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Cardiometabolic outcomes in regular immigrants in Italy: the role of the primary care

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ABSTRACT

Over the past few decades, Italy has turned into a multi-ethnic society, and in 2021 the immigrant population was 8.8% of the Italian residents. Immigrant health status is expected to transit from a low disease occurrence to the epidemiological profile of the lowest socioeconomic groups of the host population. This acculturation process, which entails an increase in risky behaviours, the adoption of a Westernized diet and a sedentary lifestyle, represents a threat to their cardiometabolic health. Furthermore, the accessibility of health services for immigrants is undermined by cultural and language barriers.

In Italy, primary care (PC) services are accessible and mostly free and are an ideal context for planning interventions to reduce health disparities. Many interventions in this setting have been demonstrated to be effective for the prevention of cardiometabolic diseases. The research focused on the analysis of inequalities by immigrant status in cardiometabolic outcomes avoidable by proper PC intervention, thus acting as a proxy for the quality of the PC received. Two kinds of outcomes were selected.

The first outcome was the hospitalization for Ambulatory Care Sensitive Conditions (ACSC). These are conditions for which timely and effective outpatient care can help to reduce the risks of hospitalisation and is an effective indicator for the accessibility and quality of PC. Two cardiometabolic conditions among the ACSCs, diabetes mellitus (DM) and heart failure (HF) were selected. Using the data of the Italian Network of Longitudinal Metropolitan Studies network, rate ratios (RRs) of avoidable hospitalization (AH) for DM and HF by citizenship were calculated for the populations of the six cities included in the network, and summarized in a random effects meta-analysis. Results for AH for HF were also adjusted for an ecological measure of socioeconomic status. The results showed higher rates of AH for DM among non-Italian men (RR: 1.63, 95% CI: 1.16-2.23), while no significant differences were found for DM among women (RR: 1.14, 95% CI: 0.65-1.99) and for HF, overall (RR: 1.26, 95% CI: 0.97–1.68) and for both sexes. Socioeconomic differences were an insufficient explanation for the increased AH in foreigners, other explanations might have been the higher risk factors among non-Italians, and a reduced access or lower quality of PC.

The next outcomes examined were the clinical and biochemical parameters collected within the health surveillance program of the Veneto Region. Differences in blood pressure (BP) and cholesterol between first-generation immigrants and Italian adults were examined, and how the migration pattern could affect health outcomes. Although no differences were observed for cholesterol and BP levels by immigrant status, heterogeneous results were observed by macro-areas of origin and sex. Acculturation led to a convergence toward the epidemiological profile of the host population, depending on the starting condition of each immigrant group. Finally, the association of immigrant status and BP was unravelled by examining the effect of covariates, with a multiple mediation analysis. The health advantage in the BP levels for the immigrant groups, net of potential mediators, was suppressed by the effect of some mediators, and in particular the body mass index (BMI) played the highest suppressive role.

This dissertation provides a comprehensive contribution on the inequalities by immigrant status in cardiometabolic outcomes that could be addressed with interventions in the PC setting, indicating the partial role played by the socioeconomic status, the effect on health of the acculturation process, and the importance of BMI in mediating these disparities. The large heterogeneity of the results by sex and macro-area of origin indicates the need for targeted interventions toward the groups at higher risk.

SOMMARIO

Negli ultimi decenni l'Italia è divenuta una società multietnica, con l'8,8% della popolazione residente rappresentata da immigrati nel 2021. Solitamente, la salute degli immigrati è buona all'arrivo, ma subisce un peggioramento, avvicinandosi allo stato di salute della popolazione autoctona più svantaggiata. L'acculturazione comporta infatti un aumento di comportamenti a rischio per malattie cardio-metaboliche, come la sedentarietà e una dieta ricca in grassi. Gli immigrati, inoltre, affrontano barriere linguistiche e culturali che limitano l'accesso ai servizi sanitari.

I servizi di assistenza primaria in Italia sono accessibili a tutti i residenti, e quasi sempre gratuiti, pertanto sono il luogo ideale per interventi volti a ridurre le disuguaglianze. Inoltre, diversi interventi in questo contesto sono stati efficaci nella prevenzione delle malattie cardio-metaboliche. Questa ricerca ha come obiettivo l'analisi delle disuguaglianze per stato migratorio negli outcome cardio-metabolici evitabili con un'adeguata assistenza primaria. I due tipi di outcome analizzati si possono considerare come dei proxy della qualità dell'assistenza primaria ricevuta.

Il primo indicatore è l'ospedalizzazione per condizioni evitabili con cure primarie adeguate e tempestive (OE). Selezionando l'OE per due condizioni cardio-metaboliche, diabete e scompenso cardiaco, sono stati calcolati i tassi di OE per italiani e stranieri, utilizzando i dati di sei città della rete italiana degli studi longitudinali metropolitani, combinandoli poi in una metanalisi ad effetti random. I risultati per lo scompenso cardiaco sono stati aggiustati anche per una misura di condizione socioeconomica. Sono stati riscontrati tassi più elevati di OE per diabete tra i maschi immigrati rispetto agli italiani (RR: 1.63, 95% CI: 1.16-2.23), mentre non vi erano differenze per DM fra le femmine (RR: 1.14, 95% CI: 0.65-1.99), né vi erano differenze di OE per HF, né complessivamente (RR: 1.26, 95% CI: 0.97–1.68) né per sesso. La diversa condizione socioeconomica non era sufficiente a spiegare le differenze tra immigrati e italiani, che probabilmente dipendono anche da una maggiore prevalenza di comportamenti a rischio tra gli immigrati e un ridotto accesso - o una minore qualità - dell'assistenza primaria.

In secondo luogo sono stati analizzati i parametri clinici e biochimici per stato migratorio, dai dati del sistema di sorveglianza della Regione Veneto. Sono state valutate differenze nei valori pressori e di colesterolo tra adulti immigrati di prima generazione e italiani, e come tali differenze variano in base all'età all'arrivo e tempo di permanenza in Italia. Anche se non vi erano differenze tra italiani e immigrati per questi indicatori, è stata riscontrata molta eterogeneità nei risultati per sesso e macro-area di origine. Si conferma che il processo di acculturazione avvicinava al profilo epidemiologico della popolazione ospite, in base alle condizioni di partenza di ciascun gruppo di immigrati. Infine, si è valutato con un'analisi di mediazione multipla il possibile effetto di alcune covariate nella relazione tra stato migratorio e pressione sanguigna appena analizzata. L'evidente vantaggio di salute che emergeva per gli immigrati al netto delle variabili di mediazione, veniva soppresso dall'effetto dei mediatori, e tra questi BMI aveva il maggior effetto soppressivo.

Gli studi raccolti in questa tesi offrono un ampio contributo alla valutazione delle disuguaglianze di salute nei pattern cardio-metabolici che possono essere mitigate con interventi adeguati nel setting delle cure primarie. Viene in particolare evidenziato il ruolo parziale dello stato socioeconomico, il ruolo dell'acculturazione e l'importanza del BMI nello spiegare tali disuguaglianze. La grande eterogeneità dei risultati per sesso e macro-area di origine indica la necessità di interventi mirati verso i gruppi a maggior rischio.

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ACSC: ambulatory care sensitive conditions
AH: avoidable hospitalization
AHRQ: agency for healthcare research and quality
BMI: body mass index
BP: blood pressure
CE: Central-Eastern
CHR: Crude Hospitalisation Rate;
CI: Confidence Interval;
CS: Central-Southern
CV: cardiovascular
CVD: cardiovascular disease
DALY: disability-adjusted life year
DBP: diastolic blood pressure
DM: diabetes mellitus
EHIC: European health insurance card
ENI: Europeo non iscritto (European citizen not registered)
EU: European union
GP: general practitioner
HbA1C: glycosylated haemoglobin
HDC: high developed countries
HF: heart failure
HMPC: high migratory pressure countries
HRR: hospitalization rate ratios
ID: index of deprivation
IN-LiMeS: Italian network of longitudinal metropolitan studies
IOM: international organization of migration
IPD: Individual Participant Data;
ISTAT: istituto di statistica (the national institute of statistic)
LDL-C: LDL-cholesterol
LM: linear regression model
LMM: linear regression mixed model
LMPC: low migratory pressure countries
LMS: longitudinal metropolitan studies
LRT: likelihood ratio test
NHS: national health system
NIHMP – INMP: national institute for health, migration and poverty
OENES: national epidemiological observatory for equity in health
OR: odds ratio
PASSI: Progresses in Health in the Italian Local Health Units
PC: primary care
PFAS: perfluoroalkyl substances
PR: prevalence ratio
PY: Person-year

RR: Rate Ratios
SBP: systolic blood pressure
SD: standard deviation
SHR: Standardised Hospitalisation Rate
SS: Sub-Saharan
STP: straniero temporaneamente presente (foreigner temporarily present)
TC: Total cholesterol
UK: United Kingdom
US: United States.
WHO: World health organization

1. INTRODUCTION

"Why treat people and send them back to the conditions that made them sick?"
Sir Michael Marmot, The Health Gap: The Challenge of an Unequal World, 2015

"All'immaginario collettivo italiano non appartiene il concetto di Assistenza Primaria, tentativo impreciso di tradurre Primary Health Care. Mentre per ogni italiano risulta chiarissima l'immagine di pronto soccorso o di sala operatoria o di reparto di chirurgia o di rianimazione - e a chiunque risulta chiaro che tutte queste entità afferiscono al "sistema ospedale" - il termine Assistenza Primaria è privo di significato."
Salute per tutti: miti, speranze e certezze della Primary Health Care, 2021

1.1. IMMIGRATION IN ITALY: A SHORT OVERVIEW

During the last decades, Italy experienced a dramatic transition from an emigrant nation (there are currently four million Italians still living abroad) to an immigrant destination (1,2). In 1990, just over 2% of the population living in Italy was born abroad (3). First, the fall of the iron curtain in 1989 brought to a migration flow from central and eastern Europe towards western and southern Europe. Italy, in particular, experienced the first 'mass immigration' from Albania to its coasts. Large waves of migration from the former socialist countries of eastern Europe continued throughout the 1990s and, more recently, the 2004 and 2007 enlargements of the European Union pushed the number of new arrivals (with the largest share of immigrants coming from Romania, Albania, Ukraine, Moldova, and Poland). Furthermore, the new 'migration frontier' along the northern shores of the Mediterranean interested Italian borderers, with immigrants from North Africa (in particular Moroccans) becoming the main immigrant group in Italy in the early 2000s. Furthermore, in recent years, growing migration flows from Asia-Pacific (notably China and the Philippines) and Latin America (Peru and Ecuador) have been recorded (4).
This process played a relevant role in the growth of the resident population in the first ten years of the 21st century and compensated for the birth decrease of the autochthonous population in the same years. As a result, the increase of 2.66 million residents that was recorded between the 2001 and 2011 Italian census was completely attributable to the increase of the immigrant population. This increase was not homogeneous and mainly interested the Northern Regions of Italy (5).
In the last few years, though, the migration flow to Italy contracted, with a contextual increase in the outflows to other countries (with an underestimation of this flow due to the missing cancelations from the municipal registries) (4), leading to a progressive stabilisation of the number of immigrants residing in Italy (6). The progressive reduction of the need for workers that followed the economic crisis of 2008 and the acquisition of Italian citizenship, mainly due to family reunification, resulted in a reduction in the overall number of citizens with non-Italian citizenship living in Italy (7).
Some words should also be spent on the recent phenomenon of arrivals that followed the Arab Spring and the Middle East and Northern African conflicts. Since 2011, considerable flows of people have reached the Italian borders through land or sea, asking for asylum. Asylum requests have been more than 400,000 in the years between 2011-2015 and became the second main

reason for the release of the residence permit, after the family reunification and overcoming the work permit requests (4).
Coming to the current situation, in 2021 the resident immigrants (defined as people with a non-Italian citizenship) are estimated to be 5,193,669 individuals (8), 8.8% of the total Italian population. In 2021, Romanians made up the largest foreign community in the country (1,076,412) followed by Albanians (433,171) and Moroccans (428,947). The fourth and fifth largest communities of foreign residents in Italy were represented by Chinese (330,495) and Ukrainians (235,953) (9). There are wide interregional differences not only in the total number of resident immigrants, but also in the most prevalent citizenship. In 2019 in Veneto, out of 501,085 foreigners (10.2% of the total population), the most prevalent citizenships were Rumanian, Moroccan, Chinese, Albanian, and Moldavian (10).

1.2. LEGAL STATUS OF IMMIGRANTS IN ITALY

1.2.1. Residence permit and obtainment of citizenship

In Italy, an immigrant person can have two types of residence permits: a temporary and a permanent one. To obtain permanent residency in Italy, a temporary residence permit must first be obtained. **Temporary residence permit** types are for seasonal work (max 9 months), subordinate employment (max 2 years), self-employment (max 2 years), study (depending on the length of the study course), medical treatment, family reunification (max 2 years), or other reasons, like elective residence, religious or business reasons. The time needed to obtain the temporary residence permit is generally up to three months. The temporary residency visa must be obtained by non-EU citizens when first arriving in Italy and should be renewed in the 60 days before or after the expiry date.
A temporary residence permit can also be obtained through the acknowledgement of an international protection, as regulated by European Directives[1,2]: **refugee status**[3] (5 years, with automatic renewal if requested), **subsidiary protection**[3] (three years) and **special protection**[4] (2 years).
Non-EU citizens must live for a minimum period of 5 years of legal temporal residence before applying for **permanent residence** in Italy[5]. Apart from living in the country for 5 years, applicants must also prove that they earn sufficient money to support themselves and that they speak Italian fluently and know the national customs. They must also have a clean criminal record. There are also categories of persons who cannot apply for permanent residence permits in Italy: students who come to Italy based on student visas, which permit a limited duration of stay, and those who

[1] Directive 2011/95/EU on "standards for the qualification of third-country nationals or stateless persons as beneficiaries of international protection, for a uniform status for refugees or for persons eligible for subsidiary protection, and for the content of the protection granted".

[2] Directive 2013/32/EU on "common procedures for granting and withdrawing international protection"

[3] D.lgs 251/2007 "Attuazione della direttiva 2004/83/CE recante norme minime sull'attribuzione, a cittadini di Paesi terzi o apolidi, della qualifica del rifugiato o di persona altrimenti bisognosa di protezione internazionale, nonchè norme minime sul contenuto della protezione riconosciuta."

[4] D.lgs 286/98, "Testo unico delle disposizioni concernenti la disciplina dell'immigrazione e norme sulla condizione dello straniero, art. 19, comma 1.1", as modified by law n. 173/2020

[5] D.lgs 286/98, art. 9, as modified by Directive 2003/109/CE

come for scientific purposes or for vocational training to Italy. Asylum seekers who are in the process of obtaining recognition as refugees also cannot apply for permanent residence until their status is clarified. Similarly, those who enter Italy for humanitarian reasons seeking temporary protection cannot apply for permanent residency in Italy.

All **citizens of the European Union (EU)** have the right to freely enter and reside in Italy or in another Member State other than the one they are citizens for three months. An EU citizen has the right to reside in Italy for a period exceeding three months when he/she is an employed or self-employed worker, has sufficient economic resources for himself and his family members, is enrolled in a public or private institute to follow a study course or professional training and has sufficient economic resources for himself and his family members; is a family member accompanying or joining a citizen of the Union who has the right to reside for a period exceeding three months. An EU citizen who has resided legally and continuously (with some exceptions) for five years in the national territory automatically acquires the right of permanent residence.

Obtainment of citizenship[6]

The Italian law for the recognition of citizenship is based on ***Ius sanguinis***, meaning that a child born to an Italian citizen mother or father (even if born abroad) is an Italian citizen by birth. The most common ways to obtain citizenship for people with parents with another citizenship are the following:

- ***By adoption***: the right to nationality is extended to any child who is adopted by an Italian citizen (even for those adopted abroad, if rendered valid in Italy by means of an order from the Juvenile Court);
- ***by descent:*** the applicant should provide evidence of having a blood tie with an Italian national (by direct line of descent);
- ***by marriage or civil partnership with an Italian citizen***: the applicant should provide evidence on the marriage with an Italian citizen. For applicants who live in Italy with their spouses, the procedure can be started after 2 years of residency, for those living outside Italy, it is possible after 3 years. If the couple has children, the required time can be reduced by 50% for both situations. The applicant must also have Italian language skills (B1 level minimum).
- ***By residency (naturalisation process):*** The applicant must live in Italy for 10 years before applying for citizenship. EU citizens benefit from a shorter residency requirement – only 4 years. The main requirements to apply for a naturalisation process are: to provide evidence of legal residence in Italy for the required years, have fluency in Italian of a minimum B1 level, provide evidence of having a minimum yearly income that is regulated by the law (the threshold can vary whether the applicant is single or married), and a clean criminal record. Children under 18 years of age living with naturalised parents automatically obtain Italian citizenship. The obtainment of citizenship by naturalisation requires several years from the request (it can last up to 24 months, extendable up to a maximum of 36 months from the request). Refugees (but not subsidiary protection holders) can request Italian citizenship after 5 years of residency in Italy.
- The *Ius soli* (receiving Italian citizenship by being born on the Italian soil) is available only for children born to stateless parents or of unknown parents; apart from this case, the Italian law does not entitle anyone to acquire Italian citizenship for the mere fact of being born on the Italian territory. In addition to this, Art. 4 of Law 91/1992 subordinates the ***acquisition of Italian citizenship to the legal and continuous residence in Italy from the person's date of birth***

[6] L.91/1992 "Nuove norme sulla cittadinanza"

until his/her coming of age (18 years old). Minimum annual income and a clean criminal record are not required. The applicant with these requirements must start the process within the 19th year of life and should receive an answer in maximum 120 days.

In Italy, the right to immigrate through a work permit (either seasonal, subordinate, or autonomous) must be regulated by an annual 'inflow decree' establishing the need for workers. However, in recent years, no political coalition has succeeded in planning and implementing the expected periodic provision within the institutional expected timescales (8). As a consequence, many non-EU immigrants coming to Italy enter with other permits, and obtain a subsequent regularisation of their stay through extraordinary mass legalisation measures. The most notable process in this sense was included in law 189/2002, aiming at better regulating the Italian flows and including a provision for the regularisation of immigrants working in domestic service and as caretakers, followed by a decree law in September 2002 to legalise the non-EU irregular workers employed in industry. These provisions led to the presentation of 705,000 applications for regularisation of which around 650,000 were approved. This was by far the most important policy initiative of its kind in Italian history, and it made a decisive contribution to bringing the total number of regular immigrants to almost 2.8 million at the beginning of 2006 (1).
In addition, recent modifications of the laws that regulate humanitarian protection[7] brought to a lower level of protection for asylum seekers, with an increase in requests denied. In 2021, the commissions considered that the applicants did not qualify for any type of protection for 58% of the request (8). However, due to difficulties in increasing the return of immigrants to their countries of origin, the number of undocumented immigrants stuck in the country has increased in recent years. All these things considered, it is not surprising that the presence of irregular immigrants in Italy remains considerable, and the rates of irregular to the overall number of immigrants increased from an estimated 7.4% in 2016, to 9% in 2021 (519.000) (11).

1.2.2. The right to health of immigrants to Italy

The Italian constitution safeguards health as a fundamental right of the individual and equitable access to health care is a core objective of the Italian National Health Service (NHS)[8]. The NHS is tax-funded and has universal coverage. Universal coverage entitles all Italian citizens and legal residents, regardless of their social status, to equal access to essential health care services that are necessary and appropriate for promoting, maintaining, and restoring health in the population according to the principle of universalism. Essential health services are provided free of charge or at a minimal charge and include general medical and paediatric services, essential drugs (including chronic diseases), and treatments administered during hospitalisation. Rehabilitation and long-term post-acute inpatient care, instruments, and laboratory diagnostics, as well as other specialised services for early diagnosis and prevention (12).
Documented immigrants, those who hold a valid residence permit, must enrol in the NHS and can access healthcare services in public and private accredited facilities through an official NHS registration code, as Italian citizens do. Additionally, women are entitled to a temporary

[7] D.L. 113/2018 "Disposizioni urgenti in materia di protezione internazionale e immigrazione, sicurezza pubblica, nonché misure per la funzionalità del Ministero dell'interno e l'organizzazione e il funzionamento dell'Agenzia nazionale per l'amministrazione e la destinazione dei beni sequestrati e confiscati alla criminalità organizzata".
[8] Constitution of the Italian Republic, Title II, Article 32

residence permit during pregnancy and up to 6 months after delivery and are always granted prenatal and postnatal care.[9]

Undocumented immigrants, instead, are guaranteed emergency and first-aid care, essential treatments (all pathologies not immediately dangerous but that could worsen in the future), paediatrics and geriatrics. However, they are not entitled to an official NHS registration code and access the NHS through an anonymous code (STP, which means "Straniero Temporaneamente Presente", foreigner temporarily present), which expires after 6 months. In addition, they cannot access general practitioners (GPs). In general, undocumented immigrants access the NHS through emergency departments or voluntary not-for-profit health organisations, although differences exist between regions.

Citizens of the European Union, in Italy for a temporary stay, can receive medically necessary (hence, not only urgent) care through the European Health Insurance Card (EHIC). Although citizens of countries that joined the European Union from the 2004 EU enlargement (New EU) are entitled to legally reside in Italy, they often experience difficulties in access to the NHS, because they lack the EHIC needed to receive health care (13). These EU-citizens are provided with a specific code (ENI, Europeo Non Iscritto, European not registered), which guarantees emergency and essential treatments as it happens for the STP-owners.

Finally, the Italian Constitution guarantees the right of asylum to foreigners to whom the actual exercise of the democratic freedoms guaranteed by the Italian Constitution is denied in their own country[10]. As a consequence of this principle, immigrants who are in serious psycho-physical conditions ascertained by suitable documentation issued by the NHS, such that the return to the country of origin would cause significant damage to their health, are entitled to receive a medical treatment permit, whether they are regular immigrants or not[11].

1.3. EXPOSURE: DEFINITION OF IMMIGRANT STATUS

1.3.1. Immigrant status

According to the International Organization for Migration (IOM), immigrants can be defined as 'a person who moves into a country other than that of his or her nationality or usual residence, so that the country of destination effectively becomes his or her new country of usual residence' (14). Epidemiologists have used different indicators to identify immigrant status, according to available sources and the purposes of the study. The different ways of classifying immigrant status can lead to disparate outcomes in studies conducted on these populations. For these reasons, it is essential to take into account the definition used when interpreting and comparing the results of different studies. Two definitions of immigrant status are found mainly in the literature:

Foreign-born (15): a person born in a country other than their current country of residence. It is easily defined by selecting the ***country of birth*** from administrative data or surveys. The country of birth defines an invariable status but excludes second and third generations of immigrants.

[9] D.lgs 286/98, Article 35

[10] Constitution of the Italian Republic, Title I, Article 10

[11] D.lgs 286/98, Article 19

Foreigner/non-national (14): A person in a State of which he/she is not a citizen or national. In this case, the exposure variable is the ***citizenship/nationality***, often retrieved by linkages with municipal registries or through surveys. It must be pointed out that citizenship (and in general, the legal status of immigrants) must be understood as a fluid characteristic that can change over the course of an individual's lifetime owing to personal circumstances (e.g., marriage) and shifting policy environments (e.g., legalisation). The ways to acquire citizenship vary from one country to another. As mentioned, in Italy, the acquisition of citizenship in a way other than the *ius sanguinis* is often long and complex, therefore, the citizenship can reflect an immigrant background also in the second-generation immigrants.

In some studies, the terms **ethnicity and/or race** have been used as a proxy of immigrant status. An 'ethnic group' has been defined as 'a named social category of people based on perceptions of shared social experience or ancestry.' Race, instead, is defined as the geographic pattern of variation in some biological traits that distinguish different human populations. Information on race/ethnicity is collected through administrative databases in some countries. This happens mainly in studies from the US, but an extensive example in a European country is represented by the Scottish Health and Ethnicity Linkage Study, linking the health data to the Scottish census (providing ethnic group) (16). In Italy, discourses on race and ethnicity became a taboo after the open discriminations of the fascist period. Therefore, ethno-racial statistics are not allowed, apart from the specific case of those historic ethnolinguistic minorities guaranteed by the Constitution and law (17). Other studies retrieved the mother tongue (from administrative databases) as a proxy of ethnicity/immigrant background (18,19). The concepts of 'immigrant group' and 'ethnic minority group' can overlap only in countries where the migration process is recent, and particularly in some European countries. However, in countries where migration is well established, such as the United States, New Zealand or Australia, the 'immigrant group' and the 'ethnic minority group' cannot be considered synonymous (20).

As described above, none of the definitions can by itself exhaustively describe the immigrant condition, they can be only used as proxies of the immigrant status. Nevertheless, each definition can be suitable according to the research question (e.g. the country of birth can adequately select the first-generation immigrants, but the second-generation immigrants would be left out, citizenship instead defines people who do not have the same rights of natives, but may change with time). If available, a combination of single definitions can describe more complex concepts and distinguish different categories (such as first-/second-generation immigrants).
For the purposes of our studies presented in chapters 2 to 5, the definition of immigrant status is presented in the methods section, and subjects that meet that definition are then called 'immigrants' throughout the text, irrespective of the chosen definition.

1.3.2. Classification of immigrants

There is a broad agreement among epidemiologists that immigrants cannot be considered as a homogeneous group. As a preliminary remark, it should be noted that immigrants represent a 'fuzzy' set, their status changed over time and according to the changes in legislation, therefore, it is difficult to apply dichotomous categories as a classification (i.e., regular / irregular, economic / forced, etc.) (21). Furthermore, a complete review of this topic goes beyond the purpose of this dissertation. Nonetheless, a specific focus should be made on the geographical classification of the countries of origin/citizenships. In fact, immigrants from countries that are geographically

and culturally close to the host country (as happens for central-eastern European countries in relation to EU countries) can have similar lifestyle habits, health beliefs, health-seeking behaviour, or reduced language barriers. On the contrary, subjects coming from countries with a very diverse culture might have a different attitude towards health services. In addition, immigrants can face challenges in integrating in the host country depending on the different perceptions of the specific ethnic and physical characteristics (e.g., skin colour) or cultural habits (e.g., wearing a veil), and related discrimination (22). These aspects may bring on one side to a different physical and psychological stress and on the other side to some obstacles in the approach toward health services related to prejudices or opinions of the healthcare practitioners. In chapters 2 to 5 we have shown how different the health outcomes are in relation to the macro-area of origin and some possible explanations for these differences related to each specific outcome. Once again, there are multiple categorisations, and the classification should be chosen according to the available sources and the purpose of the study. On the other hand, excessive fragmentation (e.g. subdivision by country of origin) would lead to very small samples and to a loss of statistical significance. Therefore, the immigrant population should be classified into (not too) small subgroups as homogeneous as possible in access to health services and health outcomes in the hosting country. Hereafter, some of the most common categorisations are presented.

Classification by income (World Bank) The World Bank assigns world economies to four income classifications: low-, lower middle-, upper middle-, and high-income countries. These classifications are based on each country's Gross National Income per capita for the previous fiscal year, derived from the sum of the gross domestic product of the country and the net income of the residents, converted into US dollars (23). This is a rough but precise and comparable classification of countries in an economic perspective, but it groups together countries from very diverse World Regions and has not the purpose of grouping the countries according to a similar cultural background.

Classification by geographical macro-area: many different international organisations group the countries for administrative purposes. The geographical macro-areas do not necessarily correspond to the continents, e.g. the World Bank classifies the countries by Region: East Asia and Pacific, Europe and Central Asia, Latin America & the Caribbean, Middle East and North Africa, North America, South Asia, Sub-Saharan Africa. This classification is often used also in epidemiologic studies concerning immigrants, but does not take into account in any way the heterogeneous socioeconomic conditions of the single countries in each Region of the world (e.g. western and central eastern Europe).

High Migratory Pressure Countries vs High Developed Countries: A categorisation that is often used in Italian studies concerning immigrants' health has been proposed by the national institute of statistic (ISTAT) and tries to mix the latter two concepts, also considering the migratory trajectories that characterise each specific country (24).
Subjects are divided into immigrants from so-called 'high developed countries"-HDC (also called 'low migratory pressure countries" – LMPC), which comprises Western Europe, North America, Oceania, Israel, and Japan; and immigrants from high migratory pressure countries (HMPCs), further divided by macro-area of origin: Central-Eastern (CE) Europe, Central and South (CS) America, North Africa, sub-Saharan (SS) Africa, and Asia (except for Israel and Japan).

This categorisation was chosen in all the studies included in this dissertation, for its ability to differentiate immigrants originating from LMPCs from those coming from HMPCs who, as a whole, generally differ from both immigrants from LMPCs and natives in terms of socioeconomic and demographic characteristics. Furthermore, other categorisations that consider immigration trajectories, such as 'non-Western immigrants' or 'immigrants from outside European Union', do not include immigrants coming from Romania and other eastern European countries, which are some of the most frequent countries of origin of immigrants coming to Italy (25).
Other classifications that can be useful in specific studies, take into account the religious background of immigrants, (e.g. immigrant coming from Muslim vs non-Muslim countries) (26) that can be considered a proxy of the religious beliefs, and can influence the approach towards health practices or lifestyles.
A few words should be spent to describe the categorisation of immigrants according to the variables of the migratory pathway, such as age at arrival or length of stay in the hosting country. These variables can be considered as proxies of the acculturation process, and can therefore deeply influence the attitudes towards health practices and the modification of lifestyle. As hypothesized since 1976 by Marmot and Syme (27), the acculturation process may play a relevant role in the risk of cardiovascular disease. Unfortunately, in Italy no routine administrative data collect information on age at arrival or the length of stay in Italy. This information can be retrieved from surveys or large databases that collect data on the specific questions. In chapter 4 we provide an example of clinical parameters that are risk factors for CV diseases, analysed considering this categorisation, retrieved within the health surveillance plan of the Veneto Region (see paragraph 1.4.2).

1.4. SOURCES OF DATA OF IMMIGRANTS' HEALTH IN ITALY

In recent years, the Italian public's attention has focused on immigrant arrivals through the Central Mediterranean route and the Western Balkan route. This has somehow limited the discussion around immigration to the irregular border crossing and the consequent asylum requests, giving the impression that the majority of immigrants arrive and resides irregularly on the Italian soil. Although it is important to raise attention to tragedies related to this flow, in terms of number of deaths and travel conditions, it must be noted that most of the immigrant population in Italy lives and resides regularly, and it is essential to explore their differential health status, to reduce health inequalities. Also, as my dissertation focusses on regular immigrants, in this paragraph and the following one I will mainly focus on the epidemiologic research on the regular (stable) group, while I will only make a short overview on irregular immigrants at the end of paragraph 1.5.

Describing and monitoring inequalities by immigrant status in health is an essential step toward policy changes aimed at promoting fair outcomes in the population. However, information on the socioeconomic attributes is rarely available (or affordable) from health and mortality data sources. In the Italian scenario, data to examine the differential health status/access to health services of immigrants compared to natives have been retrieved by either population administrative archives or surveys.
In **population studies**, sources of health data are the health administrative archives, collected routinely in the health practices, and analysed as outcomes. These studies are either cross-sectional or longitudinal.

Cross-sectional studies create indicators of health or health access based on routine mortality or morbidity statistics to obtain frequencies and, when available, use official estimates of the population as denominators to compute rates. At the national level, replicable approaches have been developed to facilitate comparison between different areas (28,29). Two projects supported by the Ministry of Health, the National Centre for Disease Prevention and Control, first experimented and then implemented a system of indicators in several regions, creating an interregional network. Activities to update the above indicators have been included in the objectives of the National Epidemiological Observatory for Equity in Health (OENES, within the National Institute for Health, Migration, and Poverty (NIHMP - INMP)), which has made it possible to complete the collection of indicators for the years 2016 and 2017 (30). The denominators were provided by ISTAT in 2013, publishing data on the resident population by age, sex, and citizenship, and an update should be available soon. However, as mentioned, these data cover only resident immigrants, leaving out those who are not resident (e.g., seasonal workers, immigrant from UE not formally enrolled in the NHS, as well as irregular immigrants). Also, the Ministry of Interior releases data on valid residence permits, but European citizens (many of which constitute a large fraction of immigrant population, e.g. Romanians) are not included. Another limitation of administrative health records in the analysis of health outcomes for the immigrant population is that some relevant information is not available, such as family immigration history, which could give essential information in studies on the second generations of immigrants. The reason depends on the decisions of the data protection authority related to fear of possible discriminations.
Longitudinal studies collect individual information from official sources and follow the population up to death or migration. The benefit of a longitudinal design that allows to detect developments or changes in the characteristics of the target population is particularly important when dealing with a 'fluid' population as the immigrant one. In addition, it is possible to establish sequences of events and raise hypotheses on causation. Contrary to Nordic European countries, where longitudinal data are usually available for the entire population, census-based longitudinal metropolitan studies (LMS) in Italy have been implemented only in some cities since the 1980s (31–35). They integrate, for the resident population, individual information coming from the population registers at municipal level with microdata from the census and from the health information system. The LMSs worked independently or in collaboration with other municipalities, to investigate socioeconomic inequalities in health (24,32,36–39). To enhance and coordinate these national efforts, the Italian Network of Longitudinal Metropolitan Studies (IN-LiMeS) has been officially created and included in the National Statistical Programme (40,41). The IN-LiMeS is widely described in paragraph 1.4.1.

In **sample studies, surveys** data that collect information on immigrant status and health outcomes are used. These may come from ad hoc surveys or from surveys conducted for other purposes. There are some examples of Nationally representative surveys that have been often used in studies on this topic and are worth noting.
The ***multipurpose national health surveys*** conducted by ISTAT have been used since 2005 also for the comparison of health outcomes between the Italian population and the resident foreign population, as the immigrant status is defined using citizenship (42).
In the last years, a more articulated survey dedicated to the "***Condition and social integration of foreign citizens***" has been developed (43), allowing for an in-depth analysis of the dynamics of migration, the conditions of daily life and their impact on health of the foreign population (as the target population was composed of families with at least one non-Italian citizen). A collection of

studies that exploit these data has been published, coordinated by ISTAT and carried out in collaboration with universities and public and research bodies (44). With respect to health, the objective of the contribution was to analyse how the relationship between immigrant status (immigrants were defined as non-Italian citizens who were born abroad) and health indicators (perceived health, lifestyles, and access to health services) according to the individual migration pathway, integration history and individual socioeconomic characteristics and context.
Another source of information on major public health issues is the *PASSI Surveillance System* (Health Progresses in Italian Local Health Units) (45), a national risk factor surveillance system. PASSI collects data on overall perceived well-being and symptoms of depression, the more frequent risk/protection factors for the most frequent diseases (smoking, alcohol, physical activity, and nutritional aspects), and the adherence to the main individual prevention programmes (screening and vaccinations). This last piece of information is also an indicator of access to public health services and the quality of the promotion of correct lifestyles within primary care services. These data, too, have led to important publications on the health status of the foreign population residing in Italy (46).
All these surveys allow us to conduct studies with a cross-sectional design. In recent years, a longitudinal extension of the National Health Interview Survey (conducted periodically) has been set up to follow up the nationally representative sample included in the survey (47).

Administrative and survey data allowed one to track and analyse the health conditions of the immigrant or foreign population. However, until now there is little evidence (or evidence limited to very small samples) on health disparities in clinical parameters and on serum biomarkers that focus on inequalities by immigrant status. Since clinical alterations can be detected before the onset of related diseases, analysis of their distribution and emergence mechanisms could help detect health differences earlier than analysis on confirmed diseases. Early detection of these risk factors could provide more chances for early treatment and reduce future health inequalities. In paragraph 1.4.2 I describe the health surveillance plan of the Veneto Region, which is the source of data in chapters 4 and 5.

