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Contribution to the epidemiology of the metabolic syndrome in Luxembourg

Ala'a ALKERWI, MD

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Ala'a ALKERWI, MD

Supervisor

Professor M. Guillaume

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For the memory of my

FATHER AND MOTHER
For the uncompromising principles that guided their lives

For my beloved

HUSBAND
For his magnificent devotion to his family
CHILDREN
For making everything worthwhile

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Summary

The metabolic syndrome (MS) is a cardiometabolic complex cluster characterised by hyperinsulinaemia, low glucose tolerance, dyslipidaemia, hypertension and obesity. It represents a significant marker of increased risk for both cardiovascular disease and type 2 diabetes. To efficiently combat the forecasted type 2 diabetes epidemic and its cardiovascular and metabolic complications, evidence-based strategies focusing on target groups of the population at risk are needed to tailor prevention programs.

In this context, the overall aim of this thesis was to investigate, for the first time, the epidemiological profile of the MS, its variations and its potential socio-economic and behavioural determinants among the presumably healthy adult population residing in Luxembourg. Such data should offer new possibilities for successful intervention to prevent and treat the MS before the coronary heart disease and type 2 diabetes develop in susceptible individuals and groups.

This PhD thesis originated from joint collaboration between the Public Health Research Centre in Luxembourg (CRP-Santé), Centre for Health Studies, and public health research institutions and universities in other neighbouring countries, under the auspices of the Interreg IIIA authorities. Most research work was based on the ORISCAV-LUX study, the first nationwide, epidemiological survey aimed to observe the cardiovascular risk factors among adult residents in Luxembourg. The data collection took place between November 2007 and January 2009 under the auspices of the Ministry of Health and co-financed by the Ministry of Research.

The ORISCAV-LUX survey was performed according to the Declaration of Helsinki and was fully approved by the *Comité National d'Ethique de Recherche* and the *Commission Nationale pour la Protection des Données*. In a representative stratified random sample of 1432 subjects aged 18-69 years residing in Luxembourg, the research considered a range of demographic, socio-economic and behavioural factors, as well as anthropometric and biological markers of the MS. All participants answered a comprehensive questionnaire, had a physical and clinical examination and underwent blood sampling for cardiovascular risk profile evaluation.

The present dissertation comprises four major parts, Introduction, Research method, Results, and Discussion and Conclusion, which further sub-divide into ten chapters, most of which were published as papers in peer-reviewed journals.

The first part (Introduction) examines closely the relevant literature to demonstrate the scientific context and the state-of-the-art of the research topic, namely the metabolic syndrome. It is arranged into four chapters: the first three chapters examine in-depth the problematic of MS, as regards the historical development of the concept, the different definitions, the place of MS in CVD risk assessment and diabetes prediction, the clinical utility and relevance, and the evolution towards a new concept of global cardiometabolic risk. The fourth chapter highlights an insight about the worldwide epidemiology of the MS, in terms of prevalence variation, and determinants. As part of the initial literature review phase, a meta-analysis study was published aiming to support the evidence available regarding the relationship between alcohol consumption and the MS, as well as to identify the gender-specific dose-response.

The second part (Research method) describes the methodology to achieve the defined objectives. Chapter 5 details the ORISCAV-LUX study design, target population, sample planning, field work procedures, recruitment calendar, data collection stages, quality control measures, and survey response rate. The statistical analysis and the variables analysed are described in chapter 6.

The third part illustrates the research findings in four distinct chapters. Chapter 7 deals with the description of ORISCAV-LUX study population and sample representativeness. Alike, this part of work has been published in two separate articles. The first describes the rationale, objectives, method of recruitment and salient outcomes regarding the prevalence of potentially modifiable and

preventable cardiovascular risk factors. The findings revealed that dyslipidemia (69.9%), hypertension (34.5%), smoking (22.3%), obesity (20.9%), and diabetes (4.4%) were the most predominant cardiovascular risk factors. All prevalence rates increased with age (except smoking) with marked gender differences (except diabetes). Moreover, the multiple-risk profile was a more highly prevalent condition in men than in women, and even in younger age groups. In fact, these risk factors prepare the path to the clustering of metabolic disorder embraced under the descriptive term of MS. The second article addresses the ORISCAV-LUX study sample representativeness, a phenomenon which has become increasingly important when planning and performing epidemiological studies. It provides an insight regarding the strategies applied to increase response rate, sample representativeness and the characteristics of non participants. Basically, the 32.2% participation rate obtained represents the realistic achievable for this type of multiple-stage survey, and corresponds to the expected rate, upon which the sample size was calculated. In sum, this research demonstrated an absence of divergence in the known demographic and cardiovascular health-related profiles of participants and non-participants. This work also ensured the external validity of our findings and hence possible generalization of the results to the general population. In Chapter 8, the overall, gender- and age-specific prevalence rates of the MS among the Europid population residing in Luxembourg are described and were recently published in a research article. It deals with the problem of absence of unified standard criteria to define the MS. In spite of the current general consensus regarding the main components of the MS, namely glucose intolerance, obesity, raised blood pressure and dyslipidaemia (elevated TG, low levels of HDL-C), different cut-off points and different mandatory inclusion criteria are still debated by numerous groups and organizations. The lack of diagnostic concordance between different definitions led to confusion among researchers and hampered a relevant international comparison. Therefore we sought to determine the prevalence of the MS, according to different widely accepted criteria, taking as reference those most recently released by the joint Interim Statement (JIS). This definition suggests using ethnic and country-specific cut-off points for waist circumference (WC). Given the dual references for the Europid population (102/88 versus 94/80), the prevalence of MS was assessed solely among the European participants to ORISCAV-LUX survey (1349 individuals), according to both high and low WC thresholds (24.7% and 28% respectively). The estimated prevalence was found to be higher in men and to increase with advancing age, but varied only slightly according to the cut-off value adopted for waist circumference. Interestingly, though the MS prevalence was higher in men, the prevalence of abdominal obesity was higher in women for all

age strata, stressing the importance of high blood pressure and dyslipidemia in the determination of the syndrome. The appropriateness of suggested MS definitions, with particular emphasis on the WC thresholds to define the prevalence, was further addressed together with considerations regarding inter-definitions agreement. The Framingham Risk Score (FRS), to assess the association between MS and risk of coronary heart disease, was used as a surrogate for a longitudinal follow-up study.

The last two chapters of the thesis analyse the study outcomes with regard to the significant socio-economic and behavioural determinants of the MS in the studied population. Beside descriptive analyses, multivariate logistic regression models were developed to examine the independent impact of the socioeconomic and lifestyle factors on the odds of having the MS. Our models revealed that the likelihood of being diagnosed with the MS increased with age and was higher in men than in women, in subjects with family history of diabetes or hypertension, in those with primary level of education and who exhibit specific lifestyle behaviours, in particular, inactivity and inadequate protein intake. Ideally, such models are developed from an experimental or cohort longitudinal database and not from cross-sectional study. As a result, causal pathways underlying the observed associations between the lifestyle factors examined in this study and the MS need to be supported by further prospective data. From a public health point of view, it is important to monitor over time the lifestyle-related risk factors of subjects with the MS.

As part of this research work, two articles are currently underway. The first one basically aims at describing the socio-economic and behavioural variation in the prevalence of the MS and at exploring the potential determinants among the general resident population in Luxembourg. It highlights the importance of lifestyle and socioeconomic factors in shaping cardiovascular risk strategies. The second manuscript focuses principally on the nutritional aspect of the studied population. This work describes for the first time the dietary intake of the participants and aims to construct a European Diet Quality Index in order to assess the degree of adherence to the current national and European dietary guidelines.

In the final (Discussion and conclusion) part of this thesis, we reflect on the main findings of the previous chapters and discuss their implications for the adult cardiovascular disease prevention in Luxembourg.

Noteworthy is that the ORISCAV-LUX study is integrated into a cross-border survey, entitled "Nutrition, Environment and Cardiovascular Health (NESCAV)", joining together four neighbouring regions: Grand-Duchy of Luxembourg, Wallonia (Belgium), Lorraine (France) and Saarland (Germany). The NESCAV survey is based on a standardised monitoring method and collection tools that enable a relevant comparison between the four regions in terms of observation of cardiovascular health and lifestyles-related risk factors among the population of the Greater region. The study protocol has been published recently in an article focusing on the interregional context of ORISCAV-LUX survey.

The views expressed in this PhD thesis are those of the author and not necessarily those of the Directorate of Health (Ministry of Health) or the Centre for Health Studies.

Résumé

Le syndrome métabolique peut être défini comme un ensemble cardio-métabolique regroupant plusieurs facteurs de risques cardiovasculaires, à savoir hyperinsulinémie, intolérance au glucose, dyslipidémie, hypertension et obésité abdominale. Il représente un marqueur important de risque accru de maladies cardiovasculaires et de diabète de type 2. Pour combattre l'épidémie de diabète de type 2 et ses complications cardiovasculaires, des programmes de prévention appropriés sont indispensables. Pour ce faire, des stratégies fondées à partir d'arguments scientifiques validés et ciblant les groupes à risques de la population doivent être développés.

Dans ce contexte, l'objectif global investigué par la présente thèse, fût d'établir pour la première fois dans la population adulte résidante au Luxembourg, le profil épidémiologique du syndrome métabolique, ses variations et ses déterminants socio-économiques et de style de vie, Ces données devraient amener des enseignements nouveaux pour la planification d'interventions mieux adaptées aux besoins de cette population pour la prise en charge du syndrome métabolique et éviter que la maladie coronarienne et le diabète de type 2 ne se développent et ne s'installent.

Cette thèse s'inscrit dans le cadre d'une collaboration entre le Centre de Recherches Publiques en Santé au Luxembourg (CRP-Santé), Centre d'Études en Santé, et d'autres établissements publics de recherches en santé et universités des pays voisins, sous l'égide des autorités Interreg III A. Dans ce cadre interrégional, le Grand-Duché du Luxembourg a réalisé la première enquête épidémiologique nationale visant à observer les facteurs de risque cardiovasculaire chez les adultes résidant au Luxembourg, l'étude ORSCAV-LUX. La collecte des données a eu lieu entre novembre 2007 et janvier

2009 sous les auspices du Ministère de la Santé et cofinancée par le Ministère de la recherche. La présente thèse se base sur les données collectées dans ce cadre.

L'enquête ORISCAV-LUX a été effectuée conformément à la déclaration d'Helsinki et a été approuvée par le Comité national d'éthique et de recherches et de la Commission nationale pour la protection des données. A partir d'un échantillon représentatif aléatoire, stratifié, la recherche a examiné auprès de 1432 sujets âgés de 18 à 69 ans et résidant au Luxembourg, une série de facteurs démographiques, socio-économiques et de style de vie, ainsi que des marqueurs anthropométriques et biologiques du syndrome métabolique. Tous les participants ont d'une part, répondu à un questionnaire détaillé, d'autre part, passé un examen physique et clinique et enfin, ont subi des prélèvements sanguins pour l'évaluation du profil de risque cardiovasculaire.

