthening the interpretation of the results
▪ Unable to answer what specific quantitative and qualitative characteristics of the natural environment have a positive effect on health and well-being, through what pathways is still largely unknown.	▪ Make classifications for the type and level of the indicators, which is important for policy makers. ▪ Examine the importance of both quantitative (amount, type, access, use) and qualitative characteristics (acoustic quality, identity, variety, safety) of the natural environment
▪ Limited research exploring the sustained affective, cognitive and physiological responses to a single exposure and the effects of a repeated exposure to the same natural environment ▪ Unable to explain how policymakers and planners can design a natural environment to maximise health benefits	▪ Explore longer-term changes in affect, cognitive function and physiological indicators that have to date only been studied during, or immediately after, engagement with the natural environment. ▪ Explore the immediate, maintained and long-term effects of repeated engagement with the same natural environment on

	affect, cognitive function, and physiological indicators of well-being .
▪ Guidelines of lifestyle, health and well being have largely undervalued local populations	▪ Include lifestyle, health and well being factors of the local populations.

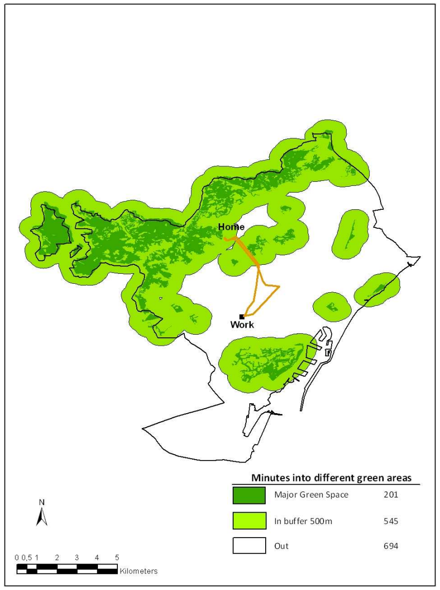
Annex-websfigures



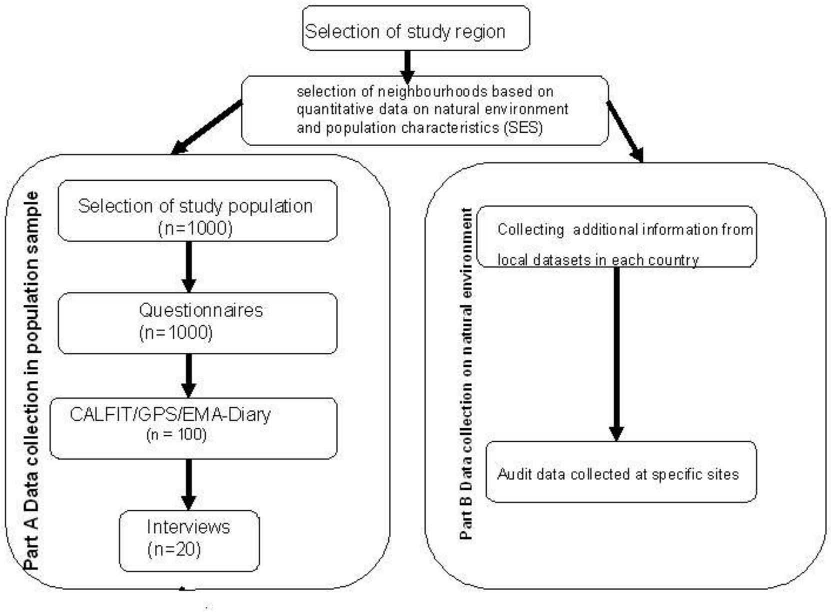
Web Figure 1 Natural outdoor environment, mechanisms and health data input in PHENOTYPE



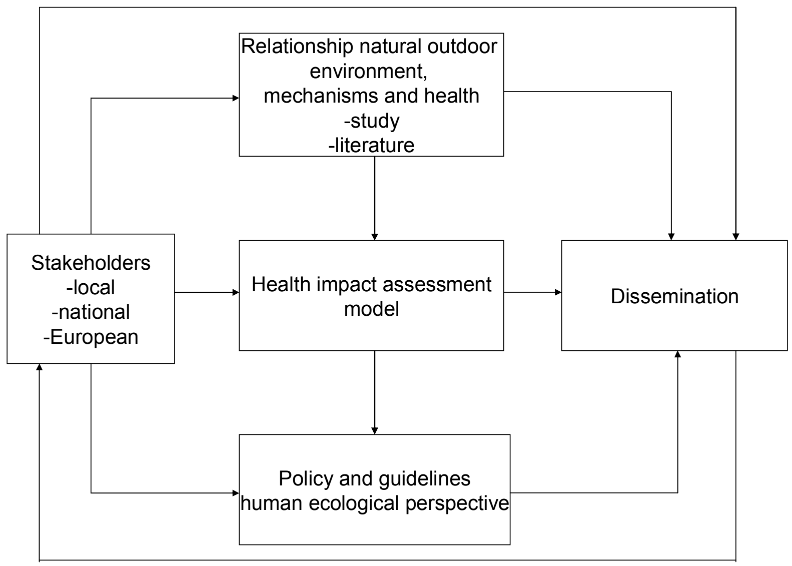
Web Figure 2 NDVI map of Barcelona and buffers around major green space areas



Web Figure 3 Mobility pattern for a subject in Barcelona obtained with the Calfit tool



Web Figure 4 Design of data collection in 4 European case cities to study the underlying mechanism



Web Figure 5 Stakeholder input and dissemination

Web Table 1 Currently available databases and cohorts for inclusion in PHENOTYPE

Study	n	Population	Collected outcomes	Relevant covariate and mechanism data
CREAL Spain				
PISCINA	3000	Children 6-9, 2006, Sabadell, Catalonia	Respiratory health BMI	Social economic status Physical activity Air pollution
INMA	3000	Children, 2-10, ongoing around Spain	Birth weight and gestation, respiratory health, neural development	Social economic status Physical activity Stress Air pollution
PAC-COPD	342	Patients with chronic obstructive pulmonary disease (PAC-CODP)	Hospital admissions All cause and specific mortality Functional data (lung function, cardiovascular function) Symptoms and co-morbidities Quality of life Mental status Body weight and composition	Social economic status Physical activity Air pollution

ECRHS	8500	Adult population in many cities around Europe	Respiratory health Short form SF36	Social economic status Physical activity Air pollution
Routine data Catalonia	Pop 7M 0.5 million deaths	All, 1999-2006, Catalonia	All cause and specific mortality	Social economic status
Hospital clinic database	16000	Births, 2000-2005 Barcelona	Birth weight and gestation	Social economic status Air pollution
Netherlands				
Cohort of Dutch inhabitants Netherlands	Pop 16M	All, 2000-2008	All cause and specific mortality and morbidity	Social economic status
Doetinchem cohort	Approximately 5000 over a period of 5 years	See: Verschuren WMM, Blokstra A, Picavet HSJ, Smit HA. The Doetinchem cohort study (cohort profile) Int J Epidemiol 2008; 37(6):1236-1241	Body weight, serum cholesterol, mortality, morbidity, health-related quality of life (RAND-36)	Social economic status, physical activity
Health survey Utrecht	3475	Adults 3475 (19-99 years)	lifestyle, perceived health, chronic diseases	Socioeconomic status, physical activity
United Kingdom				
Born in Bradford	12000	Babies, ongoing, England (large ethnic population) and their parents for a subgroup	Birth weight and gestation General and mental health parents in a	Social economic status Air pollution Detailed

			subset of 1500	ethnicity
Routine hospital emissions/ disease incidence		Small area-level data for Stoke-on-Trent/Staffordshire	Rates and nature of hospital episodes (e.g., respiratory, CVD), morbidity and mortality	Social economic status Air pollution
National health data		Small area-level health data for UK	Nature and rates of morbidity and mortality	Social economic status Air pollution
Lithuania				
Routine morbidity data Lithuania	0.5 million	Lithuania population, all age groups. Classification of all registered cases causes according to ICD-10 revision codes	Urban-rural area, age, sex, cardiovascular, respiratory, cancer, and other morbidity by districts	Social and demographic status
Routine mortality data Lithuania	0.5 million	Lithuania population, all age groups. Classification of all registered cases causes according to ICD-10 revision codes	Urban-rural area, age, sex, cardiovascular, respiratory, cancer, and other morbidity by districts	Social and demographic status
Detailed Health survey	7000	Representative sample adults of Kaunas citizens, Lithuania	General health including Blood pressure, high cholesterol and diabetes, Depression Physical functioning Cognitive function Psychosocial factors	Social economic status Air pollution Physical activities Stress
Kaunas birth	4,260	Kaunas babies and their parents for a subgroup	Birth weight and	Social,

cohort		http://www.birthcohorts.net/Cohort.Show.asp?cohortid=87	gestational age	demograpgic, economic status Air pollution

Web Table 2. Summary of proposed experimental design in each partner country in PHENOTYPE

	Country	Sample	Summary design	Measures				
				Affect	Cognition	Physiological	Environment	Other
Preventive	UK: study 1	Healthy adults (n=40)	- Field-based - Within-subjects - 30-minute exposure to natural green, natural green/blue, and urban environment - Measures at baseline (pre-exposure), 30 and 60-minutes post exposure	Mood	Cognitive function	- Salivary cortisol - HR - HRV - BP	Perceived restoration	RPE Walking speed
	UK: study 2	Healthy adults (n=40)	- Field-based - Between groups - 30-minute exposure to natural *or* urban environment on three consecutive days - Measures at baseline (day 1), 0, 30 and 60-minutes on exposure days (days 2-4) and final follow-up on day 5	Mood	Cognitive function	- Salivary cortisol - HR - HRV - BP	Perceived restoration	RPE Walking speed Hedonic and eudemonic life satisfaction
	Netherlands: study 1	Healthy adults (n=50)	- Laboratory-base - Within subjects - Shown images of natural and urban environment before a stressor (model 1) and after a stressor (model 2) stressor (to explore buffering and restorative effects, respectively)	Mood	Cognitive function	- Salivary cortisol - HR - HRV - BP	Perceived restoration	
	Netherlands: study 2	Healthy adults (n=25)	- Laboratory-based - Within subjects - Shown images of natural and urban environment before a stressor (model 1) and after a stressor (model 2) stressor (to explore buffering and restorative effects, respectively)	Mood	Cognitive function	- Neurological response (fMRI) - Salivary cortisol - HR - HRV - BP	Perceived restoration	
Therapeutic	Spain	Adults with elevated stress levels (n=20-40)	- Field-based - Exposure to natural green, natural green/blue, and urban environment over several hours - Measures at baseline (pre-exposure), 30 and	Mood	Cognitive function	- Salivary cortisol - HR - HRV - BP	- Perceived restoration - Air pollution - Noise	RPE Walking speed Social interaction

			60-minutes post exposure - Participants given CALFIT phones for some days for longer term monitoring (mood, social interaction, physical activity)				pollution	and physical activity (CALFIT)
	Lithuania	Adults with CAD (n=20)	- Field-based - Between-subjects - 30-minute exposure to natural green *or* urban environment on two consecutive days (days 2 and 3) - Measures at baseline (pre-exposure), 30 and 60-minutes post exposure - Walking treadmill test at baseline (day 1) and follow-up (day 2)	Mood	Cognitive function	- Exercise capacity (treadmill test) - Salivary cortisol - HR - HRV - BP	Perceived restoration	RPE Walking speed

CAD, coronary artery disease; HR, heart rate; HRV, heart rate variability; BP, blood pressure, RPE, rate of perceived exertion; fMRI, functional magnetic resonance imaging

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POSITIVE HEALTH EFFECTS OF THE NATURAL OUTDOOR ENVIRONMENT IN TYPICAL POPULATIONS IN DIFFERENT REGIONS IN EUROPE (PHENOTYPE)-A STUDY PROGRAMME PROTOCOL

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POSITIVE HEALTH EFFECTS OF THE NATURAL OUTDOOR ENVIRONMENT IN TYPICAL POPULATIONS IN DIFFERENT REGIONS IN EUROPE (PHENOTYPE)-A STUDY PROGRAMME PROTOCOL

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Abstract

Introduction: Growing evidence suggests that close contact with nature brings benefits to human health and well-being, but the proposed mechanisms are still not well understood and the associations with health remain uncertain. The **P**ositive **H**ealth **E**ffects of the **N**atural **O**utdoor environment in **Ty**pical **P**opulations in different regions in **E**urope (PHENOTYPE) project investigates the interconnections between natural outdoor environments and better human health and well-being..

Aims and methods: The PHENOTYPE project explores the proposed underlying mechanisms at work (stress reduction/restorative function, physical activity, social interaction, exposure to environmental hazards) and examines the associations with health outcomes for different population groups. It implements conventional and new innovative high tech methods to characterize the natural environment in terms of quality and quantity. Preventive as well as therapeutic effects of contact with the natural environment are being covered. PHENOTYPE further addresses implications for land-use planning and green space management.

The main innovative part of the study is the evaluation of possible short and long term associations of green space and health and the possible underlying mechanisms in 4 different countries (with quite different type of green space and use of green space) using the same methods and methodology in one research program. This type of holistic approach has not been undertaken before. Furthermore there are technological innovations such as the use of remote sensing and smartphones in the assessment of green space.

Conclusion: The project will produce a more robust evidence base on links between exposure to natural outdoor environment and human health and well-being, in addition to a better integration of human health needs into land use planning and green space management in rural as well as urban areas.

Keywords: green space, blue space, health, well being, physical activity, social contacts, restoration, stress, air pollution, remote sensing, GIS, audit, questionnaire survey, smartphones

Article summary

Strengths

The PHENOTYPE project is the largest European project on green space and health

The PHENOTYPE project examines simultaneously the possible underlying mechanisms (stress reduction/restorative function, physical activity, social interaction, exposure to environmental hazards) for the relationship between green space and health in 4 different countries in Europe

The PHENOTYPE project examines a range of possible associations of the natural outdoor environment and health using 16 different cohorts and/registries in 4 different European countries

The PHENOTYPE project uses a range of novel tools and methods to assess access and use of green space including remote sensing, smartphones, audits and interviews.

The PHENOTYPE project works closely with stakeholders and produces new information for stakeholders.

Introduction

Positive health effects have been observed between green space and mortality longevity[1-3], cardiovascular disease[4], people's self reported general health[5,6], mental health[7-11], sleep patterns[12], recovery from illness[13], social health aspects[14-18] and birth outcomes[19-21]. Some of the associations were shown to be modified by social economic status and level of urbanity, with greater benefits for populations with lower socioeconomic class[20,22] and those in more urban areas[6,22]. Furthermore gender has been shown to modify the relationship[11].

Increased physical activity and social contacts, psychological restoration/stress reduction, and a reduction in pollutants such as noise and air pollution, and temperature have been proposed as possible mechanisms for the health benefits of green space. Access to and/or use of green space has been associated with higher levels of physical activity[23-33] and lower levels of obesity within communities[25,27,34-38]. Studies even suggested that 'green exercise' can have even more positive mental health benefits than other kinds of exercise[39-42].

Psychological restoration[43-45] and reduced stress and anxiety[7,8,17,46,47] have all been associated with access to and/or use of green and natural space. An inner city study in a deprived estate in Chicago showed the benefits of green space both to cognitive restoration[48,49], self-discipline[48], reduced aggression[49] and reduced crime[50], with the latter also observed elsewhere recently[51]

Furthermore a few studies have suggested that green space is associated with more social contacts and cohesion[16,17,52]. And finally reduction of personal exposure to air pollution has been observed in areas with more green space[53], while vegetation has been suggested to reduce air pollution levels, and temperature[54-57], with some suggestion that the benefits are greater for socially disadvantaged groups[55]. It has also been suggested that vegetation (trees, plants) and soil may have an impact on the sound level[58-63]. Part of the appeal of green spaces may be related to pleasant acoustic environments. This may have its own, direct beneficial health effect (Health Council of the Netherlands, 2006).