1.4.1. The Network for Longitudinal Metropolitan Studies

As mentioned above, in order to enhance and coordinate local longitudinal metropolitan studies set up throughout the country, IN-LiMeS has been officially created and included in the National Statistical Programme (40,41).
The IN-LiMeS is a multicentre and multipurpose pool of metropolitan population cohorts enrolled in nine Italian cities, namely Turin, Venice, Reggio Emilia, Modena, Bologna, Florence, Leghorn, Prato, and Rome. The purpose of IN-LiMeS is to create a harmonised system of cohorts that provides a powerful, coherent, and nationally widespread source of integrated data on morbidity and mortality outcomes, demographic and socioeconomic information, and denominators through the exact estimation of the person / time at risk.
IN-LiMeS functions as an integrated monitoring system that collects demographic, socioeconomic, and clinical information at the individual level. The core of population data includes four sources: 1) the municipal population register, 2) the archives of the 2001 population census from ISTAT, 3) the archives of mortality registers, and 4) the electronic health records, namely hospital discharge archives. The population registry databases include exact dates of registration (birth and/or immigration) and cancelation (emigration and/or death) for each individual. Therefore, they keep a dynamic and updated record of the residential histories

of all inhabitants, including episodes of emigration, reimmigration, and / or death. The estimated level of accuracy of the population registration system is greater than 99% nationally (48).
The population register, the 2001 census, the mortality, and the hospital discharge records are combined, at the individual level, through stepwise deterministic record linkage procedures. The linkage between population registers and census is performed using a specific set of keys (codes from the census questionnaire). The linkage rates, calculated as the proportion of subjects who were legal residents according to the official 2001 census figures and those retrieved in the population registers, were 98% for Venice, Bologna, and Modena, 97% for Reggio Emilia, 96% for Turin, 92% for Prato, and 84% for Florence, Leghorn, and Rome.
Confidentiality is guaranteed through the deletion of personally identifiable information from individual records and the assignment of internal IDs to allow the linkage of multiple data sources. The inclusion in the National Statistical Programme is in accordance with the national legislation on the processing of personal data for statistical and scientific research purposes, for both the IN-LiMeS and each LMS (41).
Figure 1.1 shows the structure of the IN-LiMeS and the population entries and exit and availability of the data of each LMS. All LMSs can be used in multicentre studies with a closed design, in which all subjects are enrolled at the same point in calendar time, that is, the 2001 census date. At that time, all cities together counted around five million inhabitants, representing about 9% of the Italian population. In these closed cohorts, individuals can exit (i.e., death or emigration) but new entries are not allowed.
Instead, an open cohort design depends on the possibility to acquire dynamic information on the new entries from the population registers. This design gives the possibility of accounting for the changing dynamics of the population (and this is of paramount importance when considering the immigrant population), although only a few indicators of SES may be available. In the open cohort design, enrolment is based on municipal population registers, and members can enter (e.g., newborn or new residents) and leave (e.g., death or emigration) the cohort over time. Eligible individuals are those who have resided in the cities at any time since the 2001 census day until the latest available follow-up update. Turin and Reggio Emilia were the first cohorts to become open. To date, also Venice, Modena, Bologna, Prato, and Rome have adopted this design.
Future updates will include the addition of 2011 census data, a periodic update of the follow-up for new entries and exits (including mortality data), and the opening of the remaining cohorts.

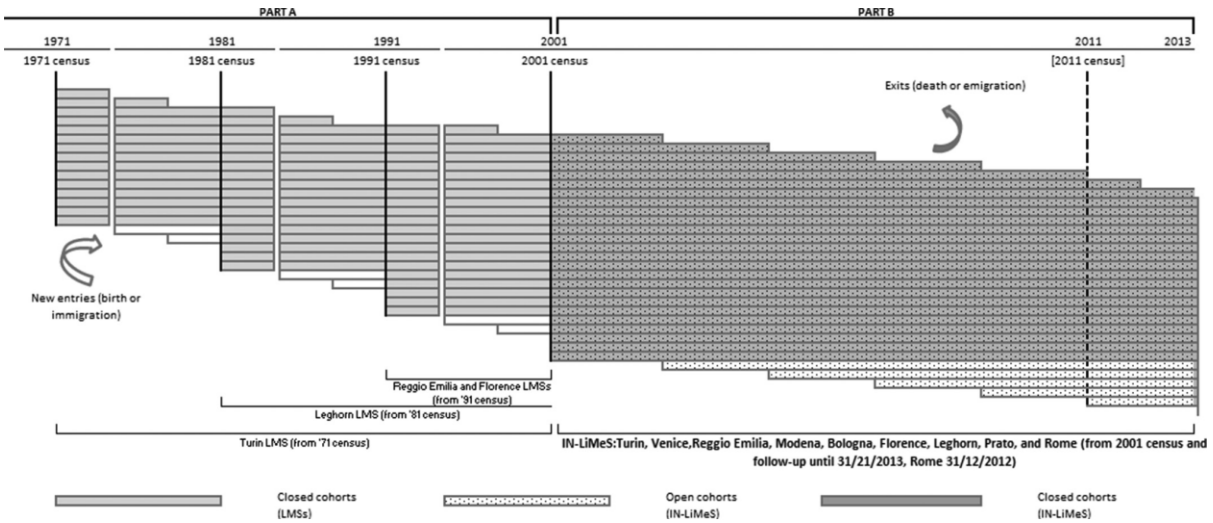

Figure 1.1. Structure of the Italian Network of Longitudinal Metropolitan Studies (IN-LiMeS): population entries and exits and availability of data.

The IN-LiMeS published in 2019 an exhaustive monograph on various health outcomes of resident foreigners compared to Italian citizens (49). The multicentre study included Venice, Modena, Bologna, Reggio Emilia, Turin, and Rome, six cities with an open cohort design. Subjects between 18 and 64 years of age who resided in one of the six cities for at least one day between January 1, 2001 and December 31, 2013 were enrolled, reaching a population of nearly 4.5 billion. The exposure variable was citizenship, retrieved from the municipal population registry, used as a proxy of immigrant status. My research group and I wrote a chapter dedicated to the overall indicator of avoidable hospitalisation (see paragraph 1.6). Chapters 2 and 3 of this dissertation focus on the differences by immigrant status for AH for two specific cardiometabolic outcomes.
With the inclusion of the whole resident population of six cities located in the north-centre of Italy, the results obtained for this population are generalisable to the whole immigrant population who legally reside in the cities of north and centre of Italy. Two categories of immigrants are inherently left out: people regularly present in Italy who are not formally enrolled in any population register (e.g., seasonal workers) and undocumented immigrants. Additionally, by using citizenship as a proxy of immigrant status, subjects born abroad but already naturalised were considered as Italian citizens (see chapter 6).

1.4.2. The health surveillance plan of the Veneto Region

In 2011, surface water and groundwater in a large area of the Veneto Region in northern eastern Italy were found to be contaminated with perfluoroalkyl substances (PFAS) that were also found in drinking water samples. PFASs are manufactured chemicals widely used for a variety of commercial and industrial applications due to their grease-, stain-, and water-repelling properties. A manufacturing plant located in the town of Trissino that produced PFAS since the late 1960s was identified as the only likely source of water contamination.
The so-called 'Red Area', interested with groundwater contamination, extends over an area of 30 municipalities and approximately 140,000 inhabitants in the provinces of Vicenza, Verona, and Padova (Figure 1.2). To address public concerns about exposure to PFAS, and in accordance with a precautionary principle, the regional health authorities established from January 2017 a health surveillance program for residents of the Red Area to aid in the prevention, early diagnosis, and treatment of some of the chronic disorders with epidemiological evidence of associations with PFAS exposure (50). The programme started by targeting the population born between 1951 and 2022, and is still ongoing, with extended recruitment of the paediatric population. At least one follow-up examination is planned for all participants in the first round of the health surveillance program.
Eligible subjects have been identified through the regional health registry. Invitation letters indicating an appointment date and time have been sent by mail, followed by a second invitation if there was no response to the first. Residents who decided to participate in the program completed a structured interview administered by a trained public health nurse, followed by blood pressure measurement, and blood and urine sampling. Programme visits have been made at public health facilities located throughout the contaminated area to ensure easy accessibility. The structured interview investigated residential history, education, occupation, dietary habits, drinking water intake and sources, smoking habits, alcohol consumption, physical activity, family and personal history of disease, medications, reproductive history, and self-reported height and weight [with automatic calculation of body mass index (BMI)]. During the interview, the public health nurse took the opportunity to inform the patient about a healthy lifestyle and

recommended behavioural changes using motivational counseling techniques. The questionnaire was conducted in Italian, but the trained nurses who administered it mediated possible language barriers for some subjects by explaining the questions. Additionally, when communication was hindered by language problems, the interviewee was invited to return a second time with an interpreter. Despite these measures to avoid a selection depending on the knowledge of the Italian language, the complexity of the questionnaire could have brought to a selection bias in the responders. Furthermore, the need for a mediator in the administration of the questionnaire, was it the nurse of a different ethnic background or an interpreter, could have brought about an interviewer bias, according to his/her interpretation of the question or answer, or depending on his/her expectations or opinions towards the interviewees (51).

The population to whom the health surveillance plan was offered lives in a rural area of the Veneto Region, and all the subjects included live in towns with no more than 25.000 inhabitants. Therefore, it is a very peculiar population and we cannot assume that it is representative of the overall population of the Veneto Region or of Italy. For this reason, the results that we obtained by analysing this population cannot be generalisable and should be referred only to this population. To characterise immigrants within this population, we provide the number and percentage of subjects from each country of birth, subdivided by the macro-areas of origin included in the health surveillance plan (Table C.4). Most of the foreign-born subjects come from Central-Eastern Europe, of them 35% were from Romania, 24% from Albania, 17% from Serbia, and 8% from Moldavia. The other two most represented macro-areas were North Africa (almost all born in Morocco - 96%) and Asia (68% from India and 17% from Pakistan). In order to understand the characteristics of these subjects, we considered the database of the employment centres, that collects data of all the labour contracts stipulated each year. We retrieved this information from centres located within the Red Area, Lonigo, and Legnago (52). It should be noted that the referral areas of these employment centres do not overlap with the Red Area, but their data can give us an idea of the labour market conditions, stratified by citizenship. We analyse the new contracts activated in 2021 stratified by the most represented subgroups: CE Europe, Morocco, India and Bangladesh pooled together. Overall, foreigners were mostly employed in agricultural sector (61% of men, 43% of women), services for companies and for people (including a vast area of jobs, such as domestic workers and cleaning workers, 13% of men and 27% of women) and manufacturing (9% of both sexes). The greatest differences with Italian citizens are that 19% of the latter were employed in educational services (only 0.2% of immigrants) and that only 11% of the Italians were employed in agriculture. Among macro-areas of origin, Moroccans were by far mainly employed in agriculture (65% men and 68% women), while among Indians and Bangladeshis a relevant percentage was employed in services for companies and people (25% of men and 40% of women). Furthermore, CE Europeans had higher percentages of employment in these services, with a peak of 45% of women from eastern European non-EU countries (Albanians, Moldavians, Serbians, Ukrainians) employed in this sector.
In chapters 4 and 5 I used the data of the Veneto Region Health Surveillance plan to analyse disparities in these outcomes in a large number of individuals, thus opening the possibility of implementing PC programmes to reduce health inequalities.

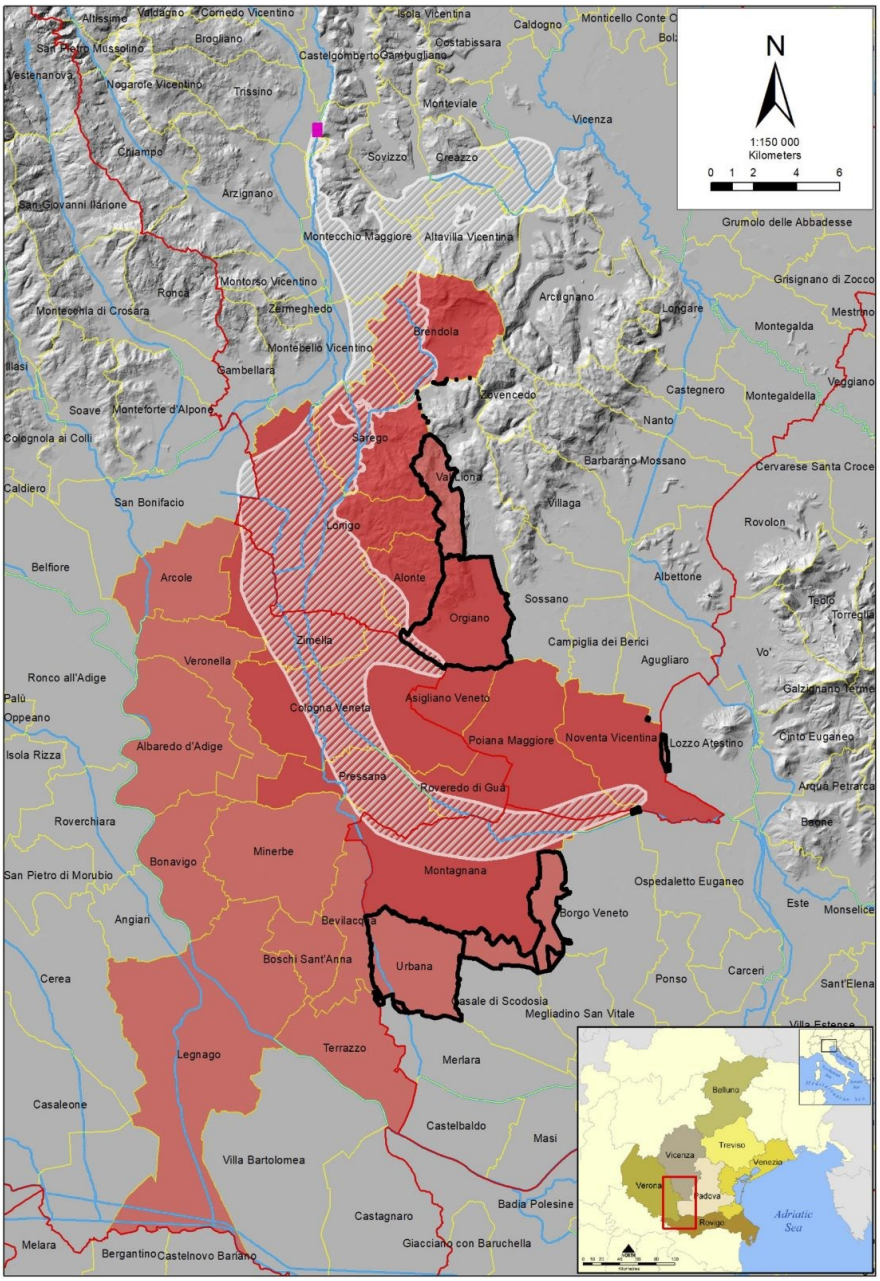

Figure 1.2. The Red Area of the Health surveillance plan

1.5. OUTCOME: CARDIOMETABOLIC HEALTH OF IMMIGRANTS IN ITALY

1.5.1. Documented (and stable) immigrants

With the steep increase in the immigrant population of the last decades, the probability of meeting a foreign-born patient, or a patient with non-Italian citizenship in the Italian health structures is relatively high. Despite these relevant changes, the scientific and cultural training of health workers on the health needs of minority groups is still limited and focusses on the risk of infectious diseases. However, current data about individuals born in low-income countries who permanently live and work in Europe or about subjects with a citizenship outside the EU indicate

that their main health issues are more likely to be chronic diseases. In fact, the health condition of immigrants compared to the host population is expected to transition from a low disease occurrence in the first period after arrival (the so-called 'healthy migrant effect') (53) to a progressive convergence toward the health behaviours and epidemiological profile of the lowest socioeconomic groups of the host population. Nowadays, in several European countries, the prevalence of hypertension, diabetes, obesity, and metabolic syndrome is found to be higher in most immigrant groups than in the host population (26). Therefore, it is essential to increase the knowledge of health practitioners about the health of immigrants and, in particular cardiometabolic health. This is especially relevant not only for the transition of the epidemiological profile described, but also due to the ageing of immigrant populations (54). If elderly people face many and complex health and care related problems, the combined experience of ageing and migration often results in additional health challenges (55). To a large extent, the health profile of elderly immigrants overlaps with those faced by socioeconomically disadvantaged ageing people in the host country (56). As for the rest, the ability to identify key health needs of ageing immigrants is severely restricted by the limited evidence with few studies reported so far (56). Ageing immigrants from non-Western countries in Europe may be less likely to drink alcohol, whereas ageing immigrant women may be less likely to smoke compared to native populations. Lack of physical activity and intake of a diet high in fat is relatively more common among immigrant groups compared to the native population.
In terms of disease-specific morbidity, for cardiovascular disease, some populations, in particular of South Asian origin, are at increased risk of both diabetes and cardiovascular disease. As is the case in the general ageing population, multimorbidity is common among immigrant groups in Europe (56). All these things considered, the challenges related to the health problems of ageing immigrants may further increase the risk of overburdening the healthcare system.
This dissertation deals with the risks of developing cardiometabolic diseases among immigrants in Italy and how these can be prevented through an adequate primary care intervention. Most studies reporting evidences of the national sources described in paragraph 1.4 provide data on cardiometabolic health comparing immigrants and natives or Italian and non-Italian citizens.

Lifestyle behaviours and risk factors: alcohol, smoke, and overweight

Exhaustive national data on lifestyle behaviours and in particular risk factors for cardiometabolic outcomes are available in the three surveillance systems previously described: the PASSI surveillance system, the Multipurpose National Health survey, and the survey on *condition and social integration of foreign citizens* (44,46,57). Overall, the surveys showed that foreigners were generally comparable to Italians in several dimensions (46,57). The smoking and alcohol consumption of non-Italian men was similar to that of Italian men. For women, there was a higher risk of being overweight and a lower risk of smoking in the foreign population (44). Sex appeared to play a similar role among Italians and foreigners, whenever the prevalence was higher for women than men among Italians, it was higher also for women among non-Italians and vice versa (46). Relevant differences have been found within the foreign population, confirming that citizenship had a major influence on health behaviours and attitudes (46). In particular, among men, those from CE Europe were at increased risk of all risky behaviours (44). Among women, those from CE Europe had a higher consumption of alcohol and smoke, while women from North Africa were at increased risk of overweight and obesity, but had less alcohol and smoke consumption, probably due to religious habits (44). For changes in the migratory pattern, the probability of being overweight was found to be higher if the length of stay in Italy was longer

than 11 years (57). In general, foreigners appeared to be more similar to Italians as the length of stay increased, confirming the assimilation process (44,46).

Access to health services

The two ISTAT surveys (44,58) also collected information about the use of medical visits. The National Health Multipurpose analysed access to outpatient visits by GPs or specialists, both for 'diseases or disorders' and for preventive purposes only. According to this work, foreigners were less likely than Italians to receive a medical examination, motivated by any health problem, and even less in the case of preventive medical examination (58). The survey dedicated to the *condition and social integration of foreign citizens* reported that foreigners also declared to assume less drugs compared to Italians (44). These findings could indicate a better health status, but this hypothesis is disproved by the fact that non-Italians accessed emergency rooms or hospital services more frequently. Therefore, it is likely that the lower access to preventive and outpatient services reflected a delayed handling of the diseases and the lower drug consumption reflected a worse management of health conditions (44). The same results on access to emergency service was found in the indicator system of indicators implemented in several regions, with higher rates of access for foreigners compared to Italians in all degrees of severity of the diseases (triage codes) (30).

Prevalence and management of chronic cardiometabolic diseases

Comparisons by citizenship in the prevalence of cardiometabolic diseases and indicators of appropriate management have been analysed through the VALORE project, a study that involved six Italian regions. It was organised by the National Agency for Regional Health Systems to assess the link between quality of care for chronic diseases and the organisation of primary care (59). Data were retrieved from the administrative health records of selected local health units within the involved Regions. Subjects diagnosed with specific cardiometabolic diseases (diabetes (DM), ischaemic disease, and heart failure) were selected by means of an algorithm based on diagnoses indicated in hospital discharge records or disease-specific drug-dispensing records, or disease-specific healthcare co-payment exemptions. The findings of this study showed that the age-standardised prevalence of coronary heart disease and heart failure was significantly lower in foreigners than in Italian citizens, but the age-standardised prevalence of DM was significantly higher among HMPC citizens than among Italian citizens. The higher prevalence of DM among foreigners from all macro-areas compared to Italians has been widely confirmed in the literature (60,61).

Once the disease has been diagnosed, adequate care and secondary prevention of acute events are essential. The process indicators of this study were chosen among those defined by scientific associations as quality measures to improve patient outcomes within primary care services and included laboratory tests, diagnostic examination, and adherence to therapy. The results for foreigners were systematically lower in all quality management indicators compared to Italians, for all the cardiometabolic conditions considered (62). Organisation and indicators of primary care quality are better described in paragraph 1.6, and this dissertation will deepen the analysis of specific outcomes concerning health disparities by citizenship in this context.

Hospitalisation and mortality for cardiometabolic outcomes

For these outcomes, the results of the IN-LiMeS longitudinal studies are extremely relevant (49). These data are representative of the population living in a metropolitan context of Northern and Central Italy. Overall, citizens of HMPC showed lower hospitalisation rates compared to their

Italian counterpart, both in general and specifically for cardiometabolic diseases. Higher rates of hospitalisation were seen among non-Italians compared to Italians for infectious diseases and blood diseases for both sexes, among women due to pregnancy, childbirth, and genitourinary system, while injury and poisoning represented a critical health area among men. Citizens from Africa seemed to be at a higher risk of hospitalisation compared to subjects from other macro-areas. Regarding mortality, foreigners showed lower all-cause mortality rates and mortality rates for cardiometabolic conditions than Italians. When stratified by macro-area, Sub-Saharan Africans experienced a significantly higher mortality rate than Italians. The only cause-specific mortality rates higher in the foreign population than Italians are tuberculosis, some site-specific tumours, and homicides.

1.5.2. Undocumented immigrants

As mentioned in paragraph 1.2, the health rights of immigrants in Italy mostly depend on their legal status, which generates very different health outcomes and attitudes towards health services. Therefore, when analyses focus on the health status of immigrants, the legal status (documented or undocumented) of the population must be considered. Anyway, in most epidemiological studies, only those who are officially residents and registered can be tracked and followed, leaving out undocumented immigrants (and people regularly present in Italy who are not formally enrolled in any population registry, like seasonal workers). Also, as mentioned before, the denominators of the health indicators provided by ISTAT only include resident immigrants. As a consequence, evidence on undocumented immigrants is scant and based mainly on nonrepresentative samples. Most studies on irregular immigrants, although interesting and valuable efforts, are isolated experiences based on small populations, collecting data in single centres, and often depend on the cooperation and work of voluntary associations (63).
Some exceptions represented by studies conducted at national level are worth noting. First, today there is important evidence that the 'healthy migrant effect" can also be applied to incoming international protection seekers, as demonstrated, for example, by the low prevalence of imported infectious diseases (including tuberculosis) (21). These data have been collected through a syndromic surveillance system that includes 13 potentially alarming syndromes activated in 2011, after the increased influx of immigrants on the Italian coasts. The aim was to obtain a demographic profile of the arriving population and to foster early detection and timely response to any event that could represent an epidemic emergency (64). On the contrary, while mental health of asylum seekers deserves special attention and a particular final focus, unfortunately it is still not adequately addressed, in spite of the high incidence of psychic problems, caused by violence endured either before or during the journey (21).
Another important study has been recently published on national data (13), and it deserves to be described, as it explores the same outcome of chapters 2 and 3 (see paragraph 1.6). The authors used the distinction between the legal status of foreigners and the type of access to NHS treatment to identify undocumented immigrants in anonymised hospital discharge records, using an administrative financing code. The potential effects of poor access to primary care were measured by focussing on the incidence of avoidable hospitalisation (on overall hospitalization), comparing Italian citizens, documented and undocumented non-Italian citizens. They showed that documented and mainly undocumented foreigners face a considerably higher risk of AH compared to Italians.

1.6. CONTEXT: PRIMARY CARE AND ITS ORGANISATION IN ITALY

1.6.1. Definition

According to the World Health Organisation (WHO), primary care is defined as "a model of care that supports first contact, accessible, continuous, comprehensive, and coordinated person-focused care. It aims to optimise population health and reduce disparities across the population by ensuring that subgroups have equal access to services" (65).

WHO identified five core functions of primary care:

1) **First contact accessibility** creates a strategic entry point for and improves access to health services.
2) **Continuity** based on the development of long-term personal relationships between a person and a health professional or a team of providers.
3) **Comprehensiveness** a diverse range of promotive, protective, preventive, curative, rehabilitative, and palliative services are provided.
4) **Coordination** services and care across levels of the health system and over time are organized.
5) **People-centred care** people should have the education and support needed to make decisions and participate in their own care.

1.6.2. Organization of PC in Italy.

General Practitioners and Paediatricians (12)

As already mentioned in paragraph 1.2, health care in Italy is a constitutional right granted to all Italian citizens. All Italians are registered with the NHS from birth and have the right to select a paediatrician or GP according to their place of residence. GPs and paediatricians are self-employed physicians who work for the NHS through a national agreement that pays them mainly on a capitation basis according to the number of people registered on their list.

People may choose any GP or paediatrician they prefer within the catchment area (district, see below) at any time, provided that the physician's list has not reached the maximum number of patients allowed (1500 for GPs and 800 for paediatricians). As a result, the actual freedom of choice depends on the prompt availability of a GP. Patients have free access to their GPs according to opening hours. GPs must be open five days a week, with at least two opening times in the afternoon or mornings. The number of hours is regulated according to the size of the patient list. Patients can receive primary care services during nights, weekends, and public holidays from professionals other than their regular GP or paediatrician, the so-called out-of-hours physicians usually working in different premises (such as independent ambulatories of local health authorities).

Since 2005, public authorities to achieve integration of GPs' developing networks, associations, and other forms of grouping, with other GPs and other health care professionals. The aim is to create new organisational models based on the integration of different professionals (e.g., GPs, paediatricians, out-of-hours physicians, nurses, specialists working in outpatient facilities, social workers, administrative personnel, etc.) working together to improve accessibility, equity, and continuity of care for patients.

GPs and paediatricians are the first contact for the most common health problems, they initially assess the patient and are expected to provide most primary care. They act as gatekeepers for

access to secondary services, write pharmaceutical prescriptions, and visit patients at home if necessary, as well as vaccinate patients against influenza during the vaccination campaign period.

GP prescriptions and specialist outpatient services (12)

Specialist outpatient services, including visits and diagnostic and curative activities, are provided by local health authorities or by accredited public and private hospitals. People are allowed to access specialist care in two ways:

- Indirect access (referral): after approval by their GP, people are free to choose their provider among those accredited by the NHS (with no cost besides limited co-payments);
- Direct access: patients can obtain an appointment through central telephone booking systems for some specific health services: gynaecology, dental care, psychiatric services, immunisation procedures, screening practices. In emergency cases, direct access is allowed to all health services. Urgency is established directly by the doctor.

Concerning the relationship with specialists, GPs act as case managers for their patients (based on a trust-based relationship). When a patient is discharged from the hospital, he receives a referral letter to be given to the GP so that he or she can be informed about the care delivered in the hospital. However, specialists can call GPs directly and these latter also have free access to visit patients during their stay in hospitals.

Patients do not have to pay for visits or prescriptions from the GPs. Co-payments exist for certain drugs or specialist visits when these are prescribed by the physician. There are exemptions to any co-payment (specialist consultations, diagnostics and rehabilitation services) for patients with oncological problems, chronic diseases, rare diseases, and disabilities. Also, citizens with a family income below a certain level, with children below the age of 6 or adults above the age of 65, and those who are unemployed or receiving a minimum pension are exempted.

Since waiting lists can be very long and the quality of services is not always satisfactory, many people seek care in private clinics, paying the associated costs fully out of pocket or through voluntary health insurance. The possibility of bypassing long waiting lists through private services increases health inequalities in a system that should, in theory, be fair and universally accessible. Instead, subjects with low incomes (including most immigrants) are likely to wait longer than wealthy subjects before receiving specialist visits or diagnostic care, thus slowing the diagnostic process and postponing therapy. One of the consequences of this effect is the probable increase in avoidable hospitalizations, conditions for which appropriate and timely outpatient care could prevent the need for hospitalization (see the following paragraph).

The districts (66)

Organisationally, both GPs and paediatricians are included within health districts (60,000 inhabitants on average), the operative branches of the local health unit that are responsible for guaranteeing the provision of primary care services. Each health district is expected to plan and provide health and social care according to the 'essential levels of care' established at the national level and based on population needs. Multidisciplinary teams of professionals (GPs and paediatricians, specialists, nurses, social assistants, social care staff, and other technical and administrative staff) work within health districts to provide different types of services to meet community needs (e.g., GP and specialised ambulatory care, maternal–infant care, frail care, mental health care, etc.). The district is also in charge of providing home healthcare for non-self-sufficient elderly and disabled people. A multi-disciplinary team, which is composed of home nurses, doctors (GPs or paediatricians and specialists, if needed) and can be integrated with actors of social care (provided by the municipalities), ensures the best home care for non-self-

sufficient citizens. The aim of this structure is to avoid unnecessary hospitalisations and to guarantee a continuum of care for discharged subjects.

1.6.3. Indicators of quality of the primary care

Evaluation of quality of the primary care has always been a problematic issue. Since the 1970s, several quality indicators for primary care have been proposed, but their validity has often remained questionable (67). Among others, the reasons for the complexity of this assessment are the lack of health information systems, which are always much less developed than in the hospital setting, and the diversity of the target of this care setting. Furthermore, the different organisation of health services between countries does not allow us to transpose a set of indicators established for a country to another country.
Indicators retrieved through administrative data are easier to compare and retrieve with respect to indicators from *ad hoc* surveys. Indicators to evaluate primary care through administrative data can be divided into three macro-areas.

a) **Proxy indicators**, which describe the quality of home and outpatient care through outcomes that are avoidable with proper intervention in this setting. A widely used example in this category is the Avoidable Hospitalization (AH) for Ambulatory Care Sensitive Conditions (ACSC). ACSCs are defined as conditions for which the provision of timely and effective outpatient care can help reduce the risks of hospitalisation by preventing the onset of a disease or condition, controlling an acute episodic illness, or managing a chronic disease or condition. Many different definitions of ACSC have been proposed; the most widely used was the one suggested by the Agency for Healthcare Research and Quality (AHRQ) (20). Chapters 2 and 3 of this dissertation analyse two specific cardiometabolic outcomes of this indicator (diabetes mellitus and heart failure), exploring possible differences in these outcomes by migrant status.
b) **Process indicators**, created through a *linkage* procedure through health administrative databases, which evaluated the appropriateness of the care pathway. Examples can be vaccination coverages, or the percentages of diabetic patients who undergo at least a measurement of glycated haemoglobin each year, or number of patients diagnosed with heart failure who receive at least an electrocardiogram yearly, or the appropriateness of drug prescription. A process indicator that is also adopted in Italy is the percentage of patients in charge of home care and the degree of intensity of this care. The 'Coefficiente di Intensità Assistenziale' (Coefficient of intensity of care) stratified the patients followed at home in four levels according to the number of days of effective care, with at least one care provider visiting the patient on the number of days of care. A process indicator can also analyse the accessibility of primary care, that is, indicating the number of GPs per 1000 inhabitants. These indicators can be easily computed at the local health unit or Regional level, and can be used to compare single practitioners, groups of practitioners, local health units or Regions.
c) **Outcome indicators**, created to evaluate the health status of patients. Examples are glycated haemoglobin (HbA1C) levels in diabetic patients or patients with optimal/normal blood pressure levels. These indicators are difficult to calculate at a centralised level, because the clinical outcomes at the single patient level are saved in the database of GPs (which is not owned by the health system) or in ad hoc databases created by specific health services, which do not know general population data (that is,

information on the denominator). In chapters 3 and 4 we analyse biochemical and clinical cardiometabolic outcomes and compare them according to the migrant status.

An Italian example (68)
In recent years, the Tuscany Region adopted a system of performance evaluation, which was recently adopted by several Italian regions. The authors used quantitative indicators retrieved by administrative data, mainly those of the first and third group described above. The authors suggested classifying primary care health indicators according to the health needs of patients, which are very diverse in this setting. In fact, primary care services are directed at healthy people, to individuals with single or multiple needs, and individuals that require end-of-life treatments. Table 1.1 lists the targets considered and the primary care interventions that are offered to these categories according to their needs, as well as examples of indicators to measure the quality of these interventions.

Table 1.1. Examples of primary care according to health needs and primary care interventions

Target	*Primary care interventions*	*Examples of indicators (process/proxy)*
Healthy subjects	• Health promotions • Primary/secondary prevention	• Cancer screening indicators (% of offer and adherence) • Immunisation coverage
Subjects with single health needs	• Family planning centres • Outpatient specialist services • Drug prescriptions	• N° of musculoskeletal magnetic resonances in elderly (>65 years) • Antibiotic prescriptions • Compliance with antidepressants
Subjects with chronic diseases	• Chronic care in general practice • Prevention of hospitalisation • Rehabilitation • Continuum of care	• Process indicators of chronic diseases • Rates of chronic subjects who started physical activity courses • Avoidable hospitalisation rates • Hospitalization lasting >30 days
Non-self-sufficient patient	• Home care • Intermediate care • Long-term care	• Home care rates among the elderly (>65 ys or 75 ys) • Rates of elderly people in long term care
End-of-life	• End-of-life assistance • Palliative care	• Rates of patients dead in hospice

1.6.4. Use of primary care services for immigrants

Along the following chapters, differences among immigrants and non-immigrants for some indicators of the quality of the primary care will be explored. In this paragraph, I will briefly summarise what is known about the use of primary care services among immigrants in Europe and, when available, in Italy.

Preventive services
For what concerns vaccination uptake, many European studies reported lower rates among immigrants (3). In particular, an Italian study found that influenza vaccination coverage among foreign citizens was 16.9% compared to 40.2% among Italian citizens (69). Similar differences

have been found for screening programs. In several countries, low mammography referral and attendance have been found for various groups of immigrant women compared to non-immigrants (3). Similarly, immigrant women have a lower acceptance of cervical cancer screening, even in organized and free screening programs (70). Disparities in utilisation for prenatal care have also been identified, and the higher rates of induced abortions for non-Western immigrants in Europe indicate difficulties in accessing preventive measures related to reproductive health (3).
According to Gimeno-Feliu "Health and illness are socially-construed concepts, varying gratly according to the cultural environment. Migrants may generally have a more 'utilitarian' concept of health, associated with the ability to work" (71). Therefore, preventive services may not be considered priorities, as they are not associated with improved physical condition, and therefore not acknowledged as needs (72). Additionally, for interventions aimed at preventing diseases and ensuring early detection of disease among ageing adults, there is a substantial social gradient in uptake (56).

General practitioners

For what concerns access to GP, results are not uniform. Several European studies show overall higher access to GPs among immigrants compared to non-immigrants (3), but some other countries reported a higher use of emergency services for immigrants, bypassing GP services (72). An Italian study showed a significant underutilization of services prescribed by a GP (drug prescriptions, second level health care services) for elderly immigrants compared to non-immigrants (73). The reasons for these differences are unclear, but they might be related to easier access to GPs in some countries, the wide range of services in general practice, and the pattern of disease burden among immigrants. It should also be kept in mind that arrangements and functions of the GPs or primary care differ in European countries, as do referral systems to higher levels of care. An explanation of the over utilization may be that immigrants may report unclear symptoms to the GP and poor communication skills, resulting in the need for repeated visits and additional diagnostic activities. GPs have been reported to communicate differently with immigrants, compared to native patients, and the consultations with immigrants were shorter (74). On the other hand, poor familiarity with their rights and the local health system (e.g., the role of gatekeeper of the GP) can influence the access of immigrants to care patterns. Additionally, emergency services are free of charge in many European countries, making these services more affordable and accessible (72).

Outpatient services

Most of the studies of specialist or outpatient care show a general tendency towards underutilization by immigrant populations of all ages (3,73), suggesting the existence of many barriers to accessing these services. Also, as previously stated, the role of gatekeeper of the GP might be of lower quality for immigrants. Interestingly, it appears that this different pattern of health care use may vary according to the immigrant generation. Due to the higher level of acculturation, second-generation immigrants show health care utilization pattern more similar to the native-born population (72).

1.7. DISSERTATION AIM AND OUTLINE

In the following chapters, I analysed two types of cardiometabolic outcomes, with the aim of exploring possible inequalities by immigrant status in the quality and accessibility of PC provision.

In **chapters 2 and 3** I focused on proxy indicators of the quality of the PC. I selected two cardiometabolic conditions among the ACSCs, diabetes mellitus (DM) and heart failure (HF).

