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DE DOCTEUR EN MÉDECINE

Relation entre la marchabilité du quartier et les facteurs de risque cardio-vasculaire dans le Nord de la France

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Liens d’intérêts

L’auteur et son directeur de thèse ne déclarent aucun lien d’intérêt en rapport avec le sujet traité au cours des trois années précédent la présentation de cette thèse.

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Avants-Propos

Cette thèse d'exercice a été réalisée au sein du Laboratoire INSERM U1167 du Professeur Philippe Amouyel à l'Université de Lille, au Centre Hospitalier et Universitaire de Lille et à l'Institut Pasteur de Lille. Ce travail s'inscrit dans le cadre de l' *Enquête Littorale Souffle Air Biologie Environnement* (ELISABET). Il a été réalisé sous la direction du Docteur Luc Dauchet.

Les résultats obtenus ont été suivis de la publication de l'article:

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Résumé

Relation entre la marchabilité du quartier et les facteurs de risque cardio-vasculaire dans le Nord de la France

Contexte. Bien que l'on sache que la marchabilité est associée à l'obésité et à l'hypertension par le biais d'une activité physique accrue, les données sur les facteurs de risque cardiovasculaire (en particulier en Europe) sont rares. Nous avons évalué la relation entre la marchabilité des quartiers et les facteurs de risque cardio-vasculaire (notamment l'obésité, l'hypertension, le profil lipidique sanguin et les taux sériques d'hémoglobine glyquée (HbA1c)) chez des adultes vivant dans le nord de la France.

Méthodes. Les données ont été extraites de la base de données de l'étude ELISABET (2011-2013). Les participants (âgés de 40 à 65 ans) résidaient dans ou autour des villes de Lille et Dunkerque. Pour chaque adresse résidentielle, nous avons déterminé un indice de marchabilité du quartier (à l'aide d'un système d'information géographique) et le Walk Score®. Des modèles de régression linéaire multiples et logistiques ont été utilisés afin d'évaluer les relations entre la marchabilité des quartiers d'une part et l'indice de masse corporelle (IMC), l'obésité, la pression artérielle, l'hypertension, les taux sériques de HDL-C, LDL-C, triglycérides et HbA1c, et le niveau d'activité physique d'autre part.

Résultats. 3218 participants ont été inclus. Après ajustement sur les variables individuelles et du quartier, nous avons constaté qu'un indice de marchabilité plus élevé était associé à un IMC plus faible (-0,23 kg. m^{-2}; intervalle de confiance (IC) à 95% [-0,45;-0,01] pour un incrément d'un intervalle interquartile (IQR)), à une pression artérielle systolique plus faible (-1. 66 mmHg ; IC 95 % [-2,47;-0,85] par IQR), une plus faible prévalence de l'hypertension (odds ratio (OR) : 0,86 ; IC 95 % [0,78:0,95] par IQR), et une plus faible prévalence d'un faible niveau d'activité physique (OR = 0,80 ; IC 95 % [0,73:0,88] par IQR). L'indice de marchabilité n'était pas significativement associé à d'autres facteurs de risque cardiovasculaire. Des résultats similaires ont été observés pour le Walk Score®.

Conclusion. Nos résultats ont montrés que le fait de résider dans un quartier plus propice à la marche était associé à une prévalence plus faible des facteurs de risque vasculaire. La promotion de la marchabilité pourrait contribuer à améliorer la santé cardiovasculaire de la population.

Abstract

The relationship between neighbourhood walkability and cardiovascular risk factors in northern France

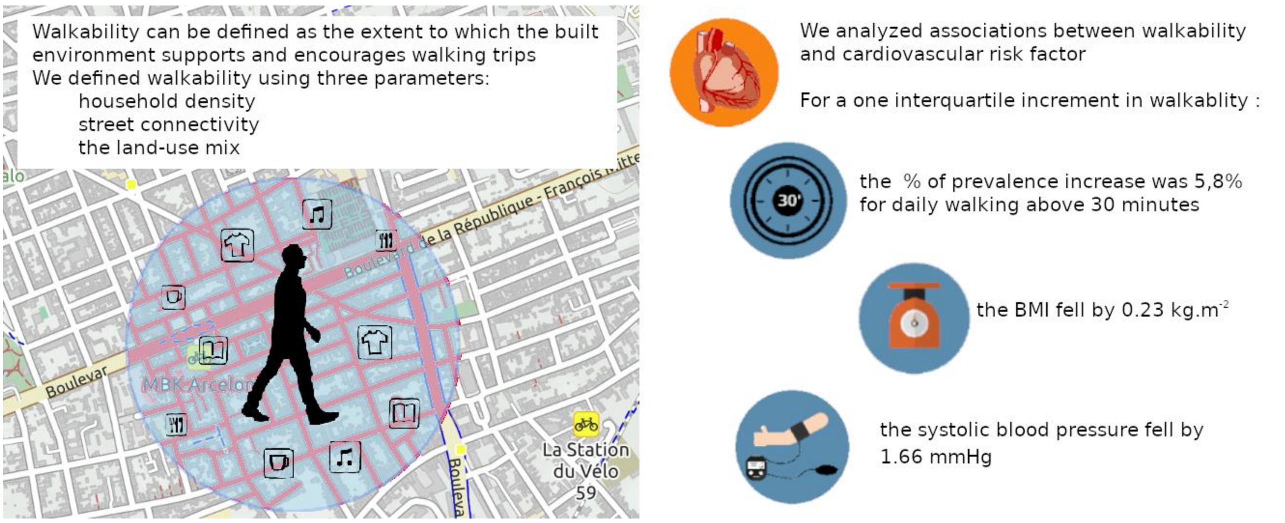
Background. Although walkability is known to be associated with obesity and hypertension through increased physical activity; data on cardiovascular risk factors (especially in the Europe) are scarce. We assessed the relationship between neighbourhood walkability and cardiometabolic factors (including obesity, hypertension, the blood lipid profile, and serum glycated haemoglobin (HbA1c) levels) among adults living in northern France.

Methods. Data were extracted from the ELISABET study database (2011-2013). The participants (aged between 40 and 65) resided in or around the cities of Lille and Dunkirk. For each residential address, we determined a neighbourhood walkability index (using a geographic information system) and the Walk Score®. Multilevel linear and logistic models were used to assess the relationships between neighbourhood walkability on one hand and body mass index (BMI), obesity, blood pressure, hypertension, serum HDL-C, LDL-C, triglyceride and HbA1c levels, and physical activity level on the other.

Results. 3218 participants were included. After adjusting for individual and neighbourhood variables, we found that a higher neighbourhood walkability index was associated with a lower BMI (-0.23 $kg.m^{-2}$; 95% confidence interval (CI) [-0.45;-0.01] for a one interquartile range (IQR) increment), a lower systolic blood pressure (-1.66 mmHg; 95% CI [-2.47;-0.85] per IQR), a lower prevalence of hypertension (odds ratio (OR): 0.86; 95% CI [0.78:0.95] per IQR), and a lower prevalence of a low level of physical activity (OR = 0.80; 95% CI [0.73:0.88] per IQR). The walkability index was not significantly associated with other cardiovascular risk factors. Similar results were observed for the Walk Score®.

Conclusion. Our results showed that residence in a more walkable neighbourhood was associated with a lower prevalence of vascular risk factors. Promoting neighbourhood walkability might help to improve the population's cardiovascular health.

Graphical abstract



Keywords: walkability; built environment; vascular risk factor; obesity; physical activity

Liste des abréviations

BMI Body Mass Index

CVD Cardiovascular Disease

CI Confidence Interval

DBP Diastolic Blood Pressure

GIS Geographic Information System

GPS Global Positioning System

HDL High-Density Lipoprotein

INSEE Institut National de la Statistique et des Etudes Economique

IQR Interquartile Range

IRIS Îlots Regroupés pour l'Information Statistique

LDL Low-Density Lipoprotein

MCV Maladie Cardiovasculaire

SBP Systolic Blood Pressure

TG Triglyceride

WS Walk Score®

WHO World Health Organization

WI Walkability Index

1 Contexte

1.1 Historique de l'urbanisme et la Santé

L'origine des villes serait née de l'apparition de l'agriculture pendant la période Néolithique (élevage, domestication des plantes, système d'irrigation et détournement d'eau, etc…) qui engendre des excédents agricoles et demande beaucoup de main d'œuvre. Très vite, des marchés pour vendre ses excédents et organiser la planification du travail apparaissent et constituent les premières organisations urbaines(2)

La ville regroupe des hommes et des femmes sur un territoire donné qui souhaitent vivre ensemble, l'espace publique apparait comme un élément primordial. En occident, dans la ville médiévale, des repères organisent cet espace public:

-l'église paroissiale est implantée au cœur de la ville, et, à partir du X^{ème} siècle, les sépultures sont disposées aux bords de l'église. Au XVII^{ème} siècle, les facultés de médecines recommandent de déplacer les cimetières hors les murs et d'éviter les puits à proximité pour protéger les nappes phréatiques(3)

-les établissements de santé par leur nature et leur taille ont aussi charpenté les villes. Les hospices, qui délivraient un accompagnement plutôt qu'un soin des personnes âgées ou malades, étaient initialement implantés à proximité des cathédrales. Progressivement, les équipements sanitaires ont été redirigés de l'autre côté des fleuves faisant œuvre de barrière sanitaire (à l'instar de l'Hôtel Dieu de Nantes ou l'Hospice civil de Lyon)(4)

Ainsi pendant cette période, la place de la santé publique dans le développement urbain est dirigée par pragmatisme sans réelles réflexions urbaines. La question d'abord était celle de l'isolement des malades pour éviter les contagions et les épidémies.(4)

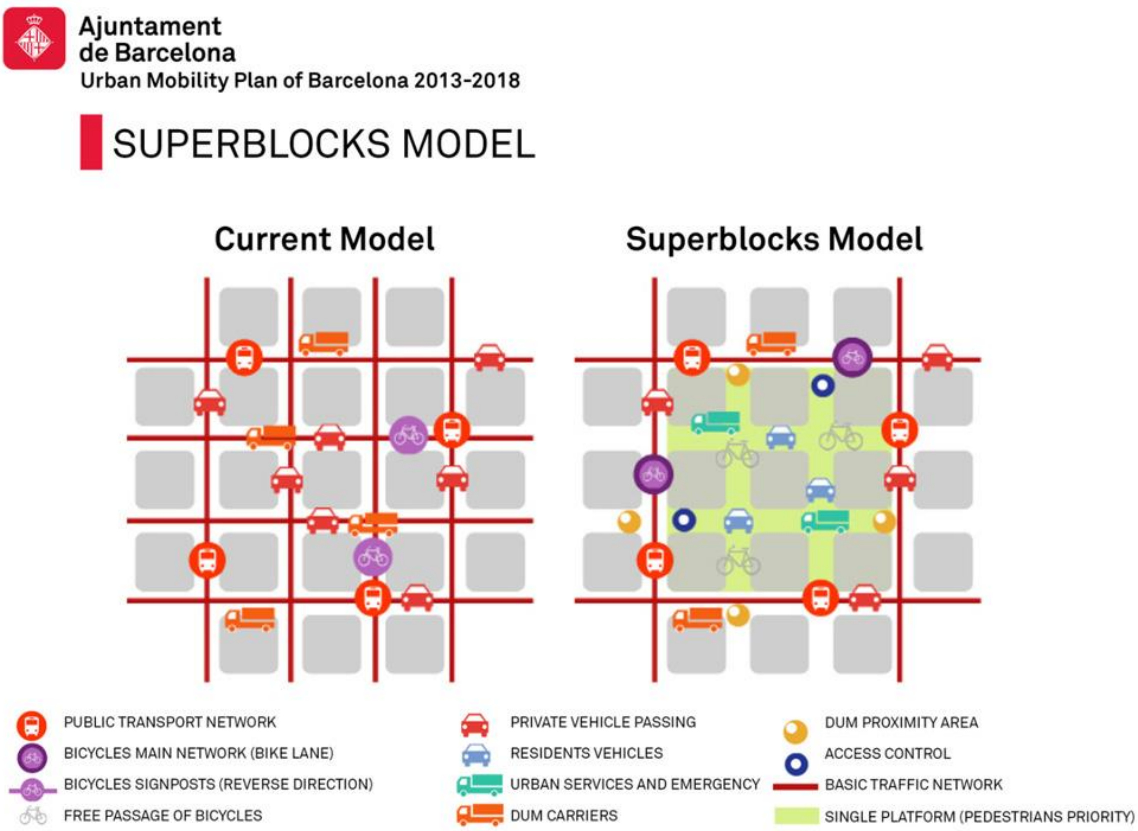
Au XIX^{ème} siècle, les notions de pureté de l'air et d'hygiénisme apparaissent avec la ville industrielle. Grace au progrès de la science, il ne s'agit plus d'accueillir mais de soigner et de prévenir. L'organisation des échanges interurbains et les épidémies, entraînent une réflexion intellectuelle sur la ville (2). La législation et les règlements urbains instaurés conçoivent la ville pour une meilleure santé (mise en place d’’espaces verts, squares, élargissement des voies, alignement du gabarit des immeubles permettant de faire entrer le soleil dans les habitations). Le baron Haussmann aura une grande influence, soutenu par Napoléon III. Sa rénovation de la capitale est fondée sur le thème : “Paris embellie, Paris agrandie, Paris assainie”(3)

La préoccupation croissante pour l’hygiène publique sera cristallisée pour la première fois par la Loi Cornudet en 1919 qui établit l’urbanisme en France et décrit trois priorités: le contrôle de la croissance des villes, la gestion des flux de circulation et vie sociale et la salubrité et l’hygiène des communes. Depuis cette loi, chaque commune est tenue de faire un plan d’urbanisme. Cependant, malgré les préceptes soulevés, aucun plan local d’urbanisme intègre un volet sanitaire.