While this growing evidence exists that close contact with nature brings benefits to human health and well-being, the proposed mechanisms are still not well understood and the associations with health remain uncertain. Furthermore, it is unclear if the possible mechanisms act in isolation or together, since with some exceptions[18] they have been studied in isolation. A coherent conceptual framework on the proposed mechanisms is currently lacking. Also, most of the research has been conducted in the North West of Europe and USA leaving questions about the generalisability to other regions. Inconsistency and variation in indicators (eg type, size and quality) for green space have often made it difficult to compare results from different studies, and a better characterisation including that of quantity and quality of green and blue spaces is needed, not only for research but also for policymakers and spatial planners. Studies have often focused on access to green space without taking into account actual use of green space. While blue space may also have a positive effect on health, probably in combination with green space, there are only a few epidemiological studies investigating this[64-66]

PHENOTYPE, a collaborative research project and explores the proposed underlying mechanisms at work (stress reduction/restorative function, physical activity, social interaction, exposure to environmental hazards). PHENOTYPE is the first study designed to examine these mechanisms simultaneously in a large sample (N=4000 subjects) in various European countries using the same methodology. This allows the study of specific factors while adjusting for others, and thereby strengthening the interpretation of the results. It further examines both the long term and short term associations with health (eg general health and wellbeing, mental health/neural development, stress, cardiovascular, cancer and respiratory mortality and morbidity, birth outcomes and obesity) for different population groups (e.g. pregnant women and/or foetus, different age groups, socioeconomic status, ethics groups, and patients), through analyses of existing cohort studies, observational studies and experiments. Preventive as well as therapeutic effects of contact with the natural environment are being evaluated. A coherent conceptual framework on the association between the natural environment and its effects on health and well-being is being developed, and it addresses implications for land-use planning and green space management.

The study includes both rural and urban settings, but the main focus is on the urban environment, for a number of reasons. Most of the population lives in urban areas (75%) in Europe, making these of greater relevance to public health, and rapid urbanization continues to reduce accessible natural environments for urban residents. Most people make more frequent use of the green spaces in their nearby living environment instead of travelling greater distances to rural areas, in particular people with lower socio-economic status, elderly people and children[67,68]. Furthermore, rural dwellers tend to have constant contact with the natural environment and it may therefore also be more difficult to assess its effects.

Lastly, the project uses an interdisciplinary and integrated approach, applying the best and most efficient methods to understand the relation between exposure to the natural environment and health. It implements conventional and innovative high tech methods to characterize the natural environment in terms of quality and quantity. This paper provides a general overview of the research methodology of PHENOTYPE.

Methods

Figure 1 summarizes the different parts of the study and the interdependencies between the different parts, namely the characterisation of the natural environment and the way it is used, examination of the underlying mechanisms in daily life settings, short and long term effects of the natural environment, and the implications for management and policy of the natural environment (see overview Figures 1 and web figure 1). In this section we will elaborate on each of these parts. A summary of the mechanisms, outcomes, populations and areas selected for investigation are given in Table 1.

Characterising the natural environment and the way it is used.

The research includes evaluation of the natural environment, which includes for the purposes of the project:

- Green spaces (e.g. roof gardens, city parks, court yards) and “greenery”; forests, nature reserves/parks, mountains, farmland, trees, landscaping

- Blue spaces; water such as canals, ponds, creeks, rivers, beaches etc.

Although many of these may actually not be ´´natural´´ since they have been man-made, for the purpose of the project we classify them as such.

One of the main aims of PHENOTYPE is to examine the importance of both quantitative (e.g. amount, type, access, use) and qualitative characteristics (e.g. acoustic quality, identity, variety, safety, rubbish) of the natural environment by collecting detailed data on these characteristics using a combination of methods. The focus lies on natural environments at different scales and distances from the home (city/town, neighbourhood, street level) and where possible also at other places where people stay (work, school, on their way to home/school, recreational). In addition, actual use of the natural environment is taken into consideration. To achieve the aim, a detailed assessment will be conducted in 4 case cities (Barcelona, Spain; Doetinchem, the Netherlands; Kaunas, Lithuania; and Stoke-on-Trent, United Kingdom), with less detailed assessment in other study areas.

PHENOTYPE uses conventional land use maps, remote sensing data from satellites and aerial photography, complemented by detailed discussions with volunteers and other stakeholder living and working in the studied areas to derive comparable classifications of the natural environment in different countries. Collected data will contribute to the characterisation of the natural environment (both quantitative and qualitative e.g. accessibility, acoustical quality, recreational activities, walkability etc). For the quantitative characterisation, PHENOTYPE makes use of available land use maps such as COordination and INformation on the Environmental programme, initiated by the European Commission (CORINE)[69] and Urban Atlas[70], and remote sensing and aerial photography to obtain comparable indices such as NDVI[71] of the natural outdoor environment in different countries. Landsat Enhanced Thematic Mapper Plus (ETM+) data are applied to a classification and regression tree (CART) model to categorise land cover types for the urban areas of interest[55]. Early application of the NDVI in Barcelona, Spain showed good results[20] (Web Figure 2)

To collect additional qualitative information on the natural environment and on other physical and social features, systematic observations (audits) are conducted by trained researchers in selected neighbourhoods in the 4 case cities using the same methods.

Since it is not feasible and not necessary to audit every street in a selected neighbourhood, a purposeful sample of streets is drawn, ensuring that important neighbourhood features are included. The selected neighbourhoods are divided into more or less homogeneous sub-areas by means of data/maps on land use/function of areas in combination with local knowledge of the area. Subsequently, trained auditors are asked to visit the sub-areas and observe them in a systematic way (auditing) using a paper form containing several close-ended questions. Every sub-area is visited by two auditors. For the first 1-2 areas, the auditors fill in the list together, discussing completion to reach consensus. In subsequent areas, where possible, the two auditors complete the audit independently and simultaneously. Furthermore, up to two natural environments of more than one hectare in size are selected per neighbourhood using GIS. Again following training in completion of the audit, two auditors visit the environments. For the first five areas, auditors undertake the interview together, discussing completion to reach consensus, thus maximizing consistency. In subsequent areas, where possible, two assessors complete the audit independently and simultaneously. In the absence of existing measures that could meet our requirements, the streetscape audit was developed for this project and the natural environment tool was adapted from an existing measures. This kind of bespoke tool development is seen in similar studies e.g. by Van Dillen[72]. One form is used for evaluating the streetscape, using indicators derived from the Street Typology developed by Leijdelmeijer et al. (2002)[73], a list of evaluating the quality of green by Van Dillen (2012)[72] and the audit tool developed by Van Lenthe et al. (2006)[74]. The natural environment audit is adapted from that developed by Gidlow et al (2012)[75] through addition of items and domains to reflect the greater diversity in natural environments to be included (i.e., different types of natural environment across four European cities). The tools were piloted and adjusted prior to use. They have not been 'validated', but there is no gold standard quality measure for natural environments against which to compare. Inter-rater reliability will be estimated through derivation of Inter-rater Correlation Coefficients (ICC) and PCA will be used to ensure that any redundant items are removed and included items are grouped sensibly into domains, before overall quality scores will be derived.

To gain insight into the way people use the natural environment, a face to face questionnaire survey is conducted to collect data on 1000 people in the 30 selected neighbourhoods in each of the 4 case cities, and an in-depth study using "Calfit", a smartphone-based monitor of time-location patterns and momentary states, on a subsample (n=100) of the participants of the questionnaire survey (for further detailed information, see next section on underlying mechanisms). The Calfit software[76,77] runs on a Google Android operating system and as currently configured can collect data on physical activity using the motion sensor and geographic location though a global positioning system (GPS), to obtain information on minutes spent and physical activity levels in different natural environments (Web Figure 3). The instrument has been validated against the Actigraph accelerometer[76], combined with other pollution measurements to assess likely inhalation[77], and lab-validated using the Cosmed metabolic monitoring system.

The work will produce different indicators of natural space that can be used in the studies described below. The aim is to make a hierarchy of indicators with on the bottom simple measures such as NDVI that can be easily obtained for all the study areas and on the top detailed measures of for example green space with actually information on the quantity, quality and use that can only be obtained for only some areas after in-depth study. As part of the work, we will examine the relationship between the simple and detailed measures to better understand how detailed information on small scale can help the interpretation of health studies conducted in larger areas with only simple measures available using existing epidemiological studies and registries (see below).

Examining the underlying mechanism in the daily life setting

New data will be collected to explore in detail and simultaneously the proposed mechanisms (physical activity, social contacts/cohesion, psychological restoration/stress reduction) underlying the relationship between the natural environment and health and well-being, in the four case cities. In each of these cities neighbourhoods varying in socio-economic status and in their distance to green space are selected. In these neighbourhoods the natural environment will be characterised, and (as mentioned above already) a selection of 1000 randomly selected residents (4000 in total, 18-75 years) will participate in a questionnaire survey, 100 in a smartphone study, and 20 in in-depth interviews (Web Figure 4).

To optimally investigate what types of natural environments and different levels of accessibility are relevant in relation with the mechanisms that we investigate (physical activity, stress and restoration, social interactions and environmental pollution), and to investigate potential differences in this mechanism among the population, we use a multiple level approach and select neighbourhoods with different socio-economic status (SES) and access to the natural environment. We use existing statistical or administrative units with Existing statistical or administrative units that were as similar as possible with regard tovariation in population size; in Stoke-on-Trent Lower Layer Super Output Areas (LSOAs), in Barcelona census areas, in Kaunas voting districts and in Doetinchem neighborhoods. Natural space and SES measures are assigned to all the units, using existing data. For natural space, Urban Atlas is used for Stoke-on-Trent, Barcelona and Kaunas. Since Urban Atlas is not available for Doetinchem, data of another Dutch database ('Top10 nl') is used. For SES no comparable data existed for the 4 cities. Therefore partners use their own local data. Then the units are ranked by each natural space and SES. Subsequently a selection of two neighbourhoods from each combination of top, middle and bottom tertiles of SES and quintiles of the natural space is made (approx. 2*3*5= 30 units). A few extra units are added to optimize contrast and reach a sufficient number of units to be able to recruit a 1000 subjects in each city (30 subjects per units). Since there are no common person registries in these countries, subjects (aged between 18 and 75) are selected using different approaches. In Doetinchem and Stoke-on-Trent, addresses are sampled randomly from the BAG Registry ('Buildings and Adresses') 2012 and a local address registry respectively and the person with the closest birthday to the interview data is selected at each address, in Barcelona subjects are randomly selected from the person registry (empadronamiento) and in Kaunas subjects are sampled randomly from a 2006-2009 survey of randomly sampled people of the city of Kaunas. In each case there is an over selection of potential addresses or subjects to be able to interview at least a 1000 subjects (and 30 per unit) in each city. The target of a 1000 subjects per city was mostly based on the available budget. To enable multi-level analysis, we estimated that a minimum of 30 participants per group (or neighbourhood) were required, with a minimum of 30 groups.

The questionnaire survey was designed to investigate three potential mechanisms in relation to natural environments and health: via physical activity, stress and restoration and social interactions as described in. In addition questions are included about environmental worries and reactions to perceived exposures (air pollution, noise, etc). The choice of indicators was based on these three mechanisms and was achieved via an interactive process of experts within the PHENOTYPE team. As much as possible questions were derived from existing and validated indices, some tailored to the specific objectives of PHENOTYPE. The questionnaire was developed in English and was translated (and back translated) into Dutch, Spanish, Catalan, and Lithuanian. The questionnaire was developed to be applied in an oral interview of at maximum 60 minutes. In Kaunas it is not common to have face-to-face interviews; therefore a written questionnaire is sent by post to the selected people. The questionnaire was piloted by all partners, with specific attention for comprehensibility, clarity and duration and was adapted at some points based on outcomes of these pilots.

The final questionnaire is structured along four main clusters of questions: I. Green and Blue Spaces; II Residential situation: Dwelling & Neighbourhood; III Wellbeing and Health; IV Personal characteristics. Per mechanism questions are asked about availability, use, importance, and satisfaction. In the sequencing of the questions we strive for a coherent set of questions per cluster moving from general to specific and from ‘’easy’’ to more intruding questions. Furthermore, most of the answer categories moved from neutral negative towards positive items. For all answers showcards have been developed by RIVM, to make it easier for both interviewers and respondents, and to speed up the interview process. A separate instruction document was developed to train the interviewers. The questionnaire ended with an optional a pencil paper attention test (Color Trails Test (CTT-A)) add ref.

Finally for the smartphone study at least 100 volunteers from each country are randomly selected from the participants of the questionnaire survey who indicated that they were willing to participate in the smartphone study. For these subjects, during 7 subsequential days the emotional state of the subject, the local environment (e.g., different quantities or qualities of natural space) and the social setting are assessed with the smartphone and the innovative Calfit technology. Besides objective geolocation and physical activity (see section Characterisation the natural environment), subjective data on stress reduction/restoration and social contacts are collected simultaneously. The latter data are collected through interactive diaries capable of eliciting ecological momentary assessment (EMA). EMA is a novel approach to elicit responses to electronic surveys throughout the course of daily life[78]. The participant receives prompts at random intervals to complete small surveys on the phone, which then have time and location stamp.

From the people who participate in both the questionnaire survey and the CALFIT study and who indicate they wanted to volunteer, 80 people (20 in each case city) are approached for semi structured interviews. These interviews are conducted to gain more detailed information on specific topics included in the questionnaire survey and CALFIT/EMA. Topics addressed include the motivation for travel routes, the associations of natural environment with mood, behaviour and well-being, the attitude towards and importance of (experiences with) natural environment, and reasons for using or not using the natural environment.

Epidemiological studies to examine long term effects of the natural environment

By using existing epidemiological studies and registries and linking these to the natural space indicators described earlier, the association between natural environment and a range of different long term health outcomes will be examined in an efficient and cost effective manner. PHENOTYPE makes use of 16 existing cohorts and registries with good health outcome data in Spain, the Netherland, Lithuania, and United Kingdom (Web Table 1), linking these to newly created natural environment indicators. Comparable estimates are produced for various regions in Europe for the associations with pregnancy outcomes, foetus development, children's health and adult population morbidity and mortality. We specifically focus on:

- the natural outdoor environment and ethnicity, socio-economic status, women´s health and pregnancy outcomes;
- the natural outdoor environment and foetus development, birth weight, and gestational age;
- the natural outdoor environment and general development, neurodevelopment, cognitive function and respiratory health in children;
- the natural outdoor environment and respiratory health in various European cities;
- the natural outdoor environment and general health, physical activity, specific morbidity and mortality.

The assessment of natural environment indicators will be mainly based on satellite data and land use maps as CORINE and Urban atlas, and sometimes local data. This will restrict to some extent the evaluation of the association with the natural environment, but this is the only realistic and achievable approach. All studies examine the role of socio-economic status, which has been suggested as an effect modifier for the relationship between exposure to the natural environment and health benefits. The European Community Respiratory Health study (ECRHS)[79] further allows for examination of exposure to the natural outdoor environment and associations with health in a range of different European cities. Some cohorts such as the Born in Bradford study[80] offers a unique opportunity to investigate the role of ethnicity in the relationship between exposure to the natural outdoor environment and health benefits, in Bradford study half of the participants are from Pakistani background, with information on both the mother and baby from pregnancy to early years in life.