Using data of the Italian Network of Longitudinal Metropolitan Studies, and using the citizenship variable retrieved by municipal registries as a proxy of immigrant status, I assessed differences in rates of hospitalization among Italians and immigrants, overall and stratified by sex and geographical macro-area. In chapter 3 I also evaluated the contribution of socioeconomic status to these disparities, adjusting these results for an ecological measure of socioeconomic status.

In chapter 4, I examined health inequalities by immigrant status in the clinical and biochemical outcomes collected within the health surveillance program of the Veneto Region. Differences in blood pressure (BP) and cholesterol levels between first-generation immigrants and Italian adults were examined, and to explore the influence of acculturation in these results, I also evaluated how the variables of the migration pattern, namely age at arrival and length of stay in Italy, could affect these health outcomes. Finally, in **chapter 5**, I disassembled the association of immigrant status and BP levels, examining the possible mediation effect of some covariates, with a multiple mediation analysis. The aim of this last work was to identify possible modifiable mediators of this association that can be targeted to reduce health disparities.

As a conclusion, I selected ten points retrieved from the results of my dissertation, that can be useful advices for practitioners working within the primary care services of the Italian NHS and for further epidemiological studies on this topic.

2. AVOIDABLE HOSPITALISATION FOR DIABETES MELLITUS AMONG IMMIGRANTS AND NATIVES: RESULTS FROM THE ITALIAN NETWORK FOR LONGITUDINAL METROPOLITAN STUDIES[12]

SUMMARY

Italy has experienced a relevant increase in migration inflow over the last 20 years. Although the Italian Health Service is widely accessible, immigrants can face many barriers that limit their use of health services. Diabetes mellitus (DM) has a different prevalence across ethnic groups, but studies focusing on DM care among immigrants in Europe are scarce. This study aimed to compare the rates of avoidable hospitalisation (AH) between native and immigrant adults in Italy. A multi-centre open cohort study including all 18- to 64-year-old residents in Turin, Venice, Reggio-Emilia, Modena, Bologna and Rome between 01/01/2001 and 31/12/2013 was conducted. Italian citizens were compared with immigrants from high migratory pressure countries who were further divided by their area of origin. We calculated age-, sex- and calendar year-adjusted rate ratios (RRs) and 95% confidence intervals (95% CIs) of AH for DM by citizenship using negative binomial regression models. The RRs were summarized using a random effects meta-analysis. The results showed higher AH rates among immigrant males (RR: 1.63, 95% CI: 1.16-2.23), whereas no significant difference was found for females (RR: 1.14, 95% CI: 0.65-1.99). Immigrants from Asia and Africa showed a higher risk than Italians, whereas those from Central-Eastern Europe and Central-Southern America did not show any increased risk. In conclusion, adult male immigrants were at higher risk of experiencing AH for DM than Italians, with differences by area of origin, suggesting that they may experience lower access to and lower quality of primary care for DM. These services should be improved to reduce disparities.

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2.1. INTRODUCTION

The unprecedented flow of immigrants towards Europe in the last few decades has turned most European countries into multi-ethnic societies. In 2018, 4.4% of the total population of the European Union (EU) was citizens of countries outside the EU (9). Italy, like other South European countries, has experienced a relevant increase in this phenomenon in the last 20 years, with the percentage of the immigrant population increasing from 1.7% of the resident population in 1998 (75) to 8.5% in 2018 (10). Once in the host country, immigrants are vulnerable to a number of threats to their physical and mental health, and their health needs may be poorly met. Moreover, the accessibility of health services for immigrants is often undermined by cultural and language barriers, creating new challenges for health systems (3).

Diabetes mellitus (DM) has been widely shown to be differently distributed among ethnic groups in Europe, with prevalence, incidence and mortality rates for such conditions being generally higher among immigrants than those among natives (76). Furthermore, the age at onset of DM is lower, and chronic complications are more common amongst immigrant populations (76). In Italy, recent large population-based studies confirmed these figures (60–62) and reported a 55% higher risk of developing DM in immigrants than in natives (61). Diabetes-related hospitalisations have also been reported to vary among different ethnic groups (77–82). Many studies, mainly from the US, have shown higher rates of hospitalisation for DM among ethnic minorities compared with their white counterparts(77–79), whereas in the European setting, the evidence is still scarce, and the results are mixed(80–82). Differences in hospitalisation between immigrants and natives can be partially explained by different accessibility to primary care (PC) for the management of DM. A recent review focusing on hospitalisation rates among people with DM highlighted that patients with access to a regular source of primary care and those with well-controlled glycosylated haemoglobin (HbA1c) levels were less likely to be admitted to the hospital (83).

An effective indicator for evaluating the accessibility and overall effectiveness of PC is the hospitalisation for Ambulatory Care Sensitive Conditions (ACSCs), hereafter called avoidable hospitalisation (AH)(84–86). ACSCs are defined as conditions for which the provision of timely and effective outpatient care can help to reduce the risks of hospitalisation by preventing the onset of an illness or condition, controlling an acute episodic illness or condition or managing a chronic disease or condition (87). AH rates have been extensively used to compare the accessibility and quality of PC among different socioeconomic groups, including different ethnic groups, or between immigrants and natives. Among chronic conditions, almost all definitions of ACSCs for the adult population include admissions for complications of DM (87–91), usually consisting of short- and long-term complications, uncontrolled DM and lower-extremity amputations due to DM. A recent review on overall AH among immigrants and ethnic minority groups (20) found that all of the studies that analysed the AH for DM, disaggregated from other diseases, in different ethnic groups were conducted in the United States (US). All of these studies reported higher rates of AH for DM in African Americans and Hispanics compared with Caucasians(78,79,92–97). Mixed findings were reported for those of Asian ethnicity. To the best of our knowledge, no studies have been published in Europe, and none have considered "immigrant status" as an exposure variable.

2.1.1. Aim of the study

The aim of this study was to compare AH rates for diabetes mellitus among Italian and immigrant adults from different geographic macro-areas of origin using open metropolitan-based cohorts of six Italian cities participating in the Italian Network of Longitudinal Metropolitan Studies (IN-LiMeS) and pooling them together through an individual participant data meta-analysis.

2.2. METHODS

2.2.1. Study population

Six of the nine metropolitan cohorts of the IN-LiMeS network, a multi-centre and multi-purpose pool of population cohorts (40), were included in this study: Turin, Venice, Reggio-Emilia, Modena, Bologna and Rome. Subjects between 18 and 64 years of age who resided in one of the six cities for at least one day between January 1, 2001 and December 31, 2013 were enrolled (except Venice, whose enrolment and follow-up periods were extended through 2014). All included cohorts had an open cohort design. In each cohort, data from municipal population registries were linked through a specific set of keys to the archive of the 2001 population census from the National Institute of Statistics (ISTAT) and to the mortality registers and hospital discharge archives. Each of the studies included in the IN-LiMeS network was part of the Italian National Statistical Program for at least the years 2017-2019 and received a positive review by the Italian Data Protection Authority. The patients' data were completely anonymised and managed in aggregate form before the analysis.

2.2.2. Avoidable hospitalisation for diabetes mellitus

The AH for DM during inpatient care episodes occurring within or outside of the area of residence between January 1, 2001, and December 31, 2013 (or 2014 for the Venetian cohort) were considered. The source of data was the Hospital Discharge Records database collected in the Hospital Information System of the region where each city is located. Only ordinary admissions for acute care were selected (day hospitals, rehabilitation and long-term care were excluded); moreover, we excluded all admissions related to childbearing as well as transfers from another hospital. Conditions related to DM that were considered avoidable through good outpatient care were those defined by the Agency for Healthcare Research and Quality (AHRQ) (91): DM short-term complications (250.1-250.3 ICD9 CM, principal diagnosis), DM long-term complications (250.4-250.9, principal diagnosis), uncontrolled DM (250.02, 250.03, principal diagnosis) and lower-extremity amputation among patients with DM (841.0-841.9 principal or secondary diagnoses AND a DM code in principal or secondary diagnoses).

2.2.3. Definition of immigrant status

The exposure variable was the immigrant status defined by citizenship as a proxy; citizenship data were retrieved from the municipal population registry. The only exception was in the Roman cohort; because information about citizenship was not available before 2007, for all subjects who left the cohort before this year the country of birth was used as a proxy of immigrant status. Subjects were grouped into three categories according to their citizenship: 1) Italians; 2)

immigrants coming from low migratory pressure countries (LMPC): Western Europe, North America, Oceania, Israel and Japan; and 3) immigrants coming from high migratory pressure countries (HMPC): Central-Eastern (CE) Europe, Central and Southern (CS) America, North Africa, Sub-Saharan Africa and Asia (except for Israel and Japan) (24). Stateless people and those with missing data were included in the "immigrants from HMPC" group. The analyses focused on the comparison between Italians and immigrants from HMPCs because the latter represented the majority of vulnerable immigrants and because the percentage of migrants from LMPCs was very low (it ranged from 0.4% in Reggio-Emilia to 1.8% in Rome).

2.2.4. Statistical analyses

Analyses were first conducted in each of the six cohorts separately. Person-years at risk were calculated with the total follow-up time being the sum of each subject's residence periods (one or more) in the corresponding city at the ages of 18e64 years during the follow-up period. Direct age-standardised rates were calculated, overall and stratified by sex, using the 2011 Italian census population as the standard population. Negative binomial regression models, suitable in the presence of overdispersion, were used to estimate the hospitalisation rate ratios (RRs) and their 95% confidence intervals (95% CIs) for AH for DM among immigrants from HMPCs (overall and by geographical macro-area) compared with Italian citizens. The RRs were adjusted for age, calendar year (treated as time-dependent covariates) and sex, which was also a stratification variable. Finally, to provide a global measure of effect, RRs for all immigrants from HMPC, stratified by geographical macro-areas, were analysed through a random effects individual participant data (IPD) meta-analysis (98) to estimate the meta-analysis hospitalisation RR and 95% CI. To assess whether the observed differences in the effect measures of each cohort were due to chance, the Cochrane heterogeneity test was performed, and to quantify such heterogeneity, the I2 statistic was calculated (99).

2.3. RESULTS

2.3.1. Description of the study population

Overall, 4 595 984 subjects aged between 18 and 64 years were enrolled in the study, for a total of 38 510,750 person-years. The cohort of Rome was the largest (58.2% of the whole study population), followed by Turin (19.6%), Bologna (8.8%), Venice (5.7%), Modena (4.1%) and Reggio-Emilia (3.6%). The overall percentage of immigrants from HMPC was 18.5%, ranging from 14.7% in Rome to 22.2% in Reggio-Emilia. Most immigrants came from Central-Eastern Europe (7.7%), followed by Asia (6%) and Central-Southern America (2.9%); however, the percentages were heterogeneously distributed among the cohorts (Table 2.1). In particular, the proportion of immigrants from Africa (North + Sub-Saharan Africa) was higher in Reggio-Emilia and Bologna (35%, 38%) and lower in Venice and Rome (8%, 16%), with a similar pattern observed in males and females. Of interest, in Venice, Bologna and Rome, the proportion of immigrants from Asia was above 30%, with a higher proportion among males (41%, 43% and 36%) than among females (24%, 26% and 26%, respectively) (Table 2.1).

Table 2.1 Study population by immigrant status, cohort and sex. Turin: entry in the cohort: October 21, 2001.

Immigrant status		Turin[a]			Venice[b]			Reggio Emilia			Modena			Bologna			Rome[c]		
		Males	Females	Total	Males	Females	Total	Males	Females	Total	Males	Females	Total	Males	Females	Total	Males	Females	Total
ITALY	n	346 760	339 740	686 500	110 533	108 582	219 115	65 997	63 647	129 644	76 910	74 975	151 885	168 093	167 663	335 756	1 101 201	1 130 723	2 231 924
	column %	81.85	80.82	81.33	84.02	82.02	83.02	77.51	77.24	77.38	80.87	80.42	80.65	83.83	82.69	83.25	83.68	83.25	83.46
LMPC	n	5 581	6 819	12 400	907	1 680	2 587	266	468	734	668	743	1 411	1 753	2 359	4 112	21 612	27 672	49 284
	column %	1.32	1.62	1.47	0.69	1.27	0.98	0.31	0.57	0.44	0.7	0.8	0.75	0.87	1.16	1.02	1.64	2.04	1.84
HMPC	n	71 336	73 830	145 166	20 120	22 123	42 243	18 885	18 285	37 170	17 521	17 506	35 027	30 669	32 750	63 419	193 099	199 886	392 985
	column %	16.84	17.56	17.20	15.29	16.71	16	22.18	22.19	22.18	18.42	18.78	18.60	15.3	16.15	15.73	14.67	14.72	14.70
Central-Eastern Europe	n	32 947	38 899	71 846	8 660	13 955	22 615	5 155	7 977	13 132	5 412	9 149	14 561	9 107	17 651	26 758	60 863	89 413	150 276
	column %	46.19	52.69	49.49	43.04	63.08	53.54	27.30	43.63	35.33	30.89	52.26	41.57	29.69	53.90	42.19	31.52	44.73	38.24
North Africa	n	17 675	10 694	28 369	1 196	545	1 741	5 128	2 450	7 578	4 543	2 131	6 674	4 860	2 322	7 182	17 064	6 938	24 002
	column %	24.78	14.48	19.54	5.94	2.46	4.12	27.15	13.40	20.39	25.93	12.17	19.05	15.85	7.09	11.32	8.84	3.47	6.11
Sub-Saharan Africa	n	5 334	5 038	10 372	1 216	609	1 825	3 143	2 170	5 313	3 948	2 544	6 492	2 246	2 075	4 321	22 435	15 264	37 699
	column %	7.48	6.82	7.14	6.04	2.75	4.32	16.64	11.87	14.29	22.53	14.53	18.53	7.32	6.34	6.81	11.62	7.64	9.59
Central-Southern America	n	8 709	13 014	21 723	774	1 646	2 420	534	1 085	1 619	536	1 061	1 597	1 279	2 217	3 496	22 911	36 700	59 611
	column %	12.21	17.63	14.96	3.85	7.44	5.73	2.83	5.93	4.36	3.06	6.06	4.56	4.17	6.77	5.51	11.86	18.36	15.17
Asia	n	6 646	6 149	12 795	8 259	5 357	13 616	4 919	4 592	9 511	3 081	2 621	5 702	13 159	8 476	21 635	69 826	51 571	121 397
	column %	9.31	8.33	8.81	41.05	24.21	32.23	26.05	25.11	25.59	17.58	14.97	16.28	42.90	25.88	34.11	36.16	25.80	30.89
Stateless and missing	n	25	36	61	15	11	26	6	11	17	1	0	1	18	9	27	0	0	0
	column %	0.04	0.05	0.04	0.07	0.05	0.06	0.03	0.06	0.00	0.01	0.00	0.00	0.06	0.03	0.04	0.00	0.00	0.00
TOTAL		423 677	420 389	**844 066**	131 560	132 385	**263 945**	85 148	82 400	**167 548**	95 099	93 224	**188 323**	200 515	202 772	**403 287**	1 315 912	1 358 281	**2 674 193**

. [a]Turin: entry in the cohort: October 21, 2001. [b]Venice: end of follow-up: December 31, 2014. [c]Rome: Birthplace for individuals residing in Rome until 2007.

2.3.2. Description of hospitalisation and hospitalisation rates

During the follow-up period, 12 678 AHs for DM were recorded in the study population: 11 738 among Italians (92.6%) and 940 (7.4%) among immigrants from HMPCs. The age-standardised rates (per 1000 PYs) ranged from 0.17 in Turin to 0.48 in Venice among Italians and from 0.15 (Turin) to 0.63 (Bologna) among immigrants. The rates were higher among males than females in all cohorts irrespective of immigrant status (Table 2.2).

Table 2.2. Discharges, person-years (PYs), crude and age-standardized hospitalization rates by immigrant status, cohort and sex.

Cohort	Migrant status	Males				Females				Total			
		n	PYs	CHR	SHR	n	PYs	CHR	SHR	n	PYs	CHR	SHR
Turin[a]	ITALY	863	2 988 124	0.29	0.23	437	3 023 196	0.14	0.11	1 300	6 011 320	0.22	0.17
	HMPC	82	408 729	0.20	0.25	22	410 588	0.05	0.07	104	819 317	0.13	0.15
Venice[b]	ITALY	854	1 023 032	0.83	0.63	493	1 025 914	0.48	0.35	1 347	2 048 947	0.66	0.48
	HMPC	45	105 305	0.43	0.31	6	115 388	0.05	0.08	51	220 693	0.23	0.19
Reggio Emilia	ITALY	245	561 514	0.44	0.38	134	554 752	0.24	0.20	379	1 116 266	0.34	0.29
	HMPC	43	101 063	0.43	0.60	32	96 484	0.33	0.41	75	197 547	0.38	0.50
Modena	ITALY	249	637 748	0.39	0.31	155	644 649	0.24	0.18	404	1 282 397	0.32	0.25
	HMPC	53	87 870	0.60	0.97	38	90 882	0.42	0.40	91	178 752	0.51	0.59
Bologna	ITALY	732	1 308 519	0.56	0.45	468	1 345 591	0.35	0.26	1 200	2 654 109	0.45	0.35
	HMPC	84	148 764	0.56	0.86	75	160 390	0.47	0.52	159	309 154	0.51	0.63
Rome[c]	ITALY	4 352	10 189 240	0.43	0.36	2 756	10 626 063	0.26	0.21	7 108	20 815 304	0.34	0.28
	HMPC	303	1 149 835	0.26	0.30	157	1 243 036	0.13	0.15	460	2 392 871	0.19	0.22

CHR: Crude Hospitalisation Rate, SHR: Standardized Hospitalisation Rate Ratios are reported x 1000. [a]Turin: entry in the cohort: October 21, 2001. [b]Venice: end of follow-up: December 31, 2014. [c]Rome: Birthplace for individuals residing in Rome until 2007.

2.3.3. Rate ratios and meta-analysis results

Overall, the risk of AH in immigrants compared with Italians approached statistical significance (RR 1.46, 95% CI: 0.99-2.14) (Fig. 2.1c). The cohort-specific results are presented in Table A.1 in Appendix A. The meta-analysis results showed higher AH rates among immigrant males than among Italians (RR 1.62, 95% CI: 1.16-2.28) (Fig. 2.1a). This pattern was common to all cohorts except for Rome (RR: 0.97 95% CI: 0.86-1.09). Among women, there were no significant differences overall (RR: 1.14, 95% CI: 0.65-1.99). However, the analysis by cohort highlighted a heterogeneous situation, with increased rates for immigrant females in Bologna (RR: 1.89, 95% CI: 1.45-2.47), Reggio-Emilia (RR: 2.04, 95% CI: 1.33-3.12) and Modena (RR: 2.92, 95% CI: 1.97-4.32) and a lower risk in Venice (RR: 0.26, 95% CI: 0.11-0.58) and Rome (RR: 0.77, 95% CI: 0.66-0.91) (Fig. 2.1b). The I^2 statistic showed a high level of heterogeneity across cohorts for both males and females (91.6% and 94%, respectively) (Fig. 2.1a and b).

The analyses disaggregated by geographical macro-areas showed that immigrants from CE Europe as well as those from CS America did not have a significantly different risk of AH compared with Italians. On the other hand, for immigrants from Asia, Sub-Saharan Africa and North Africa, increases of AH for DM of 46%, 141% and 159%, respectively, were found (Table 2.3). Significant heterogeneities were found for all groups, but they were slightly less for immigrants from CE Europe (I^2: 67%; $p = 0.01$) (Table 2.3).

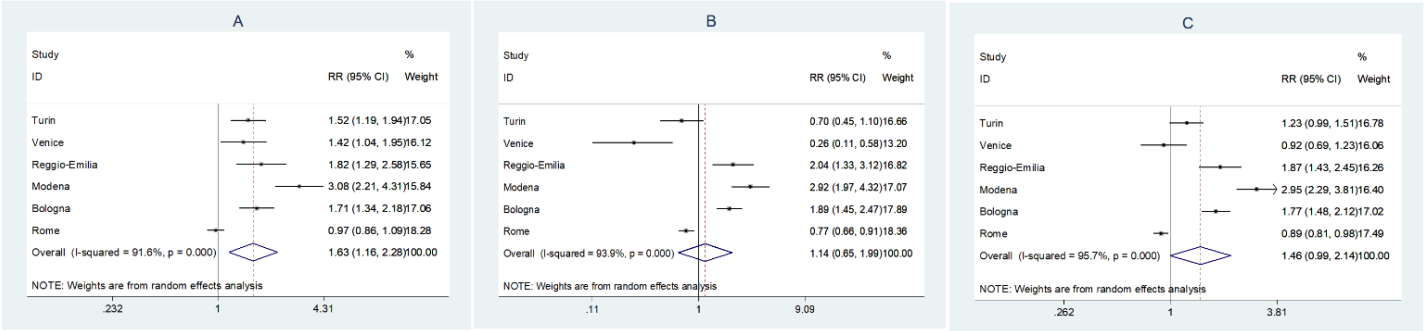

Figure 2.1. Age and calendar year-adjusted hospitalisation rate ratios (HMPC immigrants vs Italians) by cohort and sex and meta-analytic results

Table 2.3 Random effect age- and calendar year-adjusted meta-analytic hospitalization rate ratios (ref: Italy).

Geographical macro-area	RR (95% CI)	I^2	Cochran *p*-value
Central Eastern Europe	0.77 (0.58-1.01)	67%	0.01
North Africa	2.59 (1.73-3.86)	85%	<0.01
Sub-Saharan Africa	2.41 (1.30-4.45)	90%	<0.01
Central-Southern America	1.45 (0-53-3.97)	93%	<0.01
Asia	1.46 (1.00-2.14)	85%	<0.01

2.4. DISCUSSION

Overall, using a meta-analytic approach, higher AH rates for DM were found among adult immigrants from HMPC than Italians in six metropolitan Italian cohorts between 2001 and 2014. The differences in AH for DM rates, compared with Italians, were higher among men and among immigrants coming from Africa (North and Sub-Saharan) and Asia; however, the results had a high level of heterogeneity. In the cohort-specific results, women from HMPC in Rome and Venice represented an exception, showing lower AH rates compared with their Italian counterparts.

Many reasons can contribute to the increase in the risk of being hospitalised for a DM-related avoidable condition among immigrants. Their newly adopted lifestyles might play a major role (100). A study that compared Ghanaian immigrants residing in Europe with their compatriots both living in urban and rural contexts showed that the DM prevalence in immigrants was higher than the prevalence among those from rural contexts but similar to the prevalence among those living in an urban environment (101). This is probably a consequence of the process of urbanisation, where calorie-dense/low-fibre foods are available and abundant, sedentary lifestyles are more frequently adopted (101), and the same processes of urbanisation and/or westernisation are associated with migration, especially among younger immigrants (102). Genetic factors can also contribute to a greater prevalence of DM in the immigrant population, but the evidence is not conclusive (76). In this scenario, reduced access to prevention education, early diagnosis, or disease control during the early stages of the diseases - all tasks of the PC services - might widely contribute to the higher rates of AH for complications of DM. It has already

been demonstrated that immigrants are more prone to using emergency services than PC (103–105), and recent studies conducted in Italy have demonstrated that diabetic immigrants have a lower probability of HbA1C testing, annual renal function tests and lipid profile analyses (62) and a higher risk of having high levels of HbA1C (106) than Italians. Furthermore, among treated diabetic patients, immigrants have lower treatment costs [8]. Given the predisposition and vulnerability of immigrant people, cultural, socioeconomic and linguistic barriers that hamper access to care should be identified, and targeted strategies should be implemented. PC services should not only be offered equally to immigrants and natives but should also provide interventions targeted towards the populations at higher risk.

To the best of our knowledge, only two studies have been conducted in Europe comparing overall AH in immigrants and natives (49,107), and this is the first one to analyse the subgroup of AH for DM. As already mentioned, some studies have been conducted in the US context; they have highlighted that ethnic minorities showed higher rates of DM compared with their white/Caucasian counterparts and suggested the persistence of inequalities (20,82). Regardless, the results found in other settings, such as the US, are scarcely comparable because they appraise ethnic differences rather than differences by immigrant status. Furthermore, the US Health System, based on private insurance and out-of-pocket fees, would probably have a different effect on the health outcomes of patients compared with the universalistic nature of the Italian National Health Service.

Among the different geographical macro-areas, immigrants from CE Europe presented similar rates to those of their Italian counterparts, probably due to the higher cultural closeness of this group of immigrants and Italians, which facilitates access to health services. On the other hand, immigrants from North and Sub-Saharan Africa and from Asia showed a higher risk of AH for DM. These populations have also been shown to have a higher prevalence of DM at a younger age (60,100,106,108) and a higher risk of for other cardiovascular diseases than Italians (109,110). Genetic studies have confirmed a role of ethnic background in the higher prevalence of DM in South Asian people (111–113), and some authors have suggested that hypovitaminosis D, particularly relevant among people with darker skin pigmentation, increases the risk of DM (114,115). Furthermore, a study conducted in Italy in 2015 found that diabetic people of African and Asian origin had worse disease follow-up (106). Specifically, diabetic people from North Africa were at a higher risk of not being cared for in diabetic clinics and not being tested for HbA1C, and African, South Asian and other Asian immigrants were all at higher risk of having HbA1C $>$ 9% (106). These immigrants are the least rooted and stable foreign populations; therefore, they are less oriented towards addressing the health services and consequently more inclined towards avoidable hospitalisations. Furthermore, the cultural background and health practices of immigrants from Africa and Asia may be dissimilar to those of European people and health professionals, and it is essential to take particular care when dealing with these patients. For example, Muslim patients should be informed by a health care provider about Ramadan fasting and DM and about medication use during this period, but studies conducted in Europe have shown that only slightly more than half received this advice (100). All this attention is needed to act early and reduce expensive and harmful emergency interventions such as AH for DM. Our results were very heterogeneous among the different metropolitan cohorts, especially among women. One explanation may lie in the different compositions of the "immigrants from HMPC" groups in the different cities. In Venice and Rome, where immigrant women have a lower risk of AH for DM compared with their Italian counterpart, the proportions of immigrant women from Africa (over the total number of immigrants from HPMC) were 5% and 11%, respectively. These proportions were lower than those of immigrant males in the same cohorts and lower than

those of African females in the other cohorts. As immigrants from Africa have the highest risk of AH for DM, this could explain the differences between cohorts. Another explanation may arise in differential care pathways for diabetic patients. Studies conducted on diabetic patients in Turin showed that a DM care model that integrates primary and specialty care was associated with a reduction in all-cause mortality and hospitalisations compared with less structured models (114). Furthermore, integrated care models were able to reduce health inequalities among diabetic patients compared with care by a general practitioner only (116).

Immigrant males also showed higher risks of being hospitalised than immigrant females when compared with their Italian counterparts. The two groups of immigrants probably have different attitudes towards unhealthy lifestyles, health services and preventive measures. Through services for pregnant mothers, for example, women of fertile age can benefit from PC counselling and be empowered in relation to their health. According to the AHRQ definition, any discharge related to childbearing was excluded. Thus, with this analysis, we could not highlight any difference in hospitalisation relative to higher gestational diabetes prevalence, which has already been noted in some migrant groups in Europe, such as Asian women (117). Given all of these results, it is clear that when analysing the health outcomes of the immigrant population, immigrants must not be considered as a homogeneous group. Moreover, sex and the area of origin must be analysed more thoroughly to better understand the subjects who have a higher risk.

Our study has some limitations that should be noted. We used citizenship (and the birthplace in one cohort) as a proxy for immigrant status. Immigration in Italy is a quite recent phenomenon, and most adult foreigners are first-generation immigrants. Moreover, most of them still retain the citizenship of the country of origin because of the strict law in place for obtaining Italian citizenship, which requires a long and continuous stay in the country and can be acquired only after reaching the age of 18 (118). For these reasons, we believe that citizenship could still be a good proxy of immigrant status in Italy. Another limitation is that in our study only those who are officially residents and registered can be tracked and followed up. Therefore, two categories of immigrants were inherently left out: people regularly present in Italy who are not formally enrolled in any population registry (e.g., seasonal workers) and undocumented immigrants. Therefore, our results cannot be applied to the whole immigrant population. Regardless, irregular immigrants are estimated to be a minor portion of the total number of immigrants living in Italy (approximately 8%) (119).

Furthermore, we could not include other risk factors in our analysis such as the length of residence which can modify immigrants' attitudes towards health services and their lifestyles (120). The PC services in Italy are widely accessible and free at the point of use; however, different economic resources might give access to some private services, and different levels of education might affect people's approach when managing their health problems (120). Finally, considering that the prevalence of the disease is higher among immigrants (60,100), future studies should focus on cohorts of subjects with DM.

In conclusion, this study on AH for DM is the first to compare immigrants and Italians; the results showed that adult immigrants are at higher risk of AH for DM than their Italian counterparts, especially men and those from Africa and Asia. These inequalities may be reduced through an adequate and comprehensive PC service. Further studies in the Italian and European setting accounting for other socioeconomic variables and previous DM diagnosis are needed to better understand these trends.

3. AVOIDABLE HOSPITALIZATION FOR HEART FAILURE AMONG A COHORT OF 18- TO 64-YEAR-OLD ITALIAN CITIZENS AND IMMIGRANTS[13]

SUMMARY

BACKGROUND: Heart failure (HF) represents a severe public health burden. In Europe, differences in hospitalizations for HF have been found between immigrants and native individuals, with inconsistent results. Immigrants face many barriers in their access to health services, and their needs may be poorly met. We aimed to compare the rates of avoidable hospitalization for HF among immigrants and native individuals in Italy. All 18- to 64-year-old residents of Turin, Venice, Reggio Emilia, Modena, Bologna, and Rome between January 1, 2001 and December 31, 2013 were included in this multi-centre open-cohort study. Immigrants from high migratory pressure countries (divided by area of origin) were compared with Italian citizens. Age-, sex-, and calendar year-adjusted hospitalization rate ratios and the 95% CIs of avoidable hospitalization for HF by citizenship were estimated using negative binomial regression models. The hospitalization rate ratios were summarized using a random effects meta-analysis. Additionally, we tested the contribution of socioeconomic status to these disparities. Of the 4 470 702 subjects included, 15.8% were immigrants from high migratory pressure countries. Overall, immigrants showed a nonsignificant increased risk of avoidable hospitalization for HF (hospitalization rate ratio, 1.26 [95% CI, 0.97–1.68]). Risks were higher for immigrants from Sub-Saharan Africa and for males from Northern Africa and Central-Eastern Europe than for their Italian citizen counterparts. Risks were attenuated adjusting for socioeconomic status, although they remained consistent with non-adjusted results. In conclusion, adult immigrants from different geographic macro-areas had higher risks of avoidable hospitalization for HF than Italian citizens. Possible explanations might be higher risk factors among immigrants and reduced access to primary care services.

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3.1. INTRODUCTION

Heart failure (HF) represents a severe public health burden worldwide. Despite significant advances in therapies and prevention, mortality and morbidity are still high, and quality of life is poor (121).

In highly developed countries (ie, North America and Western Europe), ≈1% to 2% of people are living with HF (122). Although few data are available on the prevalence of HF in Central-Eastern Europe, the overall prevalence of cardiovascular diseases is considerably higher than in Western Europe Evidence is scarce regarding developing countries (121). One study showed that in Africa, patients with HF are younger than in other regions (123). A limited number of reports about the prevalence of HF in Asia showed that the prevalence of HF ranged from 1.26% to 6.7% in different countries (124).

In Europe, differences in the overall prevalence of hospitalization for HF have also been found between immigrants and native individuals (60,62,125–128). The results of these studies have been mixed, with immigrant groups showing either lower (62,127) or higher risk (60,125,127) of hospitalization for HF than native individuals.

These differences in hospitalization can be partially explained by different ethnic backgrounds and genetic predispositions, but they can also depend on different lifestyles and unequal access to quality ambulatory care management. It has already been demonstrated that the management of patients with HF in primary care settings may reduce avoidable readmissions (129) and that patients admitted to a hospital with HF but who were not known to have HF in their primary care experience the worst management and survival (130).

Analysing the quality and access to health care services of immigrants is of paramount importance and should be considered a priority for several reasons. First, the number of immigrants in Europe has increased considerably in the last few decades, and in Italy, the immigrant population has risen from 1.7% of residents in 1998 (75) to 8.8% in 2020 (10). Second, in the host country, immigrants are vulnerable to a number of threats to their health and their needs may be poorly met (3). Finally, immigrants may encounter many barriers in their access to health care, such as cultural and language barriers that delay their referral to appropriate services (3). Since the early 1990s, the so-called avoidable hospitalization (AH) indicator has been proposed to evaluate the accessibility and quality of primary care (PC) (87,88). The AH indicator includes hospitalizations for ambulatory care sensitive conditions that are conditions for which the provision of timely and effective outpatient care can reduce the risks of hospitalization by 1) preventing the onset of an illness or condition, 2) controlling an acute episodic illness or condition, or 3) managing a chronic disease or condition (87). AH has been widely used to compare the accessibility and quality of PC between different sociodemographic groups, including comparisons by ethnic group or by immigrant status.

Hospitalization for HF is one of the ambulatory care sensitive conditions that makes up the overall indicator of AH (87–89,91) and are by far the most common ambulatory care sensitive conditions among the chronic conditions in the adult population (49,131).

Studies analysing AH for HF disaggregated from other diseases included in the overall AH indicator, among different ethnic groups or between immigrants and native individuals, were restricted to the US population (92,131–134) and showed that Black individuals were at higher risk of AH for HF when than White Americans, while mixed findings have been reported for Hispanic and Asian individuals. To our knowledge, no study has been published in Europe on differences in AH for HF between immigrants/ethnic minorities and natives.

3.1.1. Aim of the study

Our study aimed to compare AH rates for HF among immigrants from different geographic areas with those of native adults using dynamic metropolitan cohorts of 6 Italian cities that are part of the Italian Network of Longitudinal Metropolitan Studies and pooling them together through an individual participant data meta-analysis.

3.2. METHODS

3.2.1. Study Population

Italian Network of Longitudinal Metropolitan Studies is a multi-centre and multipurpose pool of population cohorts covering the residents of 9 Italian cities (40). The Turin, Venice, Reggio Emilia, Modena, Bologna, and Rome open cohorts were included in this study.
Adults between 18 and 64 years of age who registered as residents in the population registries of the aforementioned cities for at least one day from January 1, 2001 (October 21, 2001, for Torino) to December 31, 2013 (December 31, 2014, for Venice) were enrolled.
A record linkage procedure was performed in each cohort between the municipal population registry, the 2001 population census of the National Institute of Statistics, the mortality registries, and the hospital discharge database. The linkage rates, intended as the percentage of subjects in the municipal population registry with a valid unique key for record-linkage with mortality and hospital discharge database were 100% for Venice and Turin, 99.5% for Bologna, Modena and Reggio Emilia, and 99.1% for Rome. The Italian Network of Longitudinal Metropolitan Studies is part of the Italian National Statistical Program for the years 2017 to 2019 and was approved by the Italian Data Protection Authority. No administrative permissions were required to access the raw data. Patients' data were completely anonymized, de-identified, and analysed in aggregate form for statistical purposes. Results are shown in aggregate form. Therefore, informed consent is not required.

3.2.2. Avoidable Hospitalization for Heart Failure

All AH for HF discharges occurring in the study period within or outside the city of residence were considered. These data were retrieved from the Hospital Discharge Records database found in the hospital information system of the region where each city is located.
We adopted the definition of AH for HF developed by the Agency for Healthcare Research and Quality (91). It includes all discharges of 18 to 64 years subjects with a principal International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis code for HF, not associated with cardiac procedures codes in any field. Included diagnoses and related International Classification of Diseases, Ninth Revision, Clinical Modification codes were: rheumatic heart failure (398.91), acute and chronic systolic and diastolic heart failure and congestive heart failure (428), hypertensive disease with chronic heart failure (402.01, 402.11, 402.91), benign or malignant hypertensive heart and chronic kidney disease, with heart failure (404.01, 404.03, 404.11, 404.13 404.91 404.93). International Classification of Diseases, Ninth Revision, Clinical Modification codes for cardiac procedures were 35, 36, 37.3, 37.5, 37.7, 37.8,

37.94 to 37.98, 00.5, 00.66, 38.26, 17.51/52/55. We included only inpatient discharges (with the exclusion of day hospitals, rehabilitation centres and long-term care centres). In addition, we applied the other Agency for Healthcare Research and Quality criteria, which exclude the following cases: transfer from a hospital (different facility), from a skilled nursing facility or intermediate care facility, or from another health care facility; and cases of pregnancy, childbirth, and puerperium (Major Diagnostic Criteria 14).