Le XXème siècle a connu une forte croissance de l’exode rural vers les villes. En France, la dernière migration commence à partir de 1945 et dans les années 1970, plus de 70 % de la population habite en ville(5). La taille, la forme et la structure des zones urbaines vont considérablement évoluées. A partir des années soixante, un grand nombre d’aménagements viaires vont être instaurés afin d’adapter la ville à l’automobile (rues à sens unique, des carrefours à feux, de nombreuses chaussées surdimensionnées pour la circulation existante, et de divers dispositifs instaurant la ségrégation des trafics). Ces aménagements rendraient la ville moins passante, moins lisible, plus congestionnée, en compliquant inutilement la traversée des quartiers et l’accès aux commerces, emplois, logement. Ces aménagements ont rendu la ville moins perméable et plus dangereuse pour les usagers non motorisés(6)

Cette adaptation séculaire considérable de la ville à l’automobile est parallèle à une vie de plus en plus sédentaire de la population. L’augmentation du temps de sédentarité est une des causes de l’épidémie d’obésité et est un facteur de risque favorisant les maladies cardio-vasculaires. Depuis une dizaine d’année, la tendance est à la limitation de l’usage de la voiture et nous assistons à une réappropriation de l’espace public par le piéton a l’image de la ville de Barcelone. La structure de la ville catalane, proposé par le plan Cérda en 1860, est organisé en damier continu de blocs carrés de centaine de mètres. En 2019, le modèle des « superblocks » est instauré à certains endroits de la ville. Comme le montre la figure 1, un superblocks est une cellule de 9 blocs afin de créer des quartiers compacts et connectés qui diminueraient l'exposition nocive (pollution de l'air, bruit , chaleur) et augmenteraient le niveaux d'activité physique des barcelonais (7).

Figure 1 Illustration des super blocks de Barcelone



(8)

Concevoir la ville afin de réduire la sédentarité et ses épidémies associées rentre parfaitement dans la logique d'hygiène publique. Ainsi notre travail s'intéresse à la marchabilité (la propension d'un environnement à favoriser la marche) des quartiers et sa relation avec les facteurs de risque cardiovasculaire

1.2 Marchabilité

La terme marchabilité est la traduction du terme anglais « Walkability » qui provient lui-même de l'adjectif « Walkable »(9). Initialement c'est un terme d'urbanisme afin de comprendre et d’institutionnaliser la conception de l’aménagement de l’espace pour le transport piéton. Alors que de nombreux travaux pour les transports de véhicules motorisés ont été produites à partir des années soixante, le concept pour les piétons s’est développé plus tardivement vers la fin du XX[éme](10).

Les urbanistes ont identifié des facteurs influençant la marchabilité liés directement à l’architecture et l’aménagement de l’espace (connectivité des rues, densité résidentielle, présence d’arbre et végétation, diversité des bâtiments et commerce, transparence des façades) mais aussi sa perception (sécurité, esthétisme des rues, états des voies)(9)

Comprendre pourquoi un environnement est plus « marchable » a des applications multidisciplinaires dans le champ environnemental (diminution du transport motorisé et de leur émission associé), économique (stimulation des commerces locaux) et aussi sanitaire(11).

Dans le domaine de la santé, l’étude de la marchabilité impose une quantification rigoureuse du design urbain afin d’assurer de la comparabilité des études(9). Il existe deux mesures fréquemment retrouvées dans la littérature : les indices de marchabilité, score composite qui mesure la densité résidentielle, la connectivité des rues et la diversité des aménagements, initialement développé par Frank et al en 2005 (12) et le WalkScore® développé par une entreprise privé américain. Nous avons utilisé ces deux mesures dans notre travail, ils seront détaillés en aval.

2 Introduction article (Français)

Les maladies cardiovasculaires (MCV) sont la principale cause de décès dans le monde et restent un problème de santé publique important dans les pays industrialisés(13). En France, les maladies cardiovasculaires sont la deuxième cause de décès après le cancer ; en 2017, près de 65 000 décès étaient duûs aux MCV (13). Dans le monde, plus de 70 % des cas de MCV peuvent être attribués à des facteurs de risque modifiables, tels que l'alimentation et le mode de vie (14). L'étude française ESTEBAN a trouvé des prévalences de 17% pour l'obésité (14), 30,6% pour l'hypertension (15) et 5% pour le diabète traité (16). Un mode de vie sédentaire et de mauvais choix alimentaires figurent parmi les principales causes de MCV et sont souvent liés à des variables socio-économiques et environnementales (17).

Les maladies cardiovasculaires et des faibles niveaux d'activité physique sont interdépendants (18-20). L'Organisation mondiale de la santé (OMS) recommande de pratiquer au moins 150 minutes d'activité physique d'intensité modérée ou 75 minutes d'activité physique intense par semaine (21). Cependant, près de 40% de la population française déclare ne pas suivre ces recommandations (14). Une meilleure compréhension des déterminants de l'activité physique (y compris les activités physiques liées aux déplacements et aux loisirs) pourrait permettre de mieux promouvoir un comportement plus sain, avec une activité physique pratiquée tout au long de la journée et à faible coût.

Les initiatives environnementales susceptibles de prévenir les MCV suscitent un intérêt croissant. Des études récentes ont montré que certaines caractéristiques de l'environnement urbain (notamment la marchabilité) sont associées à des niveaux plus élevés d'activité physique liée au transport et aux loisirs (22,23). La marchabilité d'un quartier est une mesure composite de la propension d'un environnement donné à entrainer la marche ; elle comprend des paramètres objectivement mesurables. Les plus fréquemment utilisés sont la densité résidentielle, la connectivité des rues et la diversité des points d'intérêts (24). De plus en plus d'études suggèrent que la marchabilité est liée aux résultats de santé cardio vasculaire (25) ;

en effet, une méta-analyse récente a trouvé des preuves solides de relations longitudinales entre la marchabilité des quartiers d'une part et l'obésité, l'hypertension et le diabète de type 2 d'autre part (26).Peu d'études ont examiné la relation avec d'autres résultats de santé cardio vasculaire (par exemple, les niveaux de cholestérol et de triglycérides (TG)) (27-29). Cependant, la plupart des études ont été réalisées en Amérique du Nord et ces associations ont rarement été évaluées dans un contexte européen. En effet, l'effet de la marchabilité sur la santé peut être influencé par les différents modèles urbains en Europe et en Amérique. Historiquement, la ville européenne médiévale s'est développée en rayonnant à partir du centre. À l'inverse, les villes américaines ont été planifiées en accordant un rôle essentiel aux voitures et avec une faible densité. L'Europe se caractérise par l'importance relative des grandes et moyennes villes et par une proximité marquée entre les villes(30). Les voitures sont plus fréquemment utilisées pour le transport dans les villes américaines que dans les villes européennes(31). Les villes européennes sont caractérisées par une plus grande variabilité structurelle que les villes américaines et certaines villes asiatiques, et par un gradient de densité uniforme concave décroissant du centre vers la périphérie, comparé à une augmentation relative de la densité à la périphérie des villes américaines(32) .

Bien que les résultats européens semblent concorder avec les résultats nord-américains pour l'hypertension (33,34), ils indiquent plutôt une absence d'association avec le diabète de type 2 et l'obésité (35,36). Cela est probablement dû aux caractéristiques spécifiques des milieux urbains et des habitudes alimentaires européens. À notre connaissance, une seule étude française a évalué la relation entre la marchabilité et les facteurs de risques cardio vasculaire (indice de masse corporelle (IMC) et pression artérielle) (34). Elle a été réalisée dans l'agglomération parisienne - un milieu urbain très dense - et a utilisé le Walk Score® (un instrument commercial qui n'est pas encore soutenu par son développeur en France, ce qui signifie qu'il est disponible mais que le développeur ne garantit pas sa validité en France) comme indicateur environnemental.

Étant donné les différences entre l'Europe et l'Amérique en termes de cadres urbains et de modèles de comportement, des preuves supplémentaires sont nécessaires dans chaque pays européen (37).

Nous avons donc analysé les données de *l' Enquête Littorale Souffle Air Biologie Environnement* (ELISABET) auprès d'un échantillon représentatif de la population vivant dans et autour des villes de Lille et Dunkerque dans le nord de la France. L'objectif principal de l'étude était de décrire l'association entre la marchabilité du quartier et les facteurs de risque cardiovasculaire chez les adultes français. À cette fin, nous avons mesuré un indice de marchabilité (WI), calculé à l'aide d'un geographic information system (GIS), et le Walk Score® (WS) comme indicateurs environnementaux.

3 III-Article

The relationship between neighbourhood walkability and cardiovascular risk factors in northern France

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3.1 Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide and remains a significant public health problem in industrialized countries(13). In France, cardiovascular disease is the second-leading cause of death after cancer; in 2017, almost 65,000 deaths were due to CVD (13). Worldwide, more than 70% of CVD cases can be attributed to modifiable risk factors, such as diet and lifestyle (14). The French ESTEBAN study found prevalences of 17% for obesity (15), 30.6% for hypertension (16) and 5% for treated diabetes (17). A sedentary lifestyle and unhealthy food choices are among the main causes of CVD and are often related to socioeconomic and environmental variables (18).

Cardiovascular disease and low levels of physical activity are interrelated (19–21). The World Health Organization (WHO) recommends doing at least 150 minutes of moderately intense physical activity or 75 minutes of vigorous physical activity per week (22). However, nearly 40% of the French population report that they do not follow these recommendations (15). A better understanding of the determinants of physical activity (including travel-related and leisure-time physical activities) might help to better promote healthier behaviour, with physical activity performed throughout the day and at low cost.

There is growing interest in environmental initiatives that might prevent CVD. Recent studies have shown that certain characteristics of the built environment (including walkability) are associated with greater levels of transport-related and leisure-time physical activity (23,24). Neighbourhood walkability is a composite measure of how friendly an environment is for walking; it comprises objectively measured parameter. The most frequently used are residential density, street connectivity, and land use diversity (12). A growing body of research suggests that walkability is related to cardiometabolic health outcomes (25); indeed, a recent meta-analysis found strong evidence for longitudinal relationships between neighbourhood walkability on one hand and obesity, hypertension, and type 2 diabetes on the other (26).Few examined the relationship with other cardiometabolic health outcomes (e.g. cholesterol and triglyceride (TG) levels)(27–29). However, most of the studies were performed in North America and those associations have rarely been assessed in a European context. Indeed, effect of walkability on health may be impacted by different pattern of urbanism in Europe and America. Historically, the medieval European city was developed radiating out from the centre. Conversely, American cites were planned with essential role given to cars and with low density. Europe is characterized by the relative importance of large and medium-sized cities and by a marked proximity between cities(30). Cars are most frequently used for transportation in US cities than in European cities(31). The European cities are characterized by higher structural variability, than American and some Asian cities, and by a decreasing uniform concave density gradient from the centre to the periphery, compared to a relative increase in density at the periphery of American cities .(32)

Although the European results appears to be consistent with the North American results for hypertension (33,34), they rather indicate a lack of association with type 2 diabetes and obesity (35,36). This is probably due to specific features of European urban settings and dietary patterns. To the best of our knowledge, only one French study has assessed the relationship between walkability and cardiometabolic factors (body mass index (BMI) and blood pressure) (34). It was performed in the Paris metropolitan area - a highly dense urban setting – and used the Walk Score® (a commercial instrument that is not yet supported by its developer in France, meaning that it is available but the developer doesn't guaranty the validity in France) as the environmental indicator.

Given the differences in urban settings and behavioural patterns between Europe and America, additional evidence is needed in each European country (37).

Hence, we analyzed data from the *Enquête Littorale Souffle Air Biologie Environnement* (ELISABET) survey of a representative sample of the population living in and around the cities of Lille and Dunkirk in northern France. The study's primary objective was to describe the association between neighbourhood walkability and cardiovascular risk factors among French adults. To this end, we assessed a walkability index (WI), calculated using a geographic information system (GIS)) and the Walk Score (WS) as environmental indicators

3.2 Methods

3.2.1 Study population and area

Our analysis was based on the cross-sectional ELISABET survey of a random sample for the electoral roll of men and women aged between 40 and 65 who have lived for at least on year in the Lille or Dunkirk urban areas, between January 2011 and November 2013. The ELISABET study's methodology has been described in detail elsewhere (38–40).