La thèse se structure en quatre parties principales et dix chapitres, une introduction, une description de la méthode de recherches, l'exposé des résultats et enfin la présentation des interprétations et conclusions. La plupart des résultats présentés dans cette thèse ont fait l'objet de publications dans des revues scientifiques.

La première partie (Introduction) est consacrée à une synthèse de la revue de la littérature afin de définir le contexte scientifique cadrant le sujet de recherche, à savoir le syndrome métabolique. Cette partie est organisée en quatre chapitres. Les trois premiers chapitres examinent en profondeur la problématique en ce qui concerne l'évolution historique du concept, les différentes définitions, la place du syndrome métabolique dans l'évaluation du risque cardiovasculaire et sa capacité de prédire le diabète, son utilité et sa pertinence clinique, et l'évolution vers un nouveau concept « le risque cardio-métabolique global ». Le quatrième chapitre met en évidence un aperçu de l'épidémiologie du syndrome métabolique à l'échelle mondiale, en termes de variations de prévalence et de ses déterminants potentiels.

La deuxième partie (Méthodes de recherche) se décline en deux chapitres. Le premier décrit la méthodologie pour atteindre les objectifs fixés. Il détaille le plan de l'étude ORISCAV-LUX, la population cible, le plan de recrutement de l'échantillon, les procédures de travail sur le terrain, la planification des étapes de collectes de données, les mesures du contrôle de qualité, et le taux de réponses. L'analyse statistique et les variables analysées sont décrites dans le second chapitre de cette deuxième partie.

La troisième partie expose les résultats de la recherche qui sont organisés en quatre chapitres distincts. Le premier chapitre décrit la population étudiée et discute la

représentativité de l'échantillon. Cette partie des travaux a fait l'objet de deux articles scientifiques. Les objectifs, la méthode de recrutement et les principaux résultats concernant la prévalence des facteurs de risques cardiovasculaires potentiellement modifiables et évitables sont décrits. Les données ont révélé que la dyslipidémie (69.9%), l'hypertension (34.5%), le tabagisme (22.3%), l'obésité (20.9%), et le diabète (4.4%) sont les facteurs prédominants dans le risque cardiovasculaire de cette population. Les taux de prévalence de ces facteurs de risque augmentent avec l'âge (à l'exception de la consommation du tabac) avec des différences marquées entre les sexes (sauf pour le diabète). En outre, le profil à risque multiple apparaît plus fréquemment chez les hommes que chez les femmes, et dans les groupes d'âges plus jeunes. Ces facteurs de risque représentent les composants sous-jacents du trouble métabolique considéré sous le terme descriptif de syndrome métabolique. La représentativité de l'échantillon de l'étude ORISCAV-LUX a été étudiée en profondeur vu l'importance que ce phénomène représente dans la planification d'études épidémiologiques. Les stratégies utilisées pour augmenter le taux de réponse et les caractéristiques des non-répondants sont présentées. Le taux de participation obtenu (32.2%) constitue un taux réaliste, correspondant au taux attendu, à partir duquel la taille de l'échantillon a été calculée. Ce travail de recherche a démontré une absence de divergence dans le profil démographique cardiovasculaire des participants et des non-participants assurant ainsi la validité externe de nos résultats et, permettant leur généralisation à la population générale. Dans le chapitre suivant, les taux de prévalence du syndrome métabolique en fonction de l'âge et du sexe dans la population europoïde résidant au Luxembourg, sont décrits et ont récemment été publiés. Le problème de l'absence de critères standards pour définir le syndrome métabolique est exploré. Malgré le consensus général actuel en ce qui concerne les principales composantes du syndrome métabolique, à savoir l'intolérance au glucose, l'obésité abdominale, l'hypertension et la dyslipidémie (triglycérides élevées, niveau bas de HDL-C), différents seuils et différents critères d'inclusion sont proposés par de nombreux groupes et organisations. Le manque de concordance entre les différentes définitions a rendu délicates les comparaisons internationales. La prévalence du syndrome métabolique dans le présent travail a été évaluée selon la définition la plus récente, publiée par la Fédération Internationale du Diabète, *Joint Interim statement* (JIS.). Cette définition suggère d'utiliser le seuil pour le tour de taille, spécifique à chaque pays et groupe ethnique. Etant donné la double référence du tour de taille pour la population europoïde (102/88 versus 94/80), la prévalence du syndrome métabolique a été évaluée uniquement parmi les 1349 sujets européens participants à l'enquête ORISCAV-LUX, selon les deux seuils haut et bas. La prévalence ainsi obtenue est respectivement de 24.7% et 28% et est plus élevée chez les hommes que chez les femmes. Elle augmente significativement avec l'âge.

Bien que la prévalence du syndrome métabolique soit plus élevée chez les hommes, la prévalence de l'obésité abdominale était plus élevée chez les femmes et ce pour tous les groupes d'âge. Le choix d'une définition appropriée du syndrome métabolique en considérant le seuil proposé du tour de taille, a également été abordé. A cet effet, le score de risque de Framingham (FRS), a été utilisé pour évaluer l'association entre le syndrome métabolique et le risque de maladies coronariennes, comme une approche alternative à l'utilisation de données prospectives.

Les deux chapitres suivants analysent les résultats de l'étude relative aux déterminants socio-économiques et de style de vie du syndrome métabolique, dans la population étudiée. Les analyses descriptives et les modèles de régressions logistiques ont été utilisés pour examiner l'impact indépendant des facteurs socio-économiques et de mode de vie sur les risques de développer un syndrome métabolique. Notre modèle a révélé que la probabilité de développer un syndrome métabolique augmente avec l'âge et était plus élevée chez les hommes que chez les femmes ainsi que chez les sujets présentant des antécédents familiaux de diabète ou d'hypertension, chez ceux ayant un niveau d'enseignement primaire et qui présentent des habitudes de vie spécifiques, en particulier, l'inactivité physique et un apport inadéquat en protéines. Idéalement, ces modèles se développent à partir d'une base de données expérimentales ou de cohorte longitudinale et non pas à partir de données transversales. En conséquence, les relations causales qui sous tentent les associations observées entre les facteurs de risques et le syndrome métabolique devront être, dans une prochaine étape, confirmées à la lueur de données prospectives. D'un point de vue de santé publique, il est important de surveiller au fil du temps les facteurs de risque liés au mode de vie des sujets atteints du syndrome métabolique.

Dans le cadre de ce travail de recherche, deux articles sont actuellement en cours de préparation, le premier vise essentiellement à décrire la variation socio-économique et le style de vie de la prévalence du syndrome métabolique. Cet article souligne l'importance des facteurs socio-économiques et liés au mode de vie dans l'élaboration de stratégies de prévention du risque cardiovasculaire. Le deuxième manuscrit se concentre principalement sur l'aspect nutritionnel de la population étudiée, ce travail décrit pour la première fois, les apports alimentaires des participants et vise à construire un score européen de la qualité de l'alimentation afin d'évaluer le degré d'adhésion aux recommandations nutritionnelles nationales et européennes.

Dans la partie finale (Discussion et Conclusion) de cette thèse, à partir des principaux résultats des chapitres précédents, leur implication est discutée en termes de prévention des maladies cardiovasculaires au Luxembourg.

Il convient de noter que l'étude ORISCAV-LUX fait partie intégrante d'un programme interrégional intitulé « Nutrition, Environnement et Santé CArdio-Vasculaire (NESCAV) », réunissant quatre régions transfrontalières, le Grand-Duché du Luxembourg, la Wallonie (Belgique), la Lorraine (France) et la Sarre (Allemagne). L'enquête NESCAV est basée sur une méthode et des outils de collecte standardisés qui permettent une comparaison pertinente entre les quatre régions en matière d'observation de la santé cardiovasculaire et des facteurs de risque liés au mode de vie, parmi la population de la Grande Région. Le protocole de l'étude a été publié récemment dans un article mettant l'accent sur le contexte interrégional de l'enquête ORISCAV-LUX.

Les opinions exprimées dans cette thèse sont celles de l'auteur et pas nécessairement celles de la Direction de la Santé du Grand-Duché du Luxembourg (Ministère de la Santé) ou du Centre d'Etude en santé (CRP-Santé).

Zusammenfassung

Beim Metabolischen Syndrom handelt es sich um ein kardiometabolisches komplexes Cluster, das sich durch Hyperinsulinämie, niedrige Glukosetoleranz, Dyslipidämie, Bluthochdruck und Fettleibigkeit auszeichnet. Es wird als wichtiger Marker für ein erhöhtes Risiko für Herz-Kreislauf-Erkrankungen und Typ-2-Diabetes angesehen. Um effizient gegen die vorhergesagte Typ-2-Diabetes-Epidemie und deren kardiovaskulären und metabolischen Komplikationen anzugehen, sind wissenschaftlich fundierte Strategien erforderlich, die auf die diesbezüglich gefährdeten Bevölkerungsgruppen ausgerichtet sind und die Grundlage für Präventionsprogramme bilden.

In diesem Zusammenhang war es das primäre Ziel dieser Dissertation, erstmals das epidemiologische Profil des MS, seine Varianten sowie seine potenziellen sozioökonomischen und verhaltensspezifischen Determinanten in der vermeintlich gesunden, in Luxemburg lebenden Erwachsenenbevölkerung zu untersuchen. Die Ergebnisse dürften neue Möglichkeiten für eine erfolgreiche Vorbeugung und Behandlung des MS – bevor sich bei den disponierten Personen und Personengruppen koronare Herzerkrankungen und Typ-2-Diabetes entwickeln – schaffen.

Diese Dissertation, die unter der Federführung der zuständigen Interreg IIIA-Instanzen durchgeführt wurde, basiert auf einer Zusammenarbeit zwischen dem Forschungszentrum für Gesundheit in Luxemburg (CRP-Santé), Abteilung für Gesundheitsstudien sowie anderen, in den Nachbarländern befindlichen, öffentlichen Gesundheitsforschungseinrichtungen und Universitäten. Für einen Großteil der Forschungsarbeit wurde auf die ORISCAV-LUX-Studie zurückgegriffen, der ersten landesweiten epidemiologischen Untersuchung, die darauf abzielt, bei in Luxemburg

lebenden Erwachsenen die kardiovaskulären Risikofaktoren zu beobachten. Die Sammlung der Daten wurde zwischen November 2007 und Januar 2009 unter der Leitung des Gesundheitsministeriums und mit der finanziellen Unterstützung des Forschungsministeriums vorgenommen.