3.2.3. Definition of Immigrant Status

The exposure variable was the immigrant status as measured by the citizenship retrieved for each subject from the municipal population registry. In the cohort of Rome, the birthplace was used as a proxy for immigrant status until 2007, because information on citizenship was not available.
Subjects were then divided into 3 groups as follows: 1) Italian citizens; 2) immigrants from low migratory pressure countries: Western Europe, North America, Oceania, Israel and Japan; and 3) immigrants from high migratory pressure countries (HMPCs): Central-Eastern Europe, Central and South (CS) America, North Africa, sub-Saharan (SS) Africa, and Asia (except for Israel and Japan) (24). This categorization was chosen for its capacity to differentiate immigrants originating from low migratory pressure countries from those coming from HMPCs who, as a whole, generally differ from both low migratory pressure countries and natives in terms of socioeconomic and demographic characteristics. Furthermore, other categorizations like non-Western immigrants or immigrants from outside European Union, do not include migrants coming from Romania and other Eastern-European countries (25), which are the most frequent countries of origin of immigrants coming to Italy. Subjects with missing citizenship information, as well as stateless persons, were excluded from the analysis.
Since the group of immigrants from low migratory pressure countries was small (ranging from 0.4% in Reggio-Emilia to 1.8% in Rome), these subjects were excluded, and the analyses were limited to comparisons between Italian citizens and subjects from HMPCs.

3.2.4. Statistical Analyses

Analyses were first conducted in each of the 6 cohorts separately. To estimate person-time at risk, we built datasets containing all time periods of residence for everyone who met our inclusion criteria, from the date of enrolment until death or emigration or the end of the follow-up period. Person-years at risk were then obtained adding up each subject's residence periods (one or more) in the corresponding city at the attained ages of 18 to 64 years during the study period.
Crude (CHRs) and direct age-standardized hospitalization rates were estimated (overall and stratified by sex) using the 2011 Italian census population as the standard. Negative binomial regression models, which are suitable in the presence of overdispersion, were used to estimate the hospitalization rate ratios (HRRs) and their 95% CIs for AH for HF among immigrants from HMPCs (overall and by geographic macro-area) compared with Italian citizens. The HRRs were adjusted for age, calendar year (treated as time-dependent covariates), and sex.
Finally, to provide a global measure of effect, a random effects individual participant data meta-analysis was performed (98), overall and stratified by sex and geographic area of origin. In the analyses stratified by geographic macro-areas, we included cohorts with at least one HF hospitalization in each of the 2 sexes to avoid that only the group of males or females had a preponderant effect on the estimates. To assess whether the observed differences in the effect measures of each cohort were because of chance, the Cochrane heterogeneity test was performed,

and the I^2 statistic, which describes the percentage of variability across cohorts, was estimated (99).
Additionally, we tested the role of socioeconomic status as potential mediator of the association between migrant status and AH adjusting all the results also for an ecological measure of deprivation, computed at census block level and retrieved from the 2001 census. The index of deprivation (ID) is a summary measure of social and material deprivation based on 5 census variables (low level of education, unemployment, nonhome ownership, single-parent family, and household crowding) (135). For each subject, the first address of entry in the cohort was taken (the closest to 2001). Then, each unique geolocating address was spatially joined to the census block and the related ID. The index was applied as categorical variable by quintiles of population, standardized and categorized at regional level for each cohort.
The percentages of adult subjects 18 to 64 years with missing ID were 1.3% in Venice, 2.3% in Turin, 15.6% in Modena, 17.7% in Reggio Emilia, 17.7% in Rome, and 20.2% in Bologna, because of the data quality of individual addresses needed for geolocation. Because in some cohorts this percentage was high, to estimate the effect of the adjustment for ID, all the analyses were replicated in the subgroup without ID missing values, showing ID-adjusted and not adjusted estimates and computing their percentage changes. We considered 2-sided $P < 0.05$ as statistically significant. We managed the data using the SAS 9.4 software (SAS Institute, Cary, NC) and analysed them using the Stata software (Stata Corp LP, College Station, TX), version 13, especially the commands nbreg, and metan with options randomi.

3.3. RESULTS

3.3.1. Description of the study population

The study included 4 470 702 subjects, resulting in 38 046 677 person-years (PYs). Sizes of the included cohorts varied widely, with more than a half of the subjects belonging to the cohort of Rome (58.9%), followed by Turin (18.6%), Bologna (8.9%), Venice (5.8%), Modena (4.1%), and Reggio Emilia (3.7%). The percentage of immigrants from HMPCs was 15.8%. Of them, 41.8% were coming from Central-Eastern Europe, 25.8% from Asia, 12.6% from CS America, 10.6% from Northern Africa and 9.2% from SS Africa. There were major differences in terms of proportion of immigrants and area of origin among the cohorts (Table 3.1).

3.3.2. Description of hospitalization and hospitalization rates

In the period 2001 to 2013 (2014), 13 194 AHs for HF were recorded, 94.3% of them occurring among Italian citizens and 5.7% among immigrants from HMPCs. Age-standardized rates (per 1000 PYs) ranged from 0.26 in Turin to 0.39 in Reggio Emilia among Italian citizens and from 0.22 in Venice to 0.61 in Reggio Emilia among immigrants. Immigrant males presented greater age-standardized rates than immigrant females in all cohorts, with the exceptions of Reggio Emilia and Bologna, where immigrant women had greater or equal rates than men, respectively (Table 3.2).

3.3.3. Rate Ratios and Meta-Analysis Results

Overall, immigrants coming from HMPC presented a nonsignificant higher risk of experiencing AH for HF than Italian citizens (hospitalization rate ratio [HRR], 1.28 [95% CI, 0.97–1.69]; Figure 3.1). The overall level of heterogeneity, as expressed by the I^2 statistic, was 89% (Figure 3.1). In the analyses disaggregated by geographic macro-areas (Figure 3.2), immigrants from SS Africa had a doubled risk of AH compared with Italians. Additionally, male immigrants from Central-Eastern Europe and Northern Africa showed excess risks of AH for HF of 27% and 26%, respectively. Immigrants from Asia did not show any significant difference compared with Italian citizens. With regard to immigrants from CS America, only 2 cohorts had discharges for HF for both males and females; therefore, the meta-analysis was not performed.

Cohort specific relative risks are presented in Table B.1 in the Appendix B. Immigrants (compared with Italian citizens) experienced significantly higher risks in Turin (HRR, 1.24 [95% CI, 1.02–1.50]), Reggio Emilia (HRR, 2.07 [95% CI, 1.57–2.72]), and Bologna (HRR, 1.57 [95% CI, 1.22–2.02]); Rome was the only cohort in which immigrants presented a lower risk of AH for HF (HRR, 0.89 [95% CI, 0.80–0.99]).

Results of the analysis examining the impact of adjustment for ID on immigrant status-AH for HF associations are presented in Tables B.2 and B.3. For the overall category of immigrants from HMPC, there was a 6.2% reduction in the risk of being hospitalized for HF than Italians. A decrease in the estimates after adjustment was seen in all subgroups from geographic macro-areas, with an effect attenuation that ranged from a 3.5% among Asians, to a 14.4% among the Northern Africans, compared with Italians.

Table 3.1. Study Population by Immigrant Status, Cohort and Sex, and Median Age for Each Group, 18–64 y

Immigrant status		Turin[a]			Venice[b]			Reggio Emilia			Modena			Bologna			Rome[c]		
		Males	Females	Total	Males	Females	Total	Males	Females	Total	Males	Females	Total	Males	Females	Total	Males	Females	Total
Total Subjects		423 652	420 353	844 005	131 545	132 374	263 919	85 142	82 389	167 531	95 098	93 224	188 322	200 497	202 763	403 260	1 315 912	1 358 281	2 674 193
% ITALIANS	*Column %*	81.85	80.82	81.34	84.03	82.03	83.02	77.51	77.25	77.39	80.87	80.42	80.65	83.84	82.69	83.26	83.68	83.25	83.46
	Median age	37	37	37	37	38	38	35	36	35	36	37	37	36	37	37	36	36	36
	(1Q-3Q)	(27-50)	(27-51)	(27-50)	(27-50)	(27-52)	(27-51)	(26-47)	(26-48)	(26-48)	(27-49)	(27-50)	(27-49)	(28-49)	(28-51)	(28-50)	(25-48)	(26-49)	(26-49)
% LMPC	*Column %*	1.32	1.62	1.47	0.69	1.27	0.98	0.31	0.57	0.44	0.70	0.80	0.75	0.87	1.16	1.02	1.64	2.04	1.84
	Median age	35	33	34	37	34	35	36	32	33	36	33	34	34	31	32	38	37	38
	(1Q-3Q)	(28-43)	(27-39)	(28-41)	(29-48)	(28-42)	(29-44)	(28-42)	(27-39)	(28-40)	(29-44)	(27-38)	(28-41)	(27-42)	(27-38)	(27-39)	(30-48)	(30-48)	(30-48)
% HMPC	*Column %*	16.83	17.56	17.19	15.28	16.70	16.00	22.17	22.18	22.18	18.42	18.78	18.60	15.29	16.15	15.72	14.67	14.72	14.70
	Median age	30	30	30	30	32	31	31	31	31	31	31	31	30	32	31	31	33	32
	(1Q-3Q)	(24-37)	(24-39)	(24-38)	(24-37)	(25-43)	(25-40)	(25-38)	(25-41)	(25-39)	(25-37)	(25-41)	(25-39)	(25-47)	(25-43)	(25-40)	(25-38)	(26-42)	(26-40)
Central-Eastern Europe	*Column %*	46.20	52.71	49.51	43.07	63.11	53.57	27.31	43.65	35.35	30.89	52.26	41.57	29.71	53.91	42.21	31.52	44.73	38.24
	Median age	29	30	29	29	35	32	28	33	31	29	34	31	29	35	32	30	33	31
	(1Q-3Q)	(23-36)	(24-40)	(23-38)	(23-38)	(26-46)	(25-44)	(22-37)	(25-46)	(24-43)	(23-37)	(26-46)	(25-43)	(24-37)	(26-47)	(25-44)	(24-37)	(26-43)	(25-41)
North Africa	*Column %*	24.79	14.49	19.55	5.95	2.46	4.12	27.16	13.41	20.40	25.93	12.17	19.05	15.86	7.09	11.33	8.84	3.47	6.11
	Median age	31	30	31	32	28	31	32	29	31	32	29	31	32	30	32	34	32	34
	(1Q-3Q)	(26-37)	(24-37)	(25-37)	(27-37)	(24-35)	(26-37)	(27-38)	(24-37)	(26-38)	(27-38)	(24-36)	(26-37)	(27-38)	(24-38)	(26-38)	(28-41)	(26-42)	(28-41)
Sub-Saharan Africa	*Column %*	7.48	6.83	7.15	6.05	2.75	4.32	16.65	11.87	14.30	22.53	14.53	18.53	7.33	6.34	6.82	11.62	7.64	9.59
	Median age	31	29	30	31	28	30	31	28	30	31	28	30	30	29	29	30	32	31
	(1Q-3Q)	(26-37)	(25-34)	(25-36)	(26-37)	(24-33)	(25-36)	(25-37)	(23-33)	(24-35)	(25-36)	(23-33)	(24-35)	(25-36)	(25-35)	(25-35)	(24-38)	(26-40)	(25-38)
Central-South America	*Column %*	12.21	17.64	14.97	3.85	7.44	5.73	2.83	5.94	4.36	3.06	6.06	4.56	4.17	6.77	5.51	11.86	18.36	15.17
	Median age	30	31	31	29	30	30	30	31	31	30	31	31	31	31	31	32	33	33
	(1Q-3Q)	(23-38)	(25-40)	(24-39)	(23-35)	(25-37)	(24-37)	(23-36)	(26-39)	(25-38)	(24-38)	(26-39)	(25-39)	(25-38)	(26-40)	(25-39)	(25-41)	(27-42)	(26-42)
Asia	*Column %*	9.32	8.33	8.82	41.08	24.23	32.25	26.06	25.13	25.60	17.59	14.97	16.28	42.93	25.89	34.13	36.16	25.80	30.89
	Median age	30	31	31	30	29	29	32	33	32	30	31	31	30	30	30	32	33	32
	(1Q-3Q)	(24-38)	(25-39)	(24-38)	(25-36)	(23-36)	(24-36)	(26-39)	(26-40)	(26-39)	(25-37)	(25-39)	(25-38)	(25-37)	(24-38)	(25-37)	(26-39)	(27-42)	(26-40)

Q1: 25th percentile; Q3: 75th percentile. HMPC indicates high migratory pressure country; and LMPC, low migratory pressure country.

aTurin: entry in the cohort: October 21, 2001. bVenice: end of follow-up: December 31, 2014. cRome: Birthplace for individuals residing in Rome until 2007.

Table 3.2 Number of Avoidable Hospitalizations for Heart Failure (n), PYs, Crude, and Age-Standardized Hospitalization Rates by Immigrant Status, Cohort, and Sex

Cohort	Immigrant status	Males				Females				Total			
		n	PYs	CHR	SHR	n	PYs	CHR	SHR	n	PYs	CHR	SHR
Turin[a]	ITALY	1365	2988124	0.46	0.36	675	3023196	0.22	0.16	2040	6011320	0.34	0.26
	HMPC	88	408729	0.22	0.48	36	410588	0.09	0.14	124	819317	0.15	0.28
	CE Europe	46	204192	0.23	0.56	14	229221	0.06	0.14	60	433412	0.14	0.30
	N Africa	21	94896	0.22	0.64	7	53609	0.13	0.18	28	148504	0.19	0.38
	SS Africa	16	30548	0.52	0.49	5	27877	0.18	0.56	21	58425	0.36	0.54
	CS America	1	37458	0.03	0.02	8	60847	0.13	0.12	9	98305	0.09	0.08
	Asia	4	41635	0.10	0.22	2	39035	0.05	0.06	6	80670	0.07	0.13
Venice[b]	ITALY	688	1023032	0.67	0.49	250	1025914	0.24	0.16	938	2048947	0.46	0.32
	HMPC	31	105255	0.29	0.56	8	115323	0.07	0.06	39	220578	0.18	0.22
	CE Europe	12	45159	0.27	0.46	3	72196	0.04	0.04	15	117355	0.13	0.14
	N Africa	0	6561	0.00	0.00	0	3011	0.00	0.00	0	9572	0.00	0.00
	SS Africa	2	6062	0.33	0.12	0	2805	0.00	0.00	2	8868	0.23	0.08
	CS America	0	3315	0.00	0.00	1	8857	0.11	0.05	1	12171	0.08	0.03
	Asia	17	44159	0.38	0.94	4	28454	0.14	0.13	21	72612	0.29	0.58
Reggio-Emilia	ITALY	368	561514	0.66	0.57	146	554752	0.26	0.22	514	1116266	0.46	0.39
	HMPC	29	101030	0.29	0.57	48	96399	0.50	0.68	77	197428	0.39	0.61
	CE Europe	6	29524	0.20	0.77	11	43624	0.25	0.24	17	73148	0.23	0.33
	N Africa	9	31107	0.29	0.36	34	15053	2.26	4.83	43	46161	0.93	1.87
	SS Africa	12	18056	0.66	0.58	2	12916	0.15	0.42	14	30972	0.45	0.51
	CS America	0	2878	0.00	0.00	0	6159	0.00	0.00	0	9037	0.00	0.00
	Asia	2	19465	0.10	0.23	1	18646	0.05	0.06	3	38111	0.08	0.13
Modena	ITALY	391	637748	0.61	0.49	217	644649	0.34	0.25	608	1282397	0.47	0.37
	HMPC	19	87864	0.22	0.37	15	90882	0.17	0.19	34	178746	0.19	0.25
	CE Europe	6	28519	0.21	0.25	8	45546	0.18	0.19	14	74065	0.19	0.21
	N Africa	4	22916	0.17	0.11	2	11576	0.17	0.39	6	34492	0.17	0.28
	SS Africa	6	18737	0.32	2.07	3	13593	0.22	0.08	9	32330	0.28	1.12
	CS America	0	2563	0.00	0.00	0	5316	0.00	0.00	0	7879	0.00	0.00
	Asia	3	15130	0.20	0.29	2	14851	0.13	0.10	5	29980	0.17	0.18
Bologna	ITALY	641	1308519	0.49	0.39	363	1345591	0.27	0.20	1004	2654109	0.38	0.29
	HMPC	33	148650	0.22	0.40	40	160355	0.25	0.41	73	309005	0.24	0.42
	CE Europe	11	41685	0.26	0.42	27	79560	0.34	0.51	38	121245	0.31	0.51
	N Africa	6	23504	0.26	0.45	3	11510	0.26	0.17	9	35014	0.26	0.32
	SS Africa	3	10189	0.29	0.58	2	10449	0.19	0.23	5	20638	0.24	0.33
	CS America	0	6284	0.00	0.00	2	10946	0.18	0.19	2	17230	0.12	0.12
	Asia	13	66988	0.19	0.40	6	47890	0.13	0.32	19	114878	0.17	0.36

(continues in the next page)

	ITALY	5029	10189240	0.49	0.41	2306	10626063	0.22	0.17	7335	20815304	0.35	0.29
	HMPC	284	1149835	0.25	0.37	124	1243036	0.10	0.12	408	2392871	0.17	0.23
	CE Europe	87	369553	0.24	0.55	41	499594	0.08	0.11	128	869147	0.15	0.25
Rome[c]	N Africa	50	116684	0.43	0.60	11	46234	0.24	0.28	61	162917	0.37	0.49
	SS Africa	28	118245	0.24	0.30	26	104858	0.25	0.33	54	223103	0.24	0.31
	CS America	8	134495	0.06	0.07	21	233926	0.09	0.07	29	368421	0.08	0.07
	Asia	111	410859	0.27	0.33	25	358424	0.07	0.08	136	769282	0.18	0.20

Rates are reported per 1000 PYs. CE indicates Central-Eastern; CHR, crude hospitalization rate; CS, Central-South; HMPC, high migratory pressure country; PY, person-years; SHR, standardized hospitalization rate; and SS, Sub-Saharan. aTurin: entry in the cohort: October 21, 2001. bVenice: end of follow-up: December 31, 2014. cRome: Birthplace for individuals residing in Rome until 2007.

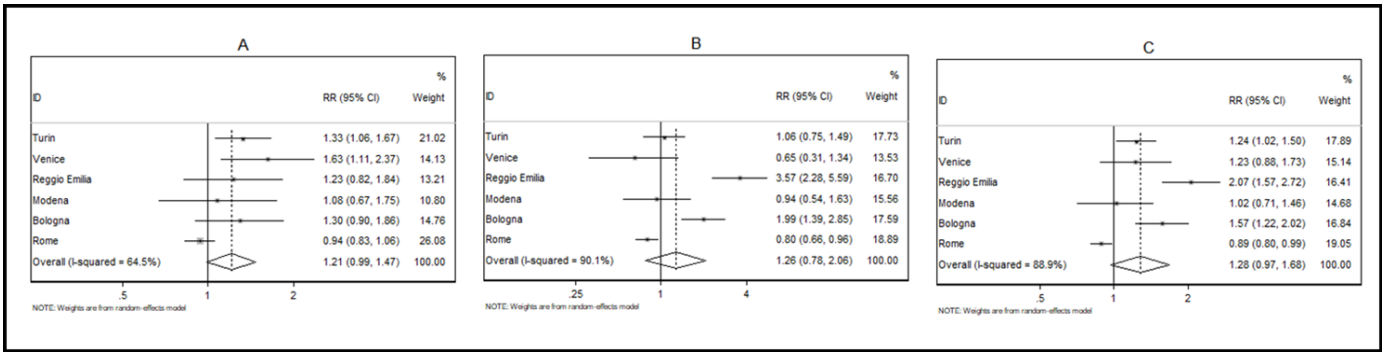

Figure 3.1 Age- and calendar year-adjusted hospitalization rate ratios (high migratory pressure country immigrants vs Italians) by cohort and sex (males, females, overall) and meta-analytic results by cohort (A, males; B, females; C, overall). RR indica

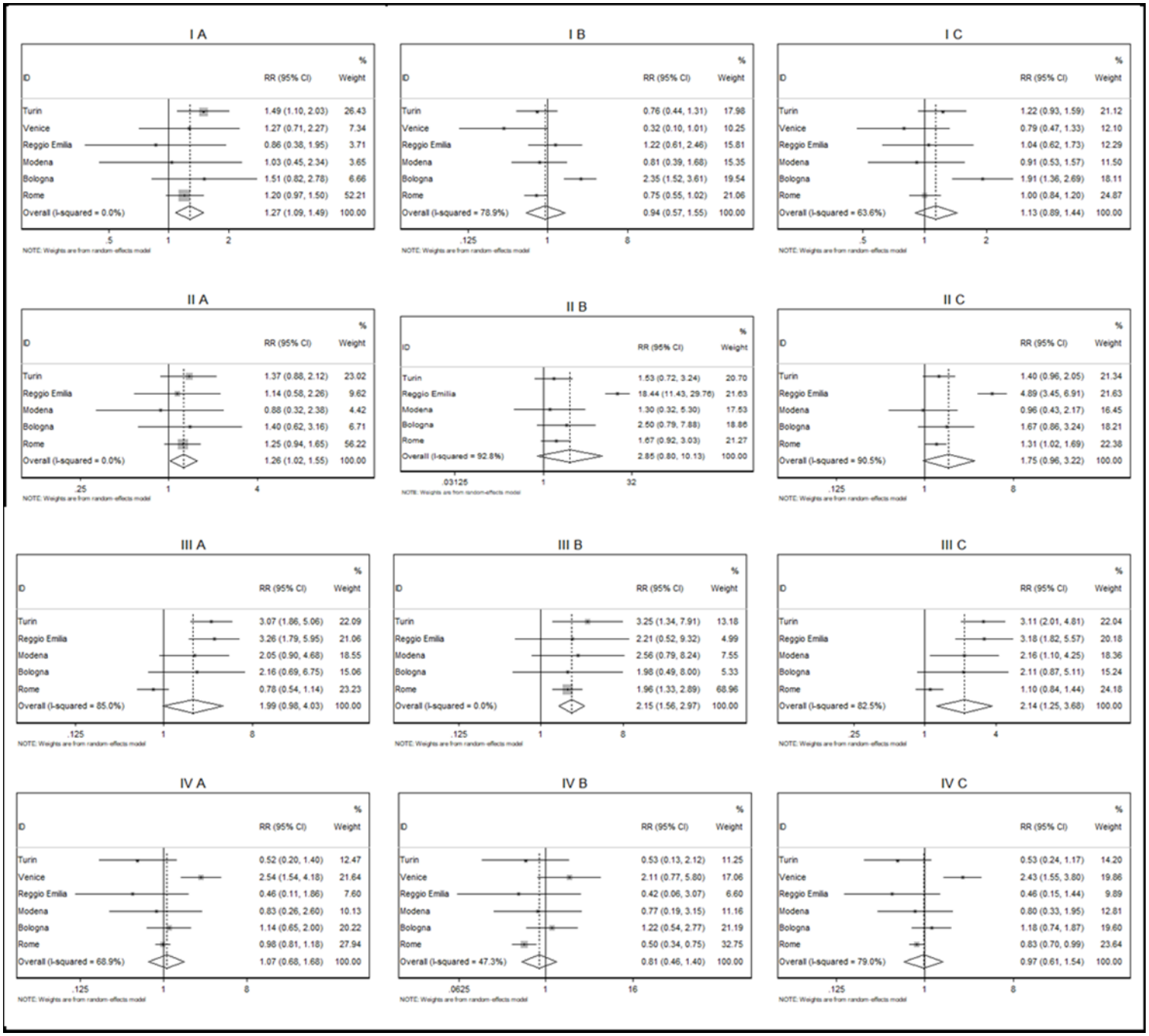

Figure 3.2 Age- and calendar year-adjusted hospitalization rate ratios by cohort and sex and meta-analytic results by cohort (A, males; B, females; C, overall). I: Immigrants from Central-Eastern Europe vs Italians; II: Immigrants from North Africa vs I Italians; III: Immigrants from Sub-Saharan Africa vs Italians; IV: Immigrants from Asia vs Italians. RR indicates rate ratios.

3.4. DISCUSSION

In 6 Italian metropolitan cohorts and during the period 2001 to 2014, immigrants coming from specific geographic macro-areas presented higher risk of experiencing AH for HF than Italian citizens. These differences were higher among immigrants coming from sub-Saharan Africa, especially females, who experienced a doubled risk, and for male citizens of Central-Eastern Europe and North Africa.

The increased risk of being avoidably hospitalized for HF is multifactorial. Lifestyle factors such as overweight, low physical activity, and cigarette smoking, as well as genetic predisposition and some predisposing diseases, such as hypertension, diabetes, and coronary heart disease, are all associated with higher incidences of HF (136). Furthermore, once the disease condition has been diagnosed, adequate and constant follow-up through outpatient care can prevent acute events from leading to hospitalization (137). Both disease prevention and monitoring of chronic conditions are key points at the primary care level.

One explanation for the increased risk of HF hospitalization in immigrants compared with Italian citizens might be influences from their countries of origin, both for genetic predisposition and different lifestyle habits. Prevalence of the aforementioned risk factors, as well as cardiovascular disease, is high in Eastern Europe (138). Also, in some central-eastern European countries, the prevalence of risk factors, such hypertension, are often coupled with lower interventions and medication control (139).

For other immigrant groups, the process of acculturation might lead to an increased risk. For instance, immigrants from SS Africa had an almost doubled risk of developing AH for HF. A study that compared Ghanaian immigrants residing in Europe with their compatriots showed that the prevalence of physical inactivity in immigrants in London was 10× higher for men and 4× higher for women than the prevalence among those living in Ghanaian rural contexts (140). In the same population, smoking prevalence was higher among Ghanaians living in Europe than those living in the country of origin (141). Furthermore, the World Health Organization estimates that the prevalence of hypertension is the highest in Africa than in other world areas, with extremely low levels of awareness and control (139). Indeed, high blood pressure levels have been found in immigrants from SS Africa living in Europe, a trend that is maintained over decades, suggesting limited efficacy of prevention strategies in such group (26). In another review, immigrants from SS Africa showed higher rates of obesity, diabetes, and hypertension when compared with the European counterpart (142).

Different access to care, and to PC in particular, can play a relevant role in explaining those disparities. Many interventions in PC settings have been demonstrated to be effective for early prevention of chronic HF. Smoking cessation, physical activity, statin treatment, and antihypertensive treatment are all recommended actions (143) that can be suggested or put into practice in the PC setting. Furthermore, the quality of the follow-up for patients with HF might be lower. An Italian study found lower adherence to HF-management guidelines (eg, therapy with angiotensin-converting-enzyme inhibitors, therapy with beta-blockers, electrolytes monitoring, annual echocardiogram) among immigrants from HMPC than among native-born individuals (62).

Our results also suggested that socioeconomic status could partially explain the high morbidity in immigrant groups. PC services in Italy are, in theory, widely accessible and mostly free at the point of use; however, different economic resources might give access to more timely private services, and different levels of education might affect people's approaches when managing their health problems (120). It has been demonstrated that socioeconomic deprivation is a powerful predictor of HF development and adverse outcomes (144). The adjustment for an ecological measure of deprivation showed a decrease of the differential risk between migrants and Italians, but it did not modify the disadvantage of the categories that had a significant higher risk of being hospitalized. In fact, a Swedish study on the risk of HF hospitalization found that foreign-born individuals were at higher risk than native-born individuals, independent of educational level and marital status (125). Also, a Scottish study examining how socioeconomic position mediate the ethnic differences in cardiovascular disease, found that the adjustment for socioeconomic

variables had little effect on relative risk of cardiovascular disease for most analysed ethnic groups, and where it did, the effect varied in direction and magnitude (145). Socioeconomic differences therefore seem to be an insufficient explanation for the increased incidence of HF hospitalizations in foreign-born individuals.

To our knowledge, all studies comparing AH for HF in immigrants/ethnic minorities have been published outside Europe, and none has compared immigrant groups to the autochthonous population (82). Concerning the available studies on overall hospitalization for HF in the European setting (also including hospitalizations accompanied by cardiac procedures codes and of subjects of all ages), the results have been mixed and have mainly depended on composition by geographic area of origin, as well as on possible differences in the study designs and methods. Two Italian studies on a large population from different regions found that immigrants from HMPC had lower hospitalization rates for HF than their Italian counterparts (62,126). Conversely, the results of a recent Italian study were partially comparable to ours, with immigrants from SS Africa at higher risk of hospitalization for HF. Contrary to our findings, though, immigrants from Eastern Europe had significant lower risk of being hospitalized for HF than native-born individuals (60). Studies conducted in the Swedish context instead found that immigrants from Central-Eastern Europe had a higher risk compared with native individuals (127,128). Indeed, in the Nordic European context, it has been shown that in many immigrant groups the risk of overweight and obesity, and consequently the risk of diabetes and CVDs, seems to be higher than the native counterpart (146).

Among the metropolitan cohorts, our results showed an increased risk of being hospitalized for HF in Turin, Reggio Emilia and Bologna, and a decreased risk in the cohort from Rome. The different compositions of the immigrants from HMPC group may be an explanation for these differences. In Rome, the 2 groups showing the lowest HRRs for HF, Asians, and CS Americans, together represent 46% of total immigrants from HMPC. On the contrary in Reggio-Emilia immigrants from Northern and SS Africa account for 34.7% of total immigrants from HMPC. Another explanation for the differences exhibited by the Roman cohort may lie in the different definition of immigrant status for those enrolled before 2007, for whom country of birth was used instead of citizenship as a proxy for immigrant status. This may have resulted in misclassification, because foreign-born people who, at that time, had been legally residing in Italy long enough to obtain Italian citizenship were included in the group of immigrants. Unfortunately, this hypothesis is difficult to test because variables that may be proxy indicators for the acculturation process, including the length of stay, are not available for our cohorts.

Given all these differences among geographic macro-areas, it is clear that immigrants should not be considered a homogenous group when exploring their health outcomes, and tailored HF prevention and follow-up programs are required to address differences and to target the worse-off groups (147).

Some advantages of the study should also be considered in its interpretation, such as the longitudinal design, the long duration of follow-up (13 years of observation) and its multicentricity, which allowed observation of how various composition of migratory flows can produce different effects on hospitalization. The use of standardized archives of data and shared procedures for the data analysis guarantee the internal validity of the results. The inclusion of cities located in North and Central Italy, where the number of immigrants is high, support the generalizability of results to other Italian cities and to cities of other European countries with universalistic health systems and immigration from HMPCs.

Our study also faced some limitations. First, citizenship was used as a proxy for immigrant status. In Italy, most adult foreigners are first-generation immigrants, with immigration having been a

relatively recent phenomenon that has reached its peak in the last 20 years. Moreover, the law in place for obtaining Italian citizenship requires a long and continuous stay in the country, and citizenship can be obtained only after the age of 18 (118); therefore, most immigrants in Italy still retain the citizenship of their country of origin. For these reasons, we think that citizenship can still be a good proxy for immigrant status.

Second, the geographic macro-areas of origin of migrant people are wide and could hide internal differences in terms of HF and risk factors prevalence, and attitudes toward health services. In particular, the Asian group could present great differences between the South, East, and South-East Asian countries (124) or between those where Islam is the main religion, and the other countries (26). Despite this, the number of HF admissions among HMPC was relatively low, and smaller macro-areas would have considerably reduced the statistical power of the analysis.

Third, our results cannot be applied to the whole immigrant population, because only those who had officially residency could be included. Undocumented immigrants and regular immigrants who were not formally enrolled in any population registry (e.g., seasonal workers) were inherently left out. Regardless, irregular immigrants are estimated to represent only 8% of the total number of immigrants living in Italy (119). Furthermore, because of the great differences in terms of health threats and accessibility of services, irregular immigrants deserve dedicated studies.

Also, we could not include the length of stay of immigrants in our analysis, which might reflect the level of acculturation and might modify immigrants' attitudes toward health services and lifestyles (148). It has been shown that immigrants residing in the United States for $\geq$10 years were more likely to be overweight/obese or hypertensive than US citizens (148), suggesting a higher risk of cardiovascular diseases.

Finally, considering that the prevalence of the condition itself partially explained the variation in AH rates for HF (149), further studies should focus on cohorts of subjects with HF.

In conclusion, this study, which analysed patterns of AH for HF among immigrants in Italy (and represents the first study of its kind in Europe), showed that male immigrants from Central-Eastern Europe and Northern Africa, as well as females from SS Africa are at higher risk of being avoidably hospitalized for HF than Italian citizens. Given the predisposition and vulnerability of immigrants, cultural, socioeconomic, and linguistic barriers that limit access to care should be identified, and targeted strategies should be implemented. PC services should not only be offered equally to immigrants and autochthonous population but should also provide interventions targeted toward the populations at increased risk.

4. ADULT FIRST-GENERATION IMMIGRANTS AND CARDIOVASCULAR RISK FACTORS IN THE VENETO REGION, NORTHEAST ITALY[14]

SUMMARY

The health condition of immigrants traditionally follows a transition from a low disease occurrence to the epidemiological profile of the deprived groups in the host country. In the Europe, studies examining differences in biochemical and clinical outcomes among immigrants and natives are lacking. We examined differences in cardiovascular risk factors between first-generation immigrants and Italians, and how migration pattern variables could affect health outcomes. We included participants between 20 and 69 years recruited from a Health Surveillance Program of the Veneto Region. Blood pressure (BP), total cholesterol (TC) and LDL cholesterol levels were measured. Immigrant status was defined by being born in a high migratory pressure country (HMPC) and subdivided by geographical macro-areas. We used generalized linear regression models to investigate differences between these outcomes among immigrants compared to native-born, adjusting for age, sex, education, BMI, alcohol consumption, smoking status, food consumption, salt consumption in the BP analysis and the laboratory in charge for cholesterol analysis. Within immigrant subjects, the results were stratified by variables of the migration pattern: age at immigration and length of residence in Italy.

37,380 subjects were included in the analysis, 8.6% were born in an HMPC. Heterogeneous results were seen by the macro-areas of origin and sex, with male immigrants from CE Europe (β=8.77 mg/dl) and Asia (β=6.56 mg/dl) showing higher levels of TC than native-born, while female immigrants from Northern Africa showed lower levels of TC (β=-8.64 mg/dl). BP levels were generally lower among immigrants. Immigrants residing in Italy for more than 20 years had lower levels of TC (β=-2.9 mg/dl) than native-born. In contrast, immigrants who arrived less than 20 years ago or arrived older than 18 years had higher levels of TC. This trend was confirmed for CE Europeans and was inverted for Northern Africans. The large heterogeneity in the results depending on sex and macro-area of origin indicates the need for targeted intervention in each specific immigrant group. The results confirm that acculturation leads to a convergence toward the epidemiological profile of the host population that depends on the starting condition of the immigrant group.

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4.1. INTRODUCTION

The unprecedented flow of immigrants toward Europe in the last few decades has turned most European countries into multi-ethnic societies. Italy, like other South European countries, has experienced a relevant increase in this phenomenon in the last 20 years, with the percentage of the immigrant population reaching 8.5% in 2018 (10). The health condition of immigrants in comparison to natives is traditionally expected to follow a transition from a low disease occurrence in the first period after arrival (so-called "healthy migrant effect") (53) to a progressive convergence toward the health behaviours and epidemiological profile of the lowest socioeconomic groups of the host population (72). This acculturation process, which entails an increase in risky behaviours (150) and the adoption of a Westernized diet and a more sedentary lifestyle (60), represents a threat to their physical and mental health. Furthermore, the accessibility of health services for immigrants is often undermined by cultural and language barriers, creating new challenges for health systems.