The ELISABET data were collected at home or in some case (10%) at the convenience of the volunteer in a health care establishment; a trained, registered nurse administered a detailed questionnaire, collected a blood sample and recorded anthropomorphic data. The study protocol was approved by the local investigational review board (*CPP Nord Ouest IV*, Lille, France; reference: 2010-A00065-34; ClinicalTrials.gov identifier: NCT02490553) in compliance with the French legislation on biomedical research. All participants provided their written, informed consent to participation in the study. Sampling frame and participation rate is described more extensively in supplemental data

According to French census data, the Lille and Dunkirk urban areas respectively comprised 1,154,103 and 203,770 inhabitants in 2014 (French National Institute Statistics and Economics Studies (*Institut National de la Statistique et des Études Économiques* (INSEE))(41). Each urban area comprises an old city centre surrounded by agglomerated cities and non-agglomerated cities separated by rural areas. leading to a wide range of walkability levels. Lille and Dunkirk both have a dense public transport network, and traffic levels vary from low to high across each urban area.

3.2.2 Definition of cardiovascular risk factors

3.2.2.1 *Physical activity and walking*

Physical activity was evaluated using the International Physical Activity Questionnaire (42). Three indicators were used to quantify physical activity: the intensity, and the frequency (per week) and average duration (per day) for each intensity level. We defined three levels of physical activity, according to the International Physical Activity Questionnaire results: high, moderate and low (see supplemental material for the definition of the categories). We also analysed self-reported daily walking time above 30 minutes as a binary variable (yes/no). For physical activity, we analysed the prevalence of moderate or high physical activity vs low and the prevalence of high activity versus low or moderate.

3.2.2.2 *Obesity*

We used the WHO definition of BMI, i.e. by the person's weight in kilograms divided by the square of his/her height in meters (kg/m²). Overweight corresponds to a BMI ≥25 kg/m² and <30 kg/m², and obesity corresponds to a BMI equal to or greater than 30 kg/m². Height and weight were measured by a trained registered nurse during examination

3.2.2.3 *Blood pressure*

Two consecutive measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were made with participants in the sitting position, after 5 minutes of rest. Examination was done in the morning, subject should be fasting for the appointment. When available, the blood pressure was the mean of two measurement. A second blood pressure measurement was taken systematically only during the last third of the study period (39) Hypertension was defined as an SBP ≥140 mmHg, a DBP ≥90 mmHg, or ongoing treatment with antihypertensive medication. To account for the effect of antihypertensive medication in our blood pressure analyses, we added 10 mmHg and 5 mmHg to the observed SBP and DBP values, respectively (43).

3.2.2.4 *Blood lipid profile and glycated haemoglobin (HbA1c) levels*

The laboratory measurements of blood markers have been described previously (26). The fasting HbA1c level in whole blood was measured using high performance liquid chromatography (VARIANT II, Bio-Rad, Hercules, CA, USA). Serum cholesterol and TG levels were measured using enzymatic assays. The level of high-density lipoprotein (HDL) cholesterol (HDL-C) was determined after the precipitation of apolipoproteins B with phosphotungstate/magnesium chloride. The level of LDL-C was calculated according to the Friedewald equation (LDL-C = Total Cholesterol - HDL-C - TG/5 in g/L). Assay samples were collected after a 10-hour fast. Throughout the project, the quality of each analysis was monitored in an internal quality control program (with the use of calibration standards, laboratory blanks, and reference materials (Seronorm™ Trace Elements Whole Blood, SERO, Billingstad, Norway)) and an external quality control program (an interlab comparison program established by the Quebec Toxicology Centre, Quebec National Institute of Public Health, Quebec, Canada). All the samples in a given batch were analysed at the same time with the same calibration standard. All biological samples were tested in the same laboratory.

3.2.3 *Exposure data*

Two frequently employed walkability measures (a WI and the WS) were used to assess neighbourhood walkability for each participant.

3.2.3.1 *Walkability index*

The WI used here was based on the index developed by Frank and al(13, 27), as a function of net residential density, street connectivity, and land use diversity. To approximate walkable areas, a 500 m radius buffer zone was created around each participant's home address, using ArcGIS software (Esri, Redlands, CA, USA) and a 500m walkable distance from the address by the network for the second. These buffer zones were then used to collect data on the built environment accessible by foot for each participant. The main analysis was made with a 500 meters Euclidean buffer. Sensitivity analysis with a 500m network buffer were realised.

The net residential density corresponded to the number of residential dwellings (houses and apartments) divided by the residential land surface within a participant's buffer zone. We used the 2010 population census data provided by the INSEE.

Street connectivity was obtained by calculating the intersection density. We used the 2013 road data from the French National Institute for Geographic and Forest Information (Institut National de l'Information Géographique et Forestière, BDTOPO® database). The ArcGIS software was first used to identify intersections of three or more walkable road segments. We excluded intersections on limited-access roads (e.g. motorways and flyovers). The intersection density was calculated by dividing the number of pedestrian-accessible street intersections in the buffer zone by the total area of the buffer zone.

Land use diversity corresponded to the types of destination that a participant could reach on foot in his/her neighbourhood. We considered retail facilities, institutions, amenities (e.g banks, post offices, hospitals, churches, etc.), recreational facilities, and residential facilities. To determine the number of destinations of each type within the buffer zone, we used data from the INSEE's 2016 Permanent Facilities Database (Base Permanente des Équipements). An entropy index was then calculated for each participant's buffer zone, using the following equation.

Entropy index of a buffer zone j = $\frac{-\sum p_{ij} \times ln p_{ij}}{ln N_i}$ (45)

where p_{ij} is the fraction of destinations of type i within the buffer zone j, and N_i is the number of different destination types (five, in the present analysis). The values range from 0 (a low diversity of destinations) to 1 (high diversity).

Lastly, each indicator was standardized as a z-score, and the neighbourhood WI was obtained by summing the z-scores. The WI was considered as both a continuous variable (per one interquartile range (IQR) increment) and as a categorical variable (in tertiles).

3.2.3.2 The WS

The WS was created by Front Seat Management LLC (Seattle, WA, USA). The algorithm calculates neighbourhood walkability by assigning a one-mile radius (1.6 km – a 30 min walk) buffer zone around the participant's residential address. Facilities present in the buffer zone are split into seven categories, including dining & drinking facilities, grocery shops, other shops, places for errands, parks, schools, and culture & entertainment. Based on the distance from the residential address (a distance decay function), points are assigned for each destination in every category. No points are given for destinations more than 1 mile away. The various (equally weighted) categories are summed and normalized as a score ranging from 0 ("Car Dependent") to 100 ("Walker's Paradise"). The WS also measures pedestrian friendliness by analysing the population density and road metrics such as block length and intersection density. The WS's data sources include Google, education.com, OpenStreetMap and places added by the WS user community.

In France, the WS is available but the score "is not yet supported in France", according to its developer; Front Seat Management LLC states that it does not have enough data to ensure an accurate score. However, a study of the Ile-de-France region (including Paris) found a strong association between objective walking time (measured with a GPS device and an accelerometer) and the neighbourhood WS (46). In the present study, each participants' residential addressed was attributed with a WS corresponding to the nearest point on a 100 m grid extracted from the WS website in January 2019.

3.2.4 Covariates

In the present analysis, we selected participants who had lived at their current address for at least one year. Participants with a non-localizable place of residence were excluded. The following variables were recorded: age, sex, urban area (Lille or Dunkirk), educational level, professional status, smoking status, marital status, and the identity of the nurse investigator having collected the study data.

The median income and population density for each neighbourhood were extracted from data provided by the French National Institute for Statistics and Economic Studies (INSEE). The geographical unit for a neighbourhood corresponded to the French “regrouped statistical information block” (IRIS) unit, as defined by the INSEE. The IRIS unit is the smallest census unit available in France(47) . We also recorded the annual mean residential PM_{10} concentration, as estimated by the ATMO Hauts-de-France monitoring organization with a spatial resolution of 25×25 m using an atmospheric dispersion modelling system. These methods have been described previously (40).

For each outcome, we only analysed participants with a full corresponding dataset.

3.2.5 Statistical analyses

In order to describe the WI tertiles in each urban area, Chi² tests were used to compare proportions of qualitative variables. Quantitative variables were assessed with Student's test (when the data were normally distributed) or a Kruskal-Wallis test.

3.2.5.1 Regression analyses

Geographical autocorrelation of quantitative outcome variables was estimated separately using Moran.I of the R package ape. All Moran indices were <0.02, therefore, auto-correlation were not addressed at the modelling stage.

To study the relationship between the outcomes (physical activity, BMI, blood pressure, blood lipid markers, and HbA1c) and neighbourhood walkability, we used multiple linear regression models for quantitative outcomes. We used Tobit regression model for blood lipids and HbA1c in order to account for treatment effect. We used logistic regression models and robust Poisson regression (glmrob of R Package robust) for binary outcomes. The WI and WS were used as explanatory variables. The main model was adjusted for age (as a continuous variable), sex (as a binary variable), urban area (Lille or Dunkirk), education level (primary education only, secondary education only, 2–4 years of higher education, or 5 or more years of higher education), smoking status (former smoker, never smoker, or current smoker), marital status (single, married or similar, divorced, widower, or other), work activity (full-time work, part-time work, or unemployment/no occupation), mobility limitation defined as answer yes to "Do you have difficulty to walk ?" or yes to "Are you breathless when you walk with other people of your age on flat ground ?", investigator (a class variable, with 12 modalities for the 12 nurse investigators), inclusion season (winter, summer, fall and spring) and the median neighbourhood household income in the IRIS unit (as a continuous variable). The variables are described in supplemental table 1.

We estimated mean differences for quantitative outcomes or the odds ratio for binary outcomes per tertile of neighbourhood walkability (using the WI and the WS, with the lowest tertile as reference) and for an interquartile range of neighbourhood walkability. We also tested for potential interactions between our main outcomes (BMI, SBP, and hypertension) on one hand and sex and urban area on the other. We tested interaction for age (years) and education (less than 2 years after high school / 2 years or more after high school) for the association between WI an outcomes .For interaction, with $p< 0.10$, we presented stratified analysis (for the age the analysis were stratified by age superior or inferior to the median (53.5 years))

3.2.5.2 Sensitivity analyses

We calculated a WI with the most recent data available (2015 for resident density, 2020 for street connectivity and 2016 for permanent facilities) and calculated spearman correlation between the two scores in order to evaluate stability of WI over time.

Anti-hypertensive therapy is very common and may bias the results, standard adjustment is not an accurate method for taking it in account. Many methods have been suggested to account the treatment effect for blood pressure (48) . Conversely, few methodologies for treatment of hyperlipemia or diabetes have been suggested. These various methodologies used for blood pressure have strength and weakness. In order to evaluate the accuracy of the model and sensitivity to the method, additional analyses were performed using three other methods. In the main model, we added 10 mmHg to the SBP and 5 mmHg to DBP for treated participants (43). The first additional method added a constant value to the participant's SBP and DBP, depending on the drug class and the drug combination. We used the constant described in the ATOM study ("blood pressure-lowering effects of antihypertensive drugs and combinations: meta-regression of published clinical trials") (49,50). In the second method, we performed censored normal regression (using a Tobit model) with right censoring on the observed blood pressure for a treated individual (48). Thirdly, we applied the non-parametric algorithm described by Levy and al. (51).

Furthermore, we adjusted our analyses for the residential PM_{10} and NO_2 concentration (as a have high concentrations of traffic-related air pollutants, which may raise the cardiovascular disease risk (40,52). Lastly, we performed mediation analysis (53), studying the mediator effect of physical activity (define as dichotomous variable low versus moderate or high) and BMI in the association between WI and blood pressure variables (SBP, DBP, and hypertension). We studied association between physical activity and BMI with blood pressure and studied the ratio of mediation using the function mediate of the R package. The confident interval was calculated by Bootstrap with 500 simulation.

We did further adjustment for household income and ethnicity. Missing data for house income were code as category of income. Ethnicity (European or Other) were determined by cluster the analysis of genetics data is currently ongoing (methodology not publish yet)(42)

In a sensitivity analysis, we take into account the sampling frame, using svydesign of the package survey and the finite population correction to take all small town were not included in Lille city area. To account the different sampling frame in Dunkirk and Lille, we did separate analysis in Lille and Dunkerque and pooled the results using rma of the metaphor package. In this analysis, participants reporting the use of diabetes medication or cholesterol medication were excluded from this sensitivity analyses of the associations with HbA1c and the blood lipid profile, respectively.