Experiments to examine short term effects of the natural environment

To examine short term effects of the natural environment on health and well-being, one or more experimental studies are conducted in each country in which individuals are exposed to different types of natural and urban environments (i.e., environmental conditions). The majority of data collection is field-based to maximise the ecological (as well as internal) validity of any observed effects.
Using a range of psychological and physiological indicators relevant to the various possible mechanisms, and 2) healthy and patient population groups (with mental and/or somatic morbidities) we will collectively explore::

- preventive and therapeutic effects of natural environments.
- immediate and sustained changes in affective, cognitive and physiological responses indicative of well-being while engaged in a natural environment, and after leaving a natural environment
- neurobiological responses to viewing natural or urban scenes before/after experiencing stress.

Through variation in experimental design, each partner makes a novel contribution(s) to the area as (details in Web Table 2):

- UK: In healthy individuals, Study 1 compares immediate and post-exposure psycho-physiological effects of urban versus natural environments to explore whether any beneficial effects are sustained following single exposures; Study 2 uses longer-term follow-up and repeated exposure to natural environments to explore whether any effects are accumulated, sustained or attenuated.
- Netherlands: an experimental functional Magnetic Resonance Imaging (fMRI) study is conducted in healthy individuals to investigate neurobiological responses to viewing natural or urban scenes before/after experiencing stress; i.e., whether viewing natural compared to urban scenery can prevent or buffer against stress responses, and how this is represented in brain activation patterns.
- Spain: in individuals with elevated stress levels, group-based exposure and Ecological Momentary Assessment (EMA, using CALFIT technology) are used to explore the role of social interaction and the nature of physical activity, in immediate and longer term responses. Ecological validity will be enhanced through 'free-living' activities within environments, rather than controlling activities, again, using EMA, GPS and accelerometry to monitor the nature (and perceptions) of this activity.
- Lithuania: a clinical population with established coronary artery disease (CAD) are recruited to evaluate the therapeutic effect of the natural environment. The outcomes of this experiment may have direct clinical applications for the use of urban and different types of natural environment in cardiac rehabilitation.

Implications, policy and guidelines and involvement of stakeholders

Guidelines

PHENOTYPE will provide recommendations for policymakers and guidelines for professional practitioners involved with spatial planning and health to create natural environments that promote health and well being. For this, we focus on a human ecological perspective which allows for a better integration of human health needs into land use planning and green space management in both rural and urban areas[81]. Currently legal standards that have been developed with economic, technological and political priorities in mind, are leading in urban design, whereas the lifestyle, sense of community, identity, and health and well being of local populations have been largely undervalued. The guidelines will reflect the importance to consider environmental, social, economic and other components of the natural and built environments in ways that also take into account and result from the point of view of citizens. PHENOTYPE will complement the common quantitative approach by valorising the social/human functions of these environments, especially their contribution to promoting health and quality of life.

Following this broad and innovative approach, PHENOTYPE will formulate, test and validate a set of recommendations and guidelines concerning the desired characteristics of different types of natural environments in urban and rural areas, specifically their characteristic features, accessibility to them for different population groups, as well as their facilities, maintenance and services. By doing so, the work will overcome the existing applicability gap between information and knowledge accumulated by much research and policy definition and implementation.

The guidelines for professional practitioners involved with spatial planning and health will consider three core topics in relation to each of the natural environment being considered:

1. Qualitative characteristics of natural environments; recommendations concerning surface area, vegetation, water sources, ambient noise levels, views and microclimate;
2. Facilities, Maintenance and Services; recommendations about the kinds of communal facilities and services provided in each type of natural environment, as well as suggested levels of maintenance;
3. Accessibility Guidelines to Natural Environments; including requirements about access to different types of natural environments such as allotments, neighbourhood parks, children's playgrounds and nature reserves.

The baseline for the work is firstly the compilation and analysis of currently available information from existing databases and literature, and later new data collected by the project as described above. This will be complemented by the engagement with the appropriate stakeholders to assess scope for development. These insights will be combined into a conceptual framework on the underlying mechanisms of the effects of the natural environment on health and well-being.

Stakeholders and dissemination

The participation provides a forum for project assurance and benefits for PHENOTYPE are summarised as follows:

- A more robust evidence base on links between exposure to natural outdoor environment and human health/well-being for various regions in Europe. Hereby we expect to develop a better understanding of the potential mechanisms.
- A better integration of human needs into land use planning and green space management in rural as well as urban areas. Furthermore, the application of these needs in practical guidelines.

Stakeholder involvement is critical for bringing outside (policy) ideas into the research planning, to increase the usefulness of the research, and to assure a better implementation of the results of the project (Web Figure 5). In a research project, this is often limited because the lack of interest of stakeholders and the limited resources and efforts of consortia.

From the start of PHENOTYPE actively sought to establish and maintain relations and dialogues with and between key stakeholders from local, regional and national health and environment authorities, institutions and the international research community. These include policy makers, architects, urban planners, natural space managers, health professionals, and the international research community. This group is highly diverse, as we are looking at a range of professions within the subject areas of environment and health, from volunteers to scientists, community workers and policy developers. PHENOTYPE has thus far been successful in its engagement activities, providing continuous opportunities for information exchange and collaborations. These contribute to strengthening networking between researchers, policy-makers and stakeholders in order to facilitate the transfer of scientific knowledge to policy development, to exchange ideas about best practice and to help identify emerging issues on the natural outdoor environment and its mechanisms to improve health.

The PHENOTYPE website www.phenotype.eu provides an overview of the project, progress, actualities, surveys and publications. The site has a sign up form for periodic newsletters through which all stakeholders are regularly informed. It guarantees continuous visibility, and provides a means for interested parties to respond to activities, or to contact us with invitations to attend workshops, etc. PHENOTYPE is also found on social media twitter (@greenhealth4eu) and LinkedIn. The PHENOTYPE databases and overall results will be exploitable by policy makers at national and international level in areas including urban planning and health.

Conclusion

The PHENOTYPE project is an FP7 collaborative action, funded by the EC to explore the mechanisms underlying positive short term and long term health effects for different population groups. PHENOTYPE applies conventional and new innovative high tech methods to characterize the natural environment in terms of quality and quantity. Preventive as well as therapeutic effects of contact with the natural environment will be covered. The proposed work aims to address the limitations of some of the studies that have been published so far (Table 2). Furthermore it addresses implications for land-use planning and green space management. The project will produce a more robust evidence base on links between exposure to natural outdoor environment and human health and well-being. This in turn will contribute to improved integration of human health needs into land use planning and green space management in rural and urban areas.

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[ENV.2011.1.2.3-2] Positive effects of natural environment for human health and well-being] Duration 1 Jan 2012-31 Dec 2015

Ethics approval was obtained for all aspects of the study by the local ethics committees in the countries where the work was conducted, and sent to the European Commission before advancement of the study.

Author statement

Mark J Nieuwenhuijsen, Hanneke Kruize, Christopher Gidlow, Michael Jerrett, Jolanda Maas, Edmund Seto, Peter Jan van den Hazel, Roderick Lawrence, and Regina Grazuleviciene and wrote the original grant proposal on which the study design and paper is based. Mark J Nieuwenhuijsen drafted the version of the paper and received input from all the authors. All authors read and commented on the paper and agree with the final version.

Competing Interests

None

Data Sharing Statement

"No additional data available yet"

"No additional data available yet".

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Table 1 PHENOTYPE study mechanisms, outcomes, populations and regions

It will explore underlying mechanisms related to:

- stress reduction/restorative function
- physical activity
- social interaction/social cohesion

exposure to environmental hazards (e.g. noise/acoustic quality, air pollution)

Both preventative and therapeutic effects (patients) will be considered. Outcomes of interest that are evaluated are:

- general health and well-being (including medically unexplained symptoms
- (MUPS))
- mental health/neural development
- stress
- cardiovascular, cancer and respiratory mortality and morbidity
- birth outcomes
- obesity

It will examine the effects for different population groups, including more vulnerable populations:

- pregnant women and/or foetus
- age groups (children, elderly)
- (lower) socio-economic status
- ethnic minorities
- patients/people with specific health complaints

It will conduct comparative studies in different regions of Europe to examine any underlying regional, social and/or cultural differences related to the meanings, uses, mechanisms and health effects of the natural environment and we will include the:

- North west (Netherlands, England)
- South (Spain)
- East (Lithuania)

Table 2 Limitations of current green space work and work undertaking by PHENOTYPE to address these

Limitations of current available work	What PHENOTYPE will do
▪ Inconsistency and variation in indicators for green or natural space have often made it difficult to compare results from different studies.	▪ Minimize the potential differences due to classification of natural space, by combining the use of conventional maps and data sources with remote sensing data and aerial photography, gather individual-level data through detailed discussions with subjects living in the areas, and use considerable stakeholder engagement to develop comparable classifications of the natural environment in different countries. ▪ Produce a more robust and comparable evidence base on links between exposure to natural outdoor environment and human health and well-being.
▪ A number of disease outcomes have been studied, but besides the routinely collected data (which use ICD coding), not always in a standardized and comparable manner in different countries	▪ Produce a more robust and comparable evidence base on links between exposure to natural outdoor environment and human health and well-being, using well studied and new outcomes with standardization between countries.
▪ Potentially very sensitive groups such as pregnant women/fetus have not been studied at all.	▪ Extend the evidence base to new outcomes and vulnerable populations e.g. pregnant women and their foetus, chronic respiratory and cardiovascular patients, ethnic minorities and

	low social economic class.
▪ Most studies focused on green space; the evidence base for the effects of blue space is very limited.	▪ Not only examine the effects of green space, but also of blue space.
▪ Most of the green space studies have been conducted in the US or the North West of Europe.	▪ Conduct comparable studies across Europe and produce evidence for North Western, Eastern and Southern Europe. This will deliver insights into regional, social and/or cultural differences in relation to natural space.
▪ Most studies do not include actual use of the natural environment.	▪ Consider actual use of the natural environment, an often neglected but fundamental indicator in relation to exposure to natural environments.
▪ There appeared to be differences by social group, with some apparently benefiting more than others from natural space, but the evidence is sparse.	▪ Produce a more robust and comparable evidence base on links between exposure to natural outdoor environment and human health and well-being, with special attention for effect modification by social groups
▪ A number of potential mechanisms have been suggested, including increased physical activity and social contacts for those living near natural space, natural environments exerting	▪ Examine the proposed mechanisms (physical activity, stress, social contacts, and environmental risk factors) simultaneously in a large sample in various countries (WP2). This will enable

stress lowering or attention restoring effects, and reducing environmental hazards (e.g. air pollution, high temperatures). However, the studies of potential mechanisms have often been limited to assessing one mechanism at the time, which increases the likelihood of unmeasured confounding effects and misses the opportunity to study these potentially interrelated mechanisms in coherence. ▪ to study the mechanisms in coherence even though they may be interrelated	us to study specific factors while adjusting for others, and thereby strengthening the interpretation of the results
▪ Unable to answer what specific quantitative and qualitative characteristics of the natural environment have a positive effect on health and well-being, through what pathways is still largely unknown.	▪ Make classifications for the type and level of the indicators, which is important for policy makers. ▪ Examine the importance of both quantitative (amount, type, access, use) and qualitative characteristics (acoustic quality, identity, variety, safety) of the natural environment
▪ Limited research exploring the sustained affective, cognitive and physiological responses to a single exposure and the effects of a repeated exposure to the same natural environment ▪ Unable to explain how policymakers and planners can design a natural environment to maximise health benefits	▪ Explore longer-term changes in affect, cognitive function and physiological indicators that have to date only been studied during, or immediately after, engagement with the natural environment. ▪ Explore the immediate, maintained and long-term effects of repeated engagement with the same natural environment on

	affect, cognitive function, and physiological indicators of well-being .
▪ Guidelines of lifestyle, health and well being have largely undervalued local populations	▪ Include lifestyle, health and well being factors of the local populations.

Figure legend

Figure 1: Interdependencies of different parts of the PHENOTYPE project

Annex-web figures

Web Figure 1 Natural outdoor environment, mechanisms and health data input in PHENOTYPE

Web Figure 2 NDVI map of Barcelona and buffers around major green space areas

Web Figure 3 Mobility pattern for a subject in Barcelona obtained with the Calfit tool

Web Figure 4 Design of data collection in 4 European case cities to study the underlying mechanism

Web Figure 5 Stakeholder input and dissemination

(All attached separately)

POSITIVE HEALTH EFFECTS OF THE NATURAL OUTDOOR ENVIRONMENT IN TYPICAL POPULATIONS IN DIFFERENT REGIONS IN EUROPE (PHENOTYPE)-A STUDY PROGRAMME PROTOCOL

POSITIVE HEALTH EFFECTS OF THE NATURAL OUTDOOR ENVIRONMENT IN TYPICAL POPULATIONS IN DIFFERENT REGIONS IN EUROPE (PHENOTYPE)

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Abstract

Introduction: Growing evidence suggests that close contact with nature brings benefits to human health and well-being, but the proposed mechanisms are still not well understood and the associations with health ~~effects~~ remain uncertain. The **Positive Health Effects of the Natural Outdoor environment in Typical Populations in different regions in Europe** (PHENOTYPE) project investigates the interconnections between natural outdoor environments ~~, in both rural and urban settings,~~ and better human health and well-being~~being in the North West, South and East of Europe. Here we provide a description of the proposed work.~~.

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Aims and methods: The PHENOTYPE project explores the proposed underlying mechanisms at work (stress reduction/restorative function, physical activity, social interaction, exposure to environmental hazards) and examines the associations with health ~~effects~~ outcomes ~~(e.g. general health and wellbeing, mental health/neural development, stress, cardiovascular, cancer and respiratory mortality and morbidity, birth outcomes and obesity)~~ for different population groups ~~(e.g. pregnant women and/or foetus, different age groups, socioeconomic status, ethnic groups, and patients)~~. It implements conventional and new innovative high tech methods to characterize the natural environment in terms of quality and quantity. Preventive as well as therapeutic effects of contact with the natural environment are being covered. PHENOTYPE further addresses implications for land-use planning and green space management.

~~**Result:**~~ The main innovative part of the study is the evaluation of possible short and long term ~~effect~~ associations of green space and health and the possible underlying mechanisms in 4 different countries (with quite different type of green space and use of green space) using the same methods and methodology in one research program. This type of holistic approach has not been undertaken before. Furthermore there are technological innovations such as the use of remote sensing and smartphones in the assessment of green space.

Conclusion: The project will produce a more robust evidence base on links between exposure to natural outdoor environment and human health and well-being, in addition

to a better integration of human health needs into land use planning and green space management in rural as well as urban areas.

Keywords: green space, blue space, health, well being, physical activity, social contacts, restoration, stress, air pollution, remote sensing, GIS, audit, questionnaire survey, smartphones

Article summary

Strengths

The PHENOTYPE project is the largest European project on green space and health

The PHENOTYPE project examines simultaneously the possible underlying mechanisms (stress reduction/restorative function, physical activity, social interaction, exposure to environmental hazards) for the relationship between green space and health in 4 different countries in Europe

The PHENOTYPE project examines a range of possible associations of the natural outdoor environment and health ~~health effects of green space~~ using 16 different cohorts and/registries in 4 different European countries

The PHENOTYPE project uses a range of novel tools and methods to assess access and use of green space including remote sensing, smartphones, audits and interviews.

The PHENOTYPE project works closely with stakeholders and produces new information for stakeholders.