In Europe, limited information is available on ethnic differences concerning biochemical and clinical parameters known as CVD risk factors, such as elevated plasma lipid levels and elevated blood pressure levels (151,152). Most of the data are derived from comparisons between studies conducted in the United States (153,154). A study conducted in the Netherlands found large ethnic differences in lipid components, both in unadjusted models and in models adjusted for multiple covariates known to affect lipid metabolism. These results suggested that, next to lifestyle factors, intrinsic differences in lipid metabolism may contribute to the observed differences in plasma lipid levels (155). A review on ethnic differences in blood pressure levels in Europe found higher blood pressure levels in immigrants from Sub-Saharan Africa over decades and lower levels in the Muslim population, suggesting the limited efficacy of prevention in some groups and that untapped lifestyle and behavioural habits may reveal advantages toward the development of hypertension (26).

In Italy, studies based on health administrative data or nationwide surveys are improving the knowledge concerning the health status of immigrant populations compared to native-born Italians. The differential disease prevalence has been widely studied, it has been shown that diabetes mellitus prevalence is higher among immigrants than among native-born Italians (62). The prevalence of other cardiovascular diseases is comparable, showing heterogeneous patterns for immigrants from different countries of origin but with worse indicators of the clinical management of the disease (62). On the other hand, studies examining differences in biochemical and clinical outcomes, known as cardiovascular risk factors, among immigrants and natives are lacking. Increased levels of total and LDL cholesterol and high blood pressure are the most prevalent conditions increasing the risk of cardiovascular disease (CVD) (156). Since biochemical alterations are detectable before the onset of the disease itself, we focused the analysis on these risk factors that could help in detecting health differences earlier than the analyses on the confirmed diseases. Early detection of these differences, especially in young populations, could provide more chances for early treatments and reduce future health inequalities.

4.1.1. Aim of the study

The objective of this study is to examine the differences in the lipid profiles and blood pressure levels between first-generation immigrants and native-born Italians in a large population of the Veneto Region, Northeast Italy. This piece of information could provide insight into

understanding the mechanisms behind emerging differences in the occurrence of cardiovascular diseases. The immigrant population is very heterogeneous and should possibly be analysed considering differences within this category. Therefore, we also analysed these data by geographical macro-area of origin to investigate how variables of the migration pathway could affect health outcomes.

4.2. METHODS

4.2.1. Participants and study design

We analysed data from a publicly funded health surveillance program implemented by the Veneto Region in 30 municipalities in this Region, located in Northeast Italy (50). This program is a population-based screening program with the aim of the prevention, early diagnosis, and treatment of chronic disorders possibly associated with the high perfluoroalkyl substances exposure – PFAS, manufactured chemicals with grease-, stain-, and water-repelling properties - that was discovered in this area in 2013. The program started in 2017, and it is still ongoing, with no cost for participants. The target population included 105,000 residents of the contaminated area born between 1951 and 2014. Eligible subjects were identified through the regional health registry, which contains personal and residency data for the entire population of the Veneto Region. Residents who decided to participate in the program completed a structured interview administered by a trained public health nurse, followed by blood pressure measurement and blood and urine sampling. Program visits were performed at public health facilities located throughout the contaminated area to ensure easy accessibility. Data were collected using centralized web-based software connected with the regional health registry. The software allows the extraction of lists of eligible residents, online compiling of interview and blood pressure data, and retrieval of laboratory test results. To maximize data quality by minimizing errors and missing values, standard data checks and cleaning procedures (e.g., range and consistency checks) were performed.
All recruited subjects until May 2021, aged between 20 and 69 years old, were included in this analysis (n=38,292, participation rate 61%). Pregnant women at the time of participation in the study and participants with missing data on relevant variables were excluded, leaving 37,710 subjects included in the analysis (Figure C.1 in Appendix C). No missing data on exposure and outcome variables were present.

4.2.2. Outcome assessment

Nonfasting blood and urine samples collected from participants were sent to three local health unit laboratories within the study area (Arzignano, San Bonifacio, Legnago). Blood pressure was measured according to the European Society of Hypertension recommendations (157).
The outcome variables include the following:

- Blood lipids (total cholesterol = TC, and LDL cholesterol = LDL-C, calculated using Friedewald formula).
- Systolic and diastolic blood pressure (SBP, DBP).
- Hypertension, defined considering any self-reported diagnosis of hypertension, reported use of antihypertensive medications, or SBP≥140 mmHg or DBP≥90 mmHg.

4.2.3. Exposure: country of birth and residential history

Immigrant status was defined as the country of birth reported by the participants. Immigrants born in high migratory pressure countries (HMPCs) were further grouped into 5 geographical macro-areas of origin: Central-Eastern (CE) Europe, Central and Southern (CS) America, North Africa, Sub-Saharan (SS) Africa and Asia (except for Israel and Japan). Immigrants born in highly developed countries (HDC) were a very small percentage (330, 0.87% of the study population) and were excluded from this study (Figure C.1).
Each participant of the surveillance program was asked about his or her residential history, including all episodes of transfer of residence to a different country/municipality. The year of immigration to Italy was calculated for immigrants from HMPC countries as the first date of residence in any Italian municipality. The age at immigration (categorized as ≥18 years old and <18 years old, as it is in Italy the age of majority) and length of residence were subsequently calculated. The latter was categorized as < 10 years, between 10 and 19 years and ≥20 years, because of the distribution of our population and the need of a sufficient statistical power. Subjects with missing information on residential history, as well as subjects with nonlinear migration pathways—such as long returns to their country of origin—were excluded from these analyses (Figure C.1).

4.2.4. Covariates

The following range of potential confounders were considered based on prior literature: age (years), sex, education (primary/middle school, high school, university or higher), BMI (from self-reported height and weight and classified as normal weight (<25), overweight (25–29.9), or obese (≥30)), alcohol consumption (0, 1–2, or 3+ alcohol units per week), smoking status (current smokers, previous smokers, or non-smokers), and food consumption. Data on food consumption (meat, fish/seafood, milk/yogurt, cheese, eggs, bread/pasta/cereals, sweets/snacks/sweet beverages, fruits/vegetables) were transformed from the number of servings per day/week/month to the number of servings per week and categorized into tertiles or quartiles to allow a harmonized diet pattern classification. Furthermore, salt consumption (categorized as low, medium, or high) was considered a possible covariate in the blood pressure analyses. Finally, information on the laboratory in charge of the analyses of serum lipids (Arzignano, Legnago and San Bonifacio) was considered a possible confounder in the statistical analyses of cholesterol levels.

4.2.5. Statistical analysis

First, the demographic and lifestyle characteristics of HMPC-born residents and natives were compared.
Participants who had reported using cholesterol-lowering medications such as statins, fibrates and red rice were excluded for serum lipid outcomes (n=1,676), and participants with a self-reported diagnosis of hypertension or under treatment with antihypertensive medications were excluded for continuous blood pressure outcomes (n=4,859), leaving 35,704 and 32,521 subjects included for the lipid and blood pressure analyses, respectively (Figure C.1).
We used generalized linear regression models (LMs) to investigate the differences between cardiometabolic outcomes (SBP, DBP, TC and LDL-C) among HMPCs and the specific macro-areas of birth compared to native-born Italians. Basic models were adjusted only for age (continuous)

and sex, while fully adjusted models were additionally adjusted for the whole set of covariates. For TC and LDL-C, a random intercept was added to the models, running linear regression mixed models (LMMs) to account for the laboratory in charge of the serum analyses. For the analyses of the association of migratory status with hypertension prevalence, a log link function was used in the models, and prevalence ratios (PRs) were calculated. Estimates and 95% confidence intervals (95% CI) were reported.
Each HMPC category based on age at arrival and length of stay in Italy was then compared to native-born Italians, using the same previously defined models for each outcome. This analysis was also conducted for each of the three macro-areas with sufficient sample sizes (CE Europe, Northern Africa, Asia). All analyses were stratified by sex.
Analyses were performed using the statistical software Stata/SE version 13.0 (Stata Corp LP, College Station, TX, USA) and R (R Development Core Team 2010, R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL: http://www.R-project.org/). We employed the "lme4" and "prLogistic" packages to run LMMs and calculate prevalence ratios, respectively.

4.2.6. Ethical aspects

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Regional (Veneto Region) Ethics Committee (24 maggio 2017 prot. N. 203638). Informed consent was obtained from all subjects involved in the study.

4.3. RESULTS

4.3.1. Characteristics of studied populations according to immigrant status

Overall, 37,380 subjects were included in the analysis, and 3,249 (8.7%) of them were born in an HMPC. Half of the immigrants came from CE Europe, 20.1% from Northern Africa, 17.7% from Asia, 6.1% from CS America and 6% from SS Africa. The characteristics of native-born Italians and immigrants are presented in Table 4.1. Immigrants were younger than native-born, and their educational attainment was much lower than that of their native-born counterparts, especially for males. Immigrants reported considerably higher percentages of non-smoking and not drinking alcohol. The percentages of obese subjects were higher among subjects born in an HMPC than among native-born Italians.
We retrieved the year of immigration from 94.7% of all immigrants (3,066 subjects). Over half of them resided in Italy for between 10 and 19 years (58.6%), and the majority of all immigrants were younger than 18 years of age upon their arrival in Italy (83.9%) (Table C.1).

Table 4.1 Characteristics of the included subjects by immigrant status.

Characteristics		HMPC (n=3249)						ITALY (n=34131)					
		Total		Males (n=1317)		Females (n=1932)		Total		Males (n=16493)		Females (n=17638)	
		Median (IQR)	*Min-Max*	*Median (IQR)*	*Min-Max*	*Median (IQR)*	*Min-Max*	*Median (IQR)*	*Min-Max*	*Median (IQR)*	*Min-Max*	*Median (IQR)*	*Min-Max*
Age (years)		40 (33-47)	20-66	41 (34-48)	20-66	39 (33-46)	20-66	42 (32-50)	20-68	42 (31-50)	20-67	43 (32-51)	20-68
		N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
BMI	**Normal weight**	1464	45.1%	510	38.7%	954	49.4%	19620	57.5%	7762	47,1%	11858	67,2%
	Overweight	1154	35.5%	574	43.6%	580	30.0%	10103	29.6%	6388	38,7%	3715	21,1%
	Obese	631	19.4%	233	17.7%	398	20.6%	4408	12.9%	2343	14,2%	2065	11,7%
Smoking Habit	**Non-smoker**	2211	68.1%	747	56.7%	1464	75.8%	19917	58.4%	8101	49,1%	11816	67,0%
	Current-smoker	593	18.3%	301	22.9%	292	15.1%	7634	22.4%	4444	26,9%	3190	18,1%
	Previous smoker	445	13.7%	269	20.4%	176	9.1%	6580	19.3%	3948	23,9%	2632	14,9%
Alcohol intake	**None**	1700	52.3%	564	42.8%	1136	58.8%	9074	26.6%	2260	13,7%	6814	38,6%
	1-2	826	25.4%	291	22.1%	535	27.7%	11892	34.8%	5017	30,4%	6875	39,0%
	3+	723	22.3%	462	35.1%	261	13.5%	13165	38.6%	9216	55,9%	3949	22,4%
Education	**Elementary/ Middle**	1586	48.8%	725	55.0%	861	44.6%	10531	30.9%	5204	31,6%	5327	30,2%
	Highschool	1353	41.6%	505	38.3%	848	43.9%	17313	50.7%	8780	53,2%	8533	48,4%
	University	310	9.5%	87	6.6%	223	11.5%	6287	18.4%	2509	15,2%	3778	21,4%
Laboratory	**Arzignano**	1880	57.9%	798	60.6%	1082	56.0%	19792	58.0%	9622	58,3%	10170	57,7%
	Legnago	771	23.7%	320	24.3%	451	23.3%	6527	19.1%	3130	19,0%	3397	19,3%
	San Bonifacio	598	18.4%	199	15.1%	399	20.7%	7812	22.9%	3741	22,7%	4071	23,1%
Central-Eastern Europe		1628	50.1%	569	43.2%	1059	54.8%						
Sub-Saharan Africa		196	6.0%	105	8.0%	91	4.7%						
Northern Africa		652	20.1%	303	23.0%	349	18.1%						
Asia		576	17.7%	279	21.2%	297	15.4%						
Central-Southern America		197	6.1%	61	4.6%	136	7.0%						
Age at arrival (years)*	**<18**	495	16.1%	222	18.0%	273	14.9%						
	≥18	2571	83.9%	1015	82.1%	1556	85.1%						
Length of Stay in Italy (years)*	**0-9**	458	14.9%	131	10.6%	327	17.9%						
	10-19	1795	58.5%	682	55.1%	1113	60.9%						
	20+	813	26.5%	424	34.3%	389	21.3%						

4.3.2. Associations between immigrant status and cardiovascular risk factors

Table 4.2 provides estimates (β coefficients) and 95% confidence intervals (95% CI) for models assessing the associations between immigrant status and the selected cardiovascular risk factors. In basic-adjusted models (adjusted for age and sex), no significant differences were observed for the TC levels between foreign-born adults and their native-born counterparts, while the LDL-C levels of immigrants were significantly higher than those of native-born Italians. Considering the results for each geographical macro-area of origin, immigrants from CE Europe had significantly higher TC and LDL-C levels than native-born Italians, while immigrants from Northern Africa showed significantly lower levels of both TC and LDL-C than native-born Italians. The higher

levels of LDL-C among immigrants disappeared in the fully adjusted model (1.09 mg/dl, 95% CI: -0.04; 2.22). Effect estimates on cholesterol levels for each geographical macro-area with the full adjustment were similar to those unadjusted, although slightly attenuated. Immigrants from CE Europe had significantly higher levels of both TC and LDL-C (TC: 3.31 mg/dl, 95% CI: 1.61; -5.01, LDL-C: 4.50 mg/dl, 95% CI: 2.98; -6.02), and immigrants from Northern Africa had significantly lower levels of both TC and LDL-C (TC: -7.69 mg/dl, 95% CI: -10.4; -4.99, LDL-C: -6.19 mg/dl, 95% CI: -8.61; -3.77).

No significant difference was observed for BP levels between foreign-born adults and their native-born counterparts in basic adjusted models. In fully adjusted models, immigrants overall had significantly lower levels of SBP and DBP (SBP: -1.27 mmHg, 95% CI: -1.81; -0.72, DBP: -0.52 mmHg, 95% CI: -0.88; -0.15) than native-born Italians. Significantly lower levels of BP were shown for the subgroups of immigrants from Northern Africa (SBP and DBP) and CE Europe (SBP only).

Figure 4.1 presents β estimates and 95% CI results for the associations between immigrant status (overall and by macro-areas) and TC (Panel a) and SBP (Panel b), stratified by sex and adjusted for the full set of covariates. Immigrant males had significantly higher levels of TC than native-born Italian males (4.29 mg/dl, 95% CI: 2.22; -6.36). Significantly higher levels also were seen for males from CE Europe (8.77 mg/dl, 95% CI: 5.8; -11.75) and from Asia (6.56 mg/dl, 95% CI: 2.26; -10.85). In contrast, females from Northern Africa had significantly lower levels of TC than native-born Italian females (-8.64 mg/dl, 95% CI: -12.2; -5.07). Male and female immigrants, overall and from CE Europe, had lower levels of SBP than their native-born Italian counterparts. No significant difference was seen for immigrants from other macro-areas when stratified by sex.

Table C.2 presents the results of the prevalence ratio for hypertension in the basic and fully adjusted models, overall and stratified by sex. The results confirmed the findings observed for blood pressure levels.

Table 4.2. β coefficients and 95% confidence intervals for the associations between immigrant status and total cholesterol, LDL cholesterol, systolic blood pressure and diastolic blood pressure.

	TOTAL CHOLESTEROL		**LDL CHOLESTEROL**	
	β1 (95% CI)	**β2 (95% CI)**	**β1 (95% CI)**	**β2 (95% CI)**
Italy	138,93	137,02	59,83	56,33
HMPC overall	0.2 (-1.03; 1.43)	0.23 (-1.03; 1.5)	**1.96** (0.86; 3.06)	1.09 (-0.04; 2.22)
Central-Eastern Europe	**4.39** (2.69; 6.09)	**3.31** (1.61; 5.01)	**5.90** (4.37; 7.42)	**4.50** (2.98; 6.02)
Sub-Saharan Africa	-4.7 (-9.43; 0.04)	**-5.00** (-9.73; -0.28)	-2.17 (-6.41; 2.07)	-3.57 (-7.78; 0.65)
Northern Africa	**-8.64** (-11.27; -6.01)	**-7.69** (-10.4; -4.99)	**-5.20** (-7.55; -2.84)	**-6.19** (-8.61; -3.77)
Asia	-0.43 (-3.24; 2.38)	0.85 (-2.01; 3.71)	1.25 (-1.27; 3.77)	1.02 (-1.54; 3.57)
South America	2.17 (-2.59; 6.93)	1.39 (-3.32; 6.11)	-0.21 (-4.48; 4.05)	-1.02 (-5.23; 3.18)
	SYSTOLIC BLOOD PRESSURE		**DIASTOLIC BLOOD PRESSURE**	
	β1 (95% CI)	**β2 (95% CI)**	**β1 (95% CI)**	**β2 (95% CI)**
Italy	109,17	105,61	64,76	65,28
HMPC overall	-0.46 (-0.99; 0.07)	**-1.27** (-1.81; -0.72)	-0.2 (-0.56; 0.16)	**-0.52** (-0.88; -0.15)
Central-Eastern Europe	-0.48 (-1.21; 0.26)	**-1.35** (-2.08; -0.63)	0.19 (-0.3; 0.69)	-0.24 (-0.73; 0.25)
Sub-Saharan Africa	0.53 (-1.64; 2.71)	-0.27 (-2.4; 1.86)	0.02 (-1.45; 1.49)	-0.43 (-1.86; 1.01)
Northern Africa	-0.09 (-1.19; 1.02)	**-1.23** (-2.36; -0.1)	**-1.06** (-1.81; -0.31)	**-1.49** (-2.25; -0.73)
Asia	-1.02 (-2.23; 0.19)	-1.21 (-2.43; 0.01)	-0.22 (-1.04; 0.6)	-0.1 (-0.92; 0.72)
South America	-0.95 (-2.98; 1.08)	-1.64 (-3.62; 0.34)	-0.57 (-1.94; 0.8)	-1.02 (-2.35; 0.31)

β1: basic adjustment, adjusting for only age and sex. β2: full adjustment, adjusting for the whole set of covariates

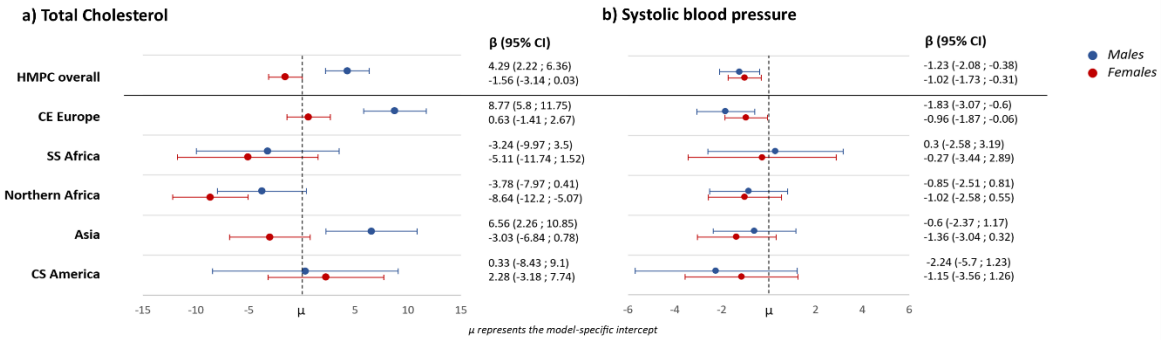

Figure 4.1 β estimates and 95% confidence intervals of the associations between country of birth (overall and by macro-areas) and total cholesterol (Panel a) and systolic blood pressure (Panel b), stratified by sex and adjusted for the full set of covariates

4.3.3. Associations between immigrant status and cardiovascular risk factors in relation to the migratory pathway

Figure 4.2 (Panels a and b) shows the association between country of birth and TC and SBP in relation to duration of residence and age at migration by sex.

Immigrants who resided for less than 10 years in Italy had higher levels of TC compared to their native-born Italian counterparts. This difference gradually decreased with a longer stay, reaching significantly lower levels of TC for those who lived in Italy for more than 20 years. This trend was particularly clear for males, with those living in Italy < 20 years showing higher levels of TC than Italian-born adults. Among females, the trend was less clear, with significantly lower levels only for those who resided in Italy between 10 and 20 years. Additionally, considering age at arrival, differences were seen for males only, with higher TC levels for males who arrived in Italy and were older than 18 years compared to native-born Italians (Panel a).

When the macro-areas of origin were considered (Table C.3), immigrants from CE Europe and Asia had patterns similar to the overall pattern. For immigrants from CE Europe, higher levels of TC also were seen for those who arrived older than 18 years. In contrast, immigrants from Northern Africa showed an opposite trend: their advantage eroded with an increasing stay in the country and with a younger age at arrival.

Immigrants who arrived under 18 years old had lower levels of SBP compared to native-born Italians, overall and for both sexes. This advantage persisted but was reduced for subjects who arrived after 18 years of age. The same advantage was seen in all groups when duration of residence was considered, but with a less clear gradient (Figure 4.2, Panel b). The greater advantage of those who arrived younger is maintained in subjects coming from all macro-areas of origin (Table C.3).

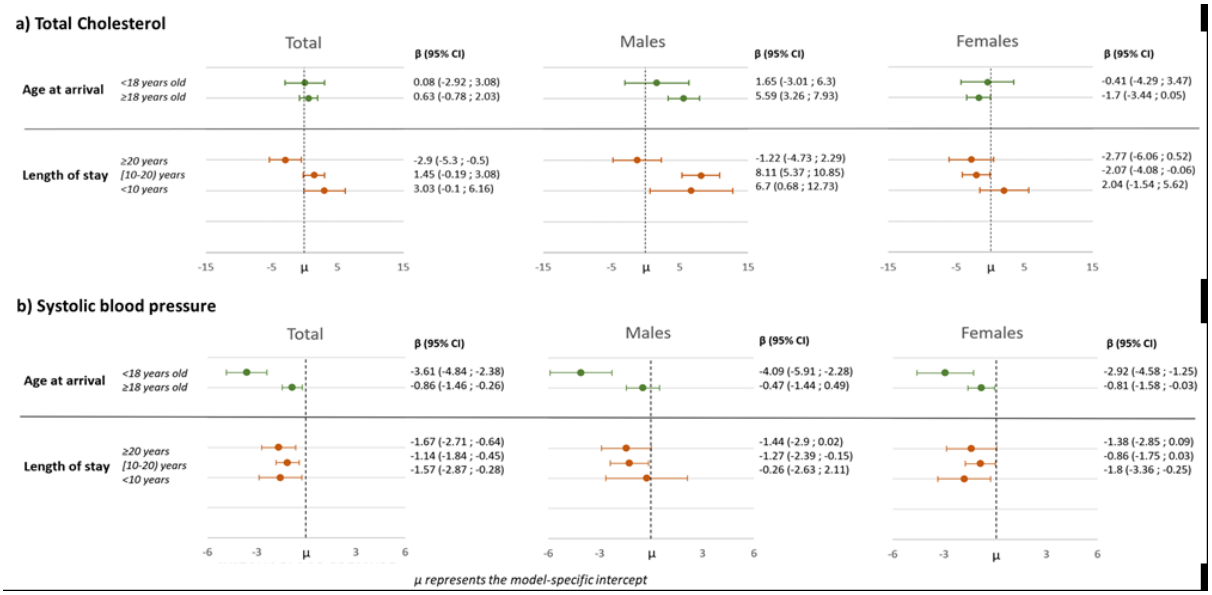

Figure 4.2. β estimates and 95% confidence intervals of the associations between country of birth and total cholesterol (Panel a) and systolic blood pressure (Panel b) in relation to duration of residence and age at migration by sex.

4.4. DISCUSSION

In our study, immigrant adult males showed higher cholesterol levels than their native-born Italian counterparts, while both immigrant males and females had lower BP levels. The higher levels of TC are mainly driven by the subjects from CE Europe, representing more than 50% of all immigrants. Immigrant males from Asia had higher levels of TC, while immigrants from Northern Africa showed lower levels of cholesterol than native-born Italians, although the results were significant for immigrant females only. Immigrants from CE Europe and Northern Africa had lower levels of SBP than native-born Italians.

After adjustments for known determinants (lifestyle factors and social determinants) of CV risk factors, the results maintained the same direction, although differences were attenuated in some cases and increased in other cases. These differences probably depend on the deep heterogeneity of the lifestyle behaviours of immigrants from different macro-areas. Regardless, the preserved direction in the adjusted results suggests that these results are only partially driven by environmental factors of the host country. Genetic factors and early living conditions can play a role in explaining these differences. The prevalence of CV risk factors, especially a high-calorie diet and cardiovascular disease, is high in Eastern Europe (138). Therefore, when immigrants from these countries arrive in Italy, they already have a background of worse health behaviours than the native population. This could explain the higher levels of TC in subjects from CE Europe. In contrast, the reduced BP levels in immigrants from CE Europe are less expected. Our results are in contrast with the European estimates of BP levels, which indicate a 10% higher prevalence of raised BP in Albania and Romania (the two most represented countries of birth in our sample; see Table C.4) than in Italy in 2014 (138). A study conducted in the same Italian region found results similar to our study, with Italian citizens having the highest rates of hypertension compared to all groups of immigrants except those coming from SS Africa (60). Regardless, it should be noted that the differences in BP levels between immigrants and natives are small in magnitude and that no differences were seen between immigrants from CE Europe and native-born Italians when considering the adjusted results for the prevalence of hypertension.

A distinct pattern of cardiovascular risk could be identified among Asians, with higher rates of TC among males than among their native-born Italian counterparts. When interpreting the results of Asian immigrants, the composition within this category is worth noting. In fact, 85% of this population in our study consisted of subjects born in the Indian subcontinent (Table C.4). The findings of our study are consistent with previous reports on ethnic differences in plasma lipid levels in the United States, Canada, the United Kingdom and the Netherlands, which have shown that South Asians are characterized by high LDL-C and triglyceride levels and low HDL-cholesterol compared to the reference population (155,158–160). The reasons for this unfavourable lipid pattern seem to be both environmental and genetic. It has been demonstrated that South Asians in the US were less physically active and had lower adiponectin and higher resistin levels than Caucasians, resulting in higher levels of LDL-C (161).

Regarding immigrants from Northern Africa, in our cohort, they are mostly represented by subjects born in Morocco (96%, see Table C4). The low prevalence of dyslipidaemia in Moroccans is consistent with the low LDL-C and triglyceride levels found by Gazzola et al. in Moroccan descendants compared to the Dutch reference population (155). Additionally, Moroccans are traditionally known to have a lower prevalence of hypertension in Europe, although this health advantage seems to be changing unfavourably through the acculturation process (162). The favourable lifestyle and behavioural habits that are linked with the Muslim population (highly prevalent in Morocco) may represent an advantage reflecting a lower predisposition toward the development of dyslipidaemia and hypertension. Differences in BP levels related to the prevalent religion have been previously found (26), and such an explanation also could be valid for the lipid pattern.

Our results on cholesterol also showed relevant sex differences: males from CE Europe and Asia had higher TC levels than native-born Italians, while no differences were seen for their female counterparts. In contrast, females from Northern Africa had lower levels of TC than native-born Italians, and this difference was less clear for males. Additionally, the trends related to acculturation, with results approaching those of the native population in immigrants with a longer stay, are stronger in males than in females. These differences may depend on the prevalence of risky behaviours: smoking and alcohol intake are more prevalent in immigrant males than in females in our population. Additionally, in the group of immigrants from CE Europe, the rate of overweight or obese people is doubled among males compared with females. This is not true for immigrants from Northern Africa, though. Additionally, these differences could be related to different approaches toward health care. In a Dutch study, women were found to have higher levels of awareness, treatment and control of hypertension than men in all ethnic groups, and this has been attributed to frequent use of health care by women (162,163).

Although environmental and socioeconomic factors play only partial roles in determining these disparities, an effort should be made to reduce the risky health behaviours and potential mediators of these differences. Many interventions in primary care settings have been demonstrated to be effective for the early prevention of cardiovascular diseases. In particular, the higher BMI of the immigrant population could be reduced with interventions on nutritional habits and physical activity. Additionally, reduced access to primary care (PC) could lead to a later diagnosis and a later start of adequate therapy. Immigrants from HMPCs have a probability of an annual LDL-C test reduced by half compared to native-born Italians (62). PC services in Italy are, in theory, widely accessible and mostly free at the point of use; however, different economic resources might provide access to more timely private services, and different levels of education might affect people's approaches when managing their health problems (164). Furthermore, the cultural backgrounds and health practices of immigrants may be dissimilar to those of European

people and health professionals, and it is essential to take particular care when dealing with these patients.

A clear gradient was seen for what concerns the levels of cholesterol by length of stay: immigrants who stayed longer than 20 years in Italy also had lower levels of TC than native-born Italians, while those who arrived less than 10 years ago had similar or higher levels of TC compared to native-born Italians. Additionally, immigrants who arrived younger than 18 years had lower levels of SBP than native-born Italians, and these results were attenuated in those who arrived older than 18 years. These results, too, were driven by the large group of immigrants from CE Europe in our population. Several studies suggest that acculturation is associated with a decline in healthy behaviours, resulting in an increase in CV risk factors (3,165), although the evidence concerning the relationships among acculturation, lifestyle behaviours, and cardiovascular risk factors is not uniform, with some examples of convergence from initially higher levels of risk factors down to local levels (166–168). These different findings mainly depend on the ethnic groups considered (169) and the starting conditions in their country of origin. In our study, the acculturation of immigrants from CE Europe seems to be a protective factor against CV risk factors. As previously said, this could reflect the higher prevalence of the aforementioned CV risk factors in CE Europe. A longer stay in Italy, as well as an arrival at a younger age, could lead to an earlier and longer adoption of healthy behaviour and result in lower CV risk factors. For other immigrant groups, the process of acculturation could lead to an increased risk. The health advantage that was seen for immigrants from Northern Africa, with lower levels of TC compared to native-born Italians, declines with an increasing length of stay and disappears for immigrants who arrived younger than 18 years. In this case, the obesogenic environment of the host country probably plays a major role in changing the virtuous lifestyle habits of immigrants. For the Asian group, the results are more heterogeneous, and it is difficult to draw any conclusion concerning this specific category.

To our knowledge, this is one of the first studies conducted in Italy analysing differences in biochemical and clinical parameters among native-born Italians and immigrants and the first that evaluates the effect of the migratory pathway in modifying these outcomes. It has been conducted on a large number of individuals and accounts for a wide number of potential characteristics associated with CV risk factors. The results also pave the way to future analysis considering other CV risk factors, such as glycated haemoglobin as indicator of the risk of developing diabetes mellitus. This could be an interesting point, to early identify subjects and groups at risk, and to tailor interventions before the development of the disease itself, which has been shown to be more prevalent in immigrants than natives (62). The study also has some limitations. First, we do not know the response rates of immigrants and natives. The questionnaire was conducted in Italian, and it was very complex, so there could have been a selection bias in the responders. The questionnaires were administered by trained nurses and not self-administered, so nurses could have mediated some language barriers by explaining the questions. Additionally, when communication was hindered by language problems, the interviewed subject was invited to return a second time with an interpreter. Second, we do not have information on the citizenship of the responders, and the “immigrant” category was built on the country of birth alone. Therefore, we could have included in this category Italian citizens but incidentally born abroad, although it is probably a quite exceptional occurrence when considering developing countries. Third, the Surveillance Program does not include people born before 1951, and this study therefore does not include elderlies. This limitation can be relevant in the analysis with hypertension as outcome, since the prevalence of this disease raises with age, although it must be pointed out that the prevalence of immigrant subjects in Italy of this age group is minimal.

In conclusion, it is clear that immigrants should not be considered a homogenous group when exploring their health outcomes. Tailored prevention and follow-up programs are required to address differences and to target the worse-off groups. Immigrants from CE Europe, especially those who arrived at older ages, arrive with a health disadvantage compared to native-born Italians, and programs raising awareness of worse habits can be useful to accelerate the process of acculturation. In contrast, immigrants from Northern Africa have a health advantage that should be preserved to avoid future increases in CV diseases.

5. MIGRANT STATUS DISPARITIES IN BLOOD PRESSURE: A MULTIPLE MEDIATION ANALYSIS OF MODIFIABLE FACTORS[15]

SUMMARY

We examined differences in blood pressure (BP) levels between first-generation immigrants and natives in a large population of adult residents in Northeast Italy, and investigated the role of lifestyle behaviours, body mass index (BMI), and education as potentially modifiable mediating factors. We included 20 to 69-year-old participants from the Health Surveillance Program of the Veneto Region (n=37,710). Immigrant status was defined as being born in a high migratory pressure country (HMPC), and immigrants were further grouped into geographical macro-areas. The outcomes were systolic BP (SBP) and hypertension, defined as abnormal BP values, self-reported diagnosis or use of antihypertensive drugs. Multiple mediation analyses were performed to determine the contribution of each mediator of the SBP/migrant status association. Of the 37,380 subjects included, 8.7% were born in an HMPC. BMI, education, alcohol, sweets and meat consumption were included as potential mediators. A small advantage in SBP was seen for immigrants compared to natives (β=-0.71, 95% CI: -1.30; -0.10). The direct effect (net of the covariates) of immigrant status on SBP was a reduction of 1.62 mmHg (95% CI: -2.25; -0.98). BMI played the highest suppressive role in this health advantage (β=1.14, 95% CI: 0.99; 1.35), followed by education. Alcohol consumption amplified the health advantage of immigrants. The suppressing effect of BMI was particularly evident among women and North Africans compared to natives. Similar results were seen for hypertension rates. Although causation cannot be proven given the cross-sectional design, our findings identify BMI as the most effective target to preserve the health advantage of immigrants with respect to BP levels.

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5.1 INTRODUCTION

Elevated blood pressure is the leading global risk factor for cardiovascular diseases (170). There is a continuous linear relationship between blood pressure levels and the risk of stroke or myocardial infarction, and treatments to lower blood pressure (BP) provide significant protection against CV events (171). The estimated worldwide trends in blood pressure levels over the past four decades have shown that the rates of increased systolic blood pressure (SBP≥140 mm Hg) have increased substantially, particularly in low- and middle-income countries with knock-on increases in disability-adjusted life years (DALYs) and deaths attributable to hypertension (172).

Disparities in BP values and in hypertension-related diseases persist in most developed countries among different ethnic groups or migrant groups compared to natives (162,173,174). A large meta-analysis on ethnic differences in blood pressure in Europe showed higher levels in immigrants from Sub-Saharan Africa and lower levels in the Muslim population compared to the native population (26). These results suggest the limited efficacy of prevention in some groups and indicate that untapped lifestyle and behavioral habits may confer advantages with respect to preventing hypertension. Our recent study conducted in northeastern Italy and presented in chapter 4 found no differences in blood pressure levels between Italians and immigrants; these effects were robust when examining the overall group of immigrants and when they were stratified by macro-area of origin. When adjusting the results for a set of potential covariates retrieved from the literature (lifestyle factors and social determinants), an advantage was observed for the immigrant group compared to Italians. This result suggests that some covariates may act as potential mediators in the relationship between migrant status and blood pressure level, with an effect similar in magnitude but opposite sign, thus acting as a suppressor of this association (175).

Different factors have been studied as possible mediators of the disparities in blood pressure levels. Racial disparities and disparities by migrant status have been found to be modified by educational level (176,177) and by behavioral (178) and clinical factors, such as body mass index (BMI) level (173,179,180). It is essential to identify which (and in what amounts) of these potentially modifiable mediators intervene in the association of migrant status and BP level. Identifying and quantifying the effects of modifiable mechanisms that link migrant status to blood pressure can improve risk stratification and guide the development of effective interventions. Furthermore, since clinical alterations such as raised blood pressure are detectable before the onset of the disease itself, the analysis of its mechanisms of emergence could help detect health differences earlier than the analyses on the confirmed hypertensive diseases or hypertension-mediated complications. An early analysis of these mechanisms, especially in young populations, could provide more chances of early treatment and reduce future health inequalities. Therefore, the aim of this study is to examine differences in blood pressure levels between first-generation immigrants and native-born Italians in a large population of adult residents in Northeast Italy and to explore the multiple factors that can explain the disparity by migrant status in blood pressure.