The threshold for statistical significance was set to $p<0.05$. Statistical analyses were performed using R software (version 3.5.1, R Core Team, 2018) (54)

3.3 Results

A total of 3276 participants had been included in the ELISABET survey, and one participant had been excluded after he withdrew his consent. The spatial distribution of the volunteers is presented in supplemental figure 1. In the present study, we excluded a further 43 participants because they had moved home within the previous year, 6 participants with missing data on their professional status, 4 with missing data on their marital status, 1 with missing data on his smoking status, and 1 who was unable to walk as the result of a known disease. Ultimately, 3218 participants were analyzed (1648 for Lille and 1570 for Dunkirk). Missing data meant that 125 participants were excluded from the physical activity analysis, 28 were excluded from the SBP analysis, and 56 were excluded from the analyses of DBP and hypertension.

The study population's characteristics are summarized by urban area and by WI level in Table 1. The participants' mean age was 53.3 yrs. In each urban area, participants living in the most walkable neighbourhood were significantly more likely to be current smokers, single, or divorced, and presented a higher educational level. In Lille, the most walkable neighbourhood had higher level of PM_{10} and a lower annual residential income; in Dunkirk, the opposite was true. The WI and WS were closely correlated (Spearman's correlation coefficient = 0.77, $p<1x10^{-15}$). The distribution of the participants' WS values is described in Table 2; most of the participants lived in a "somewhat walkable" or "very walkable" neighbourhood.

Table 1 : Participants included in the analysis and neighborhood characteristics, by urban area and level of walkability

	Lille				Dunkirk			
	Low WI	Medium WI	High WI		Low WI	Medium WI	High WI	
Individual Variables				P-Value[a]				P-Value[a]
Number n(%)	495(30.0)	592(35.9)	561(34.0)		584(37.2)	483(30.8)	503(32.0)	
Sex (Men), n(%)	240(48.5)	275(46.5)	255(45.5)	0.61	282(48.3)	246(50.9)	236(46.9)	0.44
Age, mean (SD)	53.2(6.9)	53.5(7.2)	52.6(7.4)	0.11	53.4(7.3)	53.4(7.4)	53.3(7.2)	0.942
Educational level, n(%)				$<10^{-4}$				$<10^{-4}$
5 years or more after high school	99(20)	135(22.8)	153(27.3)		58(9.9)	50(10.3)	91(18.1)	
2 years to 4 years after high school	118(23.8)	131(22.1)	114(20.3)		87(14.9)	65(13.5)	75(14.9)	
secondary education	242(48.8)	277(46.7)	239(42.6)		373(63.9)	299(61.9)	275(54.7)	
primary education	36(7.2)	49(8.3)	55(9.8)		66(11.3)	69(14.3)	62(12.3)	
Marital status, n(%)				$<10^{-4}$				$<10^{-4}$
single	25(5.0)	47(7.9)	93(16.6)		12(2.0)	24(5)	40(7.9)	
married or similar	405(81.8)	449(75.84)	363(64.7)		526(90.1)	393(81.4)	373(74.1)	
divorced	49(9.9)	70(11.82)	91(16.2)		34(5.8)	53(11)	71(14.1)	
widowed	12(2.4)	22(3.7)	10(1.8)		12(2.0)	13(2.7)	18(3.6)	
other	4(0.8)	4(0.7)	4(0.7)		0(0)	0(0)	1(0.2)	
Work activity, n(%)				0.733				0.164
no occupation/unemployed	154(31.1)	188(31.8)	178(31.7)		236(40.4)	215(44.5)	185(36.8)	
part-time work	56(11.3)	78(13.2)	78(13.9)		61(10.5)	47(9.7)	61(12.1)	
full-time work	285(57.6)	326(55.1)	305(54.4)		287(49.1)	221(45.8)	257(51.1)	

Individual Variables	Lille				Dunkirk			
	Low WI	Medium WI	High WI	P-Valuea	Low WI	Medium WI	High WI	P-Valuea
Smoking status, n(%)				0.01				0.186
Nonsmokers	582(53.6)	556(49.6)	517(49)		320(54.8)	246(50.9)	241(47.9)	
Current smokers	169(15.6)	217(19.4)	226(21.4)		97(16.6)	90(18.6)	107(21.3)	
Former smokers	335(30.8)	347(31)	312(29.6)		167(28.6)	147(30.4)	155(30.8)	
Physical activity level, n(%)[b]				$<10^{-4}$				0.003
Low	144(29.7)	149(25.9)	156(28.1)		301(51.4)	217(54.4)	203(42.5)	
Moderate	142(29.3)	249(43.3)	241(44.1)		165(28.2)	159(29.8)	192(40.1)	
High	198(41)	177(30.7)	150(27.4)		87(14.1)	80(15.7)	83(17..4)	
Daily walking >30 min, n(%)	210(42.42)	222(37.5)	251(44.74)	0.036	223(38.18)	193(39.96)	221(43.94)	0.141
BMI (kg/m^2), mean (SD)	26.9(4.7)	26.6(5.2)	26.6(5.3)	0.553	27.5(5.1)	28(5.2)	27.1(5.2)	0.039
Weight status, n(%)				$<10^{-4}$				0.025
BMI<25	202(41)	247(41.7)	239(42.6)		205(35.1)	142(29.4)	184(36.6)	
25<BMI<25	178(36)	233(39.3)	205(36.5)		236(40.4)	187(38.7)	195(38.8)	
BMI>30	115(23)	112(19)	117(20.9)		143(24.5)	154(31.9)	124(24.6)	
SBP (mmHg), mean (SD)[c]	129.2 (19.3)	126.5 (19)	126.5 (18.2)	0.035	132.1(19.3)	130 (19)	128.2(20)	0.039
DBP (mmHg), mean (SD)[d]	83.2(11.6)	81.8(11.5)	82.5(11.5)	0.158	83.7(12.3)	83.7(12.1)	81.9(12.2)	0.022
HBP, n(%)[d]	231(46.7)	253(42.7)	237(42.2)	.306	290(49.7)	235(48.6)	220(43.7)	0.132
Antihypertensive medication, n(%)	119(24)	142(24)	129(23)	0.899	145(24.8)	119(24.6)	118(23.5)	0.856
LDL-C[e] (g/L), mean (SD)	1.41(0.32)	1.37(0.36)	1.4(0.36)	0.151	1.41(0.3)	1.40(0.35)	1.42(0.34)	0.811
HDL-C[e] (g/L), mean (SD)	0.6(0.1)	0.59(0.1)	0.58(0.1)	0.17	0.58(0.14)	0.56(0.14)	0.57(0.15)	0.08
HbA1c[f] (%), mean (SD)	5.58(0.6)	5.65(0.6)	5.74(0.7)	$<10^{-4}$	5.75(0.67)	5.78(0.76)	5.78(0.76)	0.772

Environmental variables	Lille				Dunkirk			
	Low WI	Medium WI	High WI	P-Valuea	Low WI	Medium WI	High WI	P-Valuea
Walk Score®, mean (SD)	39.2(22.7)	60.4(18.7)	79.7(13)	$<10^{-4}$	33.7(24.2)	58.2(22.2)	76.8(20.8)	$<10^{-4}$
IRIS median income (×1000 euros) , median [IQR]	21.1 [19.8-22.4]	20.6[18.1-21.5]	17.2[13.4-21.6]	$<10^{-4}$	17 [16.4-20]	16.7[15.5-18.9]	18.1[14.1-20]	$<10^{-4}$
IRIS density (1000 hab/km 2), median [IQR]	1.6[0.6-3.3]	4.0[1.8-5.1]	8.5[6.0-11.3]	$<10^{-4}$	0.9[0.4-2.5]	4.1[2.3-6.3]	6.9[4.5-9.1]	$<10^{-4}$
PM10 (µg/m 3), mean(sd)	25.9(1.8)	26.9(1.8)	28.15(1.6)	$<10^{-4}$	26.2(1.1)	26.63(0.8)	25.19(0.6)	$<10^{-4}$
NO2 (µg/m 3), mean(sd)	23.2(4.9)	25.9(4.7)	28.72(4.8)	$<10^{-4}$	19.055(2.18)	20.222(2.2)	20.826(1.72)	<10-3**

WI: walkability index; n: number; SD: standard deviation.

[a] Student's t-test for quantitative variables(Kruskal-Wallis test for skewed quantitaive variables), or a chi² test for qualitative variables

b: 125 missing data, c : 28 missing data; d : 56 missing data

Individual Variables	Lille				Dunkirk			
	Low WI	Medium WI	High WI	P-Value[a]	Low WI	Medium WI	High WI	P-Value[a]
Genotype clusters ,n(%)								0.317
European	444(89.7)	539(91.05)	464(82.71)	$<10^{-4}$	532(91.1)	427(88.41)	448(89.07)	
Others	51(10.3)	53(8.95)	97(17.29)		52(8.9)	56(11.59)	55(10.93)	
Inclusion season ,n(%)				0.726				0.622
Autumn	111(22.42)	137(23.14)	141(25.13)		150(25.68)	141(29.19)	123(24.45)	
Summer	104(21.01)	140(23.65)	122(21.75)		128(21.92)	104(21.53)	110(21.87)	
Winter	129(26.06)	132(22.3)	132(23.53)		134(22.95)	110(22.77)	112(22.27)	
Spring	151(30.51)	183(30.91)	166(29.59)		172(29.45)	128(26.5)	158(31.41)	

MET,median [IQR]	2235[887.1-5040]	1806[856.5-3724]	1626[792-3360]	<10^{-4}	996[330-2346]	1039.5[280.1-2529.75]	1227.8[462-2362.75]	0.111
Annual Household income (euros),n(%)				<10^{-4}				0.036
<7000	124(25.05)	165(27.87)	158(28.16)		96(16.44)	99(20.5)	94(18.69)	
7000-15 000	4(0.81)	3(0.51)	13(2.32)		1(0.17)	1(0.21)	3(0.6)	
15 000-30 000	21(4.24)	42(7.09)	71(12.66)		15(2.57)	26(5.38)	28(5.57)	
30 000-45 000	142(28.69)	168(28.38)	154(27.45)		116(19.86)	69(14.29)	73(14.51)	
45 000-60 000	101(20.4)	109(18.41)	67(11.94)		47(8.05)	45(9.32)	41(8.15)	0.164
60 000	54(10.91)	57(9.63)	51(9.09)		29(4.97)	25(5.18)	32(6.36)	
Didn't answer the question.	49(9.9)	48(8.11)	47(8.38)		280(47.95)	218(45.13)	232(46.12)	
Mobility limitations, n(%)	36(7.27)	39(6.59)	57(10.16)	0.064	72(12.33)	60(12.42)	52(10.34)	0.505

MET: Metabolic Equivalent of Task

Table 2 : Distribution of the Walk Score® by urban area

	Lille		Dunkirk	
Walk Score®	*n(%)*	Mean	*n(%)*	Mean
Overall	1648	60.6	1570	55,1
Very car-dependent (0-24)	201(12.2)	14.7	373(23,8)	11.1
Car dependent (25-49)	215(13.0)	34.1	159(10,1)	40.6
Somewhat walkable (50 -69)	504(30.6)	60.2	418(26,6)	59.0
Very walkable (70 -89)	605(36,7)	78.8	459(29,2)	78.6
Walker's paradise (90 -100)	123(7,5)	95.1	161(10,3)	93.8

3.3.1.1 Associations between neighbourhood walkability and cardiovascular risk factors

The results of the multivariable analyses for each of the walkability indices are summarized in Table 3. In the fully adjusted model, we observed a significant negative association between neighbourhood walkability (according to the WI or the WS) and the prevalence of moderate or high physical activity was increase by 12.3% [-0.1;26.2] in the high tertile of walkability. (OR for One IQR [95%CI] = 1.25[1.13;1.38]) and at least 30 minutes of walking per day was increased by 12.1% IC95% [-2.2-28.5] (OR 1.16[1.06;1.28] for a one IQR increment in WI). WS was associated to lower prevalence of High physical activity -15.0%[-30.0;2.6] in the highest tertile of WS and OR 0.86[0.76;0.97] for one IQR. No significant association were observed with WI. There was a significant association between neighbourhood walkability and BMI; for a one IQR increment in the WI, we observed a significant difference (– 0.23 [-0.44;-0.01] kg/m²) in the mean BMI. However, we did not observe a significant association with obesity (OR 0.95[0.85;1.07] for WI). There were strong negative associations between neighbourhood walkability and blood pressure outcomes. For a one IQR increment in WI, there was a difference of – 1.66 [-2.46;-0.85] mmHg for the SBP and -0.79[-1.31;-0.27] mmHg for the DBP. The prevalence of hypertension was -8.9%[-20.2;3.9] lower in the high tertile of walkability (OR for one IQR 0.87 [0.78;0.96]) . We did not find significant associations with the biomarkers of cardiovascular risk (i.e. serum HbA1c, LDL-C, HDL-C and TG levels). All associations found for WI were also observed for WS. The only difference between the two scores was observed for a high level of physical activity.