Die ORISCAV-LUX-Studie wurde im Einklang mit der Erklärung von Helsinki durchgeführt und vom Comité National d'Ethique de Recherche sowie von der Commission Nationale pour la Protection des Données in vollem Umfang genehmigt. Basierend auf einer repräsentativen, geschichteten Zufallsauswahl von 1432 in Luxemburg lebenden Personen im Alter zwischen 18 und 69 Jahren, betrachtete die Untersuchung sowohl eine Reihe demografischer, sozioökonomischer und verhaltensspezifischer Faktoren als auch anthropometrische und biologische Marker des MS. Alle Teilnehmer beantworteten dabei einen umfassenden Fragebogen und wurden einer körperlichen und klinischen Untersuchung unterzogen. Daneben wurde ihnen, mit Hinblick auf eine Feststellung des kardiovaskulären Risikoprofils, Blut entnommen.

Die vorliegende Doktorarbeit umfasst vier Hauptteile (Einleitung, Forschungsmethode, Ergebnisse sowie Diskussion und Schlussfolgerung), die wiederum in zehn Kapitel unterteilt sind, von denen die meisten als Beiträge in wissenschaftlichen (peer-reviewed) Fachzeitschriften veröffentlicht wurden.

Im ersten Teil (Einleitung) wird die einschlägige Literatur eingehend analysiert. Ziel ist es hierbei, den wissenschaftlichen Kontext sowie die jüngsten Entwicklungen hinsichtlich des MS, das heißt des hier behandelten Forschungsthemas, aufzuzeigen. Dieser Teil ist in vier Kapitel unterteilt. Die ersten drei Kapitel behandeln ausführlich die Problematik des MS: die historische Entwicklung des Konzepts, die verschiedenen Definitionen, die Rolle des MS bei der Risikoabschätzung kardiovaskulärer Erkrankungen und bei der Vorhersage von Diabetes, den klinischen Nutzen und die klinische Relevanz sowie die Entwicklung einer neuen Auffassung bezüglich des globalen kardiometabolischen Risikos. Das vierte Kapitel bietet einen Einblick in die weltweite Epidemiologie des MS, wobei das Augenmerk auf die Unterschiede in der Prävalenz und den Determinanten gelegt wird. Als Teil der anfänglichen Literaturaufbereitung wurde eine Metaanalyse-Studie veröffentlicht, die darauf abzielt, die Erkenntnisse hinsichtlich der Verbindung zwischen Alkoholkonsum und dem MS zu untermauern und die geschlechtsspezifische Dosiswirkung zu bestimmen.

Im zweiten Teil (Forschungsmethode) wird die Methodik zur Erreichung der definierten Ziele beschrieben. Kapitel 5 behandelt ausführlich den Aufbau der ORISCAV-LUX-Studie, die Zielgruppe, die Auswahlplanung, die Vorgehensweise bei der Feldarbeit, den Zeitplan für die Anwerbung, die Datensammlungsphasen, die Qualitätskontrollmaßnahmen sowie die Antwortquote der Umfrage. Die statistischen Analysen und die untersuchten Variablen sind in Kapitel 6 beschrieben.

Der dritte Teil stellt in vier unterschiedlichen Kapiteln die Forschungsergebnisse vor. In Kapitel 7 werden die Zielgruppe der ORISCAV-LUX-Studie und die Repräsentativität der Befragten aufgezeigt. Auch dieser Teil der Arbeit ist in zwei verschiedenen Artikeln veröffentlicht worden. Der erste Artikel beschreibt das Grundprinzip, die Ziele, die Anwerbungsmethode und auffällige Ergebnisse in Bezug auf die Prävalenz möglicherweise veränderbarer und vermeidbarer kardiovaskulärer Risikofaktoren. Die Untersuchungen haben ergeben, dass zu den vorrangigen kardiovaskulären Risikofaktoren Dyslipidämie (69,9%), Bluthochdruck (34,5%), Tabakkonsum (22,3%), Fettleibigkeit (20,9%) und Diabetes (4,4%) gehören. Alle Prävalenzraten verzeichnen mit dem Alter einen Anstieg (außer beim Tabakkonsum), wobei in geschlechtlicher Hinsicht deutliche Unterschiede zu erkennen sind (außer bei Diabetes). Des Weiteren unterliegen Männer häufiger einem Mehrfachrisiko als Frauen, und dies auch in jüngeren Altersgruppen. Diese Risikofaktoren führen schließlich zu einem gemeinsamen Auftreten metabolischer Erkrankungen, die unter dem deskriptiven Begriff „Metabolisches Syndrom“ zusammengefasst werden können. Der zweite Artikel befasst sich mit der Repräsentativität der für die ORISCAV-LUX-Studie ausgewählten Personen, ein Faktor, der bei der Planung und Durchführung epidemiologischer Studien immer mehr an Bedeutung gewinnt. Hierbei bietet der Artikel einen Einblick in die zur Steigerung der Antwortrate angewandten Strategien, die Repräsentativität der Befragten sowie die Merkmale derjenigen, die nicht teilgenommen haben. Prinzipiell ist die erzielte Teilnahmequote von 32,2% für diese Art von mehrteiligen Umfragen durchaus realistisch, und entspricht der erwarteten Rate, auf deren Grundlage der Stichprobenumfang berechnet wurde. Alles in allem zeigte diese Forschungsarbeit keine Abweichung zu bereits bekannten Profilen der Teilnehmer und Nicht-Teilnehmer, was die demografischen Aspekte und die Aspekte der kardiovaskulären Gesundheit anbelangt. Diese Arbeit gewährleistete ferner die externe Validität unserer Ergebnisse und somit auch eine mögliche Übertragung dieser Ergebnisse auf die Bevölkerung im Allgemeinen. In Kapitel 8 werden die allgemeinen, geschlechtsspezifischen und altersspezifischen Prävalenzraten des MS in der in Luxemburg lebenden, europiden Bevölkerung beschrieben. Diese Ergebnisse

wurden ebenfalls kürzlich in einem wissenschaftlichen Artikel veröffentlicht. Das Kapitel behandelt außerdem das Problem fehlender einheitlicher Standardkriterien für eine Definition des MS. Trotz eines allgemeinen Konsens in Bezug auf die Hauptfaktoren des MS, nämlich Glukoseintoleranz, Fettleibigkeit, erhöhter Blutdruck und Dyslipidämie (erhöhte Triglyceride, tiefe HDL-Cholesterinwerte) diskutieren zahlreiche Gruppen und Organisationen noch immer über verschiedene Cut-off-Werte und verbindliche Einschlusskriterien. Die fehlende diagnostische Konkordanz zwischen den verschiedenen Definitionen hat unter den Wissenschaftlern zu Verwirrung geführt und bislang einen aussagekräftigen Vergleich auf internationaler Ebene erschwert. Aus diesem Grunde wurde versucht, die Prävalenz des MS auf der Grundlage verschiedener, weitgehend akzeptierter Kriterien zu bestimmen, wobei die jüngst von der Internationalen Diabetes-Föderation (IDF) im Joint Interim Statement (JIS) veröffentlichten Kriterien als Referenz zurückbehalten wurden. Diese Definition schlägt die Verwendung ethnischer und länderspezifischer Cut-off-Punkte für den Taillenumfang (WC - waist circumference) vor. Aufgrund der zweifachen Referenzen für die europide Bevölkerung (102/88 vs. 94/80) wurde die Prävalenz des MS nur unter den europäischen Teilnehmern der ORISCAV-LUX-Studie (1349 Personen), nach hoher bzw. niedriger WC-Schwelle (24,7% bzw. 28%), bewertet. Bei Männern lag die geschätzte Prävalenz höher und nahm mit dem Alter zu. Sie unterschied sich jedoch je nach für den Taillenumfang gewählten Cut-off-Wert nur geringfügig. Interessant war festzustellen, dass, obwohl die Prävalenz des MS bei Männern höher lag, die Prävalenz von abdominaler Adipositas bei Frauen in allen Altersschichten höher war, was zeigt, wie wichtig hoher Blutdruck und Dyslipidämie für die Diagnose des Syndroms sind. Des Weiteren wurde, mit den Überlegungen über eine übergreifende Definitionsvereinbarung, auf die Angemessenheit der vorgeschlagenen MS-Definitionen unter besonderer Berücksichtigung der WC-Schwellen zur Bestimmung der Prävalenz, eingegangen. Als Ersatz für eine längsschnittliche Follow-up-Studie wurde der Framingham Risk Score (FRS) zur Einschätzung des Risikos für koronare Herzerkrankungen bei einem MS verwendet.

Die beiden letzten Kapitel der Dissertation werden die Ergebnisse der Studie hinsichtlich der wichtigsten sozioökonomischen und verhaltensspezifischen Determinanten des MS in der untersuchten Bevölkerung analysiert. Neben einer deskriptiven Analyse wurden multivariate logistische Regressionsmodelle entwickelt, um die unabhängigen Auswirkungen der sozioökonomischen und lebensstilabhängigen Faktoren auf die Wahrscheinlichkeit, am MS zu erkranken, zu untersuchen. Unsere Modelle haben gezeigt, dass die Wahrscheinlichkeit, am MS zu erkranken, mit dem Alter zunimmt, bei Männern höher ist als bei Frauen, sowie bei

Personen, in deren Familie bereits Fälle von Diabetes oder Bluthochdruck vorgelegen haben. Ausserdem ist die Wahrscheinlichkeit, am MS zu erkranken, auch bei Menschen höher, die nur die Primarstufe besucht haben und die, in Bezug auf ihren Lebensstil, ein spezifisches Verhalten an den Tag legen, wie beispielsweise mangelnde Bewegung und eine unangemessene Proteineinnahme. Idealerweise basieren solche Modelle auf experimentellen Daten oder längsschnittlichen Kohortendaten und nicht auf Querschnittsdaten. Deshalb müssen Kausalitäten, die den beobachteten Verbindungen zwischen den im Rahmen dieser Studie untersuchten Lebensstilfaktoren und dem MS unterliegen, durch weitere prospektive Daten untermauert werden. Vom volksgesundheitlichen Standpunkt aus gesehen, ist es wichtig, die lebensstilbezogenen Risikofaktoren von Personen, die am MS leiden, im Laufe der Zeit zu überwachen.

Als Teil dieser Forschungsarbeit werden derzeit zwei Artikel ausgearbeitet. Der erste Artikel zielt hauptsächlich darauf ab, die sozioökonomischen und verhaltensspezifischen Varianten bei der Prävalenz des MS zu beschreiben sowie die möglichen Determinanten in der in Luxemburg lebenden Bevölkerung zu erforschen. Der Artikel unterstreicht die Bedeutung der lebensstilbezogenen und sozioökonomischen Faktoren, wenn es darum geht, Strategien in Bezug auf kardiovaskuläre Risiken auszuarbeiten. Der zweite Beitrag konzentriert sich dagegen vor allem auf Aspekte der Ernährung in der untersuchten Bevölkerung. Diese Arbeit beschreibt zum ersten Mal ausfûhrlich die Ernahrung der Teilnehmer, mit dem Ziel, einen Europäischen Ernährungsqualitätsindex auszuarbeiten und zu analysieren, inwieweit den aktuellen nationalen und europäischen Ernährungsleitlinien Rechnung getragen wird.