5.2 METHODS

5.2.1 Participants and study design

Data were retrieved from a publicly funded health surveillance program implemented by the Veneto Region in 30 municipalities located in Northeast Italy (50). This program is a population-based screening with the aim of the prevention, early diagnosis, and treatment of chronic disorders possibly associated with the high perfluoroalkyl substance (PFAS) exposure that was discovered in this area in 2013. The program started in 2017 and is still ongoing at no cost for participants. Eligible subjects born between 1951 and 2014 were identified through the regional health registry, which contains personal and residency data. A more detailed description of the health surveillance program can be found elsewhere (50). Surveillance involved the active calling of the eligible population and the free offer of health examinations, including i) a questionnaire on sociodemographic characteristics, personal health history, diet and lifestyle characteristics, self-reported height and weight; ii) measurement of blood pressure; and iii) blood and urine samples. All participants provided written informed consent. Program visits are performed at public health facilities located throughout the area to ensure easy accessibility. To maximize data quality by minimizing errors and missing values, standard data checks and cleaning procedures (e.g., range and consistency checks) are performed.
All subjects aged 20 to 69 years old recruited until May 2021 were included in this cross-sectional analysis (n=38,292, participation rate 61%). Pregnant women and participants with missing data on relevant variables were excluded, leaving a total of 37,710 subjects included in the analysis (Figure D.1 Appendix D).

5.2.2. Exposure: country of birth

Immigrant status was defined by the country of birth reported by the participants. Italian-born residents were compared to immigrants born in high migratory pressure countries (HMPC), and immigrants were further grouped into 5 geographical macroareas of origin: Central-Eastern (CE) Europe, Central and Southern (CS) America, North Africa, Sub-Saharan (SS) Africa and Asia (except for Israel and Japan). Immigrants born in highly developed countries (HDCs) were a very small proportion of the study population (n=330, 0.87%) and were excluded from the analyses, leaving 37,380 subjects (Figure D.1).

5.2.3. Outcomes: SBP and hypertension

Blood pressure was measured by trained health nurses with participants first sitting at rest for at least five minutes, according to the European Society of Hypertension recommendations (157). A validated semiautomatic sphygmomanometer with an appropriate cuff size for the arm circumference was used.
The main analysis investigated the SBP values as a continuous variable in 32,521 participants, excluding self-reported diagnosis of hypertension or under treatment with anti-hypertensive drugs (n=4,859) (Figure D1). We chose the SBP level as the only continuous outcome because it is the major risk factor for cardiovascular disease compared to DBP (181).
As a secondary outcome, we focused on hypertension prevalence, which is defined as SBP ≥140 mmHg or diastolic blood pressure ≥90 mmHg, self-reported diagnosis of hypertension, or current use of antihypertensive medications (n=9,353).

5.2.4. Statistical analysis

Covariates to be included as potential mediators or confounders of the SBP/migrant status association were selected from the available variables based on related literature, and a path diagram of mediation/confounding effects was developed. This conceptual framework (Figure 5.1) illustrates the associations of migrant status with SBP level and hypertension, the possible mediating roles of educational level, lifestyle factors (smoking, drinking habits and diet) and BMI, and the potential confounding effects of age (in years as continuous variable) and sex. Educational level was reported by the participants and was divided into three categories: primary/middle school, high school, university or higher degree. Lifestyle factors considered were alcohol consumption (0, 1–2, 3+ alcohol units per week) and smoking status (current smokers, previous smokers, nonsmokers), the diet components known to be associated with raised blood pressure (salt consumption divided into low, medium and high consumption, sweets and meat consumption in tertiles of consumption (182)). BMI (kg/m^2) was determined based on self-reported height and weight and categorized as normal weight (<25), overweight (25–29.9), and obese (≥ 30).

The selected covariates illustrated in the diagram (Figure 5.1) are potential mediators of the relationship between migrant status and the selected outcomes. A mediator is defined as a variable that is on the causal pathway between the predictor and the outcome of interest. In other words, a predictor can influence a mediator, which subsequently influences the outcome. Therefore, a variable is considered a potential mediator if two conditions are satisfied: 1) the potential mediating factor is distributed differently among the population groups; and 2) the potential mediating factor is significantly associated with the outcomes. We used t tests and chi-square tests to assess the association between migrant status and each potential mediating factor (Condition 1). We assessed the association of each covariate and the two outcomes (Condition 2) using generalized linear models adjusting for age and sex. A likelihood ratio test (LRT) was used to test the significance of each possible mediator.

We then performed multiple mediation analysis using the method based on the counterfactual framework proposed by Yu and Li (183). Note that the purpose of this study is not to identify a causal relationship but to identify factors in which the relationship between migrant status and blood pressure can be broken down. This method allows us to include factors measured in different ways (continuous, binary or categorical) and to allow correlations among factors. The method was implemented using the mma package in the statistical software R and was explained in detail elsewhere (184). We used a multiple generalized linear model (logistic regression for hypertension) to calculate the total direct effect and the total indirect effect. The total effect represents the overall effect of being an immigrant compared to natives on SBP levels. The direct effect indicates the size of the effect not explained by any of the mediating factors. The indirect effect indicates the size of the effect explained by the mediating factors. Additionally, the indirect effect of each individual mediator in the relationship of migrant status and SBP levels/hypertension prevalence was determined by the multiple mediation analysis.

Confidence intervals were computed based on the estimated mediation effects from bootstrap samples. We decided not to compute the relative effects, defined as the ratio of the corresponding (in)direct effect over the total effect, because they are hardly reasonable and interpretable when the direct and indirect effects have opposite signs (185).

All analyses were stratified by sex and by the three macroareas with sufficient sample sizes (CE Europe, North Africa, Asia). We also decided to perform a sensitivity analysis including all available mediators in the model, even those not satisfying the preliminary conditions.

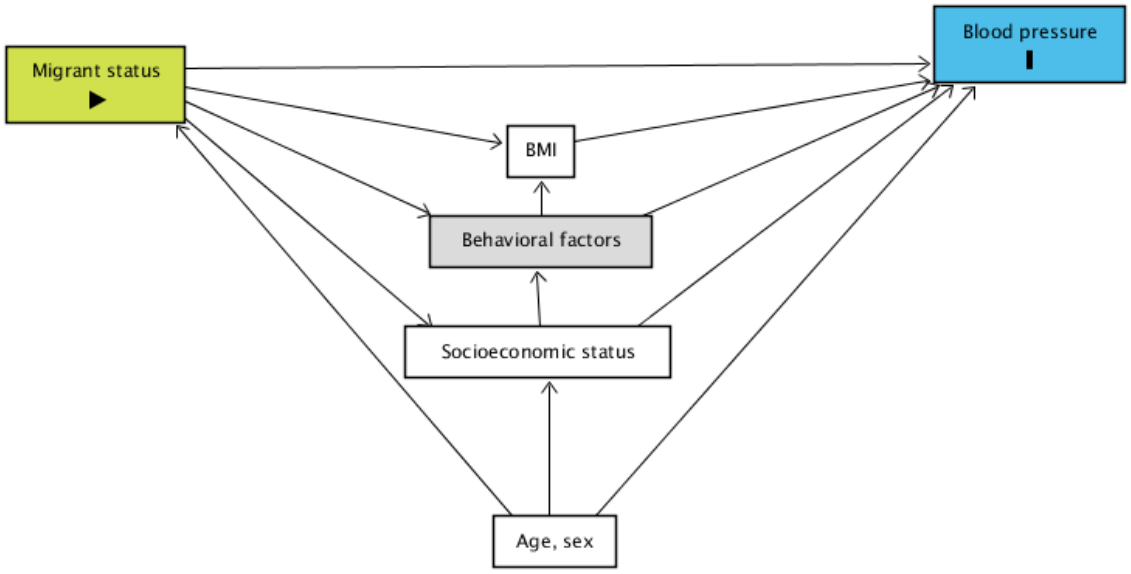

Figure 5.1 Path diagram of the association of migrant status and blood pressure

5.3. Results

5.3.1. Baseline characteristics and association of the exposure with the potential mediators

Overall, 37,380 subjects were included in the analysis, 3,249 (8.7%) of whom were born in an HMPC (Figure D.1). Baseline characteristics, SBP mean levels and hypertension rates of the population included in the analyses are listed in Table 5.1. Overall, immigrant males were older, while females were younger than natives. Immigrants had higher BMI values (especially females), lower rates of smoking, higher salt consumption but lower rates of meat, sweets and alcohol consumption. In addition, immigrants had a lower educational level than their Italian counterparts. SBP levels were higher among Italians than immigrants (mean (SD) = 121.8 (14.7) mmHg vs. 120.5 (14.6) mmHg), as was the prevalence of hypertension (25.3% vs. 21.9%). All tests performed to compare covariate distributions between immigrants and natives showed p values below 0.05, except for meat consumption among females (p value=0.08). Baseline characteristics of the study population by the three most representative macro-areas of origin are presented in Table D.1. The hypertension prevalence varied greatly among immigrants in relation to the macro area of origin: immigrants from CE Europe had the highest prevalence (23.3%), followed by those from Asia (22.0%), while the lowest prevalence was found among immigrants from North Africa (16.6%) (Table D.1).

Table 5.1. Characteristics of the included population, stratified by migrant status (Italian vs HMPC) and by sex

Characteristics (n=32,521)		Total				Males				Females			
		ITALY (n=29,644)		HMPC (n=2,877)		ITALY (n=13,954)		HMPC (n=1,138)		ITALY (n=15,690)		HMPC (n=1,739)	
continuous variables		*Mean (SD)*	*Min-Max*	*Mean (SD)*	*Min-Max*	*Mean (SD)*	*Min-Max*	*Mean (SD)*	*Min-Max*	*Mean (SD)*	*Min-Max*	*Mean (SD)*	*Min-Max*
Age (years)		39.8 (11.5)	20; 67	39.2 (9.6)	20; 66	39.2 (11.5)	20; 67	40.0 (10.0)	20; 65	40.3 (11.5)	20; 67	38.7 (9.2)	20; 66
BMI (kg/m2)		24.4 (4.3)	13.4; 54.3	25.75 (4.61)	15.6; 52.6	25.4 (3.8)	13.4; 54.3	26.2 (4.0)	16.2; 45.7	23.6 (4.6)	14. ; 54.1	25.5 (5.0)	15.6; 52.6
categorical variables		*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
BMI	*Normal weight*	18350	61,9%	1386	48,2%	7217	51,7%	478	42,0%	11133	71,0%	908	52,2%
	Overweight	8337	28,1%	1000	34,8%	5216	37,4%	479	42,1%	3121	19,9%	521	30,0%
	Obese	2957	10,0%	491	17,1%	1521	10,9%	181	15,9%	1436	9,2%	310	17,8%
Smoking Habit	*Non-smoker*	22787	76,9%	2346	81,5%	10006	71,7%	875	76,9%	12781	81,5%	1471	84,6%
	Current-smoker	6857	23,1%	531	18,5%	3948	28,3%	263	23,1%	2909	18,5%	268	15,4%
Alcohol intake	*None*	7720	26,0%	1511	52,5%	1855	13,3%	500	43,9%	5865	37,4%	1011	58,1%
	1-2	10703	36,1%	737	25,6%	4395	31,5%	247	21,7%	6308	40,2%	490	28,2%
	3+	11221	37,9%	629	21,9%	7704	55,2%	391	34,4%	3517	22,4%	238	13,7%
Education	*Elementary/ Middle*	8200	27,7%	1402	48,7%	3952	28,3%	633	55,6%	4248	27,1%	769	44,2%
	Highschool	15518	52,3%	1200	41,7%	7704	55,2%	436	38,3%	7814	49,8%	764	43,9%
	University	5926	20,0%	275	9,6%	2298	16,5%	69	6,1%	3628	23,1%	206	11,8%
Salt	*Low*	13378	45,1%	853	29,6%	5725	41,0%	319	28,0%	7653	48,8%	534	30,7%
	Medium	14664	49,5%	1759	61,1%	7323	52,5%	729	64,1%	7341	46,8%	1030	59,2%
	High	1602	5,4%	265	9,2%	906	6,5%	90	7,9%	696	4,4%	175	10,1%
Sweets	*1*	10358	34,9%	1074	37,3%	5124	36,7%	428	37,6%	5234	33,4%	646	37,1%
	2	8486	28,6%	762	26,5%	3757	26,9%	260	22,8%	4729	30,1%	502	28,9%
	3	10800	36,4%	1041	36,2%	5073	36,4%	450	39,5%	5727	36,5%	591	34,0%
meat	*1*	13483	45,5%	1368	47,5%	5143	36,9%	468	41,1%	8340	53,2%	900	51,8%
	2	5301	17,9%	469	16,3%	2508	18,0%	179	15,7%	2793	17,8%	290	16,7%
	3	10860	36,6%	1040	36,1%	6303	45,2%	491	43,1%	4557	29,0%	549	31,6%
Outcomes													
		Mean (SD)	*Min-Max*	*Mean (SD)*	*Min-Max*	*Mean (SD)*	*Min-Max*	*Mean (SD)*	*Min-Max*	*Mean (SD)*	*Min-Max*	*Mean (SD)*	*Min-Max*
systolic blood pressure		121.8 (14.7)	70; 243	120.5 (14.6)	70; 220	126.4 (13.7)	70; 243	125.2 (14.1)	75; 220	117.7 (14.3)	80; 220	117.5 (14.2)	75; 205.5
diastolic blood pressure		76.8 (10.0)	25; 148	76.14 (10.2)	25; 130	79.2 (9.7)	40; 148	79.2 (9.7)	45; 115	74.8 (9.8)	45; 115	74.5 (10.0)	45; 110
		ITALY (n=34,131)		HMPC (n=3,249)		ITALY (n=16,493)		HMPC (n=1,317)		ITALY (n=17,638)		HMPC (n=1,932)	
		N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
hypertension prevalence (n= 37,380)		8643	25.3%	710	21.9%	5380	32.6%	374	28.4%	3263	18.5%	336	17.4%

5.3.2. Associations with the outcome

The analysis of the effects of the potential mediators on the outcomes revealed important associations, as shown in Table 5.2. In the models adjusted for age and sex, SBP increased by 0.87 mmHg per increase in BMI (95% CI: 0.83-0.90, LRT p value<0.001). Additionally, the SBP levels were increased by the assumption of at least one alcoholic unit per week (LRT p value<0.001),

the increase in sweets (LRT p value<0.001) and meat consumption (LRT p value=0.002). Finally, the less educated groups had higher SBP levels than the graduated group (high school vs. university: β=1.38, 95% CI: 1.27; 1.49. Elementary/middle school vs. university: β=1.52, 95% CI: 1.40; 1.65) (Table 5.2). There were no significant associations of smoking habits and salt consumption with SBP levels. There was no association between migrant status and SBP levels in the partially adjusted model (β=-0.46, 95% CI: -0.99; 0.07), and when the model was adjusted for all covariates, immigrants had an SBP level that was 1.55 mmHg lower than that of natives (95% CI: -2.07; -1.02).

Regarding the association with hypertension prevalence, subjects with a higher BMI also had significantly higher odds of hypertension (OR=1.16, 95% CI: 1.15; 1.17). Additionally, a lower educational level (LRT p value<0.001) and an increase in sweets (LRT p value<0.001) and meat consumption (LRT p value=0.001) were associated with a higher prevalence of hypertension. No association was observed between smoking habits, alcohol consumption, salt consumption and the prevalence of hypertension. The partially adjusted model did not show a significant association between migrant status and the prevalence of hypertension (OR=0.96, 95% CI: 0.88; 1.06), while in the fully adjusted model, immigrants had a 22% lower risk of hypertension than natives (OR=0.78, 95% CI: 0.71; 0.86).

Table 5.2 Analyses of factors associated with the outcome (a significant increase in SBP, and prevalence of hypertension), adjusted for age and sex.

Characteristics		Systolic blood pressure	p-value likelihood ratio test	Hypertension	p-value likelihood ratio test
		β (95% CI)		OR (95% CI)	
Country of birth	*HMPC vs Italian*	-0.46 (-0.99; 0.07)	0,09	0.96 (0.88; 1.06)	0,434
BMI (continuous)*		0.87 (0.83; 0.90)	0,000	1.16 (1.15; 1.17)	0,000
BMI categorical	*Overweight vs normal weight*	4.50 (4.16; 4.84)	0,000	2.21 (2.08; 2.35)	0,000
	Obese vs normal weight	10.12 (9.63; 10.61)		5.68 (5.29; 6.11)	
Smoking Habit	*Current smoker vs Non-smoker /previous smokers*	0.04 (-0.32; 0.41)	0,815	1.06 (0.99; 1.13)	0,076
Alcohol intake*	*1-2 vs None*	0.75 (0.36; 1.13)	0,000	0.99 (0.93; 1.06)	0,070
	3+ vs None	0.75 (0.35; 1.15)		1.06 (0.99; 1.13)	
Education*	*Highschool vs University*	0.94 (0.54; 1.35)	0,000	1.38 (1.27; 1.49)	0,000
	Elementary/Middle School vs University	1.74 (1.28; 2.20)		1.52 (1.40; 1.65)	
salt	*Medium vs Low*	0.22 (-0.09; 0.53)	0,366	1.01 (0.95; 1.06)	0,074
	High vs Low	-0.01 (-0.68; 0.66)		1.13 (1.02; 1.26)	
sweets*	*2 vs 1*	0.42 (0.04; 0.80)	0,000	0.89 (0.83; 0.94)	0,001
	3 vs 1	0.93 (0.57; 1.29)		0.98 (0.92; 1.03)	
meat*	*2 vs 1*	1.33 (0.91; 1.75)	0,002	1.11 (1.04; 1.20)	0,000
	3 vs 1	1.78 (1.44; 2.12)		1.25 (1.18; 1.32)	

*variable selected as potential mediator (p<0.05); alcohol was forced in as potential mediators in the analysis with hypertension as outcome

5.3.3. Mediation analysis

All potential mediating factors were associated with exposure (Condition 1). However, smoking habits and salt consumption did not satisfy the second condition (association with the outcome),

and therefore, these variables were excluded from the main analysis. Although alcohol consumption was not significantly associated with hypertension (p=0.07), it was forced in the analysis as a potential mediator for this outcome because it is empirically considered important and is associated with SBP levels.

The estimates of the mediation analysis, overall and stratified by sex, are presented in Table 5.3 and Figure 5.2. The total effect of migrant status on SBP was a reduction of 0.71 mmHg (95% CI: -1.30; -0.10), that is, a rather small advantage of BP levels among immigrants compared to natives. The direct effect, obtained by removing the effect of the potential mediators, was -1.62 mmHg (95% CI: -2.25; -0.98), showing an enhanced advantage among immigrants. Such an increase reveals that the mediators act in the opposite direction compared to the direct effect of the exposure, reducing the advantage in SBP levels that immigrants would have compared to Italians if the mediators were equally distributed across the population groups. Indeed, the total indirect effect was 0.91 mmHg (95% CI: 0.72; 1.13), fairly similar in magnitude, but with an opposite sign compared to the direct effect, thus resulting in a partial suppression of the effect of migrant status on SBP levels. When the results were stratified by sex, immigrant males had an average SBP level 1.27 mmHg lower than their Italian counterpart (β=-1.27, 95% CI: -2.25; -0.40), while females had no statistically significant disparities in SBP levels by immigrant group (β=0.10, 95% CI: -0.46; 0.82) (Table 5.3).

Of the potential mediators, only BMI, alcohol intake and education reached a statistically significant indirect effect. In particular, the indirect effect of BMI is greater than the total indirect effect itself, meaning that if there was no direct effect and no other mediators, immigrants would have an average higher SBP of 1.14 mmHg compared to natives (95% CI: 0.99; 1.35) due to the differences in the BMI distribution. The educational level also played a similar role, but much smaller in magnitude (β=0.09, 95% CI: 0.04; 0.14), while the lower alcohol intake of the immigrant group was instead a protective factor for the immigrant group, having a negative indirect effect (β=-0.29 95% CI: -0.39; -0.23) (Figure 5.2a). In the analyses stratified by sex, the indirect effect of BMI was stronger among females than males. In fact, among females, the BMI increased SBP levels by an average of 1.56 mmHg for immigrants compared to natives (95% CI: 1.33; 1.81) (Figure 5.2b), while among males, BMI increased BP by only 0.76 mmHg (95% CI: 0.54-1.05). Additionally, although lower alcohol consumption is protective among immigrants of both sexes compared to natives, its negative indirect effect is stronger among males. Alcohol consumption explained an average reduction of 0.50 mmHg (95% CI: -0.64; -0.33) among immigrant males compared to their Italian counterparts (Figure 5.2c).

Table 5.3 Multiple mediation analysis for HMPC vs Italy, stratified by sex

	Systolic Blood Pressure			Hypertension		
	Total	Males	Females	Total	Males	Females
	β (95% CI)	β (95% CI)	β (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Total Effect	-0.71 (-1.30; -0.10)	-1.27 (-2.25; -0.40)	0.10 (-0.46; 0.82)	0.92 (0.83; 1.02)	0.79 (0.68; 0.94)	1.15 (1.01; 1.27)
Total Direct Effect	-1.62 (-2.25; -0.98)	-1.58 (-2.55; -0.77)	-1.28 (-1.80; -0.72)	0.78 (0.71; 0.86)	0.75 (0.64; 0.90)	0.87 (0.76; 0.97)
Total Indirect Effect	0.91 (0.72; 1.13)	0.31 (0.02; 0.56)	1.38 (1.20; 1.67)	1.19 (1.14; 1.22)	1.05 (0.99; 1.11)	1.32 (1.26; 1.38)

The sum of the percent explained effects of the individual mediators may not equal the total indirect effect because of correlation and overlapping mediation effects among mediators that is reflected in the total indirect effect but not the individual mediators

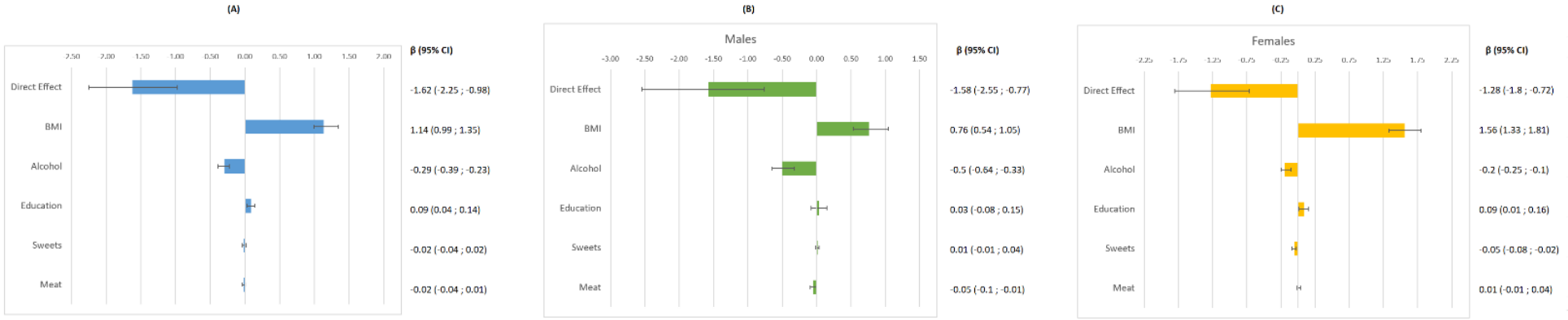

Figure 5.2 Multiple mediation analysis for SBP, HMPC vs Italy, stratified by sex. Beta and corresponding 95% Confidence Intervals in all subjects (A), Males (B), and Females (C).

5.3.4. Mediation analysis stratified by macro-area of origin

The results stratified by the macro areas of origin (presented in Table 5.4) showed a similar pattern compared to the overall results: a null total effect, explained by a negative direct effect and a positive indirect effect of the immigrant population compared to natives. Differences emerged when analysing the individual indirect effects. The BMI indirect effect was unfavorable for the immigrant groups from all the macro-areas, but its effect doubled for the group from North Africa compared to the other macro-areas (β=2.11, 95% CI: 1.8; 2.59). Additionally, education level had a positive indirect effect for immigrants from Asia, CE Europe and, to a lesser extent, North Africa compared to natives. The different alcohol consumption distributions led to a reduction in the SBP levels of immigrants from Asia and North Africa compared to natives, while it had a null effect when considering immigrants from CE Europe. Finally, the indirect effects of dietary habits reached a significant level for the Asian population. Although very small, in this population, an average reduction of 0.05 mmHg and 0.34 mmHg in SBP levels was observed due to lower sweets and meat consumption, respectively.

Table 5.4. Multiple mediation analysis for immigrants from the 3 macro-areas (Asia, North Africa, CE Europe) vs Italy

	SYSTOLIC BLOOD PRESSURE (β 95% CI)			HYPERTENSION (OR 95% CI)		
	Asia vs Italy	North Africa vs Italy	CE Europe vs Italy	Asia vs Italy	North Africa vs Italy	CE Europe vs Italy
Total Effect	-1.08 (-2.43; 0.06)	0.00 (-1.29; 1.14)	-0.90 (-1.38; 0.24)	0.95 (0.80; 1.24)	0.61 (0.48; 0.79)	1.00 (0.89; 1.14)
Total Direct Effect	-1.40 (-2.48; -0.28)	-1.65 (-3.07; -0.36)	-1.81 (-2.32; -0.83)	0.87 (0.73; 1.14)	0.47 (0.36; 0.59)	0.84 (0.75; 0.96)
Total Indirect Effect	0.31 (-0.31; 0.69)	1.65 (1.09; 2.19)	0.91 (0.83; 1.17)	1.09 (1.03; 1.18)	1.31 (1.24; 1.44)	1.19 (1.15; 1.24)
BMI	1.00 (0.55; 1.38)	2.11 (1.8; 2.59)	0.90 (0.79; 1.09)	1.13 (1.09; 1.20)	1.37 (1.30; 1.44)	1.18 (1.14; 1.22)
Alcohol	-0.48 (-0.63; -0.35)	-0.71 (-0.99; -0.45)	-0.05 (-0.09; 0.00)	0.96 (0.94; 0.99)	0.94 (0.92; 0.99)	0.99 (0.99; 1.00)
Education	0.13 (0.00; 0.25)	0.16 (-0.02; 0.33)	0.04 (0.00; 0.09)	1.02 (1.00; 1.03)	1.02 (0.99; 1.04)	1.02 (1.01; 1.03)
Sweets	-0.05 (-0.10; -0.02)	0.00 (-0.04; 0.04)	0.00 (-0.03; 0.03)	1.01 (1.00; 1.01)	1.00 (1.00; 1.01)	1.00 (1.00; 1.00)
Meat	-0.34 (-0.47; -0.24)	0.03 (-0.03; 0.09)	0.06 (0.02; 0.09)	0.98 (0.96; 0.99)	1.00 (1.00; 1.01)	1.00 (1.00; 1.01)

(The sum of the percent explained effects of the individual mediators may not equal the total indirect effect because of correlation and overlapping mediation effects among mediators that is reflected in the total indirect effect but not the individual mediators)

5.3.5. Hypertension

We found no differences in the odds of having hypertension among immigrants and natives (OR= 0.92, 95% CI: 0.83-1.02). When excluding the effect of potential mediators, immigrants had a 22% lower risk of being diagnosed with hypertension than natives (OR=0.78, 95% IC: 0.71-0.86). Similar to what happened with the continuous outcome, the total indirect effect was in the opposite direction (OR=1.19, 95% CI: 1.14-1.22), neutralizing the otherwise health advantage of immigrants compared to natives (Table 5.3). The significant mediators for this outcome were the same for SBP levels, and the order of mediating effects was roughly the same (Figure D.2). The results stratified by macro area of origin for the hypertension outcome are shown in Table 5.4.

5.3.6. Sensitivity analysis

The results of the sensitivity analysis, which included all the covariates as potential mediators, are shown in Tables D.2 and D.3. As expected, the indirect effects of salt consumption and smoking habits, which had been added as additional potential mediators, did not reach statistical significance or generated a deviation of less than 0.05 mmHg in SBP levels.

5.3.7. Ethical aspects

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Regional (Veneto Region) Ethics Committee (24 maggio 2017 prot. N. 203638). Informed consent was obtained from all subjects involved in the study.

5.4. DISCUSSION

Overall, we found that the association of migrant status with SBP levels and hypertension rates in our population can be unraveled in two effects, similar in magnitude, but with opposite signs: a negative direct effect (net of the selected mediators), which would result in a health advantage for immigrants, and a positive indirect effect, explained by the potential mediators, which played an unfavorable role for the immigrant group compared to natives. The negative coefficient of the direct effect could be interpreted as the average advantage in SBP that would appear among migrants if the covariates of the migrant population were set equal to those of the native population.

By analysing the effects of each mediator, we can assume that the suppressive role towards the association between SBP and migrant status was almost completely played by BMI. In other words, the BMI distribution was so unfavorable for the immigrant population that it suppressed the health advantage that immigrants would otherwise have had regarding BP levels. The role of BMI was more evident among women and immigrants from North Africa.

To our knowledge, only one study from the US has analysed the potential mediators (1 at a time) of the difference in hypertension incidence between black and white individuals (180). In the study by Howard et al, the dietary pattern was the largest mediating factor for differences in the incidence of hypertension between black and white individuals. Because the mean BMI was similar among black and white men, it was not a mediating factor for the excess risk of hypertension among black men. Among black women, which had a higher BMI than white women, BMI was the second largest mediating factor for hypertension (180). Other studies have identified BMI as a determinant of the effects of ethnic differences or immigrant status on BP levels, although they considered it an adjustment variable rather than a mediator and concluded that BMI could only partially explain the observed ethnic differences in hypertension prevalence (173,179).

Elevated BMI is associated with an increased risk of hypertension due to the extra load placed on the myocardium because of increased cardiac contractibility, which leads to increased heart rate and stroke volume. Therefore, by increasing cardiac output, blood pressure is subject to elevation (173). Also, two studies conducted in the US, found that people with Asian ethnicity had higher hypertension rates than other racial/ethnic groups at the same BMI levels, suggesting that the relation between BMI and BP level could be influenced by a different genetic background and that increases in weight are more detrimental than in other ethnic groups (186,187).

A smaller effect in mediating this association has been found for educational level and alcohol intake. A lower mean educational level among immigrants resulted in a suppression of the health advantage of immigrants. It is known that lower education is associated with higher levels of SBP and a higher hypertension prevalence (188), and in our study, this effect has been accounted for by other different risky behaviors or the BMI distribution, which are also known to be associated with lower educational levels (189). An explanation could be that the lower educational level could bring to lower access to health services, although a large study conducted using national data showed that men with lower levels of education had higher access to the general practitioner, who is usually the health provider in charge of detecting a raised BP (47). However, among immigrants, lower education could be related to lower language skills, lower adaptability to a different culture, and consequently higher barriers to accessing health services. A low educational level could also be related to worse working conditions and can be considered a proxy. Psychosocial factors related to physical working conditions, job strain and job control have been demonstrated to explain socioeconomic inequalities in health (190) and, more specifically, in cardiovascular outcomes (191).

Regarding alcohol intake, the lower average alcohol consumption of immigrants contributed to reducing SBP levels among immigrants compared to natives. This was particularly evident among males (except those born in CE Europe), probably due to the higher rates of Italian-born males drinking alcohol. High alcohol consumption is known to be associated with a higher prevalence of hypertension (192); nonetheless, people other than Caucasians (mainly blacks) are at risk of developing hypertension with moderate alcohol consumption (192). Virtuous behaviour still present in these populations should be encouraged and maintained to prevent the effect of acculturation, which can lead to an increase in alcohol consumption (193) and a consequent risk of higher BP levels.

Other potential mediators, such as salt consumption and diet components, had no effect on the relationship between immigrant status and blood pressure. It should be noted that these variables are self-reported in our study, and we could not rely on more objective data, such as 24-hour urinary sodium excretion.

5.4.1. Results by macro-area of origin

Overall, the patterns by macro-area of origin were similar, while there were differences in the indirect effects of single mediators. In particular, the effect of BMI previously described was higher among immigrants from North Africa, who in our study are mostly represented by subjects born in Morocco (96%, see Table C.4 Appendix C). Moroccans have been found to have a lower prevalence of hypertension in Europe (162,179), suggestive of a lower susceptibility (179) and an effect of behavioral habits related to the Muslim religion, highly prevalent in Moroccans, that are protective against the development of hypertension (26). The high negative indirect effect of alcohol consumption that we found in this population can be similarly explained. Nevertheless, this health advantage seems to be changing unfavorably through the acculturation process (162), and the indirect effect of high BMI found in our study could depend on the adoption of a westernized diet and a sedentary lifestyle, similar to the lowest socioeconomic groups of the host population.

The indirect effects of individual mediators for immigrants from CE Europe compared to Italians are small in magnitude, with the exception of the effect of BMI, which is even smaller than that of Asians and North Africans. This may reflect the higher proximity of these immigrants - mainly Romanians Albanians, Serbs and Moldavians (Table C.4) - to Italian habits and culture, both in a

positive way (the lower effect of the differential educational level) and in a negative way (there is no protective effect of the alcohol distribution, reflecting a higher alcohol consumption among this category of immigrants).
The pattern of individual mediators among Asians was similar to the overall immigrant population. Eighty-five percent of the Asian population is represented by immigrants from India and Bangladesh (Table C.4). Immigrants from these countries to the UK have been found to have lower levels of BP among adults than their English counterpart, while higher levels of BP were registered among children (namely, the second generation immigrants) (194). This intergenerational change in BP difference mirrored the change in BMI difference, thus confirming once again the risks of the acculturation process in the adoption of unhealthy lifestyles.

5.4.2. The direct effect of migrant status on blood pressure

In light of the findings described thus far, it must be noted that the purpose of this approach is not to exhaustively define all factors that underlie blood pressure levels but rather to explore the existence of modifiable factors that mediate known disparities between migrants and natives. The total effect between "migrant status" and BP captures the joint effect of all factors related to the immigrant background, regardless of their modifiability (195), and the indirect effect represents the attempt to identify the specific components intrinsic to the "immigrant status" for which interventions are more conceivable than for the immigrant status itself. Otherwise, the "direct effect" of our study must be interpreted as all the other residual factors included in the fact of being an immigrant, namely, the genetic differences (that may also explain their increased BMI), the influence of the life in the country of origin, the immigration history, and related psychosocial stress. When considering this component, a health advantage appears. This result probably mainly reflects the healthy migrant effect (53), still present in this population of first-generation immigrants, meaning that those who undertook a migratory project have a better health status than others in the home country as well as the population in the host country.

5.4.3. Health interventions

All these things considered, this paper reflects the importance of acting on modifiable factors to gain a health advantage in BP levels among immigrants. This is particularly important in light of the fact that the acculturation process, the ageing of the migrant population, and the risk of experiencing racism in the host country are all factors that could lead to an increase in SBP levels and rates of hypertension (26,162,196). Finally, efforts should be made to reduce the prevalence of hypertension because levels of hypertension awareness, treatment and control differ between ethnic minorities and Europeans (174), with the risk of higher hypertension-mediated complications among them.
Many health interventions, mainly in primary care settings, have been demonstrated to be effective for the early prevention of cardiovascular diseases. In particular, the higher BMI of the immigrant population could be reduced with interventions on nutritional habits and physical activity. As an example, a large weight control and physical activity intervention in South Asian individuals in the United Kingdom (UK) has shown that modest, medium-term changes in weight are achievable as a component of lifestyle change strategies, which might control or prevent adiposity-related diseases (197). Additionally, it must be noted that the heterogeneous results among sexes and macro-area of origin indicate the need for targeted intervention towards immigrant groups with higher effects for each mediating factor.

5.4.4. Strengths and limitations

The globally observed ethnic differences in hypertension prevalence is subject of ongoing debate, and little is known about the contribution of lifestyle, psychosocial and socio-economic determinants to the observed differences in blood pressure levels and hypertension prevalence (179). To our knowledge, this is the first study analysing the potential multiple mediators of the effects of migrant status on blood pressure. It was conducted on a large number of individuals and accounts for a wide number of potential mediators associated with BP values. Furthermore, this work attempts to disentangle the effect of migrant status on blood pressure by identifying modifiable mediators that can result in feasible opportunities to implement policies to overcome disparities.