Table.3 : Association between neighborhood walkbability (defined as a walkability index (WI) or the Walk Score® (WS)) and cardiovascular risk factors

Variables	Score	% of increase					Odds ratio		Difference of Mean				
		Tertile of walkability			Linear trend for an interquartile range increment in walkability [95%CI]	*p*-Value	Odds ratio for an interquartile Linear trend for an interquartile	*p*-Value	Tertile of walkability			Linear trend for an interquartile range increment in walkability [95%	*p*-Value
		Low (ref)	Medium [95% CI]	High [95% CI]					Low (ref	Medium [95% CI]	High [95% CI]		
Physical activity													
Moderate or High activity[b]	WI	-	9.49[-2.16;22.52]	12.26[-0.12;26.16]	6.9[1.2;12.72]	0.01744	1.25[1.13;1.38]	$<10^{-3}$					
	WS	-	4.49[-6.78;17.12]	9.49[-2.49;22.94]	5.14[-1.06;11.36]	0.10413	1.17[1.06;1.3]	0.002					
High activity[b]	WI	-	-11.11[-25.24;5.69]	-12.67[-27.62;5.37]	-5.29[-14.52;4.28]	0.27489	0.94[0.83;1.05]	0.261					
	WS	-	-7.12[-22.03;10.65]	-15.02[-29.59;2.56]	-10.8[-20.25;-1.31]	0.02572	0.86[0.76;0.97]	0.010					
Daily Walking ≥ 30 min	WI	-	-4.34[-16.5;9.6]	12.1[-2.22;28.51]	7.91[1.07;14.92]	0.02306	1.16[1.06;1.28]	0.001					
	WS	-	-1.82[-14.36;12.56]	8.59[-5.36;24.59]	4.79[-2.6;12.2]	0.20438	1.1[0.99;1.21]	0.071					
MET(%)	WI								-	-15.84[-32.58;5.06]	11.73[-21.1;58.21]	11.51[1.99;21.37]	0.017
	WS								-	-11.52[-27.27;7.66]	-7.32[-28.11;19.49]	4.37[-5.54;14.32]	0.388
Weight status													
BMI (kg/m^2)	WI								-	-0.03[-0.44;0.39]	-0.3[-0.73;0.13]	-0.23[-0.44;-0.01]	0.037
	WS								-	-0.19[-0.61;0.23]	-0.32[-0.75;0.1]	-0.26[-0.48;-0.03]	0.025
Obese	WI	-	5.04[-11.91;25.26]	-5.38[-21.7;14.35]	-3.5[-12.73;6.07]	0.4687	0.95[0.85;1.07]	0.401					
	WS	-	2.68[-13.92;22.49]	-11.64[-26.97;6.91]	-5.87[-15.72;4.01]	0.24367	0.92[0.82;1.03]	0.156					
Blood pressure													
SBP (mmHg)[c]	WI								-	-2.81[-4.39;-1.24]	-2.7[-4.33;-1.07]	-1.66[-2.46;-0.85]	0,001
	WS								-	-2.09[-3.69;-0.5]	-2.28[-3.91;-0.65]	-1.52[-2.38;-0.66]	$<10^{-3}$
DBP (mmHg)[d]	WI								-	-0.92[-1.94;0.1]	-1.1[-2.15;-0.04]	-0.79[-1.31;-0.27]	0.003
	WS								-	-0.77[-1.81;0.26]	-0.89[-1.95;0.16]	-0.69[-1.25;-0.14]	0.015
Hypertension[d]	WI	-	-6.98[-17.95;5.46]	-9.42[-20.64;3.39]	-7.12[-13.56;-0.52]	0.03461	0.86[0.78;0.95]	0.002					
	WS	-	-5.93[-17.18;6.85]	-8.9[-20.16;3.94]	-6.69[-13.56;0.2]	0.05719	0.87[0.78;0.96]	0.006					
Current smoker	WI	-	2.93[-16.88;27.47]	19.51[-3.41;47.88]	12.48[1.91;23.46]	0.02026	1.2[1.07;1.35]	0.002					
	WS	-	24[-0.35;54.3]	40.22[12.78;74.33]	21[8.86;33.2]	0.00068	1.3[1.14;1.49]	$<10^{-3}$					
Hba1c (%)	WI								-	0.03[-0.03;0.08]	0.07[0.01;0.13]	0.02[-0.01;0.05]	0.158
	WS								-	0.02[-0.04;0.08]	0.05[-0.01;0.11]	0[-0.03;0.04]	0.796
Lipidemia													
LDL(g/L)	WI								-	-0.01[-0.02;0.01]	0[-0.02;0.01]	0[-0.01;0.01]	0.829
	WS								-	-0.01[-0.02;0.01]	0[-0.02;0.01]	-0.01[-0.01;0]	0.106
HDL(g/L)	WI								-	-0.01[-0.04;0.02]	0[-0.03;0.03]	-0.01[-0.02;0.01]	0.433
	WS								-	-0.03[-0.06;0]	-0.02[-0.05;0.01]	-0.01[-0.03;0.01]	0.296
TG (g/L)f	WI								-	-0.02[-0.06;0.01]	-0.01[-0.04;0.03]	-0.01[-0.02;0.01]	0.458
	WS								-	-0.04[-0.08;-0.01]	-0.03[-0.07;0.01]	-0.01[-0.03;0.01]	0.164

CI: confidence interval; IQR: interquartile range; MET: Metabolic Equivalent of Task

main model adjusted for sex, age, urban area, educational level, smoking status, inclusion season, marital status, work activity,mobility limitation and residential median income

b: 125 missing data, c : 28 missing data; d : 56 missing data

Mutiple linear regression for difference of mean; poisson regression for % of increase; logistice regression for odds ratio

3.3.1.2 Sensitivity analyses

We studied the association using network buffer of 500 m instead of the Euclidian buffer. Result were similar than in the main analysis (supplemental table 2). The spearman correlation between WI use in the main analysis and a WI calculated with the most recent data available was 0.95.

The results of the models for walkability and blood pressure after adjustment of the blood pressure values with four different approaches are summarized in Supplemental Tables 3a and 3b The associations with walkability and blood pressure were similar, although censored normal regression led to a slightly stronger association (-2.43 mmHg for the mean SBP for a one IQR increment in the WI).

The results of the models for neighbourhood walkability and cardiovascular risk factors after adjustment for the residential PM_{10} or NO_2 concentration are summarized in Supplemental Table 3. The results were similar to those of the main model, except that the association was no longer significant for the BMI. No association between walkability index or Walkscore and Hbac1 was observed after adjustment for PM_{10} Or NO_2.

After adjustment for household income and divergent ancestry, results remain consistent (supplemental table 4). In the model taking into account the stratified sample, results were consistent except for the association of WS with physical activity and walking and WI with walking which were no more significant. Results were similar in the model taking into account the sampling frame (Supplemental table 5) except for the association with physical activity which was only significant for WI and moderate or high physical activity .

3.3.1.3 Mediation analysis

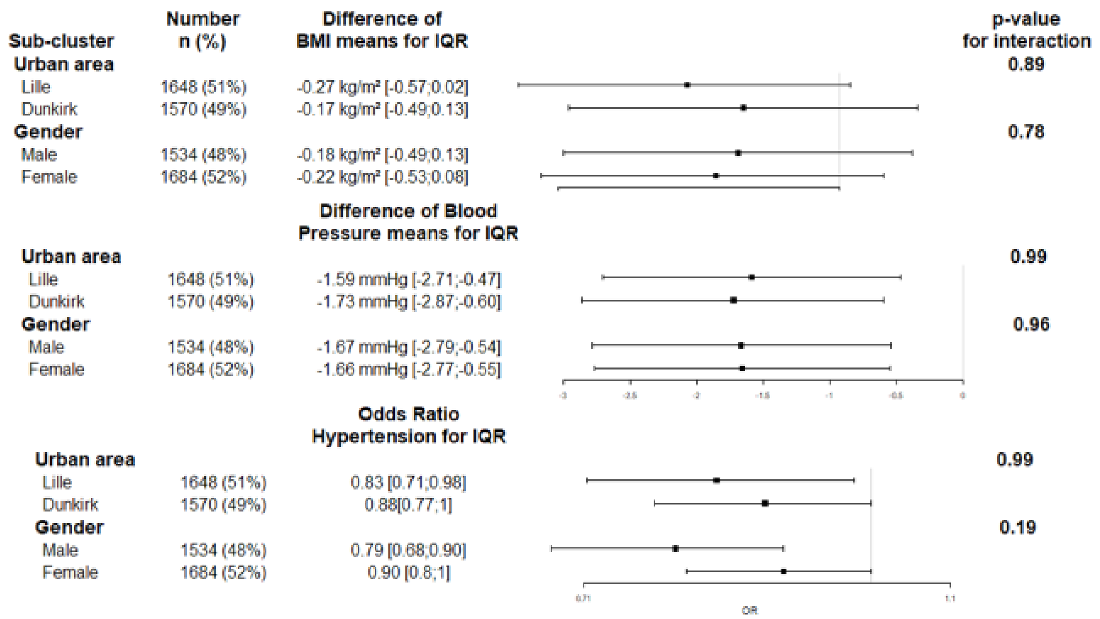
Moderate or high physical activity was associated to lower diastolic blood pressure compared to low physical activity (-0.98mmHG [-1.89; -0.08 mmHg]). No significant associations were observed between physical activity and blood systolic blood pressure or hypertension (both p>0.6). Accordingly, association ratios between WI and blood pressure explain by physical activity were small and non-significant (supplemental table 6). BMI was significantly associated to systolic blood pressure (coefficient for 1 unit of BMI 0.91 mmHg

[0.77; 1.04]), diastolic blood pressure (coefficient for 1 unit of BMI 0.57 mmHg [0.49 ; 0.63] and hypertension percentage increase or prevalence 4.9% [3.9%; 5.9%]). Association ratios explained by BMI were significant and range from 12.1%[0.4%;27%] for systolic blood pressure to 17.4%[2.1%; 45%] for diastolic blood pressure.

3.3.1.4 Interaction analysis

No significant interactions with the urban area or with sex were observed for any of the main outcomes (figure 2). For other interactions, the only significant one with WI was for education and daily walking above 30 minutes (p=0.04), the percentage increase in prevalence for one IQR of WI was 2.73 % [-5.04;11.62] in the lower education group and 9.42 % [0.19;20.16] in the higher education group. Interaction with p >0.10 are presented in supplemental table 7

Figure 2. Association with main outcomes for an IQR increment in the WI



3.3.1.5 Discussion

Our results showed that higher neighbourhood walkability was associated with a lower prevalence of low physical activity. Neighbourhood walkability had strong negative associations with blood pressure and BMI. However, we did not find a significant association with obesity or any of the blood markers.

With regard to blood pressure, the associations observed in the present study were consistent with those reported previously in the United Kingdom(33) and in France (34). In the latter study, the effect size for the association between WS and SBP (beta coefficient [95% CI] = -0.030 mmHg [-0.063;-0.0004] per unit increment in WS) was half that observed here (-0.064, [-0.095; -0.033]) (34). Our present results are also in agreement with data from North America(26,28,55) and Australia (56). Consistency is found in the Bradford Hill criteria, which reinforces the hypothesis of causality. Nevertheless these studies are mainly cross-sectional and further studies are needed to conclude on causal association . This association may be explained by increased physical activity. In the present study, neighbourhood walkability was negatively associated with a low physical activity prevalence. However, no increase of high physical activity prevalence was observed, on the contrary, a decrease in the prevalence with WS was observed. Walkability may increase moderate physical activity through walking for daily activities. High physical activity, which depends on vigorous activity (mainly accruing during sport practice), may be less impacted. Walkability may increase walking and then reduce low physical activity but may not be sufficient to achieve high physical activity. Consistently, sedentary behaviour is associated with high blood pressure (19), and moderate physical activity has a positive impact on blood pressure (57,58). The activity was not associated to blood pressure, accordingly, it does not explain the associations with SBP and DBP in the mediation analysis. One reason for this small impact might be the misclassification of self-reported physical activity and thus a lack of accuracy. Accordingly, previous studies did not clearly demonstrate mediation by physical activity of the association between walkability and changes in cardiometabolic outcomes (56,59,60). The small impact of physical activity on the association might also be due to one or more other mechanisms or cofounding factors acting alone or together. Future research should investigate additional mechanisms by which walkability is involved in cardiometabolic health outcomes.

With regard to weight status, we observed a significant association with BMI but not with obesity. The negative association with BMI was consistent with European studies (conducted in Belgium (61) and France (34)) and American studies (62,63). The effect size reported in the French study (estimated β coefficient [95% CI] for BMI = -0.010 kg/m^{-2} [-0.019;-0.002] per unit increment in WS (34)) was similar to that observed here (-0.011 [-0.020; -0.002]). The earlier French study also found that living in a low-walkability (car-dependent) neighbourhood was associated with an elevated prevalence of obesity. Furthermore, longitudinal studies in North America found a strong, protective association between higher walkability and obesity (26). In contrast, we did not find a significant association with obesity in our study perhaps because of loss of power analysing a binomial variable (obesity) instead of a continuous variable (BMI).

Lastly, the associations between neighbourhood walkability and SBP and DBP were only partly explained in the mediation analysis by BMI. The effect of walkability on blood pressure through a lowering in BMI does not seems to be predominant - probably due to a small weight reduction. Even though weight reduction diminishes blood pressure (64), other mechanisms may be involved, previous studies suggest that physical activity may reduce blood pressure through physiological pathway other than body weight (65).