Im abschließenden Teil dieser Doktorarbeit (Diskussion und Schlussfolgerungen) werden Überlegungen zu den wichtigsten Ergebnissen der vorangegangenen Kapitel vorgenommen und deren Bedeutung für die Vorbeugung kardiovaskulärer Erkrankungen bei Erwachsenen in Luxemburg debattiert.

Erwähnenswert ist, dass die ORISCAV-LUX-Studie in eine länderübergreifende Untersuchung mit dem Titel „Ernährung, Umwelt und kardiovaskuläre Gesundheit (NESCAV)" eingebunden wurde, an der vier Nachbarregionen mitwirken: das Großherzogtum Luxemburg, Wallonien (Belgien), Lothringen (Frankreich) sowie das Saarland (Deutschland). Das NESCAV-Projekt basiert auf einer standardisierten Überwachungsmethode und Datensammlungsinstrumenten, durch die ein aussagekräftiger, interregionaler Vergleich zwischen in der Bevölkerung der Großregion bestehenden und auf den Lebensstil zurückzuführenden Risikofaktoren

für die kardiovaskuläre Gesundheit vorgenommen werden kann. Das Studienprotokoll wurde kürzlich in einem Artikel über den interregionalen Kontext der ORISCAV-LUX-Studie veröffentlicht.

Diese Doktorarbeit spiegelt die Ansichten des Verfassers und nicht notwendigerweise die Meinungen des Direktorats für Gesundheit (Gesundheitsministerium) oder des Zentrums für Gesundheitsstudien wider.

Glossary

ACR	Albumin creatinine ratio
ADA	American Diabetes Association
BP	Blood pressure
CHD	Coronary heart disease
CI	Confidence interval
CRP	C-reactive protein
CT	Computed tomography
CVD	Cardiovascular disease
CVRF	Cardiovascular risk factors
DBP	Diastolic blood pressure
DEXA	Dual-energy x-ray absorptiometry
DHEA-S	Dehydroepiandrosterone sulfate
EGIR	European Group for the Study of Insulin Resistance
FI	Fasting insulin
FPG	Fasting plasma glucose
HDL-C	High density lipoprotein cholesterol
HOMA(IR)	Homeostasis model assessment (insulin resistance)

IDF	International Diabetes Federation
IFG	Impaired fasting glycaemia
IGF-I	Insulin-like growth factor 1
IGT	Impaired glucose tolerance
JIS	Joint Interim Statement
LDL-C	Low density lipoprotein cholesterol
MET	Multiples of resting energy expenditure
MI	Myocardial infarction
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MS	Metabolic syndrome
MUFA	Monounsaturated fatty acids
NCEP	National Cholesterol Education Program, Adult Treatment Panel III
NGT	Normal glucose tolerance
NHANES III	The US National Health and Nutrition Examination Survey, 1988 1994
NSP	Non-starch polysaccharides
OGTT	Oral glucose tolerance test
PAI-1	Plasminogen activator inhibitor 1 antigen
PM	Particulate matter
PUFA	Polyunsaturated fatty acids
R-ATPIII	Revised-Adults Treatment Panel III
R-IDF	Revised-International Diabetes Federation
SBP	Systolic blood pressure
SE	Standard error
SFA	Saturated fatty acids
SHBG	Sex hormone-binding globulin
STATEC	National Statistics and Economic Studies Service
TG	Triglycerides
WC	Waist circumference

WHO	World Health Organization
WHR	Waist-to-hip ratio

Contents

Part I

Introduction

1. General overview

This preamble summarizes the background, rationale and objectives of the research work.

1.1 Scope of the problem

Today around 60% of worldwide deaths and 43% of the global burden of diseases are attributed to coronary heart disease (CHD), stroke and type 2 diabetes mellitus[1]. These diseases are predicted to account for 73% of global deaths and 60% of the global burden by year 2020[2].

Multiple evidences confirmed that type 2 diabetes and cardiovascular disease (CVD), share many common risk factors such as obesity, hypertension, dyslipidemia and hyperglycemia. This cluster is named later as the "metabolic syndrome" (MS)[3-5]. The pioneer Gerald Reaven in 1988 systematized the concept of a risk factor clustering and popularized the term "syndrome X". He suggested that these metabolic abnormalities are caused by insulin resistance and are precursor to type 2 diabetes and CVD[6]. Since then, there has been a flurry of research corroborating the idea of a risk factor cluster mediated by insulin resistance.

While the role of insulin resistance as a promoter of cardiovascular risk was commonly acknowledged[7], the obesity, particularly visceral obesity, was suggested as a major determinant of insulin resistance, hence preparing the path to the clustering of metabolic and non-metabolic factors embraced under the descriptive term of "metabolic syndrome". Visceral adipose tissue may also contribute to other causes of increased atherosclerotic risk, including inflammatory, prothrombotic, and fibrinolytic factors[8].

Although the pathophysiological mechanism is so far incompletely understood, the MS concept was suggested as a multiplex risk factor for CVD and type 2 diabetes, resulting from obesity and insulin resistance[9], [10]. Currently, this multiplex is thought to be composed of the following broadly stated metabolic risk conditions: atherogenic dyslipidemia, hypertension, glucose intolerance, proinflammatory state, and a prothrombotic state.

During the last two decades, numerous scientific consensus groups proposed diverse clinical tools to identify individuals with this atherogenic cardiometabolic disorder,

however, differed in the priority given to the central obesity or to the insulin resistance. The use of different definitions to conduct research into the MS in diverse populations resulted in wide ranging prevalence rate, inconsistencies and confusion, hence, spurred on the urgent need to a single worldwide agreed definition.

In addition, years after the term "metabolic syndrome" was first coined, the existence of a distinct syndrome was still a subject of controversy. Critics of the MS concept pointed out that its components are quite common and may reasonably co-occur in some subjects independent of underlying unified pathophysiology[11]. The basic disagreement seems related to the difference in perspectives between cardiovascular and diabetes communities and how to integrate the MS into concepts of insulin resistance, pre-diabetes and type 2 diabetes[12]. In 2005, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) issued a statement discouraging the use of the term MS. In parallel, the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) released another statement encouraging use of the MS concept. The report stated that the aggregation of the factors, representing the MS, increases cardiovascular risk and should be aggressively targeted for medical intervention.

Five years later, this debate is still raging. Opinions still vary over the relevance and clinical utility of identifying and labelling individuals with this risk factors clustering. It is argued that to evaluate and manage properly global CVD risk in clinical practice, it is important to take into account the risk associated with traditional risk factors, in addition to the potential contribution of abdominal obesity/insulin resistance and related complications. Recently, this global risk is referred to as global cardiometabolic risk.

Despite those limitations, prospective outcomes data provided however substantial support for the MS hypothesis[13]. Several population studies documented that these metabolic risk factors co-occur to a far greater degree than would be predicted by chance alone[14]. [15] and can predict type 2 diabetes[16], [17], [18] and CVD [17], [19], [20, 21]. One important justification cited for the utility of the syndrome is that it changed medical perspective from a single-risk factor to the multiple-risk factors paradigm [22], [12].

During the last decade, the MS has progressively become a major public health problem, approaching epidemic proportions worldwide[23]. A total of 115 million individuals suffer from this syndrome in the US, Japan, France, Germany, Italy, Spain and the UK, a number which is set to increase rapidly, fuelled by the increase in obesity and the diabetes epidemic[24].

The pathogenesis of the MS is complex and so far incompletely understood; but the interaction of obesity, sedentary lifestyle, dietary, environmental and genetic factors are known to contribute to its development[25], [6], [26].

1.2 Rationale and motivation

Knowledge and understanding of the epidemiological profile of this emerging pathology, associated with elevate risk of diabetes and cardiovascular mortality is an essential pre-requisite to assess and address public health needs. It allows emerging possibilities for successful intervention to prevent and treat MS before the CHD and type 2 diabetes really develop in susceptible individuals and thus enables planning of an efficient prevention strategies. Until recently, there was no data indicating the frequency of the cardiovascular risk factors or the MS among the apparently healthy adults, resident in Luxembourg.

As part of the national surveillance of public health indicators, the first nationwide, population-based "Observation of cardiovascular risk factors in Luxembourg" ORISCAV-LUX survey was conducted between November 2007 and January 2009, under the auspices of the Ministry of Health and co-financed by the Ministry of Research. In a representative sample of Luxembourg's population, this study considered a range of demographic, socio-economic and behavioural factors, as well as anthropometric and biological markers of the MS. The ORISCAV-LUX study has dual significance. First, the collected ORISCAV-LUX database helped to establish national baseline statistics for a range of important pathologies and cardiovascular risk factors such as obesity, hypertension, diabetes, lipid disorder, dietary intake, smoking, and physical activity. Second, it constitutes a valid and useful database attracting researchers to investigate thoroughly the age and gender variation, interaction of various risk factors and determinants that influence population cardiovascular health. The findings allow public health authorities and health professionals to develop evidence-based prevention strategies corresponding to the real needs of the population.

The dissertation's research work exploits the ORISCAV-LUX database, in view of increasing knowledge about an escalating public health threat, called the MS that has profound public health consequences. National estimates and exploration of the problem are therefore necessary for both public health research and policy making.

1.3 Research hypothesis and objectives

In the light of the current scientific state-of-the-art concerning the research topic, the metabolic syndrome, and the initial line of investigation on the prevalence of cardiovascular risk factors among the adult residents in Luxembourg, the following hypotheses were broadly formulated:

- The MS is a significant pathology among the apparently healthy adult population residing in Luxembourg. Its prevalence rate and epidemiological profile are comparable to those in other European and worldwide populations.
- The variation in the prevalence of the MS is potentially influenced by socio-economic and behavioural factors.

Based on an inductive exploratory approach, the principal purpose of this research is to investigate, for the first time, the epidemiology of the MS in the general population resident in Luxembourg. The work tends to study the variation in its frequency, and to identify the potential socio-economic, and underlying behavioural factors that may influence and determine the prevalence variation, in order to suggest prevention strategies suitable to the real needs of the groups at risk.

Several working definitions of the MS are currently available with substantial differences in the criteria and in the cut-off points for the individual components. The multiplicity of MS definitions has led to considerable confusion, not only with respect to its clinical utility but also to compare its burden in different population. Since the recent IDF guidelines stressed the need to adopt ethnic-specific values of waist circumference, the specific objective was to initially determine the appropriate criteria to define the MS among the Europid; the dominant residing population in Luxembourg (comprising 94.2% of the total studied population). For this purpose, a prior study to assess the prevalence of MS based on inter-definition comparison according to the last 3 operating definitions (Revised-ATPIII, IDF and JIS) among the European group was performed to justify the selection. This part of dissertation is published in the BMC Public Health Journal (see Appendix).