The main limitation is its cross-sectional design, and as such, we were not able to determine the temporality between the occurrence of our exposure and the mediating effect of covariates and outcomes. Anyway, examining mediation hypotheses with cross-sectional data may be reasonable if timing is implied by the nature of their construction. In other words, it may be sensible to argue the temporal precedence of the variables in a causal chain given the chronological nature of the constructs (198). In our case, it is unlikely that the migration status has been influenced by lifestyle habits, especially those reported in the host country, and the BP values hardly have any influence on lifestyle choice or BMI. As previously stated, the purpose of this study is not to identify a causal relationship but to explore and unravel the association of BP levels and migrant status and to identify variables that can explain the disparity. However, the inferences for the two concepts are statistically identical (175). Second, as with any observational study, the results could be influenced by unmeasured confounders and mediators, such as occupation. In the Health Surveillance Plan, the information on occupation was often not reported or hardly categorizable; therefore, we decided to exclude it from the analysis. Furthermore, although considered in our survey, we did not consider physical activity due to difficulties in the harmonization of this variable, which was collected differently in two consecutive versions of the interview and was hardly comparable with the official scales measuring this indicator. Third, the questionnaire was in Italian, so there might be some measurement errors of some lifestyle variables that might have been misunderstood or wrongly interpreted by migrants. The questionnaires were administered by trained nurses and not self-administered, so the nurses could have mediated some language barriers by explaining the questions. Furthermore, when communication was hindered by language problems, the interviewed subject was invited to return a second time with an interpreter.

In conclusion, this paper provides an overview of modifiable factors associated with disparities by migrant status in SBP levels. Our results confirm that BMI and, to a lesser extent, educational level and alcohol consumption are independent mediators in the relationship between migrant status and blood pressure level. Public health measures aimed at preserving the health advantage of immigrants by targeting these factors, taking into account the specificities of each migrant group, are strongly encouraged.

6. FINAL REMARKS

In conclusion, I selected ten points retrieved from the results of the studies included in this dissertation that can be useful advices for practitioners working in the primary care services of the Italian NHS, and for epidemiologists who want to deal with the topic of immigrants' health.

1. **Specific groups of foreigners are at high risk than Italians of hospitalizations for cardiometabolic conditions that can be avoided through an adequate and accessible primary care.**

Different access and quality of care, and PC in particular, can play a relevant role in explaining disparities in the prevalence of avoidable hospitalisations. Many interventions in PC settings have been shown to be effective for early prevention of chronic CV diseases and related complications. Smoking cessation, physical activity, diet advice, statin treatment, and antihypertensive treatment are all recommended actions that can be suggested or implemented in the PC setting to reduce rates of unnecessary hospitalisations and the increased related morbidity. Immigrants have been shown to have a lower probability of being tested and followed by outpatient services, and a lower adherence to guidelines for the management of CV diseases than native-born individuals (62). As stated in the introduction, immigrants are more prone to use emergency services bypassing the GP, and poor familiarity with their rights and the local health system may influence their access to care patterns. The barriers that limit access to PC, detailed in the next point, should be identified and addressed.

2. **Cultural, socioeconomic, and linguistic barriers that hamper access to care should be identified, and targeted strategies should be implemented.**

The PC services in Italy are widely accessible and free at the point of use; however, the disparities in health outcomes that emerge in these works confirm that the access and quality of PC is not equal when considering the disparities by immigrant status.
Socioeconomic barriers might also be present in a universalistic system. Higher economic resources might give access to private services, facilitating access to care. As an example, those who can afford a private specialist visit can bypass a long waiting list and have a prompt diagnosis. Also, a higher level of education could affect people's approach when managing their health problems (120). Furthermore, among immigrants, lower education could be related to lower language skills, lower adaptability to a different culture, and consequently higher barriers to accessing health services. A low education level could also be related to worse working conditions and can be considered a proxy. Psychosocial factors related to physical working conditions, job stress, and job control have been shown to explain socioeconomic inequalities in health (190) and, more specifically, in cardiovascular outcomes (191). Additionally, health professionals should keep in mind that immigrants may not have the knowledge and skills to get oriented into the health services of the hosting country and should help those with fewer means in detecting the correct health paths for their specific needs.
Furthermore, the cultural background and health practices of immigrants may be different from those of European people and healthcare professionals, and it is essential to take particular care when dealing with these patients. For example, Muslim patients should be informed by a health care provider about Ramadan fasting and DM, and about medication use during this period, but studies conducted in Europe have shown that only slightly more than half received this advice

(100). Health professionals should be aware on the cultural habits of the country of origin and work with cultural mediators and community leaders to raise attention to harmful habits.
A cultural mediator could also be useful to overcome linguistic barriers that are particularly challenging for the newly arrived immigrants, for the elderly, and for the categories that have a lower interaction with the hosting population. Immigrants have been shown to report unclear symptoms to the GP due to poor communication abilities, resulting in the need for repeated visits and additional diagnostic activities (72). In addition, GPs communicate differently with immigrants, compared to native patients, and consultations with immigrants were shorter (74).
All these things considered, PC services should not only be offered equally to immigrants and natives, but should also provide interventions geared toward the populations with lower access.

3. The heterogeneous results among sexes and macro-area of origin of these studies indicate that immigrants should not be considered as a homogenous group.

In the chapters 2 to 5 of this dissertation it emerges that immigrants in Italy have very different profiles according to the macro-area of origin. Immigrants from CE Europe represent the majority of immigrants in Italy. As stated previously, the high prevalence of CV risk factors in CE European countries, coupled with lower interventions and medication control, is a favourable background for the development of CV diseases. Therefore, when immigrants from these countries arrive in Italy, they already have a background of worse health behaviours than the native population. As shown in chapter 4, immigrants born in CE Europe have higher levels of TC compared to Italians. In addition, male citizens of CE Europe had a higher risk of AH for HF.
On the other hand, immigrants from CE Europe show a positive effect of the acculturation process in reducing differences in TC levels with the native-born (chapter 4). Additionally, the role of lifestyle factors in explaining differences in BP levels compared to native-born individuals is smaller in magnitude than that of Asian and North Africans (chapter 5), and this may reflect the higher proximity of these immigrants to Italian habits and culture. The cultural and linguistic closeness of CE Europe with Italy, as well as the reduced ethnic segregation, can facilitate the acculturation process and reduce health inequalities, especially in the so-called 'second generation immigrants', who did not experience the influence of the country of origin. In addition to this, since 2007 the Rumanians, the most representative non-Italian group in Italy, are UE citizens. Therefore, they do not experience the stress of the risk of being expelled or living irregularly in Italy, and can return to their country of origin if they wish to do so. In summary, although the health behaviour in the country of origin may be worse than for other immigrant groups, subjects from CE Europe face less barriers in accessing the healthcare for CV diseases, and are more easily integrated in the Italian culture and society.
Foreigners from North and Sub-Saharan Africa have a higher risk of AH for DM and HF than Italians, probably reflecting a combination of higher prevalence of CV diseases, worse lifestyle behaviours (as demonstrated in chapters 4 and 5), late diagnosis and worse follow-up. A study comparing Ghanaian immigrants residing in Europe with their compatriots showed that the prevalence of physical inactivity in immigrants in London was 10× higher for men and 4× higher for women than the prevalence among those living in rural contexts (140). In the same population, smoking prevalence was higher among Ghanaians living in Europe than among those living in the country of origin (141). Furthermore, the WHO estimates that the prevalence of hypertension is highest in Africa than in other areas of the world, with extremely low levels of awareness and control (139). In fact, high blood pressure levels, high rates of obesity, and

diabetes have been found in immigrants from SS Africa who live in Europe, a trend that is maintained over decades, suggesting limited efficacy of prevention strategies in such group (26,142).
These immigrants are the least rooted and stable foreign populations; therefore, they are less orientated towards addressing the health services and, consequently, at higher risk for AH. Furthermore, the cultural background and health practises of immigrants from Africa may be different from those of European people and health professionals, and it is essential to take particular care when dealing with these patients.
Foreigners with Asian citizenship showed a higher risk of AH for DM in chapter 2. Also, Asian male immigrants showed higher TC levels, and a relevant role played by BMI in explaining the differences in BP levels (chapters 4 and 5). When interpreting the results of Asian immigrants, the composition within this category is worth noting. In fact, subjects from South Asia are extremely different than those from China, those from Central Asia, etc.
In chapters 4 and 5 most of the Asians were born in the Indian subcontinent. The findings of our study are consistent with previous reports on ethnic differences in plasma lipid levels, which have shown that South Asians are characterized by high levels of LDL-C and triglycerides and low HDL-cholesterol compared to the reference population. In addition, genetic studies have confirmed the role of ethnic background in the higher prevalence of DM in South Asian people.
Given all these differences, and other more deeply described in single chapters, it is clear that the immigrant group should always be disaggregated in the analyses to better understand the subjects more prone to develop specific health issues.

4. The definition of 'immigrant status' can influence interpretation and comparability of the results.

In chapters 2 and 3, the immigrant status was defined using the citizenship as a proxy of it, in all cohorts except the cohort of Rome (before 2007). For the cohort of Venice, the citizenship linked to each subject was the first that appeared in the linked municipal registry, whether the one owned in 2001, or at the first entering in the court. The acquisitions of citizenships before 2001 were very few (199) and therefore the criterion applied for the cohort of Venice is very precise in identifying immigrants. For the other municipalities, the only citizenship available was the most recent within the follow-up period. Therefore, in these municipalities, all immigrants who acquired the Italian citizenship between 2002 and 2013 were misclassified as Italians. The rate of acquisition of Italian citizenship between 2002 and 2013 was calculated as 20%, uniformly distributed in the four municipalities. This represents an important limit of the studies in chapter 2 and 3, not only because many immigrants who acquired the Italian citizenship have been misclassified in four cohorts, but also because of the different criteria used to identify immigrants, which prevent any precise comparison among cohorts.
The classification through citizenship as a proxy of immigrant status was chosen as the simplest one to be obtained in a study with such a complex design and can reflect a common background of lower rights and a reduced integration in the hosting country. Also, with an open-cohort design, the subjects entered in the cohort in the years after 2001 were likely to have arrived recently and had a small possibility of acquiring citizenship in such a short period of time.
Instead, the classification of immigrants by country of birth has been chosen in the studies presented in chapters 4 and 5. This classification is more stable and characterizes subjects with a common experience of displacement. Additionally, knowing the year of arrival, it permits to subclassify the subjects according to their immigration history, i.e., the length of stay and age at

arrival of immigrant people. On second-generation other hand, the immigrants have been classified as "non-immigrants", and the Italian citizens born abroad have been classified as immigrants. However, since the study is conducted on adult subjects (>20 years), and the immigration process to Italy is relatively recent, the number of second-generation immigrants not included in the immigrant group is limited.

5. **Socioeconomic status partially explains the high HF morbidity of immigrants.**

As mentioned above, different economic resources might give access to more timely private services, and different levels of education could affect people's approaches to managing their health problems. In fact, the adjustment for socioeconomic status reduces the health disparities between foreign citizens and Italians.
On the other hand, we found that adjusting the results for socioeconomic factors, the disparities persist, possibly related to genetic differences, lifestyle habits, influence of the time spent in the country of origin, immigration history, and psychosocial stress. Health professionals should receive adequate training on the peculiarities and specific health needs of these categories. In this sense, the multidisciplinary courses and seminars implemented by scientific societies such as the Italian Society for Medicine of migration (SIMM) or the Italian Association for Epidemiology (AIE), aiming at wide spreading the current evidence on immigrants' health and best practices related to the care of immigrants, are useful instruments that should also be offered also to PC practitioners (200,201).

6. **Some immigrants are at higher risk of increased cholesterol levels, and interventions should act on this. In addition, interventions to reduce the average higher BMI of immigrants are the most effective to prevent the development of hypertension.**

As already said, many interventions in primary care settings have been shown to be effective for the early prevention of cardiovascular disease, both with advices on nutritional advice and the promotion of a physically active lifestyle. These strategies can also be implemented with certain categories of immigrants, who are at increased risk of high lipid levels or high BMI due to genetic predisposition, different lifestyle habits, or less awareness of health risks. As an example, a large weight control and physical activity intervention in South Asian individuals in the United Kingdom (UK) has shown that modest medium-term changes in weight are achievable as a component of lifestyle change strategies, which could control or prevent adiposity-related diseases (197).
As mentioned in paragraph 1.6, raising awareness on prevention, or on health problems that are still silent and do not recognized as needs is challenging, especially for subjects with a different cultural background. Immigrants may generally have a more 'utilitarian' concept of health, associated with the ability to work (71). However, an attempt should be made, and it has been shown that acculturation brings about a pattern of health care utilization more similar to native-born population (72).

7. **Immigrants have some health advantages that should be preserved, acting on modifiable factors. This is particularly important in light of the ageing of the population.**

Along with the widely discussed healthy migrant effect, it has been shown in chapter 5 that in our population, a health advantage in BP levels for immigrants compared to natives would appear by

acting on modifiable factors. The most effective modifiable risk factors identified were BMI, the alcohol consumption, and level of education.
This is particularly important in light of the fact that the ageing of the immigrant population could lead to a loss of the health advantage, and an increase in rates of hypertension and other CV diseases.
The health profile of ageing immigrants may be worse than those of their native counterparts, due to exposure to different contextual risk factors. Their health condition is complicated by the influx of exposures during the lifetime and by lack of appropriate preventive care and medical treatment during migration and in the hosting country. Other cultural, contextual, and individual factors such as dietary practises or physical activity patterns, experience of discrimination and segregation, and language barriers (more common among ageing immigrants) may influence their health needs. Furthermore, competing priorities within extended family networks can reduce involvement in health promotion activities and negatively affect the ability to cope with disease. Responsibilities for the well-being of extended families and preferences for upholding care within families may negatively affect the ability to maintain health and to seek healthcare if symptoms arise. Financial obligations through sending remittances to family members in the country of origin may be an additional responsibility (56).
All these things considered, the health of ageing immigrants might be a complex challenge for the Italian health system in the future years. An investment first in their health advantage and then in ensuring a healthy ageing might be useful to prevent a higher burden of disease.

8. Acculturation leads to a convergence towards the epidemiological profile of the host population, which depends on the starting condition of the immigrant group.

In chapter 4, two opposite trends were evident: on the one hand, once in the host country, immigrants could be less aware of the health risks of some westernized habits. Therefore, they should receive health promotion advice on how to preserve their health advantage. On the other hand, some immigrants can benefit from the acculturation process when unhealthy habits are widespread in the country of origin.
Only one paper in this dissertation could account for acculturation in the presentation of the results. As previously mentioned, this information is often hard to obtain in administrative health records. To our knowledge, no studies have been proposed to study the differential rates of AH among immigrants according to their length of stay in the host country. Two hypotheses could be made on the trends of AH rates according to the length of stay: on the one hand, the healthy migrant effect would be reduced with a longer stay, with an increasing prevalence of the disease and, consequently, the AH rates. On the other hand, the acculturation process could bring about a deeper understanding of the available PC services and to a higher sensibility toward the prevention, reducing the risk of AH (72). Furthermore, as previously stated, citizenship (as a proxy of immigrant status) is not a suitable criterion to explore differences related to acculturation. In chapters 2 and 3 immigrants with a longer stay in Italy have been misclassified as 'non-immigrants' once they obtained Italian citizenship, and thus would have biased any result regarding the relationship between acculturation and length of stay.

9. Irregular immigrants might be at higher risk for some of the outcomes analyzed in this dissertation.

The works included in this dissertation do not provide any information on irregular immigrants. Anyway, the fact that the inequalities found in these works partially depend on the different

primary care access and quality suggests that the inequalities might be even higher for the irregular immigrants, as they do not even have the right of access to primary care services unless a life-threatening chronic disease is diagnosed. An aforementioned recent article on AH among regular and irregular immigrants confirmed this hypothesis, although there are no data on the disaggregated AH conditions and no comparisons on the specific CV outcomes (13). Another study indirectly confirmed this hypothesis, showing that the healthcare associated costs for undocumented diabetic immigrants are higher than for resident immigrants, because they are associated with more expensive interventions such as more urgent hospital admissions, more preventable complications, and a higher recurrence in terms of access to hospital services rather than drugs (202). In addition, in a voluntary outpatient clinic in Rome, BP levels have been found to be higher in homeless than in housed people, and in people without a residence permit compared to individuals with regular legal status (203). Although the results cannot be generalizable to the population outside the studies, the work shows that immigrants with extreme living conditions and with irregular stay have a worse control of the clinical CV parameters compared to documented and more stable immigrants. The last work also raises the attention on the essential role played by the charitable associations for the hard-to-reach groups, mainly for chronic conditions that need constant follow up. Some recent works confirmed this evidence, showing how a voluntary outpatient clinic reached a 74% attendance to the second diabetic visit for undocumented immigrants (201), and that the CV health needs of this vulnerable population in voluntary outpatient clinics are increasing (200). As previously stated, most of the evidence on undocumented immigrants is based on monocentric studies and is not generalizable but still are examples of good practices and should be collected and disseminated in dedicated congresses (200) to be implemented also elsewhere.

10. **Italy has turned into a multiethnic society, and there is a need for more analyses assessing health issues of new residents and the correct measures to address these needs.**

"One way to treat people with dignity is to understand and respond to health problems caused by their migrant status. These papers are a step in that direction"
Sir Michael Marmot, EUR J EPID, 2016

Appendix A

Avoidable hospitalisation for diabetes mellitus among immigrants and natives: Results from the Italian Network for Longitudinal Metropolitan Studies

Table A.1 Rate ratios and 95% confidence interval for each cohort overall and for geographical area

		Males			Females			Total		
Cohort	immigrant status	RR	95% CI		RR	95% CI		RR	95% CI	
			LI	UI		LI	UI		LI	UI
Turin	ITALIAN	1.00			1.00			1.00		
	HMPC	1.52	1.19	1.94	0.70	0.45	1.10	1.23	0.99	1.51
	CE Europe	0.72	0.44	1.16	0.53	0.27	1.04	0.65	0.44	0.95
	N Africa	2.82	2.01	3.97	1.44	0.64	3.24	2.47	1.81	3.38
	SS Africa	1.74	0.86	3.51	1.05	0.26	4.23	1.57	0.84	2.94
	CS America	2.07	1.14	3.78	0.60	0.19	1.87	1.37	0.81	2.33
	Asia	1.31	0.65	2.63	0.61	0.15	2.44	1.06	0.57	1.98
Venice	ITALIAN	1.00			1.00			1.00		
	HMPC	1.42	1.04	1.95	0.26	0.11	0.58	0.92	0.69	1.23
	CE Europe	0.70	0.37	1.31	0.06	0.01	0.45	0.35	0.19	0.64
	N Africa	1.36	0.44	4.25	0.00	0.00	.	1.14	0.37	3.56
	SS Africa	3.08	1.37	6.92	0.00	0.00	.	2.57	1.15	5.76
	America	0.00	0.00	.	0.58	0.08	4.14	0.38	0.05	2.74
	Asia	2.15	1.43	3.22	0.87	0.32	2.37	1.82	1.25	2.64
Reggio Emilia	ITALIAN	1.00			1.00			1.00		
	HMPC	1.82	1.29	2.58	2.04	1.33	3.12	1.87	1.43	2.45
	CE Europe	0.29	0.07	1.19	1.30	0.68	2.50	0.81	0.46	1.42
	N Africa	3.36	2.20	5.14	3.18	1.45	6.99	3.36	2.30	4.89
	SS Africa	2.96	1.63	5.39	6.15	2.98	12.67	3.87	2.44	6.14
	America	0.00	0.00	.	2.09	0.51	8.57	1.24	0.31	5.02
	Asia	0.69	0.22	2.16	1.11	0.35	3.56	0.84	0.37	1.90
Modena	ITALIAN	1.00			1.00			1.00		
	HMPC	3.08	2.21	4.31	2.92	1.97	4.32	2.95	2.29	3.81
	CE Europe	0.70	0.26	1.90	1.44	0.74	2.80	1.05	0.60	1.81
	N Africa	4.99	3.12	7.99	2.58	0.94	7.10	4.31	2.83	6.56
	SS Africa	4.02	2.22	7.27	6.31	3.19	12.49	4.85	3.10	7.59
	America	3.83	0.94	15.58	13.94	7.16	27.14	9.66	5.36	17.42
	Asia	3.67	2.02	6.68	1.83	0.67	5.01	2.93	1.76	4.89
Bologna	ITALIAN	1.00			1.00			1.00		
	HMPC	1.71	1.34	2.18	1.89	1.45	2.47	1.77	1.48	2.12
	CE Europe	1.45	0.91	2.28	1.03	0.66	1.59	1.16	0.84	1.59
	N Africa	2.13	1.30	3.48	7.59	4.73	12.19	3.46	2.46	4.86
	SS Africa	1.32	0.49	3.54	4.46	2.36	8.43	2.67	1.56	4.55
	America	1.87	0.70	5.02	1.16	0.37	3.63	1.47	0.70	3.11
	Asia	1.76	1.26	2.47	1.88	1.19	2.98	1.80	1.37	2.36
Rome	ITALIAN	1.00			1.00			1.00		
	HMPC	0.97	0.86	1.09	0.77	0.66	0.91	0.89	0.81	0.98
	CE Europe	0.84	0.66	1.07	0.65	0.48	0.88	0.74	0.61	0.89
	N Africa	1.45	1.11	1.88	1.25	0.69	2.26	1.44	1.13	1.83
	SS Africa	0.99	0.71	1.39	1.03	0.65	1.61	1.00	0.77	1.31
	America	0.68	0.47	0.99	0.52	0.34	0.80	0.60	0.45	0.79
	Asia	0.99	0.82	1.20	0.93	0.72	1.21	0.97	0.83	1.13

CI: confidence interval LI: lower limit, UI: upper limit

Appendix B

Avoidable hospitalization for heart failure among a cohort of 18- to 64-year-old Italian citizens and immigrants. Results from the Italian network for longitudinal metropolitan studies

Table B.1 Rate ratios and 95% confidence interval for each cohort overall and for geographical area

		Males			Females			Total		
Cohort	immigrant status	RR	95% CI		RR	95% CI		RR	95% CI	
			LI	UI		LI	UI		LI	UI
Turin	ITALIAN	1.00			1.00			1.00		
	HMPC	1.33	1.06	1.67	1.06	0.75	1.49	1.24	1.02	1.50
	CE Europe	1.49	1.10	2.03	0.76	0.44	1.31	1.22	0.93	1.59
	N Africa	1.37	0.88	2.12	1.53	0.72	3.24	1.40	0.96	2.05
	SS Africa	3.07	1.86	5.06	3.25	1.34	7.91	3.11	2.01	4.81
	CS America	0.15	0.02	1.04	1.37	0.68	2.76	0.71	0.37	1.37
	Asia	0.52	0.20	1.40	0.53	0.13	2.12	0.53	0.24	1.17
Venice	ITALIAN	1.00			1.00			1.00		
	HMPC	1.63	1.11	2.37	0.65	0.31	1.34	1.23	0.88	1.73
	CE Europe	1.27	0.71	2.27	0.32	0.10	1.01	0.79	0.47	1.33
	N Africa	0.00			0.00			0.00		
	SS Africa	1.85	0.46	7.45	0.00			1.59	0.39	6.40
	CS America	0.00			1.32	0.18	9.46	0.78	0.11	5.59
	Asia	2.54	1.54	4.18	2.11	0.77	5.80	2.43	1.55	3.80
Reggio Emilia	ITALIAN	1.00			1.00			1.00		
	HMPC	1.23	0.82	1.84	3.57	2.28	5.59	2.07	1.57	2.72
	CE Europe	0.86	0.38	1.95	1.22	0.61	2.46	1.04	0.62	1.73
	N Africa	1.14	0.58	2.26	18.44	11.43	29.76	4.89	3.45	6.91
	SS Africa	3.26	1.79	5.95	2.21	0.52	9.32	3.18	1.82	5.57
	CS America	0.00			0.00			0.00		
	Asia	0.46	0.11	1.86	0.42	0.06	3.07	0.46	0.15	1.44
Modena	ITALIAN	1.00			1.00			1.00		
	HMPC	1.08	0.67	1.75	0.94	0.54	1.63	1.02	0.71	1.46
	CE Europe	1.03	0.45	2.34	0.81	0.39	1.68	0.91	0.53	1.57
	N Africa	0.88	0.32	2.38	1.30	0.32	5.30	0.96	0.43	2.17
	SS Africa	2.05	0.90	4.68	2.56	0.79	8.24	2.16	1.10	4.25
	CS America	0.00			0.00			0.00		
	Asia	0.83	0.26	2.60	0.77	0.19	3.15	0.80	0.33	1.95
Bologna	ITALIAN	1.00			1.00			1.00		
	HMPC	1.30	0.90	1.86	1.99	1.39	2.85	1.57	1.22	2.02
	CE Europe	1.51	0.82	2.78	2.35	1.52	3.61	1.91	1.36	2.69
	N Africa	1.40	0.62	3.16	2.50	0.79	7.88	1.67	0.86	3.24
	SS Africa	2.16	0.69	6.75	1.98	0.49	8.00	2.11	0.87	5.11
	CS America	0.00			1.54	0.38	6.24	0.81	0.20	3.24
	Asia	1.14	0.65	2.00	1.22	0.54	2.77	1.18	0.74	1.87
Rome	ITALIAN	1.00			1.00			1.00		
	HMPC	0.94	0.83	1.06	0.80	0.66	0.96	0.89	0.80	0.99
	CE Europe	1.20	0.97	1.50	0.75	0.55	1.02	1.00	0.84	1.20
	N Africa	1.25	0.94	1.65	1.67	0.92	3.03	1.31	1.02	1.69
	SS Africa	0.78	0.54	1.14	1.96	1.33	2.89	1.10	0.84	1.44
	CS America	0.20	0.10	0.40	0.68	0.44	1.05	0.41	0.28	0.59
	Asia	0.98	0.81	1.18	0.50	0.34	0.75	0.83	0.70	0.99

CI: confidence interval LI: lower limit, UI: upper limit

Table B.2 Number of avoidable hospitalizations for heart failure (n_ric), person-years (PYs), Rate ratios and 95% confidence Intervals by immigrant status, cohort and sex, without adjustment and adjusted for Index of Deprivation (ID)

		MALES								FEMALES								OVERALL					
Cohort	Citt	n_ric	PY	Without adjustment for ID			Adjusted for ID			n_ric	PY	Without adjustment for ID			Adjusted for ID			n_ric	PY	Without adjustment for ID			Adjusted for ID		
				RR	LI	UI	RR	LI	UI			RR	LI	UI	RR	LI	UI			RR	LI	UI	RR	LI	UI
Turin	ITALY	1349	2927428							666	2971798							2015	5899226						
	HMPC	88	402202	1.33	1.06	1.68	1.15	0.91	1.45	36	403308	1.07	0.76	1.52	0.95	0.67	1.35	124	805510	1.24	1.03	1.50	1.08	0.89	1.31
	CE Europe	46	201278	1.50	1.10	2.04	1.35	1.00	1.84	14	225092	0.77	0.45	1.33	0.71	0.42	1.22	60	426370	1.23	0.94	1.60	1.11	0.85	1.45
	N Africa	21	93717	1.36	0.88	2.12	1.07	0.69	1.66	7	52770	1.55	0.73	3.29	1.18	0.56	2.51	28	146487	1.40	0.96	2.05	1.09	0.74	1.59
	SS Africa	16	29354	3.07	1.86	5.07	2.45	1.48	4.05	5	27178	3.29	1.35	8.00	2.71	1.11	6.61	21	56533	3.12	2.02	4.83	2.49	1.61	3.86
	CS America	1	37078	0.15	0.02	1.04	0.14	0.02	0.96	8	60150	1.38	0.68	2.78	1.28	0.63	2.58	9	97228	0.71	0.37	1.37	0.66	0.34	1.28
	Asia	4	40774	0.53	0.20	1.41	0.46	0.17	1.23	2	38118	0.53	0.13	2.15	0.48	0.12	1.93	6	78892	0.53	0.24	1.18	0.46	0.21	1.04
Venice	ITALY	685	1017865							246	1021715							931	2039580						
	HMPC	29	101866	1.61	1.09	2.37	1.57	1.07	2.32	8	111120	0.68	0.33	1.40	0.68	0.33	1.40	37	212986	1.24	0.88	1.74	1.22	0.87	1.72
	CE Europe	10	43423	1.13	0.60	2.14	1.09	0.58	2.06	3	69194	0.34	0.11	1.07	0.33	0.11	1.06	13	112617	0.73	0.42	1.27	0.72	0.41	1.25
	N Africa	0	6363	0.00	0.00	.	0.00	0.00	.	0	2886	0.00	0.00	.	0.00	0.00	.	0	9249	0.00	0.00	.	0.00	0.00	.
	SS Africa	2	5792	1.98	0.49	7.97	1.85	0.46	7.47	0	2714	0.00	0.00	.	0.00	0.00	.	2	8506	1.69	0.42	6.81	1.61	0.40	6.48
	CS America	0	3145	0.00	0.00	.	0.00	0.00	.	1	8547	1.38	0.19	9.90	1.37	0.19	9.83	1	11692	0.83	0.12	5.90	0.83	0.12	5.94
	Asia	17	43143	2.65	1.61	4.36	2.67	1.62	4.39	4	27780	2.16	0.79	5.95	2.16	0.79	5.95	21	70922	2.53	1.62	3.96	2.54	1.62	3.97
Reggio Emilia	ITALY	349	525937							127	525983							476	1051920						
	HMPC	18	71136	1.05	0.64	1.72	0.99	0.60	1.63	46	68791	5.11	3.26	8.00	3.75	2.31	6.08	64	139927	2.44	1.83	3.27	2.17	1.61	2.92
	CE Europe	5	21662	0.97	0.40	2.39	0.94	0.38	2.31	9	29889	1.70	0.80	3.60	1.54	0.72	3.28	14	51551	1.29	0.74	2.24	1.20	0.69	2.10
	N Africa	8	20765	1.40	0.68	2.88	1.32	0.64	2.71	34	11795	23.38	14.29	38.24	16.62	9.77	28.26	42	32561	6.41	4.51	9.11	5.57	3.89	7.97
	SS Africa	4	13281	1.41	0.52	3.86	1.31	0.48	3.60	2	9844	2.99	0.70	12.72	2.25	0.52	9.75	6	23125	1.76	0.77	4.02	1.50	0.65	3.44
	CS America	0	2181	0.00	0.00	.	0.00	0.00	.	0	4609	0.00	0.00	.	0.00	0.00	.	0	6790	0.00	0.00	.	0.00	0.00	.
	Asia	1	13246	0.32	0.05	2.32	0.31	0.04	2.20	1	12654	0.71	0.10	5.21	0.58	0.08	4.26	2	25900	0.45	0.11	1.83	0.41	0.10	1.64
Modena	ITALY	374	606019							204	618376							578	1224395						
	HMPC	16	62170	1.18	0.70	1.98	1.10	0.66	1.86	13	64075	1.27	0.71	2.28	1.19	0.66	2.14	29	126245	1.22	0.83	1.80	1.13	0.77	1.67
	CE Europe	5	20155	1.13	0.46	2.76	1.08	0.44	2.64	6	29524	1.03	0.45	2.36	1.00	0.43	2.30	11	49679	1.09	0.59	2.00	1.04	0.57	1.92
	N Africa	3	16140	0.86	0.27	2.70	0.77	0.24	2.44	2	8943	1.90	0.46	7.74	1.61	0.39	6.59	5	25083	1.09	0.45	2.65	0.95	0.39	2.31
	SS Africa	6	13539	2.60	1.13	5.94	2.36	1.03	5.42	3	10547	3.76	1.16	12.15	3.24	1.00	10.50	9	24086	2.87	1.46	5.65	2.54	1.29	5.01
	CS America	0	1875	0.00	0.00	.	0.00	0.00	.	0	3982	0.00	0.00	.	0.00	0.00	.	0	5857	0.00	0.00	.	0.00	0.00	.

	Asia	2	10461	0.72	0.18	2.90	0.69	0.17	2.78	2	11079	1.05	0.26	4.27	0.97	0.24	3.93	4	21540	0.85	0.32	2.29	0.80	0.30	2.15
Bologna	ITALY	578	1195741							338	1249142							916	2444883						
	HMPC	24	98568	1.43	0.94	2.17	1.30	0.86	1.99	20	105779	1.39	0.87	2.22	1.33	0.84	2.13	44	204348	1.41	1.03	1.92	1.31	0.96	1.80
	CE Europe	7	25225	1.66	0.78	3.53	1.53	0.72	3.25	10	46015	1.34	0.70	2.55	1.31	0.69	2.50	17	71240	1.46	0.89	2.39	1.40	0.86	2.29
	N Africa	3	14942	1.07	0.34	3.34	0.86	0.27	2.69	3	8599	3.04	0.97	9.57	2.34	0.74	7.41	6	23541	1.57	0.70	3.52	1.25	0.56	2.81
	SS Africa	2	6217	2.29	0.57	9.22	2.01	0.50	8.11	1	6789	1.34	0.19	9.60	1.17	0.16	8.35	3	13006	1.86	0.60	5.79	1.62	0.52	5.06
	CS America	0	4243	0.00	0.00	.	0.00	0.00	.	2	7520	2.07	0.51	8.37	2.04	0.50	8.24	2	11763	1.17	0.29	4.70	1.13	0.28	4.56
	Asia	12	47942	1.47	0.82	2.64	1.41	0.79	2.51	4	36856	0.94	0.35	2.55	0.94	0.35	2.55	16	84798	1.28	0.78	2.12	1.24	0.75	2.04
Rome	ITALY	3594	8965172							1684	9471300							5278	18436472						
	HMPC	184	919999	0.83	0.71	0.96	0.81	0.70	0.94	88	1076060	0.73	0.59	0.92	0.78	0.63	0.97	272	1996058	0.73	0.59	0.92	0.79	0.70	0.90
	CE Europe	68	319458	1.17	0.91	1.49	1.12	0.88	1.43	34	448841	0.73	0.52	1.03	0.75	0.53	1.05	102	768298	0.96	0.79	1.18	0.95	0.78	1.16
	N Africa	16	92845	0.59	0.36	0.96	0.57	0.35	0.93	5	38043	1.19	0.49	2.87	1.20	0.50	2.90	21	130889	0.67	0.44	1.03	0.65	0.42	1.00
	SS Africa	17	69952	0.72	0.45	1.17	0.68	0.42	1.09	15	80382	1.68	1.01	2.81	1.78	1.07	2.97	32	150335	0.99	0.70	1.40	0.94	0.67	1.34
	CS America	7	96092	0.28	0.13	0.58	0.27	0.13	0.58	13	185202	0.62	0.36	1.07	0.66	0.38	1.14	20	281294	0.43	0.28	0.67	0.44	0.28	0.68
	Asia	76	341652	0.87	0.69	1.09	0.88	0.70	1.10	21	323591	0.54	0.35	0.83	0.60	0.39	0.92	97	665242	0.76	0.62	0.94	0.79	0.65	0.97

Table B.3 Random effect age- and calendar year-adjusted meta-analytic hospitalization rate ratios (reference: Italy), without adjustment and adjusted for Index of Deprivation (ID).