~~Weakness~~

~~The limited funding may not lead to the full exploitation by the wealth of data generated within the life time of the project~~

Introduction

Positive health effects have been observed between green space and mortality longevity[1-3] ~~(Takano et al. 2002; Mitchell and Popham 2008, Villeneuve et al. 2012)~~, cardiovascular disease[4] ~~(Pereira et al. 2012)~~, people's self reported general health[5,6] ~~(de Vries et al. 2003; Maas et al. 2006)~~, mental health[7-11] ~~(Grahn & Stigsdotter, 2003; Hartig et al. 2003; Maas, et al. 2009b; Ottosson & Grahn, 2005, Richardson et al. 2013)~~, sleep patterns[12] ~~(Astell-Burt et al. 2013a)~~, recovery from illness[13] ~~(Ulrich 1994)~~, social health aspects[14-18] ~~(Kim & Kaplan, 2004; Sullivan et al. 2004; Kweon et al 1998; Maas et al. 2009a; de Vries 2010)~~ and birth outcomes[19-21] ~~(Donavan et al. 2012; Dadvand et al. 2012a, Dadvand et al. 2012b)~~. Some of the associations were shown to be modified by social economic status and level of urbanity, with greater benefits for populations with lower socioeconomic class[20,22] ~~(Mitchell & Popham, 2008, Dadvand et al. 2012a)~~ and those in more urban areas[6,22] ~~(Maas et al. 2006; Mitchell et al. 2007)~~. Furthermore gender has been shown to modify the relationship[11] ~~(Richardson and Mitchell 2010b)~~.

Increased physical activity and social contacts, psychological restoration/stress reduction, and a reduction in pollutants such as noise and air pollution, and temperature have been proposed as possible mechanisms for the health benefits of green space. Access to and/or use of green space has been associated with higher levels of physical activity[23-33] ~~(Cohen et al. 2006; Cohen et al. 2007; Coombes et al. 2010; Lachowycz and Jones 2011; Toftager et al. 2011; Rodriguez et al. 2012; Mytton et al. 2012; Annerstedt et al. 2012; Almanza et al. 2012; Astell-Burt et al. 2013b; Richardson et al. 2013)~~ and lower levels of obesity within communities[25,27,34-38] ~~(Coombes et al. 2010; Ellaway et al. 2005; Wolch et al. 2011; Toftager et al. 2011; Pereira et al. 2013; Astell-Burt et al. 2013c; Lovasi et al 2013)~~. Studies even suggested that 'green exercise' can have even more positive mental health benefits than other kinds of exercise[39-42] ~~(Bodin et al. 2003; Pretty et al. 2005; Bowler et al. 2010; Thompson Coon et al. 2011)~~.

Psychological restoration[43-45] ~~(Kaplan & Kaplan, 1989; van den Berg et al. 2003; van den Berg & Custers, 2011;)~~ and reduced stress and anxiety[7,8,17,46,47] ~~(Ulrich et al., 1991, Grahn & Stigsdotter, 2003; Hartig et al. 2003; Maas et al. 2009; Stigsdotter et al 2010)~~ have all been associated with access to and/or use of green and natural space.

An inner city study in a deprived estate in Chicago showed the benefits of green space both to cognitive restoration[48,49] ~~(Faber Taylor 2002; Kuo & Sullivan, 2001a)~~, self-discipline[48] ~~(Faber Taylor et al. 2002)~~, reduced aggression[49] ~~(Kuo & Sullivan, 2001a)~~ and reduced crime[50] ~~(Kuo & Sullivan, 2001b)~~, with the latter also observed elsewhere recently[51] ~~(Wolfe and Mennis 2013)~~

Furthermore a few studies have suggested that green space is associated with more social contacts and cohesion[16,17,52] ~~(Kuo et al. 1998; Kweon et al. 1998; Maas et al 2009)~~.

And finally reduction of personal exposure to air pollution has been observed in areas with more green space[53] ~~(Dadvand et al. 2012c)~~, while vegetation has been suggested to reduce air pollution levels, and temperature[54-57] ~~(Baldauf et al. 2009; Su et al. 2011; Park et al. 2012a, 2012b)~~, with some suggestion that the benefits are greater for socially disadvantaged groups[55] ~~(Su et al. 2011)~~. It has also been suggested that vegetation (trees, plants) and soil may have an impact on the sound level[58-63] ~~(Aylor, 1972; Fan et al. 2010; Fang & Ling, 2003, 2005; Samara & Tsitsoni, 2007; Zhang & Kang, 2007)~~. Part of the appeal of green spaces may be related to pleasant acoustic environments ~~(Brown, 2006 in: Health Council of the Netherlands, 2006)~~. This may have its own, direct beneficial health effect (Health Council of the Netherlands, 2006).

While this growing evidence exists that close contact with nature brings benefits to human health and well-being, the proposed mechanisms are still not well understood and the associations with health ~~effects~~ remain uncertain. Furthermore, it is unclear if the possible mechanisms act in isolation or together, since with some exceptions[18] ~~(de Vries et al. 2013)~~ they have been studied in isolation. A coherent conceptual framework on the proposed mechanisms is currently lacking. Also, most of the research has been conducted in the North West of Europe and USA leaving questions about the generalisability to other regions. Inconsistency and variation in indicators (eg type, size and quality) for green space have often made it difficult to compare results from different studies, and a better characterisation including that of quantity and quality of green and blue spaces is needed, not only for research but also for policymakers and spatial planners. Studies have often focused on access to green space without taking into account actual use of green space. While blue space may also have a positive effect on health, probably in combination with green space, there are only a few epidemiological studies investigating this[64-66] (Völker and Kistemann 2011, Völker and Kistemann 2013, White et al. 2013)

PHENOTYPE, a collaborative research project and explores the proposed underlying mechanisms at work (stress reduction/restorative function, physical activity, social interaction, exposure to environmental hazards). PHENOTYPE is the first study designed to examine these mechanisms simultaneously in a large sample (N=4000 subjects) in various European countries using the same methodology. This allows the study of specific factors while adjusting for others, and thereby strengthening the interpretation of the results. It further examines both the long term and short term health effects associations with health (eg general health and wellbeing, mental health/neural development, stress, cardiovascular, cancer and respiratory mortality and morbidity, birth outcomes and obesity) for different population groups (e.g. pregnant women and/or foetus, different age groups, socioeconomic status, ethics groups, and patients), through analyses of existing cohort studies, observational studies and experiments. Preventive as well as therapeutic effects of contact with the natural environment are being evaluated. A coherent conceptual framework on the association between the natural environment and its effects on health and well-being is being developed, and it addresses implications for land-use planning and green space management.

The study includes both rural and urban settings, but the main focus is on the urban environment, for a number of reasons. Most of the population lives in urban areas (75%) in Europe, making these of greater relevance to public health, and rapid urbanization continues to reduce accessible natural environments for urban residents. Most people make more frequent use of the green spaces in their nearby living environment instead of travelling greater distances to rural areas, in particular people with lower socio-economic status, elderly people and children[67,68] (Schwanen et al. 2002; Maas 2008). Furthermore, rural dwellers tend to have constant contact with the natural environment and it may therefore also be more difficult to assess its effects.

Lastly, the project uses an interdisciplinary and integrated approach, applying the best and most efficient methods to understand the relation between exposure to the natural environment and health. It implements conventional and new innovative high tech methods to characterize the natural environment in terms of quality and quantity. This paper provides a general overview of the research methodology of PHENOTYPE.

Methods ~~and results~~

Figure 1 summarizes the different parts of the study and the interdependencies between the different parts, namely the characterisation of the natural environment and the way it is used, examination of the underlying mechanisms in daily life settings, short and long term effects of the natural environment, and the implications for management and policy of the natural environment (see overview Figures 1 and web figure 1). In this section we will elaborate on each of these parts. A summary of the mechanisms, outcomes, populations and areas selected for investigation are given in Table 1.

Characterising the natural environment and the way it is used.

The research includes evaluation of the natural environment, which includes for the purposes of the project:
- Green spaces (e.g. roof gardens, city parks, court yards) and "greenery"; forests, nature reserves/parks, mountains, farmland, trees, landscaping
- Blue spaces; water such as canals, ponds, creeks, rivers, beaches etc.

Although many of these may actually not be ´´natural´´ since they have been man-made, for the purpose of the project we classify them as such.

One of the main aims of PHENOTYPE is to examine the importance of both quantitative (e.g. amount, type, access, use) and qualitative characteristics (e.g. acoustic quality, identity, variety, safety, rubbish) of the natural environment by collecting detailed data on these characteristics using a combination of methods. The focus lies on natural environments at different scales and distances from the home (city/town, neighbourhood, street level) and where possible also at other places where people stay (work, school, on their way to home/school, recreational). In addition, actual use of the natural environment is taken into consideration. To achieve the aim, a detailed assessment will be conducted in 4 case cities (Barcelona, Spain; Doetinchem, the

Netherlands; Kaunas, Lithuania; and Stoke-on-Trent, United Kingdom), with less detailed assessment in other study areas.

PHENOTYPE uses conventional land use maps, remote sensing data from satellites and aerial photography, complemented by detailed discussions with volunteers and other stakeholder living and working in the studied areas to derive comparable classifications of the natural environment in different countries. Collected data will contribute to the characterisation of the natural environment (both quantitative and qualitative e.g. accessibility, acoustical quality, recreational activities, walkability etc). For the quantitative characterisation, PHENOTYPE makes use of available land use maps such as COordination and INformation on the Environmental programme, initiated by the European Commission (CORINE)[69](EAA 2005) and Urban Atlas[70] (EAA 2010), and remote sensing and aerial photography to obtain comparable indices such as NDVI[71] (Weier and Herring, 2011) of the natural outdoor environment in different countries. Landsat Enhanced Thematic Mapper Plus (ETM+) data are applied to a classification and regression tree (CART) model to categorise land cover types for the urban areas of interest[55] (Su et al 2010). Early application of the NDVI in Barcelona, Spain showed good results[20] (Web Figure 2), Dadvand et al. 2012a)

To collect additional qualitative information on the natural environment and on other physical and social features, systematic observations (audits) are conducted by trained researchers in selected neighbourhoods in the 4 -case cities using the same methods. Since it is not feasible and not necessary to audit every street in a selected neighbourhood, a purposeful sample of streets is drawn, ensuring that important neighbourhood features are included. The selected neighbourhoods are divided into more or less homogeneous sub-areas by means of data/maps on land use/function of areas in combination with local knowledge of the area. Subsequently, trained auditors are asked to visit the sub-areas and observe them in a systematic way (auditing) using a paper form containing several close-ended questions. Every sub-area is visited by two auditors. For the first 1-2 areas, the auditors fill in the list together, discussing completion to reach consensus. In subsequent areas, where possible, the two auditors complete the audit independently and simultaneously. Furthermore, up to two natural environments of more than one hectare in size are selected per neighbourhood using GIS. Again following training in completion of the audit, two auditors visit the

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Formatted: Font: (Default) Times New Roman, 12 pt environments. For the first five areas, auditors undertake the interview together, discussing completion to reach consensus, thus maximizing consistency. In subsequent areas, where possible, two assessors complete the audit independently and simultaneously. In the absence of existing measures that could meet our requirements, the streetscape audit was developed for this project and the natural environment tool was adapted from an existing measures. This kind of bespoke tool development is seen in similar studies e.g.[72] ~~(e.g., Van Dillen et al. 2012.)~~. One form is used for evaluating the streetscape, using indicators derived from the Street Typology developed by Leijdelmeijer et al. (2002)[73], a list of evaluating the quality of green by Van Dillen (2012)[72] and the audit tool developed by Van Lenthe et al. (2006)[74]. The natural environment audit is adapted from that developed by Gidlow et al (2012)[75] through addition of items and domains to reflect the greater diversity in natural environments to be included (i.e., different types of natural environment across four European cities). The tools were piloted and adjusted prior to use. They have not been 'validated', but there is no gold standard quality measure for natural environments against which to compare. Inter-rater reliability will be estimated through derivation of Inter-rater Correlation Coefficients (ICC) and PCA will be used to ensure that any redundant items are removed and included items are grouped sensibly into domains, before overall quality scores will be derived.

~~The researchers walk through the neighbourhood, systematically coding characteristics such as the architectural character, maintenance of the landscape, and perceptions on how a place looks and feels. To collect comparable information in the 4 case cities, two standardized forms are used. One form is used for evaluating the streetscape, using indicators derived from the Street Typology developed by Leijdelmeijer et al. (2002), a list of evaluating the quality of green by Van Dillen (2012) and the audit tool developed by Van Lenthe et al. (2006). A second form is used for evaluating the natural spaces in the study areas of at least 1 ha. It is an adapted form of the Neighbourhood Green Space Tool developed by Gidlow et al. (2012).~~

To gain insight into the way people use the natural environment, a face to face questionnaire survey is conducted to collect data on 1000 people in the 30 selected neighbourhoods in each of the 4 case cities, and an in-depth study using "Calfit", a smartphone-based monitor of time-location patterns and momentary states, on a subsample (n=100) of the participants of the questionnaire survey (for further detailed

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information, see next section on underlying mechanisms). The Calfit software[76,77] (Donaire-Gonzales et al. 2013, de Nazelle et al. 2013) runs on a Google Android operating system and as currently configured can collect data on physical activity using the motion sensor and geographic location though a global positioning system (GPS), to obtain information on minutes spent and physical activity levels in different natural environments (Web Figure 3). The instrument has been validated against the Actigraph accelerometer[76] (Donaire-Gonzales et al. 2013), combined with other pollution measurements to assess likely inhalation[77] (de Nazelle et al. 2013), and lab-validated using the Cosmed metabolic monitoring system.

The work will produce different indicators of natural space that can be used in the studies described below. The aim is to make a hierarchy of indicators with on the bottom simple measures such as NDVI that can be easily obtained for all the study areas and on the top detailed measures of for example green space with actually information on the quantity, quality and use that can only be obtained for only some areas after in-depth study. –As part of the work, we will examine the relationship between the simple and detailed measures to better understand how detailed information on small scale can help the interpretation of health studies conducted in larger areas with only simple measures available using existing epidemiological studies and registries (see below).

Examining the underlying mechanism in the daily life setting

New data will be collected to explore in detail and simultaneously the proposed mechanisms (physical activity, social contacts/cohesion, psychological restoration/stress reduction) underlying the relationship between the natural environment and health and well-being, in the four case cities. In each of these cities 30 neighbourhoods varying in socio-economic status and in their distance to green space are selected. In these neighbourhoods the natural environment will be characterised, and (as mentioned above already) a selection of 1000 randomly selected residents (4000 in total, 18-75 years) will participate in a questionnaire survey, 100 in a smartphone study, and 20 in in-depth interviews (Web Figure 4).

To optimally investigate what types of natural environments and different levels of accessibility are relevant in relation with the mechanisms that we investigate (physical

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activity, stress and restoration, social interactions and environmental pollution), and to investigate potential differences in this mechanism among the population, we use a multiple level approach and select neighbourhoods with different socio-economic status (SES) and access to the natural environment. We use existing statistical or administrative units with Existing statistical or administrative units that were as similar as possible with regard tovariation in population size; in Stoke-on-Trent Lower Layer Super Output Areas (LSOAs), in Barcelona census areas, in Kaunas voting districts and in Doetinchem neighborhoods. Natural space and SES measures are assigned to all the units, using existing data. For natural space, Urban Atlas is used for Stoke-on-Trent, Barcelona and Kaunas. Since Urban Atlas is not available for Doetinchem, data of another Dutch database ('Top10 nl') is used. For SES no comparable data existed for the 4 cities. Therefore partners use their own local data. Then the units are ranked by each natural space and SES. Subsequently a selection of two neighbourhoods from each combination of top, middle and bottom tertiles of SES and quintiles of the natural space is made (approx. 2*3*5= 30 units). A few extra units are added to optimize contrast and reach a sufficient number units to be able to recruit a 1000 subjects in each city (30 subjects per units). Since there is no common person registries in these countries, subjects (aged between 18 and 75) are selected using different approaches. In Doetinchem and Stoke-on-Trent, addresses are sampled randomly from the BAG Registry ('Buildings and Adresses') 2012 and a local address registry respectively and the person with the closest birthday to the interview data is selected at each address, in Barcelona subjects are randomly selected from the person registry (empadronamiento) and in Kaunas subjects are sampled randomly from a 2006-2009 survey of randomly sampled people of the city of Kaunas. In each case there is an over selection of potential addresses or subjects to be able to interview at least a 1000 subjects (and 30 per unit) in each city. The target of a 1000 subjects per city was based on the available budget. To enable multi-level analysis, we estimated that a minimum of 30 participants per group (or neighbourhood) were required, with a minimum of 30 groups.