With regard to blood markers, we did not find an association with HbA1c and even a non-significant increase of HbA1c associated with high walkability in the main model was observed. A recent meta-analysis reported that neighbourhood walkability was associated with a lower risk/prevalence of diabetes (66). Two European studies did not find an association between walkability and type 2 diabetes. The effect of walkability might simply not be strong enough to have any observable effects on the HbAc1 level. Furthermore, HbA1c has been linked to air pollution. As regards, one possible explanation for the lack of association of HbA1c with high walkability in the main model could be due to higher air pollution in area with high density. Accordingly, air pollution was higher in walkable neighbourhoods in Lille. The non-significant, unfavourable association between walkability and HbA1c disappeared after adjustment for PM_{10} or NO_2. Although it is not sufficient to confirm it this last result is consistence of the hypothesis of a confusion by air pollution.

In sedentary people, increased light- or moderate-intensity physical activity has a positive effect on blood lipid levels by increasing the HDL-C level and decreasing the LDL-C and triglyceride levels (67–69). However, we did not find an association between neighbourhood walkability and any of the blood lipid markers. Again, the influence of walkability on physical activity might not be strong enough to produce an observable effect on the blood lipid profile. Canadians studies have observed than higher HDL cholesterol was associated to Walkability(27,29). However, these results are inconsistent to the best of our knowledge, no European studies have been conducted, and an American study did not observe any association with HDL-C or LDL-C (28). Furthermore, a recent Dutch study did not find any evidence to suggest that population density (a walkability parameter) is associated with blood lipid levels (50). Therefore, there is limited evidence for an association between walkability and blood lipids.

We observed a higher prevalence of smoking in area with high walkability. This association has been observed previously in Ontario. Nevertheless, we didn't expected walkability to have unfavourable impact on smoking. The reasons for higher rate of smoking associated to walkability remain to be explained. One hypothesis may be the greater proximity to tobacco seller(27)

Our results were consistent across cities, gender, education groups and age. A significant interaction was observed only for walking ≥ 30 min/Day and education. It seems that walkability may be more associated to walking when education level is higher. This may be due to a possible increase in health consciousness among better educated people. Il may also be due to chance due to the large number of interaction tests done.

Our study had some limitations. Firstly, its cross-sectional design prevented us from assessing the possible causal nature of the relationship between neighbourhood walkability and our outcomes. Reverse causation might be possible due to potential self-selection of neighborhood driven by physical activity preferences. Health-conscious participants may selected residential location that facilitated physical activity; in turn, that choice might lead to overestimation of the relationships between walkability and health outcomes(70). In our study, however, residents living in more walkable areas reported smoking more (i.e. arguing against this hypothesis), and previous studies have shown that reverse causation is unlikely (71,72). Secondly, there was a time interval between the collection of the ELISABET data (in 2011-2013) and the collection of geographical data (in 2019 for the WS and from 2013 to 2016 for the WI). It is possible that some neighbourhoods changed during this time, which might have led to misclassification of walkability measures. Nevertheless, any changes might have been marginal. Moreover, we did not account for fine features such as greenness, sidewalk conditions, or shade – all of which can influencing pedestrian behaviours like leisure-time walking (56) accordingly the correlation between the two WI calculated with different data periods were high. Thirdly, we could not incorporate more subjective variables, such as perceived security or aesthetics. Fourthly, the participant individual income measurement had weakness, there were lots of missing data and only household income was available. Residual confounding on socio economic level is therefore possible. Furthermore, we didn't have ethnicity information. Nevertheless, results were consistent after adjusting with a proxy of ethnicity by genetic cluster analysis which is not validated yet.

Filthy, This work has an analytic objective and representativeness of the sample is a less important issues(74). Nevertheless, we take into account the study sampling in a sensitivity analysis. The results on blood pressure remain significant. Association with physical activity were consistent but only significant for WI. The reduce number of significant results with physical activity may be explain by the lower power of this analysis. Indeed the number of degrees of freedom were increase by the stratification of the analysis by city areas. Lastly, our walkability index did not distinguish between establishments within each type of destination;

for example, the retail category included supermarkets and small convenience stores. Nevertheless, this measurement error might have been non-differential and would have biased the association towards the null

This study had several strengths. Firstly, we used objective measures of cardiometabolic risk markers. Secondly, we use two different walkability indices - one of which was GIS-based. Thirdly, we studied two different French cities with a wide range of urban settings and environmental features. The observed associations were similar in both cities. Furthermore, the observed associations were consistent with both walkability indices and all methods of adjusting the blood pressure analysis. This strengthens the level of confidence in our associations - especially for blood pressure and BMI, which do not appear to be explained by specific local features or methodological issues

3.4 Conclusion

Overall, our results evidenced favourable associations between neighbourhood walkability on one hand and blood pressure and BMI on the other. However, no association was found for other cardiovascular health outcomes (HbA1c and blood lipid markers) in the French context. Greater neighbourhood walkability might improve health at the population level. Further research in Europe is required for a better understanding of the mechanisms involved - especially for blood markers.

Acknowledgements

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Competing interest

AC, FO, PA, AM declare that they have no conflicts of interest.

LD contributed to an expert report commissioned by Lille European metropole "Rapport d'expertise à propos de la localisation de la piscine du projet d'aménagement de la gare Saint Sauveur à Lille" [Expert report on the location of the swimming pool in the Saint Sauveur station development project in Lille] but did not receive any personal fees.

4 Conclusion (Français)

Dans l'ensemble, nos résultats mettent en évidence des associations favorables entre la marchabilité des quartiers, d'une part, et la pression artérielle et l'IMC, d'autre part. Cependant, aucune association n'a été trouvée pour d'autres résultats de santé cardiovasculaire (HbA1c et marqueurs lipidiques sanguins) dans le contexte français. Une plus grande marchabilité des quartiers pourrait améliorer la santé au niveau de la population. Des recherches supplémentaires en Europe sont nécessaires pour mieux comprendre les mécanismes impliqués - en particulier pour les marqueurs sanguins.

5 Annexes

<u>Sampling frame and participation rate.</u>

participants were selected from electoral rolls by random sampling, with stratification for gender, age and centre (Lille or Dunkirk). All participants

were recruited between January 2011 and November 2013. Each selected participant received a letter asking him/her to contact the coordinating team and make an appointment for data collection.

In the absence of a reply, repeated reminders by mail and, when possible by telephone, were conducted. Data was collected at home (occasionally during a consultation in a healthcare establishment).

In all cases, a trained, registered nurse administered a detailed questionnaire and performed spirometry testing.

The sampling was stratified by town by age and Sex. All the 18 town of Dunkirk urban community were included in the study with a sample proportional to the population size of each town. In the Lille Urban Area all the town of more than 20000 inhabitant (60 % of the population of the Lille urban community) were included in the sample. 6 over the 14 town between 10000 and 20000 inhabitants were randomly include in the sample and 6 over the 58 town of less than 10000 inhabitant were randomly included. The sample size within each town were calculated to have the sample sampling probability for each inhabitant of the Lille of the same age and sex Urban Area.

We invited 9949 potentially eligible subjects to participate in the study (Fig. 1). Of these, 3684 did not reply. Among participant contacted, 52.3% (3276/6265) accepted to participate (cooperation rate). Finally, the response rate was 32.9% (3276 out of 9945 subjects).

<u>Definition of physical activity groups</u>

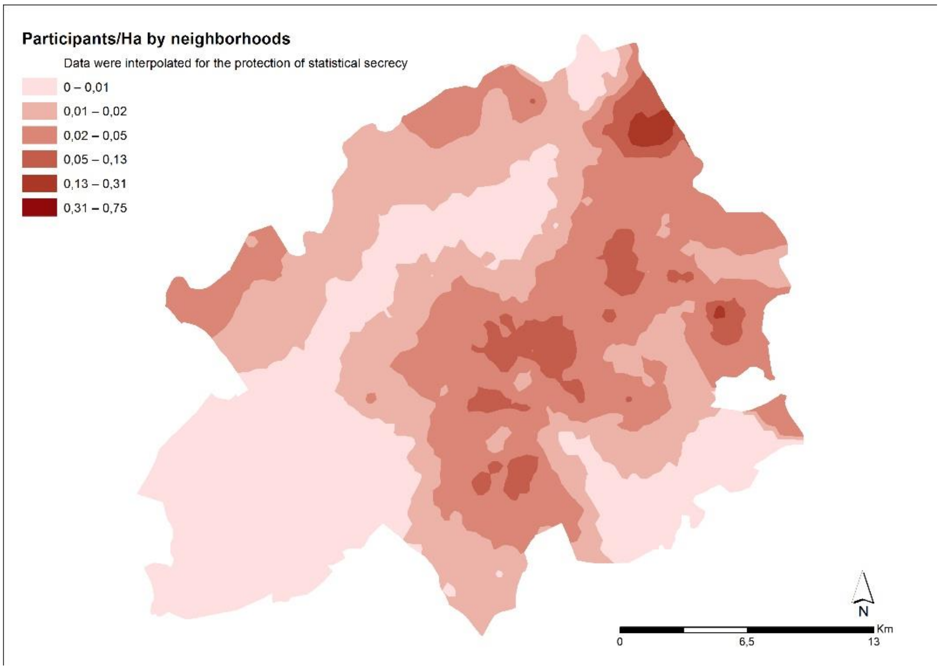
High level: at least 3 days of vigourous activity and metabolic equivalent of task (MET) of vigourous activity ≥1500. Or at least seven days of physical activity by week and total MET ≥3000

Moderate: at least 3 days of vigorous physical activity of at least 20 minutes or at least five days of moderate activity or at least 30 minutes or at least three days of walking of more than 30 minutes or at least 5 days of physical activity (any) and total MET ≥600.

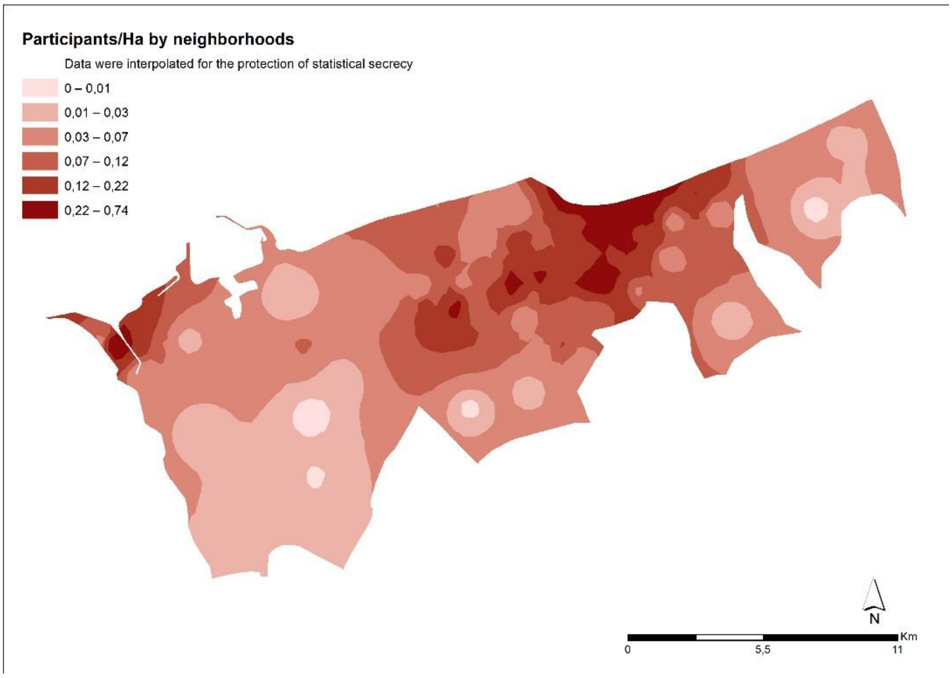
Low: Subject not include in moderate or high physical activity were

Supplemental figure 1 distribution of ELISABET volunteers in Lille(A) and Dunkirk (A) Areas

A



B



supplemental table 1 : Description of the variable used in the analysis.