1.4 Contribution of the research to knowledge development

The research establishes, for the first time, the prevalence of the MS in Luxembourg and addresses its potential determinants by investigating the relationship with the socio-economic and behavioural factors, in a representative sample of European adults residing in Luxembourg. The findings will be helpful to develop national targeted strategies for the prevention of diabetes and cardiovascular diseases. Furthermore, identifying the group of population at risk and understanding the association with the potentially modifiable lifestyles, such as physical inactivity, certain dietary patterns are of significant importance. An evidence-based strategy aiming at the prevention of this multi-component syndrome may provide a less confusing message to the public than attempting to target individual abnormalities. The results will support the evidence available about the relationship between lifestyles and MS as a comprehensive clinical entity.

In sum, the research outcomes will bring together original scientific information on MS and its components, and then transfer that knowledge into actions by the national stakeholders and decision-makers. Its ultimate aim is to fight against the modern public health challenge, represented by the cardiometabolic risk.

Chapter 1

Metabolic syndrome

1. Introduction

The term "Metabolic Syndrome" (MS) is generally used to indicate a clinical entity of substantial heterogeneity, represented by the co-occurrence of hypertension, impaired glucose tolerance, atherogenic dyslipidemia, central fat accumulation, insulin resistance, as well as prothrombotic and inflammatory states. This multiple metabolic and cardiovascular disorders cluster together in the same individual more often than might be expected by chance, leading to increase the probability of suffering from cardiovascular disease (CVD) and type 2 diabetes mellitus[19], [27], [13].

Researchers have focused intensively on this pathological disorder, mainly after the identification of the MS in 2001, by the National Cholesterol Education Program (NCEP) Adult Treatment panel ATPIII, as a secondary target (after lowering LDL-C) of CHD risk reduction[28]. Since then, several lines of evidence suggested that the components of the MS, acting together synergistically, can raise the individual's risk of developing CVD[28], [27], [17], [21], [19].

In spite of the critics of the MS concept[11], data from large prospective population-based studies, such as the Framingham offspring study[14], the Botnia study[19], the Kuopio Ischemic heart Disease study[27], the Italian study [29], and the Atherosclerosis Risk in Communities (ARIC) study[30], [15], confirmed that the presence of the metabolic syndrome was significantly associated with an increased risk of cardiovascular disease morbidity and mortality, providing thus substantial support for the MS hypothesis[13].

During the last decade, this multiplex cardiometabolic disorder has progressively become a major worldwide public health problem, because of its association with increased risk of type 2 diabetes mellitus, atherosclerotic cardiovascular disease and all-cause mortality[19], [27], [13].

This reality called for an increasing effort from the scientific community to detect the etio-pathogenic mechanisms and, consequently, to elaborate interventional initiatives to counteract this escalating health threat. Several scientific associations and public health organizations have proposed definitions and diagnostic criteria of the MS. However, this diversity of opinions has generated terminology and conceptual confusion.

2. Historical development of the MS concept

Regardless of disagreement about who first described the MS in medical literature, its concept existed for at least 80 years[23]. According to a group of researchers[24], the constellation of metabolic disturbances was initially described in 1920s by Kylin, a Swedish physician, and later by Vague in 1947. The later drew the attention to upper body adiposity (android or male-type obesity), as a metabolic abnormality commonly associated with type 2 diabetes and CVD[7], [31]. However, the frequent simultaneous presence of obesity, hypertension, diabetes and hyperlipidemia was described in 1965 by Avogaro *et al*, and then by Haller *et al* in 1977, who described their association with atherosclerosis[24].

Ten years later, the clinical importance of the syndrome was highlighted by Reaven who introduced the concept of Syndrome X, as a clustering of disturbances in glucose and insulin metabolism, dyslipidemia and hypertension. Reaven suggested that insulin resistance was a fundamental "disorder" associated with a set of metabolic abnormalities which not only increased the risk of type 2 diabetes but also contributed to the development of CVD before the appearance of hyperglycemia. He emphasized that insulin resistance was at the centre of a cluster of metabolic abnormalities, which include hypertriglyceridemia, low high-density lipoprotein (LDL) cholesterol level, increased glycemia, and elevated blood pressure. Such constellation of abnormalities was described as syndrome X[6].

Following this early conceptual contribution, numerous studies have confirmed that insulin resistance was indeed associated with metabolic abnormalities that increase the risk of both diabetes and CVD[32-34]. Syndrome X was also called Reaven's Syndrome, Insulin Resistance Syndrome[35], deadly quartet[36], and is now widely known as Metabolic syndrome.

A later key conceptual advance was the recognition of the central role of abdominal obesity[37] in the diagnosis of the MS, and its introduction as a clinically easy-measurable entity. This second hallmark put the abdominal obesity on the front line to diagnose the MS.

3. Definitions

Despite controversies with regards to its causes, the concept of the MS was increasingly accepted. In 1998, the first initiative to develop an internationally recognized definition came from the World Health Organization (WHO).

3.1 WHO definition

In an attempt to provide a tool for clinicians and researchers, the "WHO Working Group on Diabetes" proposed in 1998, a set of criteria to define the MS[38] (Table2). The consensus was finalized in 1999 and placed on the WHO website. It reported clearly that the definition would be modified as new information became available about the components and their predictive power. The WHO definition, stated that diabetes type 2 or impaired glucose tolerance (IGT), together with at least 2 of 4 other factors (hypertension, hyperlipidemia, obesity and microalbuminuria) define the MS. In case of normal glucose tolerance, the evidence of insulin resistance is needed; this is defined as the lowest quartile of measures of insulin sensitivity. The definition of obesity is based on either overall obesity assessed by body mass index (BMI), or central obesity assessed by waist-to-hip ratio (WHR)[38]. The definitive statement issued in 1999, modified the systolic blood pressure threshold from 160 to 140 mmHg and microalbuminuria as assessed by albumin/creatinine was changed from 20 to 30 mg/g[38],[4] (Table 1).

Table 1. WHO definition of the metabolic syndrome 1999[38], [4]

Glucose intolerance, Impaired Glucose Tolerance (IGT) or Diabetes mellitus and/or insulin resistance together with two or more of the following criteria listed below:
1) Obesity: BMI > 30 Kg/m^2 and / or Waist-to-hip ratio > 0.90 in men or > 0.85 in women
2) Dyslipidaemia: serum triglycerides ≥ 150 mg/dl and/or HDL-C < 35 mg/dl in men and < 39 mg/dl in women
3) Urinary albumin excretion rate ≥ 20 μg/min or albumin: creatinine ratio ≥ 30 mg/g
4) Hypertension: Blood pressure ≥ 140/90 mmHg

The potential disadvantage of the WHO criteria is that special testing of glucose status, beyond routine clinical assessment, was necessary to diagnose the MS, for example: oral glucose tolerance test (OGTT) and insulin resistance measurement by hyperinsulinemic euglycemic clamp. Since insulin clamp evaluation was impractical, most epidemiological studies used hyperinsulinemia as a surrogate for insulin resistance (fasting insulin levels in the upper quartile of the background population)[16], [27].

Another weak point was related to the non-reliable measurement of obesity by the BMI, especially in the elderly people, due to the changes in height with advancing age compared to younger adults[39]. In addition, for any given BMI tertile, subjects in the top waist tertile had a worse risk factor profile than individuals with the same BMI but with lower waist circumference (WC) measures, meaning that the BMI and WC did not predict the risk of metabolic disturbances equally[24]. The greater truncal adipose tissue was distinguished as the real risk factor for the MS[39]. Moreover, the frequency of microalbuminuria in non-diabetic individuals is very low and, therefore, this criterion was relevant only in the presence of diabetes[24].

3.2 EGIR definition

In 1999, the European Group for the Study of Insulin Resistance (EGIR) proposed an alternative definition[40], which was labeled the insulin resistance syndrome. While the WHO definition required an evaluation of insulin resistance under euglycemic hyperinsulinemic conditions and was applied alike to diabetic and non-diabetic subjects, the EGIR definition excluded the diabetic population and relied on fasting insulin as a surrogate marker of insulin resistance. The EGIR definition still retained insulin resistance, as an essential component and major etiological determinant of the MS. As beta-cell dysfunction, the key characteristic of type 2 diabetes, makes insulin sensitivity estimates unreliable[5], people with diabetes were excluded from the definition. In addition, WC was used as surrogate for obesity because it correlates better with intra-abdominal adiposity than BMI[37]. The adoption of WC rather than BMI represented a major deviation in the conceptual development of the MS. In addition, the impaired glucose tolerance was not necessary for the recognition of the MS (Table 2).

Table 2. EGIR definition of the metabolic syndrome 1999[41]

Hyperinsulinaemia defined as fasting insulin concentration above the upper quartile for the non-diabetic subjects* (age and sexes combined) in addition to two or more of the following components:
1) Central obesity: WC ≥ 94 cm in men or ≥ 80 in women
2) Dyslipidemia: serum triglycerides (TG) > 180 mg/dl and/or HDL-C < 40 mg/dl and/or drug treatment for dyslipidemia
3) Hypertension: systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg and/or drug treatment for hypertension
4) Fasting plasma glucose (FPG) ≥ 110 mg/dL

** The EGIR insulin resistance syndrome was defined only for non-diabetic subjects.*

3.3 NCEP-ATPIII definitions

- ATPIII 2001

Two years later, the National Education Program's Adult Treatment Panel III (NCEP-ATPIII) formulated another definition, designed to have clinical utility. The ATPIII did not find enough evidence to recommend routine measurement of insulin sensitivity or the 2-hour post-challenge glucose determination, but included simply a fasting glucose determination[42]. Additionally, the cut-off points for each component of the cluster and the way of combining them to define the MS differ from the previous two definitions[42]. The ATPIII definition is a simple set of diagnostic criteria based on common clinical measures, including WC to identify central obesity, raised TG, reduced HDL-C, elevated blood pressure (BP) and raised FPG level. The MS diagnosis was established, when 3 out of 5 listed characteristics were present (Table 3). The ATPIII criteria were widely used in both clinical practice and epidemiological studies. The criteria had the advantage of excluding the specific measure of insulin sensitivity, and treated all components with equal importance by avoiding the emphasis on a single cause [43].

Table 3. NCEP-ATIII definition of the metabolic syndrome 2001[44]

Any 3 of 5 following criteria constituted the diagnosis of MS
1) Central obesity: WC ≥ 102 cm in men or ≥ 88 in women
2) Hypertriglyceridamia: serum TG ≥ 150 mg/dl
3) Low HDL-C < 40 mg/dl in men and < 50mg/dl in women
4) Hypertension: SBP ≥ 130 mmHg or DBP ≥ 85 mmHg
5) FPG ≥ 110 mg/dL

- Revised ATPIII 2005

Subsequently, certain modifications of the ATPIII definition were developed later by the American Heart Association/National Heart, Lung, Blood Institute (AHA/NHLBI) included adjustment of WC to lower thresholds particularly in ethnic groups, for instance, the Asian American, who are more susceptible to insulin resistance. In addition, TG, HDL-C levels, and BP were counted as abnormal when a person was taking drug treatment for these factors. The threshold for elevated FPG was reduced from ≥110 mg/dL to ≥100 mg/dL, in accordance with the American Diabetes Association's guidelines [43] (Table 4).