~~The choice of items was based on the proposed mechanisms and was achieved via an interactive process of experts within the PHENOTYPE team and others in the institutions involved. As much as possible questions were derived from existing and validated indices. The questionnaire was piloted by the four centers separately with specific attention for comprehensibility, clarity and duration and was adapted based on these pilots. The questionnaire is structured along several main clusters of questions: i)~~

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residential situation: ii) dwelling iii) wellbeing and health, and iv) personal characteristics. It includes questions on perceived quality and use of green and blue space in the residential area and in the immediate living environment, perceived environmental and social quality including aspects as noise, amenities and social cohesion, lifestyle, subjective health and questions related to personal background. The questionnaire was developed in English and translated and back translated in Dutch, Spanish and Lithuanian. More details on the frameworks and questionnaire will be described in a forthcoming paper by Van Kamp et al. (In prep). Also we will assessment cognitive fatigue in each subject as measured by CTT.

The questionnaire survey was designed to investigate three potential mechanisms in relation to natural environments and health: via physical activity, stress and restoration and social interactions as described in. In addition questions are included about environmental worries and reactions to perceived exposures (air pollution, noise, etc). The choice of indicators was based on these three mechanisms and was achieved via an interactive process of experts within the PHENOTYPE team. As much as possible questions were derived from existing and validated indices, some tailored to the specific objectives of PHENOTYPE. The questionnaire was developed in English and was translated (and back translated?) into Dutch, Spanish, Catalan, and Lithuanian. The questionnaire was developed to be applied in an oral interview of at maximum 60 minutes. In Kaunas it is not common to have face-to-face interviews; therefore a written questionnaire is sent by post to the selected people. The questionnaire was piloted by all partners, with specific attention for comprehensibility, clarity and duration and was adapted at some points based on outcomes of these pilots.

The final questionnaire is structured along four main clusters of questions: I. Green and Blue Spaces; II Residential situation: Dwelling & Neighbourhood; III Wellbeing and Health; IV Personal characteristics. Per mechanism questions are asked about availability, use, importance, and satisfaction. In the sequencing of the questions we strive for a coherent set of questions per cluster moving from general to specific and from ‘’easy’’ to more intruding questions. Furthermore, most of the answer categories moved from neutral negative towards positive items.

For all answers showcards have been developed by RIVM, to make it easier for both interviewers and respondents, and to speed up the interview process. A separate instruction document was developed to train the interviewers. The questionnaire ended with an optional a pencil paper attention test (Color Trails Test (CTT-A)) add ref.

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Finally for the smartphone study at least 100 volunteers from each country are randomly selected from the participants of the questionnaire survey who indicated that they were willing to participate in the smartphone study. For these subjects, From the 1,000 volunteers in each of the 4 case cities who complete the questionnaire, 100 people are approached to take part in a smartphone study (400 in total). dDuring 7 subsequential days the emotional state of the subject, the local environment (e.g., different quantities or qualities of natural space) and the social setting are assessed with the smartphone and the innovative Calfit technology. Besides objective geolocation and physical activity (see section Characterisation the natural environment), subjective data on stress reduction/restoration and social contacts are collected simulataneously. The latter data are collected through interactive diaries capable of eliciting ecological momentary assessment (EMA). EMA is a novel approach to elicit responses to electronic surveys throughout the course of daily life[78] (Shiffman et al. 2008). The participant receives prompts at random intervals to complete small surveys on the phone, which then have time and location stamp.

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From the people who participate in both the questionnaire survey and the CALFIT study and who indicate they wanted to volunteer, 80 people (20 in each case city) are approached for semi structured interviews. These interviews are conducted to gain more detailed information on specific topics included in the questionnaire survey and CALFIT/EMA. Topics addressed include the motivation for travel routes, the effect associations of natural environment on with mood, behaviour and well-being, the attitude towards and importance of (experiences with) natural environment, and reasons for using or not using the natural environment.

Epidemiological studies to examine long term effects of the natural environment

By using existing epidemiological studies and registries and linking these to the natural space indicators described earlier, the association between natural environment and a range of different long term health effects outcomes will be examined in an efficient and cost effective manner. PHENOTYPE makes use of 16 existing cohorts and registries with good health outcome data in Spain, the Netherland, Lithuania, and United Kingdom (Web Table 1), linking these to newly created natural environment indicators.

Comparable estimates are produced for various regions in Europe for the ~~effects on~~associations with pregnancy outcomes, foetus development, children's health and adult population morbidity and mortality. We specifically focus on:

- the natural outdoor environment and ethnicity, socio-economic status, women´s health and pregnancy outcomes;
- the natural outdoor environment and foetus development, birth weight, and gestational age;
- the natural outdoor environment and general development, neurodevelopment, cognitive function and respiratory health in children;
- the natural outdoor environment and respiratory health in various European cities;
- the natural outdoor environment and general health, physical activity, specific morbidity and mortality.

The assessment of natural environment indicators will be mainly based on satellite data and land use maps as CORINE and Urban atlas, and sometimes local data. This will restrict to some extent the evaluation of the ~~effect of~~association with the natural environment, but this is the only realistic and achievable approach. All studies examine the role of socio-economic status, which has been suggested as an effect modifier for the relationship between exposure to the natural environment and health benefits. The European Community Respiratory Health study (ECRHS)[79] ~~(Burney et al 1994)~~ further allows for examination of exposure to the natural outdoor environment and ~~health effects~~ associations with health in a range of different European cities. Some cohorts such as the Born in Bradford study[80] ~~(Wright et al. 2012)~~ offers a unique opportunity to investigate the role of ethnicity in the relationship between exposure to the natural outdoor environment and health benefits, in Bradford study half of the participants are from Pakistani background, with information on both the mother and baby from pregnancy to early years in life.

Experiments to examine short term effects of the natural environment

To examine short term effects of the natural environment on health and well-being, one or more experimental studies are conducted in each country in which individuals are exposed to different types of natural and urban environments (i.e., environmental conditions). The majority of data collection is field-based to maximise the ecological (as well as internal) validity of any observed effects.

Using a range of psychological and physiological indicators relevant to the various possible mechanisms, and 2) healthy and patient population groups (with mental and/or somatic morbidities) we will collectively explore:Using a range of psychological and physiological indicators relevant to the various possible mechanisms, and inclusion of healthy and patient population groups (with mental and physical morbidities) collectively explore:

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- preventive and therapeutic effects of natural environments.
- immediate and sustained changes in affective, cognitive and physiological responses indicative of well-being while engaged in a natural environment, and after leaving a natural environment
- neurobiological responses to viewing natural or urban scenes before/after experiencing stress.

Through variation in experimental design, each partner makes a novel contribution(s) to the area as (details in Web Table 2):

- UK: In healthy individuals, Study 1 compares immediate and post-exposure psycho-physiological effects of urban versus natural environments to explore whether any beneficial effects are sustained following single exposures; Study 2 uses longer-term follow-up and repeated exposure to natural environments to explore whether any effects are accumulated, sustained or attenuated.
- Netherlands: an experimental functional Magnetic Resonance Imaging (fMRI) study is conducted in healthy individuals to investigate neurobiological responses to viewing natural or urban scenes before/after experiencing stress; i.e., whether viewing natural compared to urban scenery can prevent or buffer against stress responses, and how this is represented in brain activation patterns.
- Spain: in individuals with elevated stress levels, group-based exposure and Ecological Momentary Assessment (EMA, using CALFIT technology) are used to explore the role of social interaction and the nature of physical activity, in immediate and longer term responses. Ecological validity will be enhanced through ‘free-living’ activities within environments, rather than controlling activities, again, using EMA, GPS and accelerometry to monitor the nature (and perceptions) of this activity.

- Lithuania: a clinical population with established coronary artery disease (CAD) are recruited to evaluate the therapeutic effect of the natural environment. The outcomes of this experiment may have direct clinical applications for the use of urban and different types of natural environment in cardiac rehabilitation.

Implications, policy and guidelines and involvement of stakeholders

Guidelines

PHENOTYPE will provide recommendations for policymakers and guidelines for professional practitioners involved with spatial planning and health to create natural environments that promote health and well being. For this, we focus on a human ecological perspective which allows for a better integration of human health needs into land use planning and green space management in both rural and urban areas[81] ~~(Lawrence 2001)~~. Currently legal standards that have been developed with economic, technological and political priorities in mind, are leading in urban design, whereas the lifestyle, sense of community, identity, and health and well being of local populations have been largely undervalued. The guidelines will reflect the importance to consider environmental, social, economic and other components of the natural and built environments in ways that also take into account and result from the point of view of citizens. PHENOTYPE will complement the common quantitative approach by valorising the social/human functions of these environments, especially their contribution to promoting health and quality of life.

Following this broad and innovative approach, PHENOTYPE will formulate, test and validate a set of recommendations and guidelines concerning the desired characteristics of different types of natural environments in urban and rural areas, specifically their characteristic features, accessibility to them for different population groups, as well as their facilities, maintenance and services. By doing so, the work will overcome the existing applicability gap between information and knowledge accumulated by much research and policy definition and implementation.

The guidelines for professional practitioners involved with spatial planning and health will consider three core topics in relation to each of the natural environment being considered:

1. Qualitative characteristics of natural environments; recommendations concerning surface area, vegetation, water sources, ambient noise levels, views and microclimate;
2. Facilities, Maintenance and Services; recommendations about the kinds of communal facilities and services provided in each type of natural environment, as well as suggested levels of maintenance;
3. Accessibility Guidelines to Natural Environments; including requirements about access to different types of natural environments such as allotments, neighbourhood parks, children's playgrounds and nature reserves.

The baseline for the work is firstly the compilation and analysis of currently available information from existing databases and literature, and later new data collected by the project as described above. This will be complemented by the engagement with the appropriate stakeholders to assess scope for development. These insights will be combined into a conceptual framework on the underlying mechanisms of the effects of the natural environment on health and well-being.

Stakeholders and dissemination

The participation provides a forum for project assurance and benefits for PHENOTYPE are summarised as follows:

- A more robust evidence base on links between exposure to natural outdoor environment and human health/well-being for various regions in Europe. Hereby we expect to develop a better understanding of the potential mechanisms.
- A better integration of human needs into land use planning and green space management in rural as well as urban areas. Furthermore, the application of these needs in practical guidelines.

Stakeholder involvement is critical for bringing outside (policy) ideas into the research planning, to increase the usefulness of the research, and to assure a better implementation of the results of the project (Web Figure 5). In a research project, this is often limited because the lack of interest of stakeholders and the limited resources and efforts of consortia.

From the start of PHENOTYPE actively sought to establish and maintain relations and dialogues with and between key stakeholders from local, regional and national health and environment authorities, institutions and the international research community. These include policy makers, architects, urban planners, natural space managers, health professionals, and the international research community. This group is highly diverse, as we are looking at a range of professions within the subject areas of environment and health, from volunteers to scientists, community workers and policy developers. PHENOTYPE has thus far been successful in its engagement activities, providing continuous opportunities for information exchange and collaborations. These contribute to strengthening networking between researchers, policy-makers and stakeholders in order to facilitate the transfer of scientific knowledge to policy development, to exchange ideas about best practice and to help identify emerging issues on the natural outdoor environment and its mechanisms to improve health.

The PHENOTYPE website www.phenotype.eu provides an overview of the project, progress, actualities, surveys and publications. The site has a sign up form for periodic newsletters through which all stakeholders are regularly informed. It guarantees continuous visibility, and provides a means for interested parties to respond to activities, or to contact us with invitations to attend workshops, etc. PHENOTYPE is also found on social media twitter (@greenhealth4eu) and LinkedIn. The PHENOTYPE databases and overall results will be exploitable by policy makers at national and international level in areas including urban planning and health.

Conclusion

The PHENOTYPE project is an FP7 collaborative action, funded by the EC to explore the mechanisms underlying positive short term and long term health effects for different population groups. PHENOTYPE applies conventional and new innovative high tech methods to characterize the natural environment in terms of quality and quantity. Preventive as well as therapeutic effects of contact with the natural environment will be covered. The proposed work aims to address the limitations of some of the studies that have been published so far (Table 2). Furthermore it addresses implications for land-use planning and green space management. The project will produce a more robust evidence base on links between exposure to natural outdoor environment and human health and well-being. This in turn will contribute to improved integration of human health needs into land use planning and green space management in rural and urban areas.

"No additional data available yet".

Author statement

Mark J Nieuwenhuijsen, Hanneke Kruize, Christopher Gidlow, Michael Jerrett, Jolanda Maas, Edmund Seto, Peter Jan van den Hazel, Roderick Lawrence, and Regina Grazuleviciene and wrote the original grant proposal on which the study design and paper is based. Mark J Nieuwenhuijsen drafted the version of the paper and received input from all the authors. All authors read and commented on the paper and agree with the final version.

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[ENV.2011.1.2.3-2] Positive effects of natural environment for human health and well-being] Duration 1 Jan 2012-31 Dec 2015

Ethics approval was obtained for all aspects of the study by the local ethics committees in the countries where the work was conducted, and sent to the European Commission before advancement of the study.