	measurement or source of data	unit or category
Sex	questionnaire	Men/women
Age	questionnaire	years
Educational level	questionnaire	5 years or more after high school/2 years to 4 years after high school/secondary education/primary education
Marital status	questionnaire	single/married or similar/divorced/widowed/other
Work activity	questionnaire	no occupation or unemployed/part-time work/full-time work
Mobility limitation	questionnaire: defined as response yes to “do you have difficulty to walk” or yes to the question “are you breathless when you walk with other people of your age on flat ground”	YES/NO
Smoking status	questionnaire	response to the question "do you smoke or have ever smoke more than one year: No : Non smoker yes currently : Current smokers yes but I quit : Former smokers
Physical activity level	questionnaire IPAQ	low/moderate/High
Daily walking ≥ 30 min	questionnaire IPAQ	YES/NO
Body mass Index (BMI)	measurement height and Weight	Kg/m2
Weight status	measurement height and Weight	BMI<25/25≤BMI<30/BMI≥30
Obesity	measurement height and Weight	BMI≥30
Systolic blood pressure	measured a inclusion	mmHg
Diastolic blood pressure (DBP)	measured a inclusion	mmHg
High Blood Pressure (HBP)	SBP≥ 140mmHg or DBP≥ 90mmHg or ongoing treatment with antihypertensive medication	YES/NO
Antihypertensive medication, n(%)	questionnaire	YES/NO
LDL-Cholesterol	blood sample	g/L
HDL-Cholesterol	blood sample	g/L
HbA1c	blood sample	%
IRIS residential median income	Density of the neighbourhood (source INSEE)	k€
IRIS density	Density of the neighbourhood (source INSEE)	1000 hab/km 2
mean athmospheric PM10 at household	Atmospheric dispersion modelling system	µg/m 3
mean athmospheric NO2 at household	Atmospheric dispersion modelling system	µg/m 3
Walk Score® (WS)	https://www.walkscore.com/	abitrary unit from 0 to 100
Walkabilty index (WI)	function of net residential density, street connectivity, and land use diversity in a buffer of 500 m	abitrary unit
investigator		12 modalities for the 12 nurse investigators

Supplemental Table 3a : Association between neighborhood walkability (WI or WS) and cardiovascular risk factor, after adjustment for the residentiel PM10 concentration

Variables	Score	Odds ratio							Difference of Mean				
		Tertile of walkability			Linear trend for an interquartile		Odds ratio for an interquartile		Tertile of Walkability			Linear trend for an interquartile	
	Score	Low (ref)	Medium [95% CI]	High [95% CI]	ge increment in walkability [9	*p*-Value	.inear trend for an interquartil	*p*-Value	Low (ref)	Medium [95% CI]	High [95% CI]	ıge increment in walkability [	*p*-value
Weight Status													
BMI (kg/m^2)	WI								-	0.02[-0.39;0.44]	-0.2[-0.65;0.26]	-0.18[-0.41;0.05]	0.12096
	WS								-	-0.1[-0.54;0.34]	-0.19[-0.67;0.28]	-0.2[-0.46;0.06]	0.12297
Obese	WI	-	8.41[-9.38;29.68]	0.39[-17.86;22.68]	-0.53[-10.45;9.76]	0.91794	0.99[0.88;1.11]	0.83429					
	WS	-	7.06[-11.05;28.85]	-4.98[-23.16;17.5]	-2.05[-13.38;9.33]	0.7235	0.96[0.84;1.1]	0.55697					
Blood Pressure													
SBP (mmHg)[c]	WI								-	-2.82[-4.42;-1.22]	-2.71[-4.44;-0.99]	-1.72[-2.58;-0.85]	0.0001
	WS								-	-2.16[-3.84;-0.49]	-2.39[-4.2;-0.58]	-1.71[-2.7;-0.72]	0.00071
DBP (mmHg)[d]	WI								-	-0.95[-1.98;0.09]	-1.15[-2.27;-0.04]	-0.86[-1.42;-0.3]	0.00257
	WS								-	-0.85[-1.94;0.24]	-1.01[-2.19;0.16]	-0.85[-1.49;-0.21]	0.00942
Hypertension[d]	WI	-	-5.93[-17.21;6.87]	-8.55[-20.54;5.24]	-7.43[-14.3;-0.38]	0.03906	0.85[0.77;0.95]	0.00296					
	WS	-	-5.91[-17.7;7.58]	-8.3[-20.9;6.31]	-7.66[-15.59;0.3]	0.05918	0.85[0.76;0.96]	0.00716					
Hba1c (%)[e]	WI								-	0.01[-0.05;0.07]	0.04[-0.02;0.1]	0[-0.03;0.04]	0.79788
	WS								-	-0.01[-0.07;0.05]	0[-0.06;0.07]	-0.03[-0.06;0.01]	0.11262
Lipidaemia													
LDL-C (g/L)[f]	WI								-	-0.01[-0.02;0.01]	0[-0.02;0.01]	0[-0.01;0.01]	0.8237
	WS								-	-0.01[-0.02;0.01]	0[-0.02;0.01]	0[-0.01;0]	0.2408
HDL-C (g/L)[f]	WI								-	-0.01[-0.04;0.02]	0[-0.03;0.04]	0[-0.02;0.01]	0.64617
	WS								-	-0.02[-0.06;0.01]	-0.02[-0.05;0.02]	-0.01[-0.02;0.01]	0.52963
TG (g/L)f	WI								-	-0.02[-0.05;0.02]	0[-0.04;0.03]	0[-0.02;0.01]	0.63444
	WS								-	-0.04[-0.08;0]	-0.03[-0.07;0.01]	-0.01[-0.03;0.01]	0.26217

CI: confidence interval; IQR: interquartile range

Final model adjusted for sex, age, urban area, educational level, smoking status, inclusion season, marital status, work activity, mobility limitation, residential median income and residential PM10 concentration

b: 209 missing data, c : 28 missing data; d : 56 missing data

Supplemental Table 3b : Association between neighborhood walkability (WI or WS) and cardiovascular risk factor, after adjustment for the residentiel NO2 concentration

Variables	Score	Odds ratio							Difference of Mean				
		Tertile of walkability			Linear trend for an interquartile		Odds ratio for an interquartile		Tertile of Walkability			Linear trend for an interquartile	
		Low (ref)	Medium [95% CI]	High [95% CI]	ge increment in walkability [9	*p*-Value	.inear trend for an interquartil	*p*-Value	Low (ref)	Medium [95% CI]	High [95% CI]	ıge increment in walkability [	*p*-value
Weight Status													
BMI (kg/m^2)	WI								-	0.03[-0.39;0.45]	-0.19[-0.64;0.26]	-0.18[-0.4;0.05]	0.13013
	WS								-	-0.11[-0.55;0.32]	-0.19[-0.66;0.28]	-0.2[-0.46;0.06]	0.1257
Obese	WI	-	8.41[-9.38;29.69]	0.11[-18.01;22.23]	-0.15[-10.19;10.26]	0.97634	0.99[0.87;1.11]	0.81293					
	WS	-	6.54[-11.28;27.93]	-5.53[-23.42;16.53]	-1.82[-13.11;9.52]	0.75305	0.95[0.84;1.09]	0.4947					
Blood Pressure													
SBP (mmHg)[c]	WI								-	-2.87[-4.47;-1.27]	-2.81[-4.53;-1.09]	-1.78[-2.64;-0.91]	0.00006
	WS								-	-2.2[-3.85;-0.55]	-2.46[-4.25;-0.67]	-1.76[-2.73;-0.78]	0.00041
DBP (mmHg)[d]	WI								-	-0.99[-2.03;0.05]	-1.22[-2.33;-0.1]	-0.9[-1.46;-0.34]	0.00159
	WS								-	-0.88[-1.95;0.19]	-1.08[-2.24;0.08]	-0.89[-1.52;-0.26]	0.00581
Hypertension[d]	WI	-	-5.84[-17.12;6.98]	-7.72[-19.77;6.13]	-6.35[-13.29;0.77]	0.08015	0.87[0.79;0.97]	0.01156					
	WS	-	-4.43[-16.26;9.07]	-6.65[-19.3;7.99]	-5.75[-13.62;2.15]	0.15376	0.89[0.79;1]	0.04091					
Hba1c (%)[e]	WI								-	-0.01[-0.02;0.01]	0[-0.02;0.01]	0[-0.01;0.01]	0.3266
	WS								-	-0.01[-0.02;0.01]	0[-0.02;0.01]	-0.01[-0.01;0]	0.65575
Lipidaemia													
LDL-C (g/L)[f]	WI								-	-0.01[-0.04;0.02]	0[-0.03;0.03]	0[-0.02;0.01]	0.89878
	WS								-	-0.03[-0.06;0.01]	-0.02[-0.05;0.01]	-0.01[-0.03;0.01]	0.09183
HDL-C (g/L)[f]	WI								-	-0.02[-0.06;0.02]	-0.01[-0.04;0.03]	-0.01[-0.02;0.01]	0.59234
	WS								-	-0.04[-0.08;-0.01]	-0.03[-0.07;0.01]	-0.01[-0.04;0.01]	0.44388
TG (g/L)f	WI								-	-0.02[-0.06;0.01]	-0.01[-0.04;0.03]	-0.01[-0.02;0.01]	0.57028
	WS								-	-0.04[-0.08;-0.01]	-0.03[-0.07;0.01]	-0.01[-0.04;0.01]	0.2063

CI: confidence interval; IQR: interquartile range

Final model adjusted for sex, age, urban area, educational level, smoking status, inclusion season, marital status, work activity, mobility limitation, residential median income and residential NO2 concentration

b: 125 missing data, c : 28 missing data; d : 56 missing data

Mutiple linear regression for difference of mean; poisson regression for % of increase; logistice regression for odds ratio

Supplemental table 4 : Association between neighborhood walkability (defined as a walkability index (WI) or the Walk Score® (WS)) and cardiovascular risk factors after adjustment annual household income and genotyped cluster

Variables		% of increase							Difference of Mean				
		Tertile of walkability			Linear trend for an interquartile		Odds ratio for an interquartile		Tertile of walkability			Linear trend for an interquartile	
	Score	Low (ref)	Medium [95% CI]	High [95% CI]	range increment in walkability [95%CI]	*p*-Value	range increment in walkability [95%CI]	*p*-Value	Low (ref	Medium [95% CI]	High [95% CI]	range increment in walkability [95%	*p*-Value
Physical activity													
Moderate or High activity	WI	-	9.34[-2.5;22.61]	11.92[-1.14;26.72]	6.97[0.87;13.21]	0.02487	1.25[1.12;1.39]	0.00004					
	WS	-	4.29[-7.49;17.58]	9.14[-4.18;24.31]	5.26[-1.94;12.47]	0.15222	1.17[1.04;1.32]	0.01026					
High activity[b]	WI	-	-10.6[-25.14;6.76]	-11.51[-27.59;8.13]	-4.13[-14.08;6.2]	0.42805	0.95[0.84;1.08]	0.44376					
	WS	-	-6.74[-22.57;12.33]	-14.6[-31;5.71]	-12.08[-23.36;-0.75]	0.03665	0.85[0.74;0.98]	0.02207					
Daily Walking ≥ 30 min	WI	-	-3.05[-15.57;11.32]	14.79[-0.72;32.73]	9.35[2.03;16.86]	0.01196	1.2[1.08;1.32]	0.00037					
	WS	-	-0.14[-13.5;15.28]	12.08[-3.94;30.77]	7.02[-1.52;15.6]	0.10728	1.14[1.02;1.28]	0.02272					
MET(%)	WI								-	-14.47[-31.01;6.05]	16.83[-32.7;102.8]	9.24[-13.14;33.53]	0.42959
	WS								-	-4.36[-27.54;26.25]	6.14[-39.49;86.16]	1.84[-31.67;35.78]	0.91479
Weight status													
BMI (kg/m^2)	WI								-	0.02[-0.39;0.44]	-0.2[-0.65;0.26]	-0.18[-0.41;0.05]	0.12096
	WS								-	-0.1[-0.54;0.34]	-0.19[-0.67;0.28]	-0.2[-0.46;0.06]	0.12297
Obese	WI	-	8.41[-9.38;29.68]	0.39[-17.86;22.68]	-0.53[-10.45;9.76]	0.91794	0.99[0.88;1.11]	0.83429					
	WS	-	7.06[-11.05;28.85]	-4.98[-23.16;17.5]	-2.05[-13.38;9.33]	0.7235	0.96[0.84;1.1]	0.55697					
Blood pressure													
SBP (mmHg)[c]	WI								-	-2.87[-4.45;-1.3]	-2.77[-4.41;-1.13]	-1.71[-2.52;-0.9]	0.00004
	WS								-	-2.21[-3.81;-0.61]	-2.42[-4.05;-0.78]	-1.59[-2.45;-0.72]	0.00032
DBP (mmHg)[d]	WI								-	-0.93[-1.95;0.09]	-1.11[-2.17;-0.05]	-0.81[-1.33;-0.28]	0.00259
	WS								-	-0.81[-1.85;0.23]	-0.94[-2;0.12]	-0.71[-1.27;-0.15]	0.01239
Hypertension[d]	WI	-	-5.95[-17.23;6.87]	-7.93[-19.97;5.91]	-7.39[-13.84;-0.77]	0.02885	0.85[0.77;0.94]	0.00141					
	WS	-	-4.82[-16.62;8.65]	-7.17[-19.79;7.43]	-7.03[-13.92;-0.12]	0.04608	0.86[0.77;0.95]	0.00356					
Current smoker	WI	-	-1.72[-15.66;14.52]	31.8[6.76;62.71]	15.96[5.65;26.65]	0.00218	1.22[1.1;1.36]	0.00023					
	WS	-	20.53[-2.84;49.52]	37.69[9.77;72.71]	22.57[6.32;38.91]	0.00642	1.31[1.09;1.58]	0.00459					
Hba1c (%)	WI								-	0.03[-0.03;0.08]	0.07[0.01;0.13]	0.02[-0.01;0.05]	0.16873
	WS								-	0.02[-0.04;0.08]	0.04[-0.01;0.1]	0[-0.03;0.03]	0.84952
Lipidemia													
LDL(g/L)	WI								-	-0.01[-0.02;0.01]	0[-0.02;0.01]	0[-0.01;0.01]	0.97242
	WS								-	-0.01[-0.02;0.01]	0[-0.02;0.01]	-0.01[-0.01;0]	0.14816
HDL(g/L)	WI								-	-0.01[-0.04;0.02]	0[-0.03;0.03]	0[-0.02;0.01]	0.54439
	WS								-	-0.03[-0.06;0.01]	-0.02[-0.05;0.01]	-0.01[-0.02;0.01]	0.3861
TG (g/L)f	WI								-	-0.02[-0.05;0]	-0.01[-0.05;0.03]	-0.02[-0.04;0]	0.61177
	WS								-	-0.06[-0.11;-0.01]	-0.04[-0.06;-0.02]	-0.02[-0.06;0.01]	0.2402