Geographical macro-area		Cohorts included	Without adjustment for ID			With adjustment for ID		
			RR (95% CI)	I^2	Cochran *p*-value	RR (95% CI)	I^2	Cochran *p*-value
HMPC overall	Males	All	1.19 (0.92-1.55)	75.4%	0.001	1.10 (0.87-1.39)	68.4%	0.007
	Females	All	1.31 (0.73-2.35)	91.8%	<0.001	1.20 (0.76-1.91)	86.3%	<0.001
	Total	All	1.29 (0.93-1.79)	88.5%	<0.001	1.21 (0.90-1.63)	88.8%	<0.001
CE Europe	Males	All	1.27 (1.07-1.51)	0.0%	0.766	1.20 (1.01-1.42)	0.0%	0.888
	Females	All	0.91 (0.64-1.28)	42.8%	0.12	0.87 (0.63-1.21)	36.5%	0.164
	Total	All	1.08 (0.92-1.28)	16.3%	0.309	1.02 (0.89-1.17)	0.0%	0.505
N Africa	Males	TO, RE, MO, BO, RM	1.00 (0.66-1.52)	45%	0.124	0.87 (0.63-1.22)	21%	0.282
	Females	TO, RE, MO, BO, RM	3.11 (0.73-13.16)	93.2%	<0.001	2.53 (0.67-9.50)	91.5%	<0.001
	Total	TO, RE, MO, BO, RM	1.62 (0.63-4.14)	94.5%	<0.001	1.38 (0.55-3.47)	94.1%	<0.001
SS Africa	Males	TO, RE, MO, BO, RM	1.74 (0.85-3.57)	79%	<0.001	1.54 (0.80-2.95)	74%	0.004
	Females	TO, RE, MO, BO, RM	2.16 (1.46-3.20)	0.0%	0.55	2.06 (1.40-3.05)	0%	0.813
	Total	TO, RE, MO, BO, RM	1.94 (1.08-3.48)	79%	<0.001	1.68 (1.01-2.81)	72%	0.006
CS America	Males	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.
	Females	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.
	Total	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.
Asia	Males	All	1.06 (0.61-1.85)	76%	0.001	1.04 (0.59-1.82)	77%	0.001
	Females	All	0.81 (0.50-1.32)	28%	0.222	0.80 (0.52-1.23)	17%	0.302
	Total	All	0.98 (0.58-1.67)	82%	<0.001	0.95 (0.56-1.61)	82%	<0.001

TO= Turin, VE= Venice, RE=Reggio Emilia, MO=Modena, BO= Bologna, RM=Rome. N.e.= not estimated.

Appendix C

Adult first-generation immigrants and cardiovascular risk factors in the Veneto Region, Northeast Italy

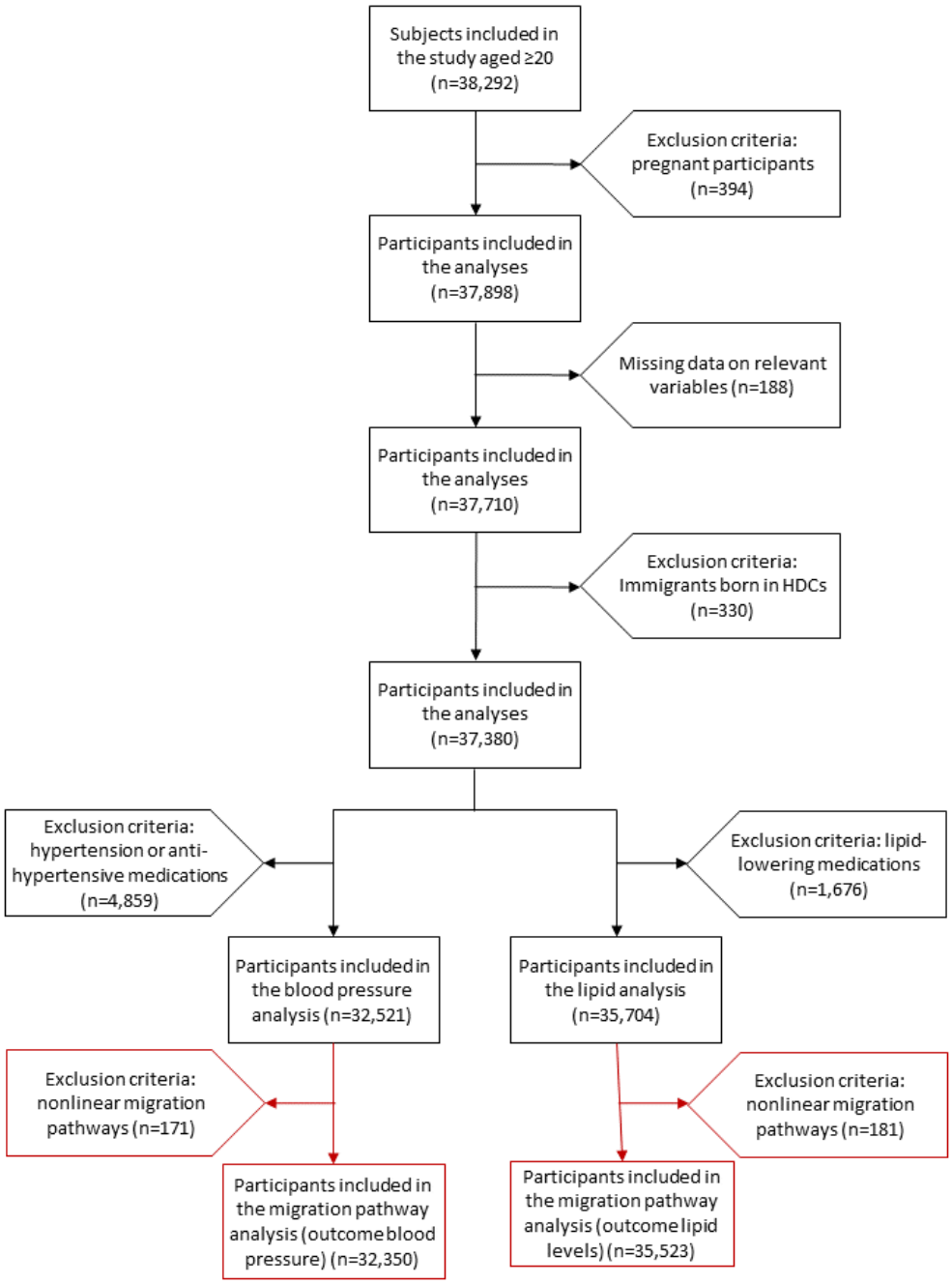

Figure C.1. Flowchart of participants included in the study

Table C.1. Characteristics of the included subjects by macro-area of origin

Characteristics (n=3066)		Asia (n=558)						North Africa (n=630)						CE Europe (n=1525)						Sub-Saharan Africa (n=185)						South America (n=168)					
		Total		Males		Females		Total		Males		Females		Total		Males		Females		Total		Males		Females		Total		Males		Females	
		Median (IQR)	*Min - Max*	*Median (IQR)*	*Min - Max*	*Median (IQR)*	*Min - Max*	*Median (IQR)*	*Min - Max*	*Median (IQR)*	*Min - Max*	*Median (IQR)*	*Min - Max*	*Median (IQR)*	*Min - Max*	*Median (IQR)*	*Min - Max*	*Median (IQR)*	*Min - Max*	*Median (IQR)*	*Min - Max*	*Median (IQR)*	*Min - Max*	*Median (IQR)*	*Min - Max*	*Median (IQR)*	*Min - Max*	*Median (IQR)*	*Min - Max*	*Median (IQR)*	*Min - Max*
Age (years)		39 (33-46)	20-65	41 (33-48)	20-64	38 (32-45)	20-65	41 (34-47)	20-66	43 (37-49)	20-65	39 (32-45)	20-66	40 (34-47)	20-66	41 (34-48)	20-66	40 (34-47)	20-66	40 (33-47)	20-61	43 (34-50)	21-61	38 (32-45)	20-56	41.5 (33-49)	20-65	40 (32-47)	21-62	42 (33-49)	20-65
Age at arrival (years)		26 (21-31)	0-55	25 (20-30)	0-55	26 (22-32)	0-55	24 (19-29)	0-49	25 (21-29)	0-43	23 (19-29)	0-49	24 (20-30)	0-55	25 (20-30)	0-53	24 (20-31)	0-55	26 (20-30)	0-40	25.5 (20-28)	0-47	15 (10-21)	2-49	23.5 (12-29)	0-48	20 (9-26)	0-47	24 (17-30)	0-48
Length of Stay in Italy (years)		13 (10-18)	1-56	16 (11-20)	1-56	11 (8-15)	1-50	17 (12-21)	1-60	18 (13-22)	1-50	15 (11-20)	1-60	16 (12-19)	0-59	17 (13-21)	0-41	15 (12-18)	1-59	26 (20-29)	0-47	16 (10-25)	2-46	14 (9-19)	2-49	18 (13-26)	3-60	19 (15-28)	8-60	17 (12-24)	3-46
% of life spent in Italy (years %)		34.9 (25.0-43.9)	2.6-100	40 (31.3-47.5)	2.6-100	30 (21.8-38.1)	4.6-100	40.9 (31.3-51.9)	3.1-100	43.2 (32.8-53.7)	3.1-100	39.2 (30-50)	4.6-100	38.7 (30.6-47.1)	0-100	40.9 (32.8-50)	0-100	37.7 (29.4-46.2)	3.7-100	37.5 (27.6-50)	5.7-100	39.0 (28.1-50.9)	5.7-100	37.0 (26.3-44.7)	7.8-100	44.7 (33.3-64.4)	7.7-100	51.2 (37.5-71.8)	23.0-100	41.2 (31.8-58.8)	7.7-100
		N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
BMI	Normal weight	251	45.0%	121	44.5%	130	45.5%	248	39.4%	142	48.5%	106	31.5%	712	46.7%	150	28.5%	562	56.3%	76	41.1%	47	47.5%	29	33.7%	94	56.0%	17	36.2%	77	63.6%
	Overweight	215	38.5%	115	42.3%	100	35.0%	234	37.1%	111	37.9%	123	36.5%	527	34.6%	256	48.7%	271	27.1%	63	34.1%	35	35.4%	28	32.6%	51	30.4%	23	48.9%	28	23.1%
	Obese	92	16.5%	36	13.2%	56	19.6%	148	23.5%	40	13.7%	108	32.0%	286	18.8%	120	22.8%	166	16.6%	46	24.9%	17	17.2%	29	33.7%	23	13.7%	7	14.9%	16	13.2%
Smoking Habit	Non-smoker	470	84.2%	196	72.1%	274	95.8%	508	80.6%	181	61.8%	327	97.0%	845	55.4%	223	42.4%	622	62.3%	159	85.9%	76	76.8%	83	96.5%	115	68.5%	27	57.4%	88	72.7%
	Current-smoker	57	10.2%	48	17.6%	9	3.1%	67	10.6%	59	20.1%	8	2.4%	383	25.1%	150	28.5%	233	23.3%	14	7.6%	13	13.1%	1	1.2%	28	16.7%	9	19.1%	19	15.7%
	Previous smoker	31	5.6%	28	10.3%	3	1.0%	55	8.7%	53	18.1%	2	0.6%	297	19.5%	153	29.1%	144	14.4%	12	6.5%	10	10.1%	2	2.3%	25	14.9%	11	23.4%	14	11.6%
Alcohol intake	None	397	71.1%	142	52.2%	255	89.2%	593	94.1%	266	90.8%	327	97.0%	482	31.6%	75	14.3%	407	40.7%	107	57.8%	53	53.5%	54	62.8%	49	29.2%	5	10.6%	44	36.4%
	1-2	85	15.2%	60	22.1%	25	8.7%	19	3.0%	14	4.8%	5	1.5%	544	35.7%	147	27.9%	397	39.7%	48	25.9%	24	24.2%	24	27.9%	58	34.5%	19	40.4%	39	32.2%
	3+	76	13.6%	70	25.7%	6	2.1%	18	2.9%	13	4.4%	5	1.5%	499	32.7%	304	57.8%	195	19.5%	30	16.2%	22	22.2%	8	9.3%	61	36.3%	23	48.9%	38	31.4%

Education	Elementary/ Middle	338	60.6 %	177	65.1 %	161	56.3 %	466	74.0 %	211	72.0 %	255	75.7 %	550	36.1 %	227	43.2 %	323	32.3 %	115	62.2 %	58	58.6 %	57	66.3 %	58	34.5 %	21	44.7 %	37	30.6 %
	Highschool	162	29.0 %	75	27.6 %	87	30.4 %	125	19.8 %	59	20.1 %	66	19.6 %	821	53.8 %	273	51.9 %	548	54.9 %	56	30.3 %	36	36.4 %	20	23.3 %	83	49.4 %	20	42.6 %	63	52.1 %
	University	58	10.4 %	20	7.4 %	38	13.3 %	39	6.2 %	23	7.8 %	16	4.7 %	154	10.1 %	26	4.9 %	128	12.8 %	14	7.6 %	5	5.1 %	9	10.5 %	27	16.1 %	6	12.8 %	21	17.4 %
Laboratory	Arzignano	398	71.3 %	203	74.6 %	195	68.2 %	258	41.0 %	128	43.7 %	130	38.6 %	982	64.4 %	361	68.6 %	621	62.2 %	107	57.8 %	62	62.6 %	45	52.3 %	89	53.0 %	23	48.9 %	66	54.5 %
	Legnago	121	21.7 %	53	19.5 %	68	23.8 %	197	31.3 %	90	30.7 %	107	31.8 %	303	19.9 %	107	20.3 %	196	19.6 %	41	22.2 %	24	24.2 %	17	19.8 %	50	29.8 %	17	36.2 %	33	27.3 %
	San Bonifacio	39	7.0 %	16	5.9 %	23	8.0 %	175	27.8 %	75	25.6 %	100	29.7 %	240	15.7 %	58	11.0 %	182	18.2 %	37	20.0 %	13	13.1 %	24	27.9 %	29	17.3 %	7	14.9 %	22	18.2 %
Age at arrival (years)	<18	78	14.0 %	45	16.5 %	33	11.5 %	124	19.7 %	53	18.1 %	71	21.1 %	217	14.2 %	90	17.1 %	127	12.7 %	26	14.1 %	15	15.2 %	11	12.8 %	50	29.8 %	19	40.4 %	31	25.6 %
	≥18	480	86.0 %	227	83.5 %	253	88.5 %	506	80.3 %	240	81.9 %	266	78.9 %	1308	85.8 %	436	82.9 %	872	87.3 %	159	85.9 %	84	84.8 %	75	87.2 %	118	70.2 %	28	59.6 %	90	74.4 %
Length of Stay in Italy (years)	0-9	133	23.8 %	45	16.5 %	88	30.8 %	81	12.9 %	25	8.5 %	56	16.6 %	181	11.9 %	38	7.2 %	143	14.3 %	45	24.3 %	22	22.2 %	23	26.7 %	18	10.7 %	1	2.1 %	17	14.0 %
	10-19	315	56.5 %	148	54.4 %	167	58.4 %	342	54.3 %	156	53.2 %	186	55.2 %	975	63.9 %	315	59.9 %	660	66.1 %	85	45.9 %	40	40.4 %	45	52.3 %	78	46.4 %	23	48.9 %	55	45.5 %
	20+	110	19.7 %	79	29.0 %	31	10.8 %	207	32.9 %	112	38.2 %	95	28.2 %	369	24.2 %	173	32.9 %	196	19.6 %	55	29.7 %	37	37.4 %	18	20.9 %	72	42.9 %	23	48.9 %	49	40.5 %
% of life spent in Italy (years %)	0%-24%	132	23.7 %	38	14.0 %	94	32.9 %	83	13.2 %	31	10.6 %	52	15.4 %	189	12.4 %	41	7.8 %	148	14.8 %	36	19.5 %	17	17.2 %	19	22.1 %	23	13.7 %	3	6.4 %	20	16.5 %
	25%-49%	351	62.9 %	184	67.6 %	167	58.4 %	363	57.6 %	169	57.7 %	194	57.6 %	1029	67.5 %	351	66.7 %	678	67.9 %	102	55.1 %	54	54.5 %	48	55.8 %	73	43.5 %	17	36.2 %	56	46.3 %
	≥50%	75	13.4 %	50	18.4 %	25	8.7 %	184	29.2 %	93	31.7 %	91	27.0 %	307	20.1 %	134	25.5 %	173	17.3 %	47	25.4 %	28	28.3 %	19	22.1 %	72	42.9 %	27	57.4 %	45	37.2 %

Table C.2. Prevalence ratio (PR) for hypertension, basic- and full-adjusted models, overall and stratified by sex

	HYPERTENSION					
	TOTAL		MALES		FEMALES	
	Basic-adj PR (95% CI)	Full-adj PR (95% CI)	Basic-adj PR (95% CI)	Full-adj PR (95% CI)	Basic-adj PR (95% CI)	Full-adj PR (95% CI)
Italy	1	1	1	1	1	1
HMPC overall	0.96 (0.88-1.06)	0.80 (0.72-0.88)	0.82 (0.73-0.93)	0.79 (0.69-0.90)	1.21 (1.06-1.38)	0.87 (0.75-1.00)
Central-Eastern Europe	1.10 (0.97-1.24)	0.88 (0.77-1.00)	1.05 (0.88-1.25)	0.84 (0.69-1.02)	1.19 (1.01-1.41)	0.95 (0.79-1.15)
Sub-Saharan Africa	1.42 (1.03-1.97)	1.12 (0.79-1.57)	0.92 (0.61-1.40)	0.94 (0.60-1.47)	2.93 (1.83-4.69)	1.61 (0.97-2.68)
Northern Africa	0.61 (0.49-0.75)	0.49 (0.39-0.61)	0.46 (0.34-0.61)	0.53 (0.39-0.72)	0.99 (0.72-1.35)	0.50 (0.36-0.70)
Asia	0.98 (0.79-1.21)	0.87 (0.70-1.09)	0.86 (0.66-1.12)	0.94 (0.71-1.24)	1.28 (0.93-1.77)	0.89 (0.63-1.26)
South America	0.86 (0.59-1.26)	0.78 (0.53-1.15)	0.74 (0.41-1.33)	0.66 (0.36-1.22)	0.99 (0.61-1.59)	0.87 (0.53-1.43)

Table C.3. Association between country of birth and TC and SBP in relation to duration of residence and age at migration, by macro-area of origin.

Variables of migratory pattern	TOTAL CHOLESTEROL								
	CE EUROPE			NORTH AFRICA			ASIA		
Age at arrival	β	95% CI		β	95% CI		β	95% CI	
Italy	141.01			141.10			141.34		
HMPC with <18 yo at arrival	2.38	-2.07	6.83	-4.53	-10.40	1.35	2.14	-5.39	9.67
HMPC with >18 yo at arrival	4.27	2.38	6.16	-7.88	-10.94	-4.83	0.74	-2.37	3.86
Lenght of stay									
Italy	140.80			141.20			141.25		
HMPC from >20 years in Italy	-0.55	-4.08	2.98	-5.64	-10.31	-0.97	-3.77	-10.15	2.62
HMPC from 10-19 years in Italy	5.27	3.12	7.43	-7.80	-11.44	-4.16	1.58	-2.22	5.39
HMPC from <10 years in Italy	5.96	1.07	10.86	-8.64	-15.94	-1.34	3.27	-2.48	9.02
Variables of migratory pattern	**SYSTOLIC BLOOD PRESSURE**								
	CE EUROPE			**NORTH AFRICA**			**ASIA**		
Age at arrival	β	95% CI		β	95% CI		β	95% CI	
Italy	108.40			108.46			108.38		
HMPC with <18 yo at arrival	-4.74	-6.55	-2.93	-2.72	-5.16	-0.28	-2.73	-5.79	0.32
HMPC with >18 yo at arrival	-0.75	-1.56	0.07	-1.03	-2.30	0.24	-0.75	-2.09	0.59
Lenght of stay									
Italy	108.24			108.43			108.41		
HMPC from >20 years in Italy	-2.12	-3.64	-0.60	-1.64	-3.61	0.34	-0.46	-3.30	2.37
HMPC from 10-19 years in Italy	-1.17	-2.09	-0.25	-1.40	-2.91	0.11	-0.09	-1.71	1.53
HMPC from <10 years in Italy	-1.17	-3.21	0.88	-0.64	-3.59	2.30	-3.63	-6.01	-1.25

Table C.4. Number and percentage of subjects from each country of birth in each macro-area of origin

CENTRAL-EASTERN EUROPE	**N**	**%**
ROMANIA	568	34,9%
ALBANIA	398	24,4%
SERBIA	277	17,0%
MOLDAVIA	125	7,7%
POLAND	64	3,9%
UKRAINE	43	2,6%
BULGARIA	37	2,3%
BOSNIA	36	2,2%
RUSSIA	14	0,9%
BELARUS	10	0,6%
SLOVAK REPUBLIC	10	0,6%
CROATIA	9	0,6%
HUNGARY	7	0,4%
CZECH REPUBLIC	6	0,4%
MACEDONIA	6	0,4%
YUGOSLAVIA	5	0,3%
LATVIA	3	0,2%
LITHUANIA	3	0,2%
KOSOVO	2	0,1%
SLOVENIA	2	0,1%
ESTONIA	1	0,1%
MONTENEGRO	1	0,1%
OTHER	1	0,1%
SUB-SAHARAN AFRICA	**N**	**%**
IVORY COAST	50	25,5%
SENEGAL	44	22,4%
NIGERIA	32	16,3%
GHANA	28	14,3%
ETHIOPIA	9	4,6%
BURKINA FASO	7	3,6%
GUINEA	4	2,0%
KENYA	3	1,5%
TOGO	3	1,5%
BURUNDI	2	1,0%
CHAD	2	1,0%
GUINEA BISSAU	2	1,0%
SOUTH AFRICA	2	1,0%
RWANDA	2	1,0%
CAMEROON	1	0,5%
CONGO	1	0,5%
GABON	1	0,5%
MADAGASCAR	1	0,5%
MALI	1	0,5%
ZAMBIA	1	0,5%
NORTHERN AFRICA	**N**	**%**

MOROCCO	630	96,6%
TUNISIA	10	1,5%
EGYPT	5	0,8%
ALGERIA	4	0,6%
LIBYA	3	0,5%
ASIA	**N**	**%**
INDIA	393	68,2%
BANGLADESH	100	17,4%
CHINA	43	7,5%
GEORGIA	14	2,4%
SRI LANKA	7	1,2%
LEBANON	3	0,5%
PHILIPPINES	2	0,3%
IRAN	2	0,3%
KAZAKHSTAN	2	0,3%
NEPAL	2	0,3%
SYRIA	2	0,3%
THAILAND	2	0,3%
ARMENIA	1	0,2%
KYRGYZSTAN	1	0,2%
PAKISTAN	1	0,2%
UZBEKISTAN	1	0,2%
CENTRAL-SOUTHERN AMERICA	**N**	**%**
BRAZIL	65	33,0%
ARGENTINA	40	20,3%
PERU	20	10,2%
COLOMBIA	12	6,1%
CUBA	12	6,1%
DOMINICAN REPUBLIC	12	6,1%
VENEZUELA	11	5,6%
GUATEMALA	6	3,0%
CHILE	5	2,5%
PARAGUAY	5	2,5%
MEXICO	3	1,5%
ECUADOR	2	1,0%
BOLIVIA	1	0,5%
COSTA RICA	1	0,5%
HONDURAS	1	0,5%
NICARAGUA	1	0,5%

Appendix D

Migrant status disparities in blood pressure: a multiple mediation analysis of modifiable factors

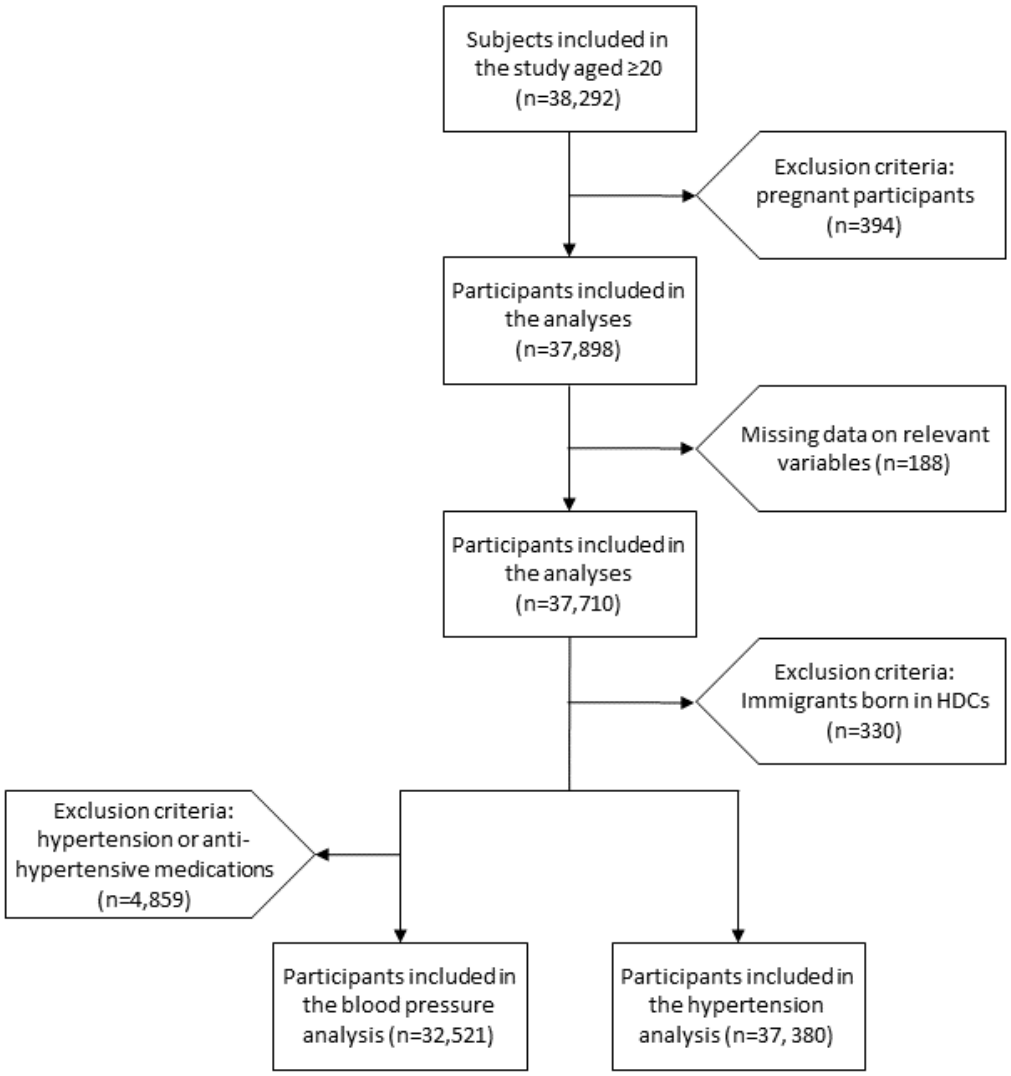

Figure D.1. Flowchart of the study population.

Table D.1. Characteristics of the subgroups by macro-area of origin: Asia, North Africa and Central-Eastern Europe

Characteristics		Asia (n=508)		North Africa (n=608)		CE Europe (n=1,426)	
Covariates							
continuous variables		*Mean (SD)*	*Min-Max*	*Mean (SD)*	*Min-Max*	*Mean (SD)*	*Min-Max*
Age (years)		38.3 (9.4)	20; 65	40.0 (9.2)	20; 64	39.3 (9.6)	20; 66
BMI (kg/m2)		25.5 (4.3)	16.0; 45.7	26.9 (4.6)	15.6; 52.6	25.5 (4.6)	15.6; 51.6
categorical variables		*N*	*%*	*N*	*%*	*N*	*%*
Sex	*Females*	271	53.3%	323	53.1%	951	66.7%
	Males	237	46.7%	285	46.9%	475	33.3%
BMI	*Normal weight*	243	47.8%	239	39.3%	727	51.0%
	Overweight	186	36.6%	224	36.8%	485	34.0%
	Obese	79	15.6%	145	23.8%	214	15.0%
Smoking Habit	*Non-smoker/Previous*	458	90.2%	544	89.5%	1058	74.2%
	Current-smoker	50	9.8%	64	10.5%	368	25.8%
Alcohol intake	*None*	364	71.7%	573	94.2%	426	29.9%
	1-2	79	15.6%	19	3.1%	541	37.9%
	3+	65	12.8%	16	2.6%	459	32.2%
Education	*Elementary/Middle*	305	60.0%	449	73.8%	497	34.9%
	Highschool	155	30.5%	121	19.9%	786	55.1%
	University	48	9.4%	38	6.3%	143	10.0%
salt	*Low*	116	22.8%	187	30.8%	423	29.7%
	Medium	357	70.3%	369	60.7%	856	60.0%
	High	35	6.9%	52	8.6%	147	10.3%
sweets	*1*	211	41.5%	213	35.0%	507	35.6%
	2	124	24.4%	171	28.1%	388	27.2%
	3	173	34.1%	224	36.8%	531	37.2%
meat	*1*	389	76.6%	263	43.3%	570	40.0%
	2	57	11.2%	94	15.5%	263	18.4%
	3	62	12.2%	251	41.3%	593	41.6%
Outcomes							
		Mean (SD)	*Min-Max*	*Mean (SD)*	*Min-Max*	*Mean (SD)*	*Min-Max*
systolic blood pressure		120.4 (15.2)	80; 220	121.7 (14.1)	80; 196	120 (14.5)	75; 185
diastolic blood pressure		76.2 (10.3)	50; 110	75.8 (9.6)	45; 104	76.3 (10.2)	45; 111
		Asia (n=576)		**North Africa (n=652)**		**CE Europe (n=1,628)**	
		N	*%*	*N*	*%*	*N*	*%*
hypertension prevalence (n=37,380)		127	22,0%	108	16,6%	380	23,3%

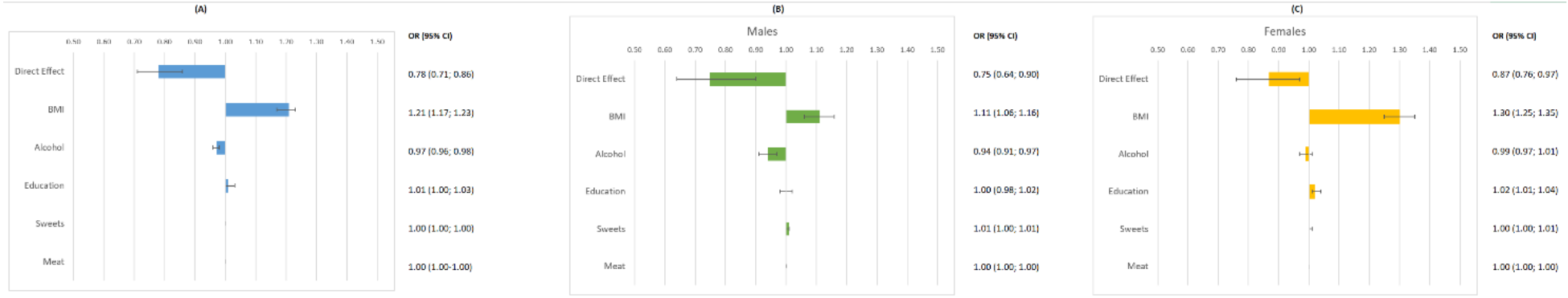

Figure D.2. Multiple mediation analysis for HMPC vs Italy, stratified by sex. ORs and corresponding 95% Confidence Intervals in all subjects (A), Males (B), and Females (C).

Table D.2. Sensitivity analysis: Multiple Mediation Analysis for HMPC vs Italy, all covariates included, stratified by sex

	Systolic Blood Pressure			Hypertension		
	Total β (95% CI)	**Males β (95% CI)**	**Females β (95% CI)**	**Total OR (95% CI)**	**Males OR (95% CI)**	**Females OR (95% CI)**
Total Effect	-0.6 (-1.24; 0.1)	-1.23 (-2.15; -0.57)	0.12 (-0.62; 0.85)	0.91 (0.80; 1.01)	0.79 (0.68; 0.90)	1.14 (1.00; 1.31)
Total Direct Effect	-1.53 (-2.1; -0.91)	-1.52 (-2.16; -0.95)	-1.25 (-2.00; -0.55)	0.78 (0.69; 0.85)	0.76 (0.64; 0.86)	0.88 (0.76; 1.01)
Total Indirect Effect	0.93 (0.69; 1.18)	0.29 (-0.19; 0.57)	1.37 (1.20; 1.57)	1.17 (1.12; 1.23)	1.05 (1.00; 1.10)	1.30 (1.22; 1.39)
BMI	1.22 (1.06; 1.32)	0.88 (0.50; 1.11)	1.61 (1.47; 1.78)	1.20 (1.16; 1.24)	1.12 (1.07; 1.16)	1.30 (1.24; 1.37)
Smoke	0.01 (-0.01; 0.03)	0.01 (-0.02; 0,04)	0.02 (0.00; 0.03)	1.00 (1.00; 1.00)	1.00 (1.00; 1.00)	1.00 (1.00; 1.00)
Alcohol	-0.30 (-0.41; -0.18)	-0.51 (-0.65; -0.35)	-0.21 (-0.29; -0.18)	0.97 (0.96; 0.99)	0.94 (0.92; 0.97)	0.99 (0.97; 1.00)
Education	0.10 (0.03; 0.17)	0.05 (-0.05; 0.07)	0.10 (0.00; 0.15)	1.01 (1.00; 1.03)	1.00 (0.98; 1.02)	1.02 (1.00; 1.04)
Salt	-0.05 (-0.09; 0.00)	-0.05 (-0.10; -0.03)	-0.04 (-0.17; 0.06)	0.99 (0.99; 1.00)	0.99 (0.98; 1.00)	0.99 (0.98; 1.01)
Sweets	-0.02 (-0.03; 0.01)	0.01 (-0.01; 0.03)	-0.06 (-0.10; 0.00)	1.00 (1.00; 1.00)	1.00 (1.00; 1.00)	1.00 (1.00; 1.00)
Meat	-0.02 (-0.03; 0.00)	-0.05 (-0.11; -0.01)	0.01 (-0.01; 0.04)	1.00 (1.00; 1.00)	1.00 (1.00; 1.00)	1.00 (1.00; 1.00)

(The sum of the percent explained effects of the individual mediators may not equal the total indirect effect because of correlation and overlapping mediation effects among mediators that is reflected in the total indirect effect but not the individual mediators)

Table D.3. Sensitivity analysis: Multiple Mediation Analysis for HMPC vs Italy, all covariates included, stratified by area of origin

	SYSTOLIC BLOOD PRESSURE (β 95% CI)			HYPERTENSION (OR 95% CI)		
	Asia vs Italy	**North Africa vs Italy**	**CE Europe vs Italy**	**Asia vs Italy**	**North Africa vs Italy**	**CE Europe vs Italy**
Total Effect	-1.01 (-2.52; 0.16)	-0.11 (-1.16; 0.91)	-0.82 (-1.47; -0.16)	0.97 (0.74; 1.18)	0.62 (0.53; 0.76)	1.00 (0.90; 1.11)
Total Direct Effect	-1.32 (-2.68; 0.07)	-1.62 (-2.71; -0.75)	-1.73 (-2.38; -1.09)	0.90 (0.68; 1.09)	0.47 (0.40; 0.59)	0.84 (0.76; 0.94)
Total Indirect Effect	0.31 (-0.34; 0.58)	1.51 (1.15; 2.06)	0.91 (0.66; 1.18)	1.08 (1.02; 1.15)	1.31 (1.21; 1.40)	1.19 (1.14; 1.22)
BMI	1.03 (0.66; 1.19)	2.12 (1.74; 2.53)	0.92 (0.69; 1.14)	1.15 (1.08; 1.21)	1.38 (1.28; 1.43)	1.18 (1.13; 1.22)
Smoke	0.04 (-0.01; 0.10)	0.03 (0.01; 0.08)	-0.01 (-0.02; 0.00)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)	1.00 (1.00; 1.00)
Alcohol	-0.51 (-0.67; -0.36)	-0.75 (-1.02; -0.48)	-0.05 (-0.08; -0.01)	0.96 (0.93; 1.00)	0.94 (0.91; 0.99)	0.99 (0.99; 1.00)
Education	0.15 (0.01; 0.24)	0.18 (0.02; 0.36)	0.04 (0.01; 0.08)	1.02 (1.00; 1.04)	1.02 (0.99; 1.05)	1.02 (1.01; 1.02)
Salt	-0.04 (-0.12; 0.03)	-0.04 (-0.11; 0.02)	-0.06 (-0.11; -0.01)	0.99 (0.98; 1.00)	0.99 (0.98; 1.00)	0.99 (0.98; 1.00)
Sweets	-0.05 (-0.1; -0.01)	0.00 (-0.04; 0.05)	-0.01 (-0.02; 0.02)	1.00 (1.00; 1.01)	1.00 (1.00; 1.01)	1.00 (1.00; 1.00)
Meat	-0.36 (-0.48; -0.23)	0.04 (0.00; 0.08)	0.06 (0.04; 0.1)	0.98 (0.96; 0.99)	1.00 (1.00; 1.01)	1.00 (1.00; 1.01)

(The sum of the percent explained effects of the individual mediators may not equal the total indirect effect because of correlation and overlapping mediation effects among mediators that is reflected in the total indirect effect but not the individual mediators)

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