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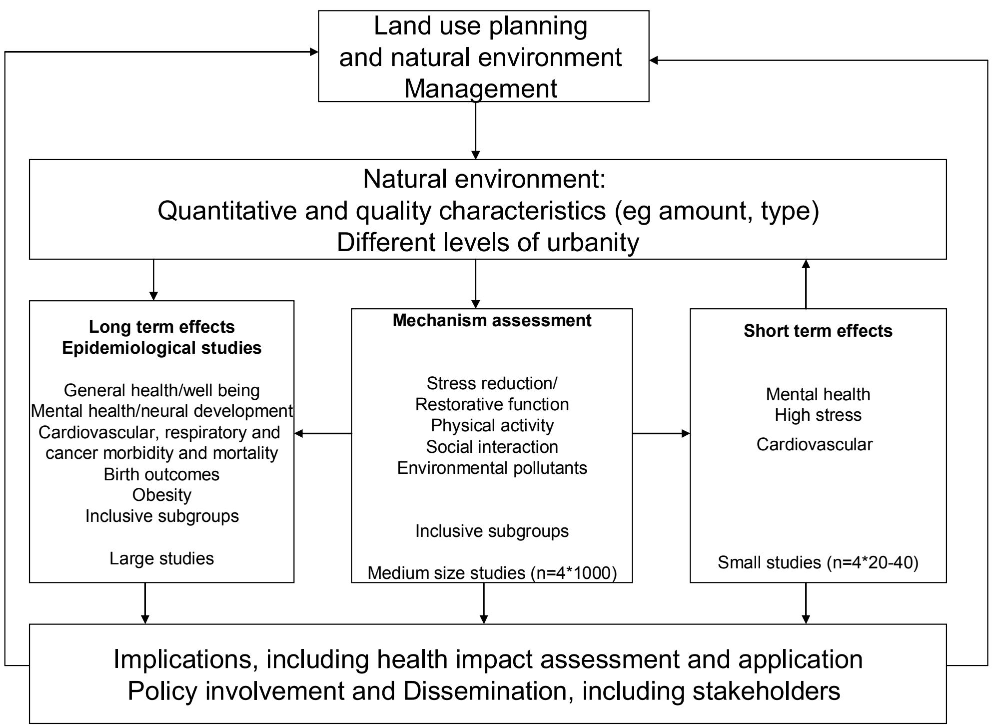


Figure 1: Interdependencies of different parts of the PHENOTYPE project

Table 1 PHENOTYPE study mechanisms, outcomes, populations and regions

It will explore underlying mechanisms related to:

- stress reduction/restorative function
- physical activity
- social interaction/social cohesion

exposure to environmental hazards (e.g. noise/acoustic quality, air pollution)

Both preventative and therapeutic effects (patients) will be considered. Outcomes of interest that are evaluated are:

- general health and well-being (including medically unexplained symptoms
- (MUPS))
- mental health/neural development
- stress
- cardiovascular, cancer and respiratory mortality and morbidity
- birth outcomes
- obesity

It will examine the effects for different population groups, including more vulnerable populations:

- pregnant women and/or foetus
- age groups (children, elderly)
- (lower) socio-economic status
- ethnic minorities
- patients/people with specific health complaints

It will conduct comparative studies in different regions of Europe to examine any underlying regional, social and/or cultural differences related to the meanings, uses, mechanisms and health effects of the natural environment and we will include the:

- North west (Netherlands, England)
- South (Spain)
- East (Lithuania)

Table 2 Limitations of current green space work and work undertaking by PHENOTYPE to address these

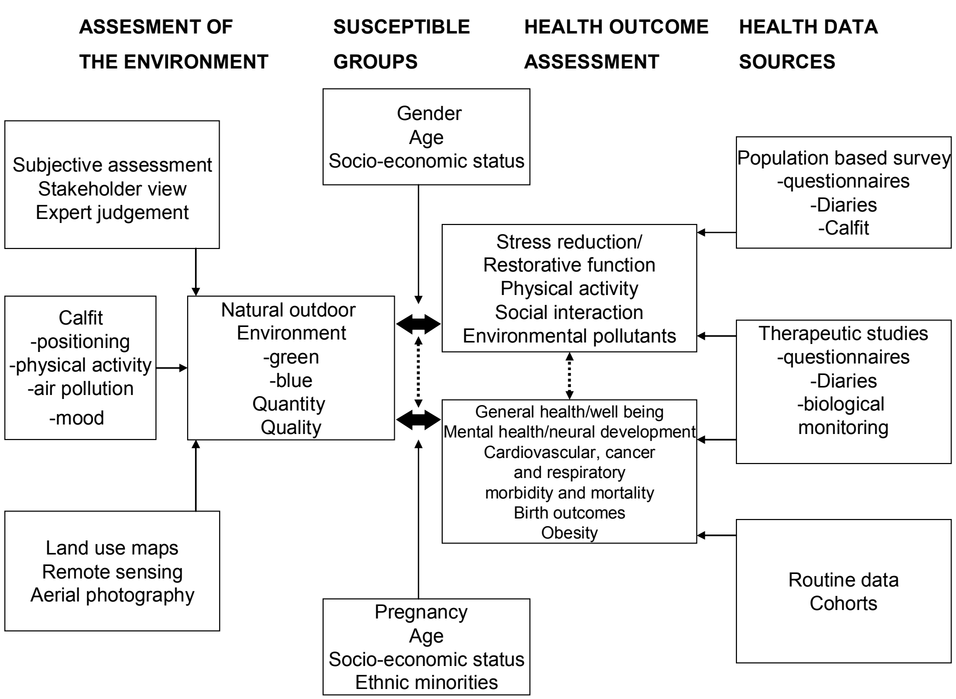
Limitations of current available work	What PHENOTYPE will do
▪ Inconsistency and variation in indicators for green or natural space have often made it difficult to compare results from different studies.	▪ Minimize the potential differences due to classification of natural space, by combining the use of conventional maps and data sources with remote sensing data and aerial photography, gather individual-level data through detailed discussions with subjects living in the areas, and use considerable stakeholder engagement to develop comparable classifications of the natural environment in different countries. ▪ Produce a more robust and comparable evidence base on links between exposure to natural outdoor environment and human health and well-being.
▪ A number of disease outcomes have been studied, but besides the routinely collected data (which use ICD coding), not always in a standardized and comparable manner in different countries	▪ Produce a more robust and comparable evidence base on links between exposure to natural outdoor environment and human health and well-being, using well studied and new outcomes with standardization between countries.
▪ Potentially very sensitive groups such as pregnant women/fetus have not been studied at all.	▪ Extend the evidence base to new outcomes and vulnerable populations e.g. pregnant women and their foetus, chronic respiratory and cardiovascular patients, ethnic minorities and

	low social economic class.
▪ Most studies focused on green space; the evidence base for the effects of blue space is very limited.	▪ Not only examine the effects of green space, but also of blue space.
▪ Most of the green space studies have been conducted in the US or the North West of Europe.	▪ Conduct comparable studies across Europe and produce evidence for North Western, Eastern and Southern Europe. This will deliver insights into regional, social and/or cultural differences in relation to natural space.
▪ Most studies do not include actual use of the natural environment.	▪ Consider actual use of the natural environment, an often neglected but fundamental indicator in relation to exposure to natural environments.
▪ There appeared to be differences by social group, with some apparently benefiting more than others from natural space, but the evidence is sparse.	▪ Produce a more robust and comparable evidence base on links between exposure to natural outdoor environment and human health and well-being, with special attention for effect modification by social groups
▪ A number of potential mechanisms have been suggested, including increased physical activity and social contacts for those living near natural space, natural environments exerting	▪ Examine the proposed mechanisms (physical activity, stress, social contacts, and environmental risk factors) simultaneously in a large sample in various countries (WP2). This will enable

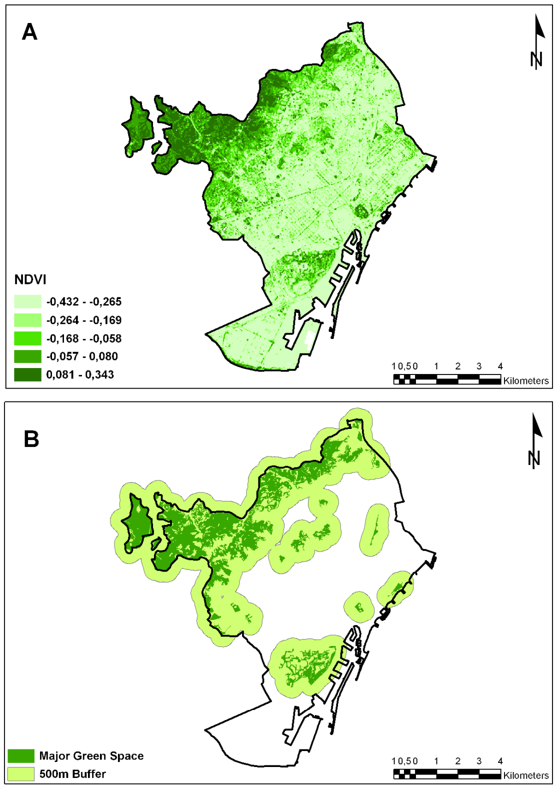
stress lowering or attention restoring effects, and reducing environmental hazards (e.g. air pollution, high temperatures). However, the studies of potential mechanisms have often been limited to assessing one mechanism at the time, which increases the likelihood of unmeasured confounding effects and misses the opportunity to study these potentially interrelated mechanisms in coherence. ▪ to study the mechanisms in coherence even though they may be interrelated	us to study specific factors while adjusting for others, and thereby strengthening the interpretation of the results
▪ Unable to answer what specific quantitative and qualitative characteristics of the natural environment have a positive effect on health and well-being, through what pathways is still largely unknown.	▪ Make classifications for the type and level of the indicators, which is important for policy makers. ▪ Examine the importance of both quantitative (amount, type, access, use) and qualitative characteristics (acoustic quality, identity, variety, safety) of the natural environment
▪ Limited research exploring the sustained affective, cognitive and physiological responses to a single exposure and the effects of a repeated exposure to the same natural environment ▪ Unable to explain how policymakers and planners can design a natural environment to maximise health benefits	▪ Explore longer-term changes in affect, cognitive function and physiological indicators that have to date only been studied during, or immediately after, engagement with the natural environment. ▪ Explore the immediate, maintained and long-term effects of repeated engagement with the same natural environment on

	affect, cognitive function, and physiological indicators of well-being .
▪ Guidelines of lifestyle, health and well being have largely undervalued local populations	▪ Include lifestyle, health and well being factors of the local populations.

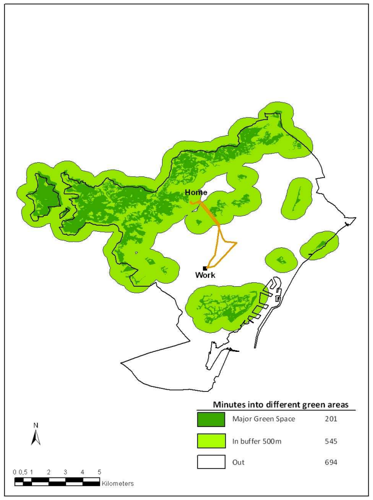
Annex-websfigures



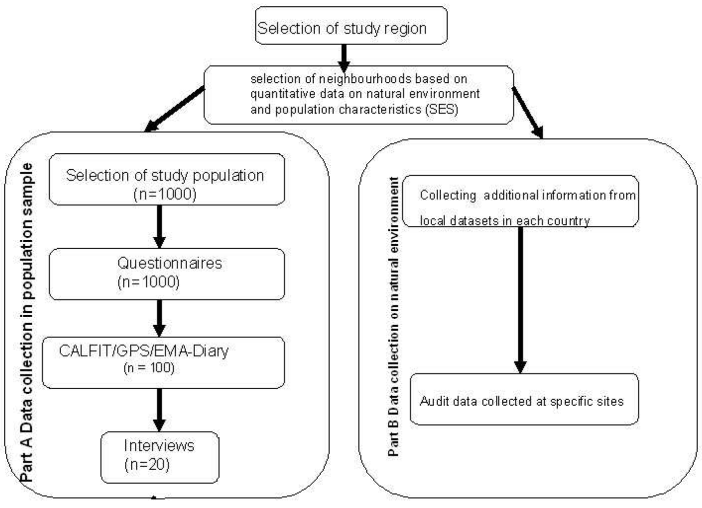
Web Figure 1 Natural outdoor environment, mechanisms and health data input in PHENOTYPE



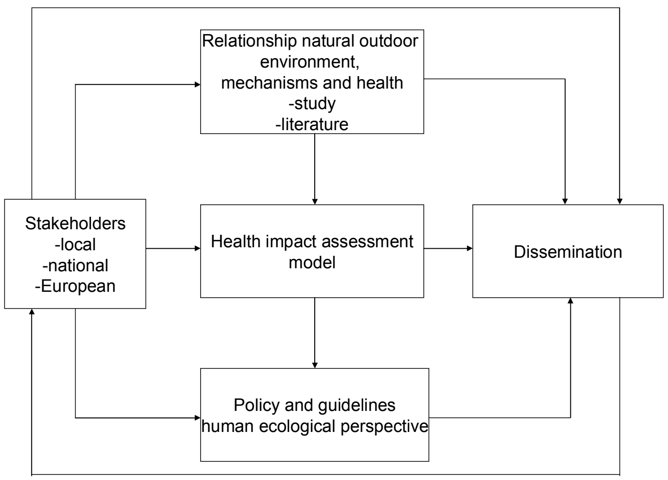
Web Figure 2 NDVI map of Barcelona and buffers around major green space areas



Web Figure 3 Mobility pattern for a subject in Barcelona obtained with the Calfit tool



Web Figure 4 Design of data collection in 4 European case cities to study the underlying mechanism



Web Figure 5 Stakeholder input and dissemination

Web Table 1 Currently available databases and cohorts for inclusion in PHENOTYPE

Study	n	Population	Collected outcomes	Relevant covariate and mechanism data
CREAL Spain				
PISCINA	3000	Children 6-9, 2006, Sabadell, Catalonia	Respiratory health BMI	Social economic status Physical activity Air pollution
INMA	3000	Children, 2-10, ongoing around Spain	Birth weight and gestation, respiratory health, neural development	Social economic status Physical activity Stress Air pollution
PAC-COPD	342	Patients with chronic obstructive pulmonary disease (PAC-CODP)	Hospital admissions All cause and specific mortality Functional data (lung function, cardiovascular function) Symptoms and co-morbidities Quality of life Mental status Body weight and composition	Social economic status Physical activity Air pollution

ECRHS	8500	Adult population in many cities around Europe	Respiratory health Short form SF36	Social economic status Physical activity Air pollution
Routine data Catalonia	Pop 7M 0.5 million deaths	All, 1999-2006, Catalonia	All cause and specific mortality	Social economic status
Hospital clinic database	16000	Births, 2000-2005 Barcelona	Birth weight and gestation	Social economic status Air pollution
Netherlands				
Cohort of Dutch inhabitants Netherlands	Pop 16M	All, 2000-2008	All cause and specific mortality and morbidity	Social economic status
Doetinchem cohort	Approximately 5000 over a period of 5 years	See: Verschuren WMM, Blokstra A, Picavet HSJ, Smit HA. The Doetinchem cohort study (cohort profile) Int J Epidemiol 2008; 37(6):1236-1241	Body weight, serum cholesterol, mortality, morbidity, health-related quality of life (RAND-36)	Social economic status, physical activity
Health survey Utrecht	3475	Adults 3475 (19-99 years)	lifestyle, perceived health, chronic diseases	Socioeconomic status, physical activity
United Kingdom				
Born in Bradford	12000	Babies, ongoing, England (large ethnic population) and their parents for a subgroup	Birth weight and gestation General and mental health parents in a	Social economic status Air pollution Detailed

			subset of 1500	ethnicity
Routine hospital emissions/ disease incidence		Small area-level data for Stoke-on-Trent/Staffordshire	Rates and nature of hospital episodes (e.g., respiratory, CVD), morbidity and mortality	Social economic status Air pollution
National health data		Small area-level health data for UK	Nature and rates of morbidity and mortality	Social economic status Air pollution
Lithuania				
Routine morbidity data Lithuania	0.5 million	Lithuania population, all age groups. Classification of all registered cases causes according to ICD-10 revision codes	Urban-rural area, age, sex, cardiovascular, respiratory, cancer, and other morbidity by districts	Social and demographic status
Routine mortality data Lithuania	0.5 million	Lithuania population, all age groups. Classification of all registered cases causes according to ICD-10 revision codes	Urban-rural area, age, sex, cardiovascular, respiratory, cancer, and other morbidity by districts	Social and demographic status
Detailed Health survey	7000	Representative sample adults of Kaunas citizens, Lithuania	General health including Blood pressure, high cholesterol and diabetes, Depression Physical functioning Cognitive function Psychosocial factors	Social economic status Air pollution Physical activities Stress
Kaunas birth	4,260	Kaunas babies and their parents for a subgroup	Birth weight and	Social,

cohort		http://www.birthcohorts.net/Cohort.Show.asp?cohortid=87	gestational age	demograpgic, economic status Air pollution