Table 4. Revised ATPIII definition of the metabolic syndrome 2005[43]

Any 3 of 5 criteria listed below constitute the diagnosis of MS
1) Elevated WC ≥ 102 cm in men or ≥ 88 in women
2) Elevated TG ≥ 150 mg/dl and/or drug treatment for elevated TG*
3) Reduced HDL-C < 40 mg/dl in men and < 50 mg/dl in women and/ or drug treatment for reduced HDL-C
4) Elevated BP ≥ 130 mmHg systolic BP or ≥ 85 mmHg diastolic BP or drug treatment for hypertension
5) Elevated FPG ≥ 100 mg/dL and/or drug treatment for elevated glucose

* *Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and reduced HDL-C. Patients taking 1 of these drugs were presumed to have high TG and low HDL*

3.4 IDF definition

In parallel, a consensus group, comprising members of the International Diabetes Federation (IDF) and representatives from organizations contributed to the previous definitions was formed in 2005, to establish a unified definition for the MS that would be suitable for use worldwide, in both epidemiological and clinical practice. A major issue of the IDF consensus was that central (abdominal) obesity, easily assessed using WC, was a prerequisite risk factor for the diagnosis of the syndrome. The IDF provided, for the first time, different obesity cut-off points for different ethnic groups[45] (Table 5&6). WC was a well accepted proxy measurement for abdominal obesity and served as the first screening test for the MS. The added advantage is that insulin resistance which is difficult to measure in routine clinical practice was not an essential requirement[5].

Table 5. The IDF definition of the metabolic syndrome 2005[5], [45]

Central obesity (defined as WC with ethnicity specific values) plus any two of the following four factors:
1) Raised serum TG ≥ 150 mg/dl or specific treatment for this lipid abnormality
2) Reduced HDL-C < 40 mg/dl in men and < 50 mg/dl in women and/or specific treatment for this lipid abnormality
3) Elevated BP ≥ 130 mmHg systolic BP or ≥ 85 mmHg diastolic BP and/or treatment of previously diagnosed hypertension
4) Elevated FPG ≥100 mg/dL or previously diagnosed type 2 diabetes. If FPG was above 100 mg/dL, oral glucose tolerance test (OGTT) was strongly recommended but was not necessary to define the presence of the MS

Table 6. Ethnic specific values for waist circumference[45]

Country/Ethnic group		Waist circumference
Europids In the USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes	Male Female	≥ 94 cm ≥ 80 cm
South Asians Based on a Chinese, Malay and Asian-Indian population	Male Female	≥ 90 cm ≥ 80 cm
Chinese	Male Female	≥ 90 cm ≥ 80 cm
Japanese	Male Female	≥ 90 cm ≥ 80 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available	
Sub-Saharan Africans	Use European data until more specific data are available	
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available	

The underlying principle behind the ethnic-specific thresholds was that for a given WC, Asians, blacks, Caucasians showed different levels of intra-abdominal adiposity, putting the subjects at different risk levels of CVD and diabetes[46].

However, the IDF believed that the new IDF criteria were not the final word. Thus a list of potential additional criteria, called "Platinum standard" definition was established. It included several biomarkers that should be investigated in future epidemiological studies and research in order to determine their predictive power for CVD and/or diabetes[45] (Table 7).

Table 7. "Platinum standard" definition-additional metabolic criteria for research[45]

Abnormal body fat distribution	General body fat distribution (DEXA) Central fat distribution (CT/MRI) Adipose tissue biomarkers: leptin, adiponectin Liver fat content (MRS)
Atherogenic dyslipidaemia (elevated triglyceride and low HDL)	ApoB (or non-HDL-C) Small LDL particles
Dysglycaemia	OGTT
Insulin resistance (other than elevated fasting glucose)	Fasting insulin/proinsulin levels HOMA-IR Insulin resistance by Bergman Minimal Model Elevated free fatty acids (fasting and during OGTT) M value from clamp
Vascular dysregulation (beyond elevated blood pressure)	Measurement of endothelial dysfunction Microalbuminuria
Pro-inflammatory state	Elevated high sensitivity C-reactive protein Elevated inflammatory cytokines (eg TNFalpha, IL-6) Decrease in adiponectin plasma levels
Pro-thrombotic state	Fibrinolytic factors (PAI-1, etc) Clotting factors (fibrinogen, etc)
Hormonal factors	Pituitary-adrenal axis

3.5 Joint Interim Statement definition

In 2009, a Joint Interim Statement (JIS) of the IDF Task force on Epidemiology and prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of obesity was published, in an attempt to harmonize the definition. The new definition is also known as Revised IDF 2005 (R-IDF 2005). Unlike the first IDF definition, the abdominal obesity should not be an obligatory criterion, though the WC was agreed to be a useful preliminary screening tool. The remaining 4 diagnostic criteria were essentially identical to those provided by the R-ATPIII and IDF. The presence of 3 components out of 5 establishes the diagnosis of MS (Table 8).

Table 8. Joint Interim Statement definition of the metabolic syndrome 2009[47]

Any 3 of 5 criteria listed below constitute the diagnosis of MS
1) Elevated WC according to population- and country-specific definitions (either the IDF or AHA/NHLBI cut points for people of European origin)
2) Elevated TG ≥ 150 mg/dl or drug treatment for elevated TG
3) Reduced HDL-C < 40 mg/dl in men and < 50 mg/dl in women or drug treatment for reduced HDL-C
4) Elevated BP ≥ 130 mmHg systolic BP or ≥ 85 mmHg diastolic BP and/or drug treatment for hypertension
5) Elevated FPG ≥ 100 mg/dL or drug treatment for elevated glucose

The new R-IDF 2005 definition recognizes that the risk associated with a particular waist measurement varies in different populations and ethnic groups. The WHO identified 2 levels of abdominal obesity in European population depending on risk for metabolic complications[48]. An increased risk occurs at waist circumferences of ≥ 94 cm in men or ≥ 80 in women, but risk is substantially higher at ≥ 102 cm in men or ≥ 88 in women. Until more data from research work were available, it was suggested to use national or regional cut-off points for WC.

To sum up, the abundance of widely varying data, comparing the prevalence of MS by using different criteria across different population reinforced the need for a standardized definition internationally. Now after the release of the JIS, the actual question is whether this new definition is the last word or whether the scientific community needs further reconciliation.

Chapter 2

Place of metabolic syndrome in CVD risk assessment and diabetes prediction

1. Introduction

This chapter attempts to elucidate the place of the MS in the predictability of type 2 diabetes and CVD risk assessment. However, it is important to highlight beforehand the traditional CVD risk assessment tools.

2. Risk assessment algorithms

CVD is a leading cause of disability and death. Primary and secondary prevention measures help to reduce cardiovascular events and improve the overall health of patients. Several risk prediction methods have been implemented in large prospective epidemiological studies to identify individuals at high risk of CHD or CVD. The prediction models varied from one study to another in terms of the statistical method, endpoints and included risk factors for risk assessment. Table 9 presents the most widely known CVD risk assessment algorithms, originated from SCORE project, Framingham study and PROCAM study.

Table 9. CVD risk assessment algorithms, originated from SCORE project, Framingham study and PROCAM study

Risk assessment algorithms	Framingham risk algorithm[49]	PROCAM risk algorithm[50]	European SCORE risk algorithm [51]
Included risk factors	Age 30-74 years	Age 35 to 65 years of age	Age 40-65 years
	Gender (men, women)	Men only	Gender (men, women)
	Smoking	Smoking	Smoking
	SBP or DBP	SBP	SBP
	T-C and HDL-C	LDL-C HDL-C Triglycerides	T-C and cholesterol/ HDL-C ratio
	Diabetes mellitus	Diagnosis of diabetes	
	ECG-LVH (left ventricular hypertrophy identified by electrocardiography	Premature CHD in 1st degree family relative	
Risk prediction method	Stepwise logistic regression	Cox proportional hazards model	Weibull model
Endpoint	Incidence of fatal and non-fatal CVD	Risk of acute coronary events (fatal or non-fatal myocardial infarction or acute coronary death)	Ten-year risk of fatal atherosclerotic CVD

The American Framingham Heart study led to the development of a CVD risk prediction model, called the Framingham risk score. It was designed to estimate the absolute risk of developing CHD, in a 30-74 years age group, white population [52]. The score was based on traditional risk factors; cigarette smoking, blood pressure, diabetes, total cholesterol, and LDL-C, as well as to ECG-identified left ventricular hypertrophy[49].

The Prospective Cardiovascular Münster (PROCAM) study in Germany developed also a risk prediction model that used some of the risk factors included in the Framingham risk score along with other variables, such as TG-C and family history of clinical signs of premature CHD[50]. The PROCAM was based only on male population.

The Systematic COronary Risk Evaluation (SCORE) project assembled a pool of data from 12 European cohort studies, carried out mainly in general population settings, to provide a picture of person's overall or global risk of CHD[51]. In comparison to the other models, the European SCORE charts considered only the principal risk factors, such as age, gender, smoking, SBP and T-cholesterol.

Additional risk charts and scores have also been developed from other studies such as the United Kingdom Prospective Diabetes Study (UKPDS) [53], and the Italian CUORE project[54]. All these risk scores are useful tools for evaluating a patient's global CHD risk in clinical practice[46].

3. Metabolic syndrome and traditional tools

The above-mentioned risk assessment algorithms take into account traditional risk factors such as age, sex, family history, blood pressure, smoking, cholesterol (both LDL and HDL), and diabetes. However, these CVD risk assessment tools did not capture the risk of abdominal obesity and the related abnormalities of the MS. This is especially important with the recent sweeping epidemic of abdominal obesity. It has been suggested that the CVD risk of abdominal obesity and/or MS may be independent from or go beyond the risk predicted by traditional risk factors[46]. Many individuals are at increased risk of CVD because of the presence of a constellation of metabolic abnormalities. However, the Framingham risk score does not assess properly lifetime risk particularly among young adults with abdominal obesity and MS who may not be considered at elevated risk of CVD because of their young age[10]. Therefore, the existing CVD risk assessment tools proved cumbersome in clinical practice and were not sufficient to adequately capture the additional risk related to the MS, such as the abdominal obesity, insulin resistance and related complications[46].

4. Predictability of the metabolic syndrome to CVD

Many prospective studies documented the relation of MS to cardiovascular risk, particularly to cardiovascular morbidity, mortality as well as all-cause mortality. In the Kuopio Ischemic Heart Disease Risk Factor Study, a population-based, prospective cohort study of 1209 Finnish men aged 42 to 60 years, the 10-year CVD risk was increased 2.1- and 2.5-fold with the ATP III and WHO MS definitions, respectively[27]. The same study found that the risk of death from CVD was increased by 2.6–3 times, and the risk of all-cause mortality was increased 1.9–2.1 times with the presence of MS.

The DECODE project based on 11 prospective European cohort studies, that followed up 6156 men and 5356 women for 8.8 years. It reported that the overall hazard ratios for all-cause and cardiovascular mortality in non-diabetic persons with the MS were 1.44 and 2.26 in men and 1.38 and 2.78 in women, respectively[25].