CI: confidence interval; IQR: interquartile range

model adjusted for sex, age, urban area, educational level, smoking status, inclusion season, marital status, work activity, mobility limitation, annual household income, genotyped cluster and residential median income

b: 125 missing data, c : 28 missing data; d : 56 missing data

Mutiple linear regression for difference of mean; poisson regression for % of increase; logistice regression for odds ratio

Supplemental Table 5 : Association between neighborhood walkbability (defined as a walkability index (WI) or the Walk Score® (WS)) and cardiovascular risk factors model taking in account the stratified sampling frame

Variables	Score	% of increase							Difference of Mean				
		Low (ref)	Tertile of walkability Medium [95% CI]	High [95% CI]	Linear trend for an interquartile range increment in walkability [95%CI]	*p*-Value	Odds ratio for an interquartile Linear trend for an interquartile	*p*-Value	Low (ref)	Tertile of walkability Medium [95% CI]	High [95% CI]	Linear trend for an interquartile range increment in walkability [95%CI]	*p*-Value
Physical activity													
Moderate or High activity[b]	WI	-	3.28[-3.82;10.9]	9.27[-11.72;35.25]	6.98[-3.04;17.37]	0.17468	1.26[1.08;1.47]	0.00276					
	WS	-	0.61[-11.64;14.57]	6.81[-16.34;36.37]	4.06[-9.26;17.44]	0.5511	1.1[0.79;1.53]	0.58478					
High activity[b]	WI	-	-8.32[-27.67;16.21]	-7.9[-36.64;33.86]	-2.25[-14.07;10.1]	0.71581	0.98[0.8;1.2]	0.85654					
	WS	-	-5.82[-23.93;16.6]	-18.41[-34.99;2.38]	-9.35[-21.53;2.89]	0.13397	0.89[0.68;1.16]	0.38778					
Daily Walking ≥ 30 min	WI	-	-8.27[-18.62;3.39]	8.04[-4.38;22.07]	2.46[-4.01;9.08]	0.46002	1.07[0.95;1.21]	0.24593					
	WS	-	-4.76[-33.48;36.36]	4.32[-13.83;26.31]	0.31[-13.29;13.99]	0.96393	1.02[0.8;1.3]	0.88088					
MET(%)	WI								-	-15.91[-31.96;3.92]	12.37[-30.78;82.41]	7.25[-12.45;28.43]	0.42959
	WS								-	-7.33[-30.75;24]	0.71[-38.4;64.65]	-1[-31.82;30.18]	0.91479
Weight status													
BMI (kg/m^2)	WI								-	0.08[-0.37;0.54]	-0.08[-0.44;0.28]	-0.2[-0.38;-0.01]	0.03992
	WS								-	-0.34[-1.13;0.44]	-0.23[-0.44;-0.02]	-0.34[-0.53;-0.15]	0.00053
Obese	WI	-	5.2[-23.34;44.38]	-2.81[-19.46;17.29]	-1.22[-9.97;7.82]	0.78835	1.01[0.91;1.13]	0.83927					
	WS	-	1.79[-13.88;20.31]	-9.42[-23.46;7.21]	-3.62[-11.82;4.6]	0.38716	0.95[0.86;1.04]	0.28844					
Blood pressure													
SBP (mmHg)[c]	WI								-	-3.02[-4.74;-1.3]	-3.16[-4.93;-1.4]	-1.95[-2.95;-0.95]	0.00013
	WS								-	-1.48[-2.66;-0.29]	-2.57[-4.16;-0.99]	-1.75[-2.74;-0.75]	0.00058
DBP (mmHg)[d]	WI								-	-1.06[-2.84;0.71]	-1.46[-2.49;-0.44]	-1.05[-1.66;-0.44]	0.00079
	WS								-	-0.39[-1.33;0.55]	-0.92[-2.39;0.55]	-0.76[-1.71;0.2]	0.11934
Hypertension[d]	WI	-	-8.6[-18.09;1.98]	-12.05[-22.21;-0.57]	-8.12[-14.62;-1.44]	0.0174	0.88[0.8;0.96]	0.00389					
	WS	-	-1.99[-14.45;12.28]	-7.7[-19.13;5.35]	-6.74[-15.17;1.71]	0.1178	0.86[0.72;1.02]	0.07935					
Current smoker	WI	-	-1.72[-15.66;14.52]	31.8[6.76;62.71]	15.96[5.65;26.65]	0.00218	1.22[1.1;1.36]	0.00023					
	WS	-	20.53[-2.84;49.52]	37.69[9.77;72.71]	22.57[6.32;38.91]	0.00642	1.31[1.09;1.58]	0.00459					
Hba1c (%)[e]	WI								-	0.02[-0.03;0.08]	0.08[-0.05;0.21]	0.02[-0.03;0.08]	0.39978
	WS								-	0.02[-0.01;0.04]	0.06[-0.02;0.14]	0.01[-0.02;0.04]	0.48012
Lipidemia[f]													
LDL(g/L)	WI								-	-0.01[-0.03;0]	-0.01[-0.02;0.01]	-0.01[-0.01;0]	0.07544
	WS								-	0[-0.02;0.01]	0[-0.02;0.02]	-0.01[-0.03;0.01]	0.23205
HDL(g/L)	WI								-	-0.02[-0.04;0]	0[-0.03;0.03]	-0.01[-0.03;0]	0.04019
	WS								-	-0.04[-0.07;-0.01]	-0.02[-0.05;0]	-0.01[-0.04;0.01]	0.25487
TG (g/L)f	WI								-	-0.03[-0.05;-0.01]	-0.01[-0.06;0.03]	-0.02[-0.05;0]	0.0694
	WS								-	-0.06[-0.11;-0.01]	-0.04[-0.07;-0.01]	-0.02[-0.06;0.02]	0.2738

CI: confidence interval; IQR: interquartile range; MET: Metabolic Equivalent of Task

main model adjusted for sex, age, urban area, educational level, smoking status, inclusion season, marital status, work activity,mobility limitation and residential median income

b: 125 missing data, c : 28 missing data; d : 56 missing data; e : 522 missing data, f : 198 missing data

Mutiple linear regression for difference of mean; poisson regression for % of increase; logistice regression for odds ratio

Supplemental Table 6 : Mediation analysis with bootstraping of BMI and low physical activity level on the association between WI blood pressure adjusting and hypertension

Mediator	Variables	Linear trend for an interquartile WI	coefficient of effect of WI on variable adjusted for mediator	mediation ratio (%)	*p*-Value
Low physical activity					
	SBP (mmHg)	-1,599 [-2,438;-0,798]	-1,58 [-2,425;-0,798]	-1,18% [-8;4]	0.532
	DBP (mmHg)	-0,717 [-1,196;0,193]	-0,668 [-1,154;-0,138]	6,82% [-4,3;27,2]	0.256
	High Blood Pressure	-6.867%[-11.487;-0,814]	-6.749%[-11.455;-0,715]	1,5%[-7,6%;11,5%]	0.960
BMI					
	SBP (mmHg)	-1,655 [-2,445;-0,881]	-1,456 [-2,248;-0,661]	12,07% [0,4;27,4]	0.044
	DBP (mmHg)	-0,789 [-1,293;-0,275]	-0,666 [-1,154;-0,193]	15,52% [1,6;41,2]	0.036
	High Blood Pressure	-7.89%[-12.655;-0.980]	-6.36%[-11.480;-0.724]	17.2%[2.8%;51,6%]	0.016

CI: confidence interval, IQR: interquartile range

main model adjusted for sex, age, urban area, educational level, smoking status, inclusion season, marital status, work activity, mobility limitation, annual household income,genotyped cluster and residential median income

number of simulation = 500

Supplemental table 7 Association with outcomes for an IQR increment in the WI by Age and education

Variables	Sub cluster	Number n (%)	Linear trend for an interquartile range increment of WI [95%CI]	p-Value for interaction
		% of increase		
Daily Walking >30 min	Education			0.05214
	less than 2 years after high school	2042 (63%)	3.2[-5.52;12.07]	
	2 years or more after high school	1176 (37%)	14.31[3.7;25.03]	
	Age			0.04496
	< 53.5 years	1609 (50%)	14.1[3.89;24.49]	
	> 53.5 years	1609 (50%)	2.76[-6.2;11.83]	
Hypertension	Education			0.29032
	2 years or more after high school		-4.86[-12.88;3.29]	
	2 years or more after high school		-11.48[-21.94;-0.86]	
	Age			0.07965
	< 53.5 years		-3.94[-14.67;7.06]	
	> 53.5 years		-8.99[-16.83;-1.05]	
		Difference of Mean		
Systolic blood	Education			0.685967
	less than 2 years after high school		-1.89[-2.95;-0.83]	
	2 years or more after high school		-1.49[-2.68;-0.3]	
	Age			0.09761
	< 53.5 years		-1.03[-2.14;0.08]	
	> 53.5 years		-2.39[-3.5;-1.28]	

Main model adjusted for sex, age, urban area, educational level, smoking status, inclusion season, marital status, work activity, mobility limitation, annual household income,genotyped cluster and residential median income

Mutiple linear regression for difference of mean; poisson regression for % of increase

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Titre de la thèse :
Relation entre la marchabilité du quartier et les facteurs de risque cardio-vasculaire dans le Nord de la France

Thèse - Médecine - Lille 2021

Cadre de classement : *Santé Publique*

DES + spécialité : *Santé publique*
Mots-clés : marchabilité, environnement urbain, facteurs de risque vasculair, obésité, activité physique

Résumé :
Contexte. Bien que l'on sache que la marchabilité est associée à l'obésité et à l'hypertension par le biais d'une activité physique accrue, les données sur les facteurs de risque cardiovasculaire (en particulier en Europe) sont rares. Nous avons évalué la relation entre la marchabilité des quartiers et les facteurs de risque cardio-vasculaire (notamment l'obésité, l'hypertension, le profil lipidique sanguin et les taux sériques d'hémoglobine glyquée (HbA1c)) chez des adultes vivant dans le nord de la France.
Méthodes. Les données ont été extraites de la base de données de l'étude ELISABET (2011-2013). Les participants (âgés de 40 à 65 ans) résidaient dans ou autour des villes de Lille et Dunkerque. Pour chaque adresse résidentielle, nous avons déterminé un indice de marchabilité du quartier (à l'aide d'un système d'information géographique) et le Walk Score®. Des modèles de régression linéaire multiples et logistiques ont été utilisés afin d'évaluer les relations entre la marchabilité des quartiers d'une part et l'indice de masse corporelle (IMC), l'obésité, la pression artérielle, l'hypertension, les taux sériques de HDL-C, LDL-C, triglycérides et HbA1c, et le niveau d'activité physique d'autre part.
Résultats. 3218 participants ont été inclus. Après ajustement sur les variables individuelles et du quartier, nous avons constaté qu'un indice de marchabilité plus élevé était associé à un IMC plus faible (-0,23 kg. m^{-2}; intervalle de confiance (IC) à 95% [-0,45;-0,01] pour un incrément d'un intervalle interquartile (IQR)), à une pression artérielle systolique plus faible (-1. 66 mmHg ; IC 95 % [-2,47;-0,85] par IQR), une plus faible prévalence de l'hypertension (odds ratio (OR) : 0,86 ; IC 95 % [0,78:0,95] par IQR), et une plus faible prévalence d'un faible niveau d'activité physique (OR = 0,80 ; IC 95 % [0,73:0,88] par IQR). L'indice de marchabilité n'était pas significativement associé à d'autres facteurs de risque cardiovasculaire. Des résultats similaires ont été observés pour le Walk Score®.
Conclusion. Nos résultats ont montrés que le fait de résider dans un quartier plus propice à la marche était associé à une prévalence plus faible des facteurs de risque vasculaire. La promotion de la marchabilité pourrait contribuer à améliorer la santé cardiovasculaire de la population.

<u>Composition du Jury</u> :

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