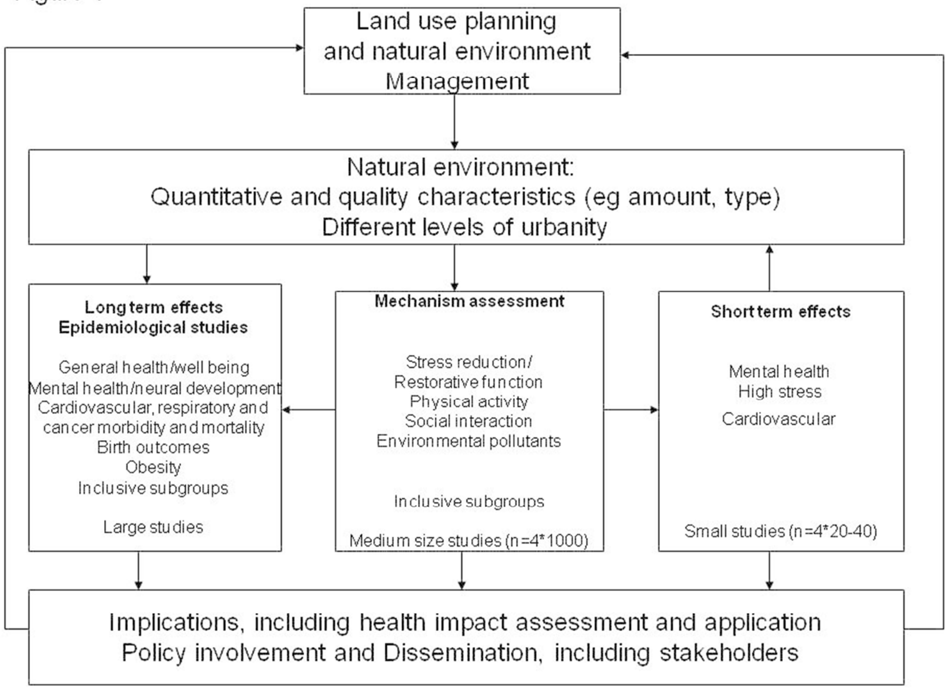
Web Table 2. Summary of proposed experimental design in each partner country in PHENOTYPE

	Country	Sample	Summary design	Measures				
				Affect	Cognition	Physiological	Environment	Other
Preventive	UK: study 1	Healthy adults (n=40)	- Field-based - Within-subjects - 30-minute exposure to natural green, natural green/blue, and urban environment - Measures at baseline (pre-exposure), 30 and 60-minutes post exposure	Mood	Cognitive function	- Salivary cortisol - HR - HRV - BP	Perceived restoration	RPE Walking speed
	UK: study 2	Healthy adults (n=40)	- Field-based - Between groups - 30-minute exposure to natural *or* urban environment on three consecutive days - Measures at baseline (day 1), 0, 30 and 60-minutes on exposure days (days 2-4) and final follow-up on day 5	Mood	Cognitive function	- Salivary cortisol - HR - HRV - BP	Perceived restoration	RPE Walking speed Hedonic and eudemonic life satisfaction
	Netherlands: study 1	Healthy adults (n=50)	- Laboratory-base - Within subjects - Shown images of natural and urban environment before a stressor (model 1) and after a stressor (model 2) stressor (to explore buffering and restorative effects, respectively)	Mood	Cognitive function	- Salivary cortisol - HR - HRV - BP	Perceived restoration	
	Netherlands: study 2	Healthy adults (n=25)	- Laboratory-based - Within subjects - Shown images of natural and urban environment before a stressor (model 1) and after a stressor (model 2) stressor (to explore buffering and restorative effects, respectively)	Mood	Cognitive function	- Neurological response (fMRI) - Salivary cortisol - HR - HRV - BP	Perceived restoration	
Therapeutic	Spain	Adults with elevated stress levels (n=20-40)	- Field-based - Exposure to natural green, natural green/blue, and urban environment over several hours - Measures at baseline (pre-exposure), 30 and	Mood	Cognitive function	- Salivary cortisol - HR - HRV - BP	- Perceived restoration - Air pollution - Noise	RPE Walking speed Social interaction

			60-minutes post exposure - Participants given CALFIT phones for some days for longer term monitoring (mood, social interaction, physical activity)				pollution	and physical activity (CALFIT)
	Lithuania	Adults with CAD (n=20)	- Field-based - Between-subjects - 30-minute exposure to natural green *or* urban environment on two consecutive days (days 2 and 3) - Measures at baseline (pre-exposure), 30 and 60-minutes post exposure - Walking treadmill test at baseline (day 1) and follow-up (day 2)	Mood	Cognitive function	- Exercise capacity (treadmill test) - Salivary cortisol - HR - HRV - BP	Perceived restoration	RPE Walking speed

CAD, coronary artery disease; HR, heart rate; HRV, heart rate variability; BP, blood pressure, RPE, rate of perceived exertion; fMRI, functional magnetic resonance imaging

Figure 1



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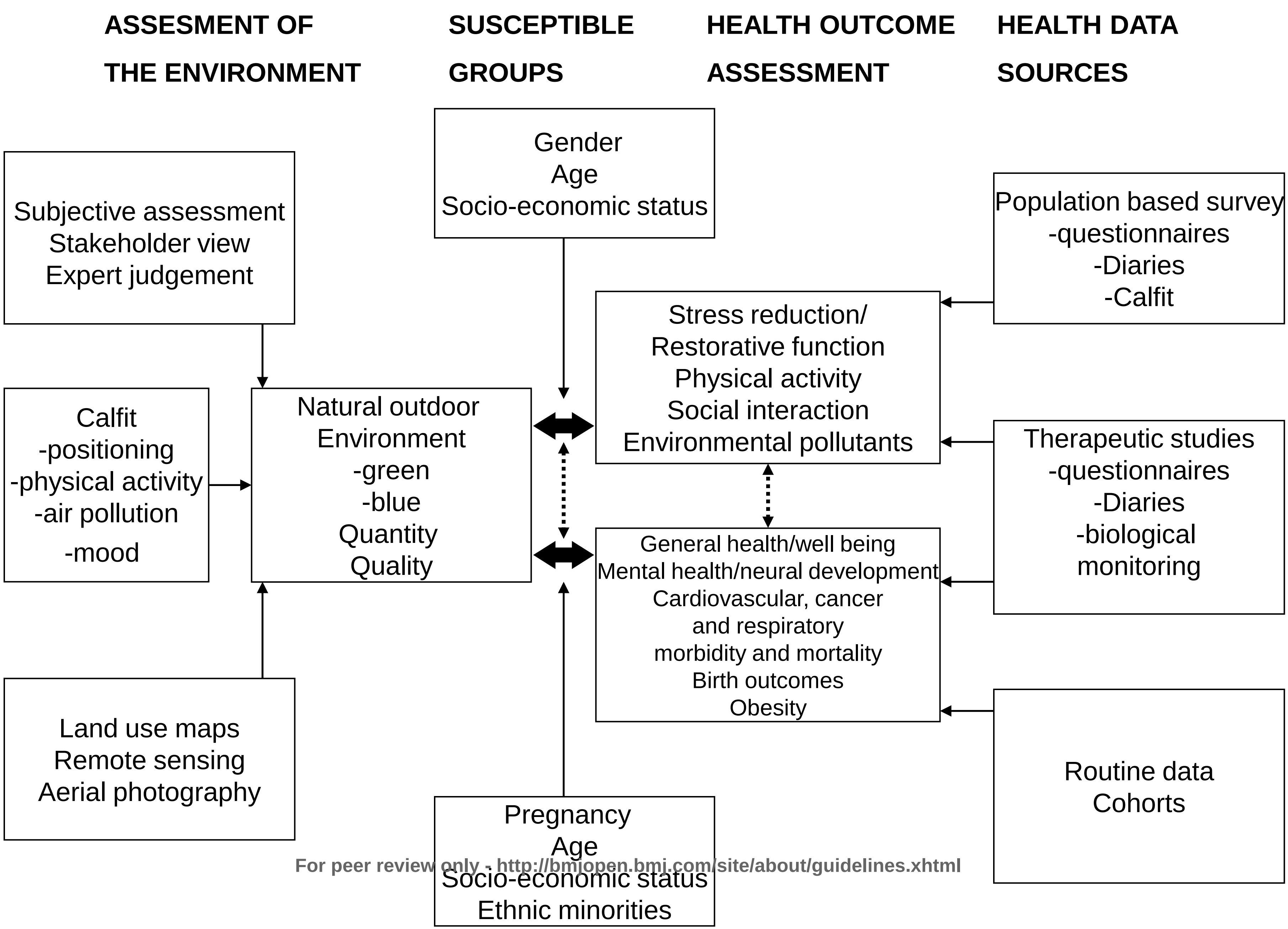
Web figure 1


ASSESMENT OF THE ENVIRONMENT
SUSCEPTIBLE GROUPS
HEALTH OUTCOME ASSESSMENT
HEALTH DATA SOURCES
Gender
Age
Socio-economic status
Subjective assessment
Stakeholder view
Expert judgement
Population based survey
-questionnaires
-Diaries
-Calfit
Stress reduction/
Restorative function
Physical activity
Social interaction
Environmental pollutants
Calfit
-positioning
-physical activity
-air pollution
-mood
Natural outdoor
Environment
-green
-blue
Quantity
Quality
Therapeutic studies
-questionnaires
-Diaries
-biological
monitoring
General health/well being
Mental health/neural development
Cardiovascular, cancer
and respiratory
morbidity and mortality
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Remote sensing
Aerial photography
Routine data
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Pregnancy
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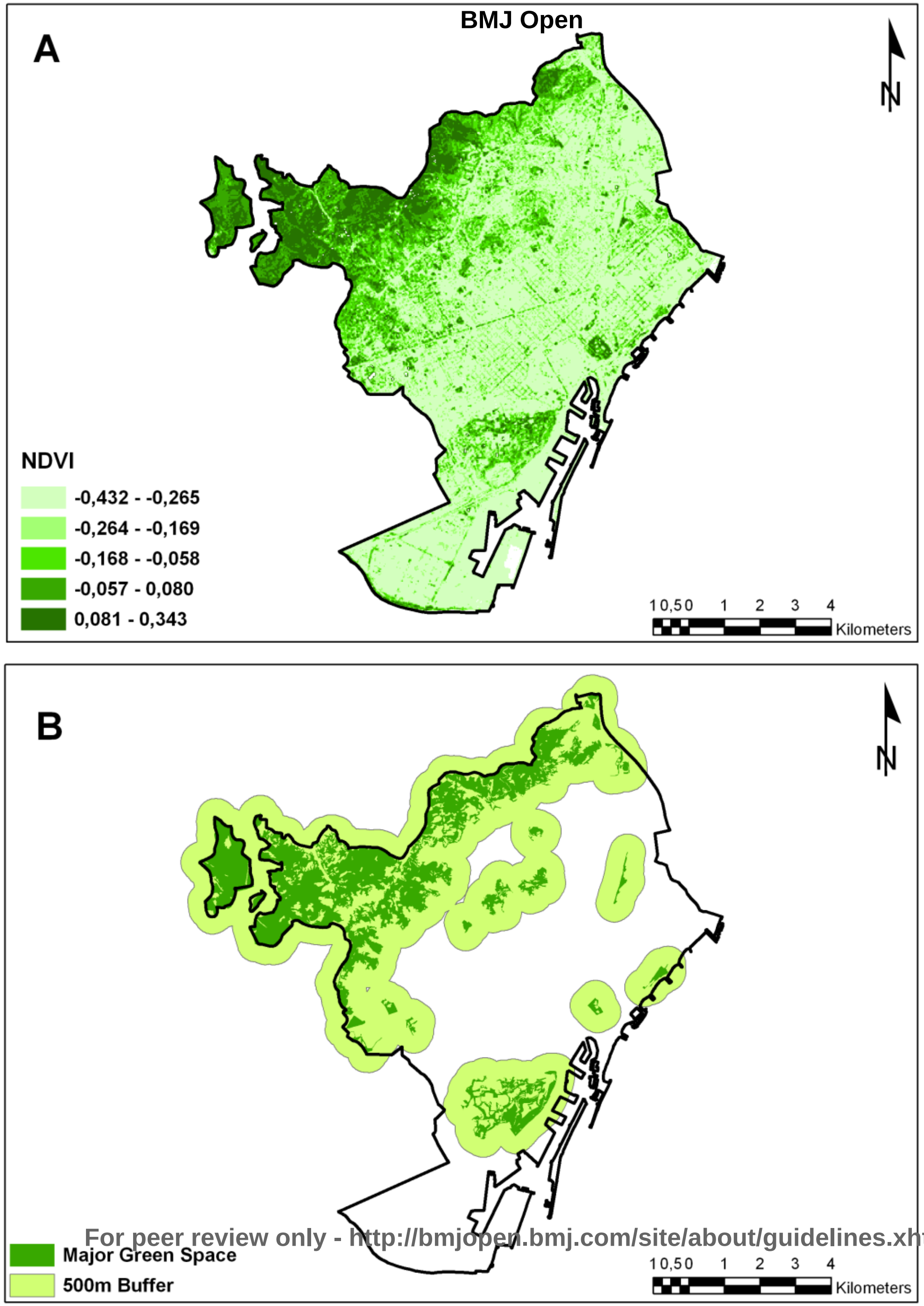
Socio-economic status
Ethnic minorities