In the WOSCOPS (West of Scotland Coronary Prevention) Study, a modified NCEP-MS definition predicted CHD events, in the multivariate model incorporating conventional risk factors (hazard ratio=1.30). Men with 4 or 5 features of the MS had a 3.7-fold increase in risk for CHD and a 24.5-fold increase for diabetes compared with men without the syndrome[55].

In Botnia study, carried out on 4483 subjects, aged 35-70 years, followed for 7 years in Finland and Sweden, the risk for coronary heart disease and stroke was increased 3-fold in subjects with the WHO-MS definition. Cardiovascular mortality was also markedly increased in subjects with the syndrome compared to those without it (12.0 vs. 2.2%, $P < 0.001$)[19].

Nevertheless, the use of different definitions of the MS led to inconsistent results on its association with the risk of CVD[56]. Systematic research reviews showed that the cardiovascular risk, conferred by the different definitions, varied between populations; in most studies, it was lower with the IDF definition as compared to other alternatives[57], [56].

In addition, two recent meta-analysis, reviewed longitudinal studies, showed that the relative risk of CVD associated with the MS was higher in women compared to men[58], and higher in studies that used the WHO definition compared to studies that used the NCEP-ATP III definition[56].

These findings suggested that the MS is an important risk factor for CVD incidence and mortality, as well as all-cause mortality. However, several physicians and academics disputed the syndrome's relevance and its cardiovascular risk predictability. The crucial question of the debate was whether the gathering of the MS components in a single person can express a risk of heart disease greater than that conveyed by each component individually. The relevance of the MS as a CVD risk assessment tool will be considered in details in chapter 3.

5. Predictability of the MS to type 2 diabetes

The most important clinical dimension of the MS is its association with the risk of development of type 2 diabetes. Several prospective studies indicated that the MS predicts type 2 diabetes [17-19], [59] . People with the syndrome were over 4 times as likely to develop type 2 diabetes compared with subjects who did not have the MS[13]. However, without excluding the diabetic subjects, this might not be a surprise, since impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are components of the suggested WHO definition[7]. In addition, neither the ATP III nor the IDF criteria excluded hyperglycaemia as 1 of the 5 criteria for the diagnosis of the MS. By these criteria, most patients with type 2 diabetes mellitus have the MS. In San Antonio Heart Study, the NCEP definition of the MS predicted diabetes better than the WHO definition, independently of other factors. It was suggested therefore to lower the fasting glucose cut-off points to improve the diabetes prediction [18].

Despite the above data, there is ongoing controversy as to whether the MS is associated with increased cardiovascular and diabetes risk or is simply a sum of the risk of the associated components: reduced glucose tolerance, elevated blood pressure, dyslipidemia, and abdominal obesity[22]. According to a recent review, aiming to examine the ability of the MS to predict vascular events and incident diabetes, the number of existing studies appeared limited to draw definite conclusions[57] and the MS predicts diabetes much more efficiently in non-diabetic individuals[60].

Chapter 3

Relevance of metabolic syndrome

1. Introduction

After a plethora of publication on the MS worldwide, the MS is still an ill-defined concept that has many unanswered questions[24], [61], [62]. So far, evidence-based outcomes are limited. The MS components and cut-off values are the results of expert consensus[63], [64].

Although the suggested definitions provided some uniformity to research efforts over the past 10 years, a considerable confusion about the relevance and the precise clinical utility of the concept "metabolic syndrome" remains controversial.

Several researchers believe that the MS is a simple useful tool to call attention to patients who are at high lifetime risk for both atherosclerotic CVD and diabetes; such persons deserve increased attention in clinical management and monitoring[38], [40], [43], [64],[65]. Others[9], [64], [66] debated the future of the MS and asked whether it offers advantages over existing models for the prediction of cardiovascular events[17]. Moreover, creating a diagnostic category of the MS was criticized by Reaven himself who was a pioneer in systemizing the concept of a risk factor syndrome. Reaven believes that this effort has little clinical or pedagogic utility and if necessary the WHO approach is the most rational one[65].

The major polemic was emerged in 2005 when a joint committee of the American Diabetes Association (ADA) and from the European Association for the Study of Diabetes (EASD) published a critical appraisal of the MS concept, and of its diagnostic utility in clinical practice[64].

Most recently, the WHO Expert Consultation, who edited the first definition 10 years earlier, has released in 2009 a Position Statement, pertaining to evaluate the relevance and the clinical utility of the MS concept[67]. The statement critically concluded that though the MS may be considered useful as an educational concept, it has limited practical utility as a diagnostic or management tool. Disappointingly, the statement has suggested that in the light of the current knowledge, further efforts to refine the MS are inappropriate and further comparative epidemiological studies are of limited utility[67].

Several debated key points, regarding the concept of the MS are elucidated in the following sections.

2. Debated key points

2.1 Diversity of definitions

During the last decade, several definitions of MS were produced by a number of expert groups; the World Health Organization (WHO)[38], the European Group for the Study of Insulin Resistance (EGIR)[40], the National Cholesterol Education program–Third Adult Treatment Panel (NCEP-ATPIII)[42], the American Heart Association/National Heart, Lung, and Blood Institute[43], and the International Diabetes Federation (IDF)[5]. Most recently, a Joint Interim Statement (JIS) has been released in 2009, by several major organizations, in an attempt to unify the criteria[47].

Generally, the preceding definitions were either difficult to use or gave inconsistent results in clinical practice or epidemiological surveys when applied to identify individuals with the MS. Although these definitions were similar in their focus on such constituent criteria as, obesity, dyslipidemia, hyperglycemia, and hypertension, substantial differences remained concerning the insulin resistance.

Studies and research papers attempting to compare the diagnostic adequacy of each definition found difficulty in making direct comparisons to identify the syndrome across different populations. In addition, the use of different definitions had an impact on the estimated prevalence and confused the interpretation of epidemiological studies.

For instance, in the DECODE study which regrouped seven cross-sectional European surveys, WHO, EGIR and NCEP-ATPIII were poorly agreed in non-diabetic subjects[68]. In another methodological study, comparing the different definitions, the higher agreement was found between definitions require measurement of insulin (WHO, EGIR) compared to those not require (NCEP-ATPIII, R-ATPIII, IDF)[69].

As yet, no general agreement has been reached, and published prevalence estimates using various definitions are still controversial. This problem was approached in detail in the article “Prevalence of the metabolic syndrome in the adult population of Luxembourg estimated from the ORISCAV-LUX study”. This publication aimed to estimate the prevalence of MS in the general population resident in Luxembourg, and examined the degree of concordance by comparing the last suggested R-ATPIII, IDF and the JIS definitions.

2.2 Ambiguous pathophysiologic mechanism

The pathogenesis of the MS is currently a subject of crucial discussion. The criteria of MS are interrelated, but the pathophysiology of their relation is not yet fully understood. The little consensus about the underlying unified mechanism is well illustrated by the long-standing debate about how to define this syndrome. This led to the appearance of two distinct schools of thought: the insulin resistance-based and the ectopic fat deposition-based theory. So far, both suggested mechanisms remain equivocal and debated.

The basic scientists and endocrinologists support the point of view that the insulin resistance and compensatory hyperinsulinemia are squarely responsible for the MS[6], [62], [9]. According to this group, obesity is thought to exacerbate insulin resistance and thus increase the likelihood of an associated adverse clinical condition, but it is not considered as a fundamental component of the syndrome, as the clustering of risk factors can occur in insulin resistant individuals of normal weight[70], [71]. The primary goal of this pathophysiological approach is to alert physicians to the idea that patients with insulin resistance are not only at risk for CVD, but also to other multiple adverse clinical conditions such as polycystic ovarian syndrome, nonalcoholic fatty liver disease, breast cancer, sleep apnoea. CVD is just one of these important conditions. This group of researchers do not seek strict clinical definition for the syndrome[67].

The other group presents the cardiologists and clinical epidemiologists who support the term "metabolic syndrome" and seek to assemble a group of related metabolic risk factors useful for the prediction of cardiovascular events, for prevention perspectives. In line with this viewpoint, obesity is considered as a core component of the MS rather than a modulator of the effects of insulin resistance[72]. The primary clinical goal of this school of thought is to suggest an operational tool to be used for long-term risk stratification of atherosclerosis patients [73], [43]. This group supports the idea that the abdominal obesity is the predominant driving force behind the MS and is a particularly detrimental factor in persons who have concomitant metabolic susceptibility from other causes.

Chronologically, the pathophysiological "Insulin Resistance Syndrome" transmuted into clinical "metabolic Syndrome" in the 1990s[74]. This shift happened to help the scientists to translate science into practice in an area of major medical and public health concern. As insulin resistance was difficult to be measured by the glucose clamp technique, at the population level, fasting plasma insulin levels was used as a proxy to prompt the research for cheap, easy surrogates of insulin resistance[74]. However,

this introduced a confusion because of the partial difference in the physiology of hyperinsulinemia and insulin resistance[75], as well as lack of measurement standardization across studies[74].

Then after, anthropometric measures were suggested to replace insulin resistance in new definitions of the MS. The NCEP-ATPIII and particularly, the IDF took the position that obesity (especially abdominal obesity) is a dominant factor behind the multiplication of risk factors. According to the NCEP, the onset of obesity elicits a clustering of risk factors in persons who are metabolically susceptible[73] (Figure 1). Metabolic susceptibility has many contributing factors, including genetic forms of insulin resistance, increased abdominal fat, ethnic and racial influences, physical inactivity, advancing age, endocrine dysfunction, and genetic diversity[76]. However, the relevance of this application has not yet exclusively establish by the research[74].

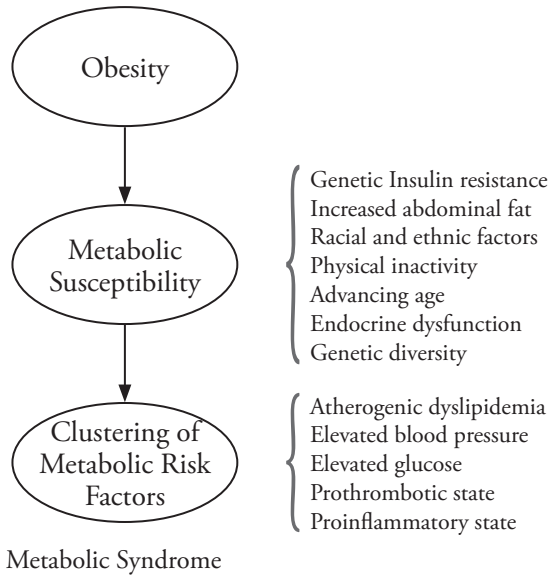

Figure 1 Proposed pathogenesis of the clustering of cardiovascular disease risk factors of metabolic origin, Grundy 2006[76].