Web figure 2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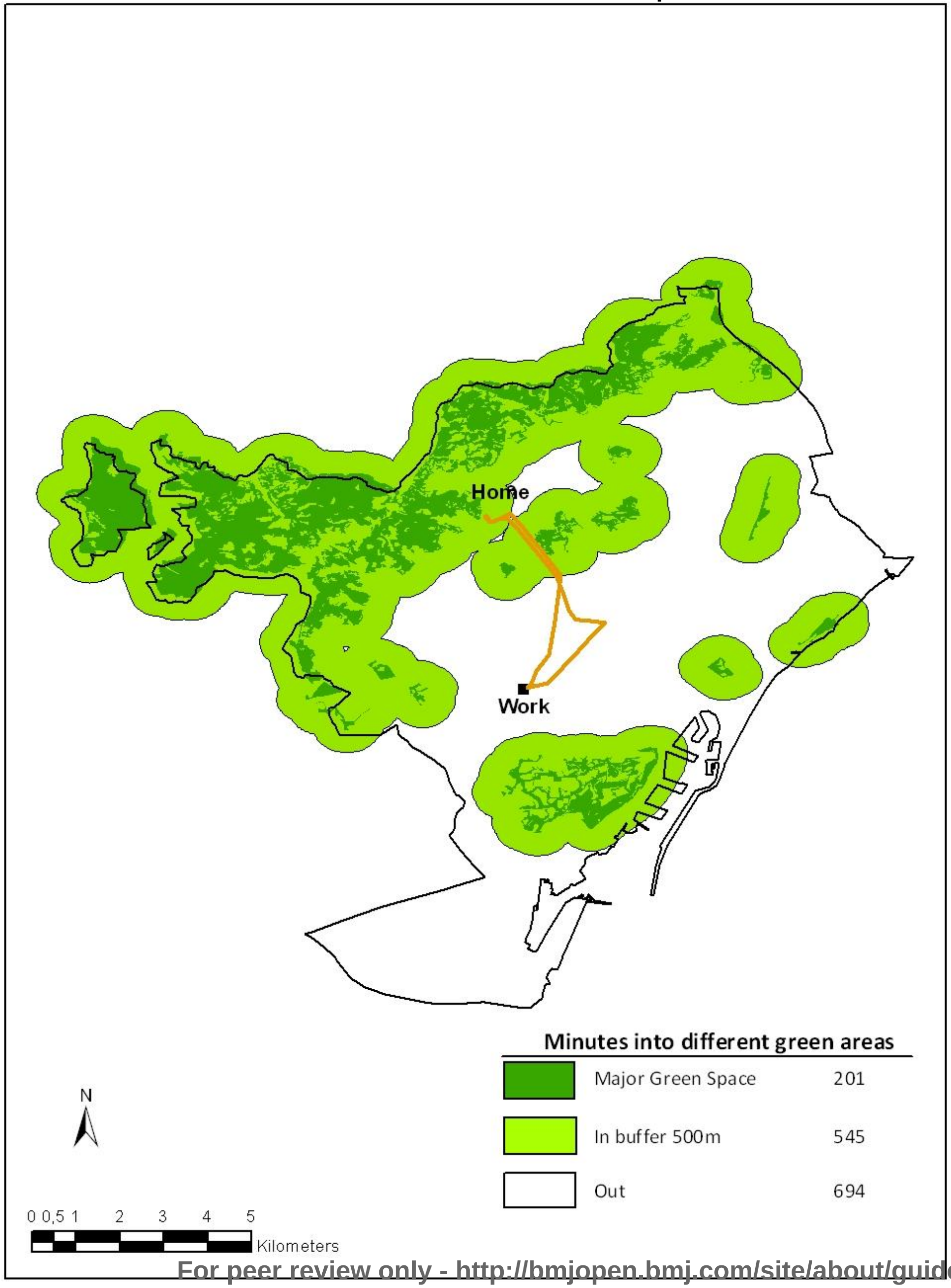
Web figure 3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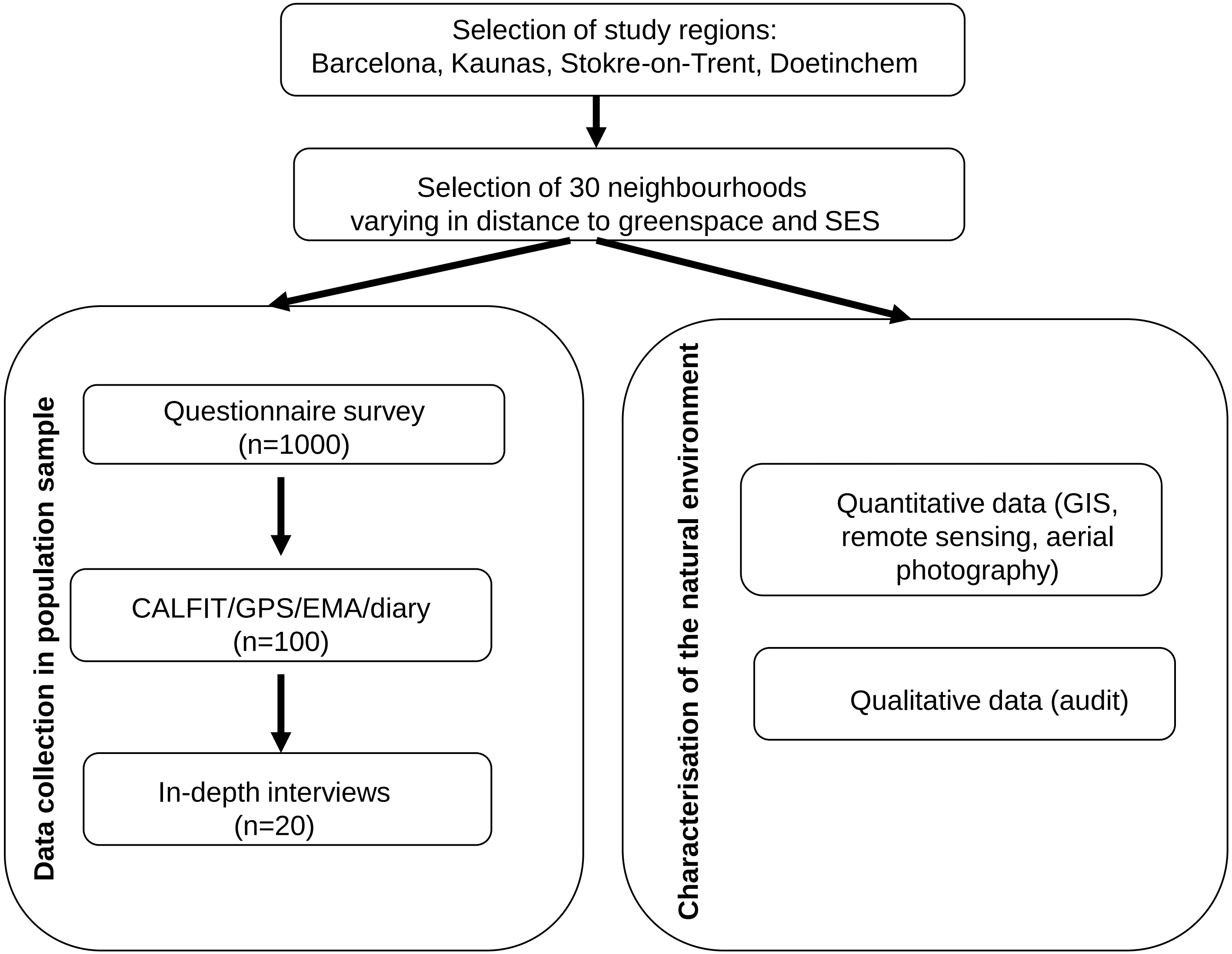
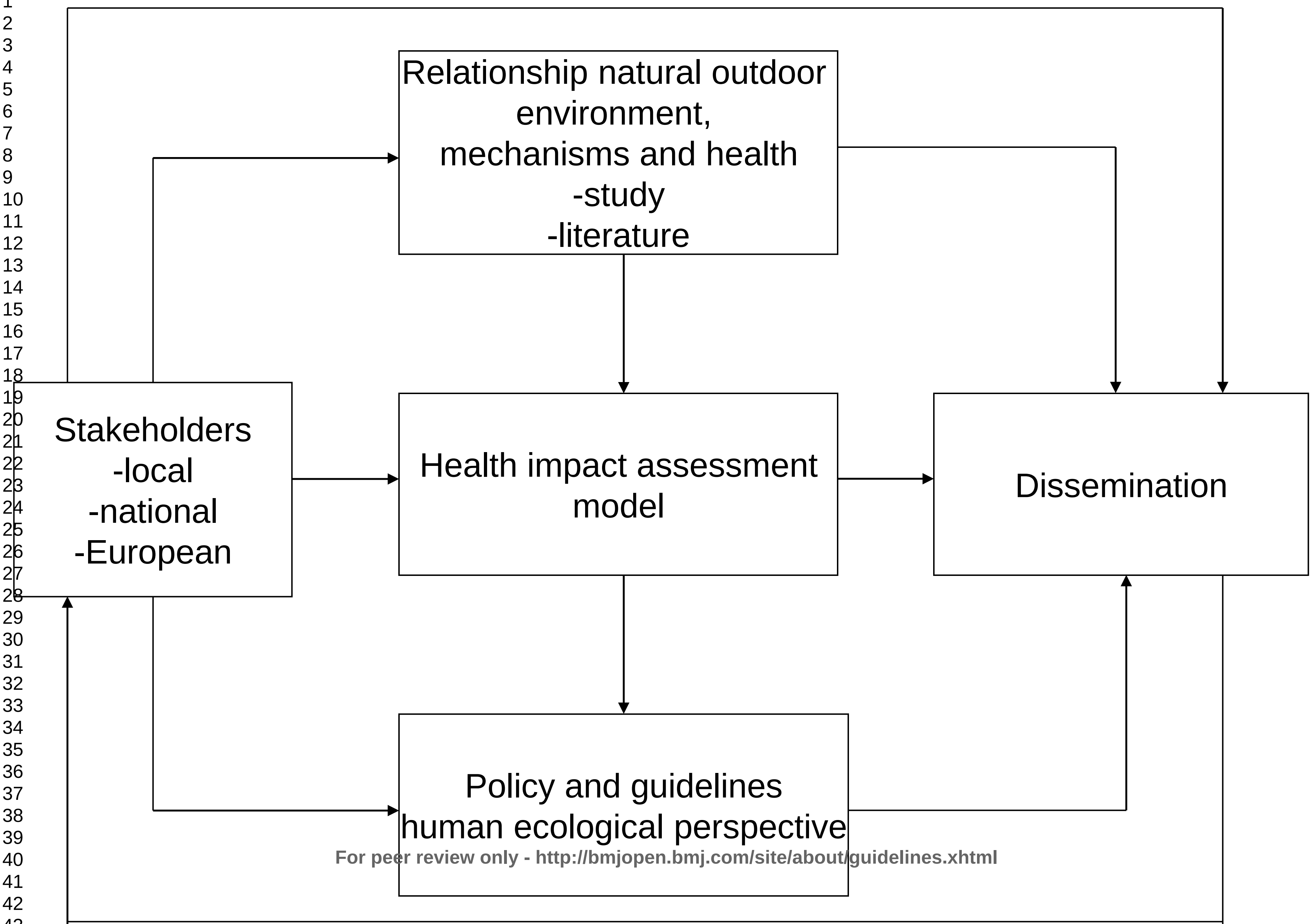
Minutes into different green areas
Major Green Space 201
In buffer 500m 545
Out 694
N
0 0,5 1 2 3 4 5
Kilometers

Web figure 4


Selection of study regions:
Barcelona, Kaunas, Stokre-on-Trent, Doetinchem
Selection of 30 neighbourhoods
varying in distance to greenspace and SES
Data collection in population sample
Questionnaire survey
(n=1000)
CALFIT/GPS/EMA/diary
(n=100)
In-depth interviews
(n=20)
Characterisation of the natural environment
Quantitative data (GIS, remote sensing, aerial photography)
Qualitative data (audit)

Web figure 5


Relationship natural outdoor environment, mechanisms and health
-study
-literature
Stakeholders
-local
-national
-European
Health impact assessment model
Dissemination
Policy and guidelines human ecological perspective

Web Table 1 Currently available databases and cohorts for inclusion in PHENOTYPE

Study	n	Population	Collected outcomes	Relevant covariate and mechanism data
CREAL Spain				
PISCINA	3000	Children 6-9, 2006, Sabadell, Catalonia	Respiratory health BMI	Social economic status Physical activity Air pollution
INMA	3000	Children, 2-10, ongoing around Spain	Birth weight and gestation, respiratory health, neural development	Social economic status Physical activity Stress Air pollution
PAC-COPD	342	Patients with chronic obstructive pulmonary disease (PAC-CODP)	Hospital admissions All cause and specific mortality Functional data (lung function, cardiovascular function) Symptoms and co-morbidities Quality of life Mental status Body weight and composition	Social economic status Physical activity Air pollution
ECRHS	8500	Adult population in many cities around Europe	Respiratory health Short form SF36	Social economic status Physical activity

				Air pollution
Routine data Catalonia	Pop 7M 0.5 million deaths	All, 1999-2006, Catalonia	All cause and specific mortality	Social economic status
Hospital clinic database	16000	Births, 2000-2005 Barcelona	Birth weight and gestation	Social economic status Air pollution
Netherlands				
Cohort of Dutch inhabitants Netherlands	Pop 16M	All, 2000-2008	All cause and specific mortality and morbidity	Social economic status
Doetinchem cohort	Approximately 5000 over a period of 5 years	See: Verschuren WMM, Blokstra A, Picavet HSJ, Smit HA. The Doetinchem cohort study (cohort profile) Int J Epidemiol 2008; 37(6):1236-1241	Body weight, serum cholesterol, mortality, morbidity, health-related quality of life (RAND-36)	Social economic status, physical activity
Health survey Utrecht	3475	Adults 3475 (19-99 years)	lifestyle, perceived health, chronic diseases	Socioeconomic status, physical activity
United Kingdom				
Born in Bradford	12000	Babies, ongoing, England (large ethnic population) and their parents for a subgroup	Birth weight and gestation General and mental health parents in a subset of 1500	Social economic status Air pollution Detailed ethnicity
Routine hospital		Small area-level data for Stoke-on-Trent/Staffordshire	Rates and nature of hospital episodes (e.g.,	Social economic status

emissions/ disease incidence			respiratory, CVD), morbidity and mortality	Air pollution
National health data		Small area-level health data for UK	Nature and rates of morbidity and mortality	Social economic status Air pollution
Lithuania				
Routine morbidity data Lithuania	0.5 million	Lithuania population, all age groups. Classification of all registered cases causes according to ICD-10 revision codes	Urban-rural area, age, sex, cardiovascular, respiratory, cancer, and other morbidity by districts	Social and demographic status
Routine mortality data Lithuania	0.5 million	Lithuania population, all age groups. Classification of all registered cases causes according to ICD-10 revision codes	Urban-rural area, age, sex, cardiovascular, respiratory, cancer, and other morbidity by districts	Social and demographic status
Detailed Health survey	7000	Representative sample adults of Kaunas citizens, Lithuania	General health including Blood pressure, high cholesterol and diabetes, Depression Physical functioning Cognitive function Psychosocial factors	Social economic status Air pollution Physical activities Stress
Kaunas birth cohort	4,260	Kaunas babies and their parents for a subgroup http://www.birthcohorts.net/Cohort.Show.asp?cohortid=87	Birth weight and gestational age	Social, demograpgic, economic status Air pollution

Web Table 2. Summary of proposed experimental design in each partner country in PHENOTYPE

	Country	Sample	Summary design	Measures				
				Affect	Cognition	Physiological	Environment	Other
Preventive	UK: study 1	Healthy adults (n=40)	- Field-based - Within-subjects - 30-minute exposure to natural green, natural green/blue, and urban environment - Measures at baseline (pre-exposure), 30 and 60-minutes post exposure	Mood	Cognitive function	- Salivary cortisol - HR - HRV - BP	Perceived restoration	RPE Walking speed
	UK: study 2	Healthy adults (n=40)	- Field-based - Between groups - 30-minute exposure to natural *or* urban environment on three consecutive days - Measures at baseline (day 1), 0, 30 and 60-minutes on exposure days (days 2-4) and final follow-up on day 5	Mood	Cognitive function	- Salivary cortisol - HR - HRV - BP	Perceived restoration	RPE Walking speed Hedonic and eudemonic life satisfaction
	Netherlands: study 1	Healthy adults (n=50)	- Laboratory-base - Within subjects - Shown images of natural and urban environment before a stressor (model 1) and after a stressor (model 2) stressor (to explore buffering and restorative effects, respectively)	Mood	Cognitive function	- Salivary cortisol - HR - HRV - BP	Perceived restoration	
	Netherlands: study 2	Healthy adults (n=25)	- Laboratory-based - Within subjects - Shown images of natural and urban environment before a stressor (model 1) and after a stressor (model 2) stressor (to explore buffering and restorative effects, respectively)	Mood	Cognitive function	- Neurological response (fMRI) - Salivary cortisol - HR - HRV - BP	Perceived restoration	
Therapeutic	Spain	Adults with elevated stress levels (n=20-40)	- Field-based - Exposure to natural green, natural green/blue, and urban environment over several hours - Measures at baseline (pre-exposure), 30 and	Mood	Cognitive function	- Salivary cortisol - HR - HRV - BP	- Perceived restoration - Air pollution - Noise	RPE Walking speed Social interaction

			60-minutes post exposure - Participants given CALFIT phones for some days for longer term monitoring (mood, social interaction, physical activity)				pollution	and physical activity (CALFIT)
	Lithuania	Adults with CAD (n=20)	- Field-based - Between-subjects - 30-minute exposure to natural green *or* urban environment on two consecutive days (days 2 and 3) - Measures at baseline (pre-exposure), 30 and 60-minutes post exposure - Walking treadmill test at baseline (day 1) and follow-up (day 2)	Mood	Cognitive function	- Exercise capacity (treadmill test) - Salivary cortisol - HR - HRV - BP	Perceived restoration	RPE Walking speed

CAD, coronary artery disease; HR, heart rate; HRV, heart rate variability; BP, blood pressure, RPE, rate of perceived exertion; fMRI, functional magnetic resonance imaging