2.3 Clinical utility

Certain researchers, representing mainly the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), opposed extending the concept of the MS to clinical practice and objected to characterize the MS as a risk factor for heart disease or diabetes[64], [65]. The claim was that the primary clinical emphasis should remain on treating the individual risk factors and that aggregating them into a syndrome has little clinical utility. In 2005, the ADA and EASD issued their own joint statement calling for a critical appraisal of the metabolic syndrome, its designation as a syndrome, and its clinical utility[64]. Recently, a new study published in 2010 analyzed data from the INTERHEART study, a case-control study of incident acute MI that involved 12 297 cases and 14 606 controls from 52 countries. The results suggested that patients with MS are no more at risk of future MI than those with diabetes or hypertension alone[77]. The results strongly suggested that treating the individual risk factors is rather better than focusing on the metabolic syndrome, supporting therefore, the individual risk-factor approach.

The counter arguments, represented by the IDF, AHA, and NHLBI advocated that the diagnosis of the MS helps physicians to discover persons at increased lifetime risk for CVD and directs the attention to the underlying causes, notably obesity and other lifestyle factors. The last group thereby reinforces its utility through the early detection for needs of lifestyle changes in clinical practice[10], [78]. In spite of this disagreement over clinical strategy, most investigators agree that clustering of metabolic risk factors is a real and relatively common phenomenon[79].

Grungy was the scientist who most thoroughly advocated the clinical utility of MS, by linking the importance of clinical MS recognition to an "iceberg phenomenon"[76]. He explained that identifying the metabolic syndrome provides a simple means of recognising the risk, submerged in a tangle of metabolic derangement[76]. According to Grundy, "*seeing the tip of the iceberg can be lifesaving but it seems fruitless to dissect surface configuration of an iceberg when most of the danger lies below. The same is true for a finding of the aggregation of the metabolic signs such as high TG, low HDL-C, impaired FPG, and mildly elevated BP in a patient with an increased WC*"[76].

Although the MS seemed to provide little advantage over the available risks scores (the Framingham or the European SCORE)[80], [64], several clinicians believe that the clinical diagnosis is useful because it determines the therapeutic strategy in patients at higher risk[76]. Moreover, the application of the available CVD risk scores is still cumbersome

and not routinely used in clinical practice. The MS may thus represent a simple convenient alternative tool to identify individuals at increased risk of atherosclerotic CVD or type 2 diabetes mellitus[81], [78].

Beyond risk assessment, the presence of the MS can alert clinicians to the likelihood of related pathological conditions, e.g. obstructive sleep apnoea, fatty liver, cholesterol gallstones, and polycystic ovarian disease[10]. In addition, it helps to recognize that patients with a clustering of measured risk factors usually have several hidden metabolic risk factors, e.g, a prothrombotic state, a proinflammatory state, and multiple lipoprotein abnormalities[43], [78].

As previously elucidated, full understanding of the pathophysiology responsible for the MS can help in determining the best treatment options. However, this issue is still a matter of discussion. Globally, there are 2 viewpoints about the best therapeutic strategy for patients with the MS. One conventional approach holds that each of the metabolic risk factors should be singled out and treated separately. However, the concern about this prescription is that it may lead to an aggressive use of medications at the expense of lifestyle therapies, particularly, weight reduction and increased exercise[76]. Alternatively, the other view emphasizes the global approach that aims to implement lifestyle therapies to reduce all risk factors simultaneously. It targets multiple risk factors together by striking at the underlying causes. Treating the underlying causes does not rule out the management of individual risk factors, but it may reinforce the control of multiple risk factors[76]. In practice, there is a tendency to switch from a vertical approach (by speciality) to a multidisciplinary horizontal approach, which enables early detection of the combination of risk factors, sometimes without obvious illness, as measure of effective prevention.

So far, there is no proof that the lifestyle modification interventions targeting the MS are superior to those targeting the individual components[64], [81].

2.4 Public health utility

Around the world, the MS is now considered as one of the major public health challenges of the 21st century, associated with a 5-fold and 2- to 3-fold increase in type 2 diabetes and CVD respectively [46]. In consequence, the related premature morbidity and mortality could overcharge the health care system budgets of both developed and developing countries[7], [82].

Although, there is limited research addressing directly the impact of MS on public health and/or health promotion activities[67], the MS was suggested to provide an easily comprehensive public health message. For example, in Japan, the Government recently introduced a national screening programme using the MS concept as a single point of entry to identify people at high risk who might benefit from an intervention to reduce CVD risk[83].

In the scientific research field, the introduction of the MS concept led to a large number of epidemiological, metabolic, and genetic studies that moved up the understanding of its prevalence and pathogenesis. Over years, the MS was a stimulus for the development of new drugs or drug combinations that may modify multiple risk factors simultaneously[10].

In addition, the MS was considered as a comprehensive approach to a major public health problem, called atherosclerosis[84], [44]. It constituted an educational tool for patients and health professionals, focusing on the multi-factorial nature of the atherosclerotic diseases. This approach recommended the same prevention and management strategies for both metabolic syndrome and its individual components (e.g. a healthy diet, regular physical activities, smoking cessation, weight loss and control, plus pharmacological intervention where necessary)[67].

2.5 Tool for CVD risk assessment

One of the most important criticisms addressed to the concept of the MS was its efficiency to properly evaluate the *global* CVD risk in clinical practice. The current recommendations stress the need to focus on the assessment of the total burden of risk, the so-called global risk profile, rather than on individual or particular risk factor. This is because, the absolute risk of an acute coronary event depends on the totality of interacting risk determinants; some associated with adult lifestyle, others operating from early childhood[50].

The plethora of epidemiological, metabolic and clinical studies, published over the last 2 decades, demonstrated that the different definitions of the MS were able to identify subgroups of patients at greater risk of type 2 diabetes[85] and at increased *relative* risk of CHD[56], [58]. Nevertheless, none of these definitions can properly assess *global* CVD risk[46].

In comparison to the available CVD risk algorithms, the MS, as a clinical entity, could not improve prediction of future (lifetime) risk of CVD[80], [64]. The related studies did not always take into account all potential confounding variables, which made the inter-studies comparison to establish evidence rather difficult [46]. Furthermore, the MS did not incorporate important traditional risk factors, such as smoking, age and gender[10].

For this purpose, the scientific communities emphasized the importance of using global risk calculators such as Framingham risk score, the PROCAM algorithm or the European SCORE, to evaluate the short-term risk of developing CHD[86], [64], [51]. Conversely, these CVD risk assessment tools did not capture the risk of abdominal obesity and the related abnormalities of the MS.

On the whole, the presence of MS alone cannot predict global CVD risk, nor do the available risk scores. Meanwhile, better risk assessment algorithms are needed to quantify diabetes and CVD risk on a global scale[86]. This global risk is referred to as global CardioMetabolic Risk (CMR), which will be explained in the following section.

3. Toward a new global "cardiometabolic risk" concept

The unremitting debate, as to whether the MS increases CVD risk beyond the risk posed by traditional CVD risk factors, has spurred the creation of a new concept named the global "cardiometabolic risk".

In order to move the field forward, a multidisciplinary International Chair on CMR was created, at the end of 2005, to provide a platform to discuss the concepts of abdominal obesity, metabolic syndrome, and global CVD risk [46].

Global CMR is defined as the risk of CVD resulting from the presence of traditional risk factors along with features of the MS[46], [86]. Under this model, CMR encompasses the overall CVD risk, resulting from traditional risk factors (age, sex, smoking, hypertension, LDL cholesterol, HDL cholesterol, diabetes) and from the additional risks of intra-abdominal obesity or related features of the MS. Under this working model, the MS cannot be used to assess the global CVD risk but is at best one more modifiable CVD risk factor [46].

Figure 2 illustrates the "building blocks" of global CMR, adapted from Després et al [46] and the interactive graph available on line at: http://www.cardiometabolic-risk.org/. It has been suggested that the CVD risk of abdominal obesity/metabolic syndrome may be independent of or go beyond the risk predicted by traditional risk factors. However, this hypothesis of considering MS as an independent "building block" needs to be confirmed by further research.

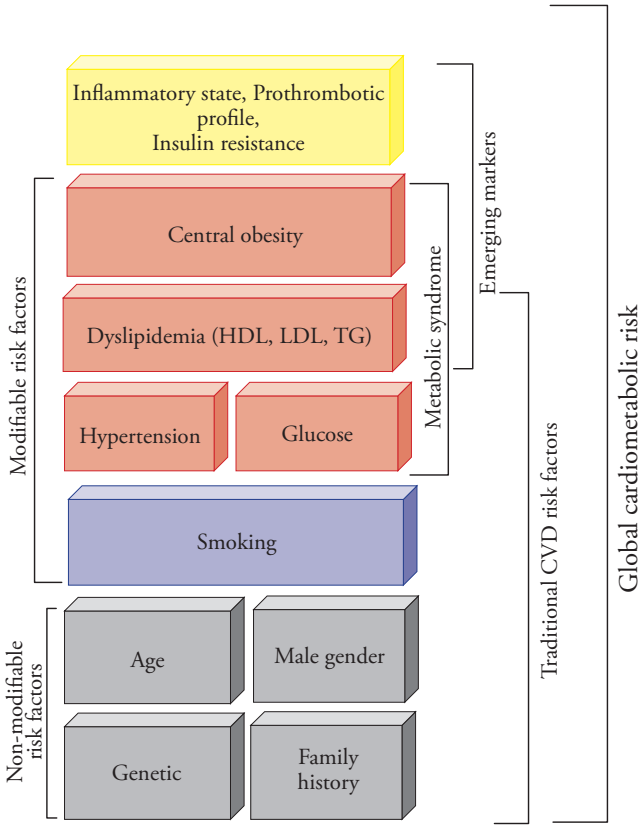

Figure 2. The "building blocks" of global cardiometabolic risk, with adaptation from Després et al [46].

Chapter 4

Epidemiology of metabolic syndrome

1. Introduction

The epidemiology is the study of how often and why diseases occur in different groups of people. The epidemiological information is used to plan and evaluate strategies to prevent illness and as a guide to the management of patients in whom disease has already developed. Like the clinical findings and pathology, the epidemiology of a disease is an integral part of its basic description. A key feature of the epidemiology is the measurement of disease outcomes in relation to a population at risk.

The MS is a cluster of CVD risk factor abnormalities associated with increased risk of type 2 diabetes mellitus and cardiovascular morbidity and mortality[27]. Understanding the epidemiology of the MS, knowledge about the variation of its frequencies and its potential determinants are essential pre-requisites to assessing and addressing public health needs. It enables decision-makers to plan efficient prevention programmes, which lead in the long term towards reducing the burden and consequently to health promotion of the general population.

This chapter aims to shed light on the current sate-of-art with regards to the prevalence of the MS worldwide and its key determinants.

2. Prevalence of metabolic syndrome

Multiple prevalence data suggested that the MS is very common worldwide, especially among older people and in certain ethnic populations[23]. The syndrome will undoubtedly become even more common over time, in parallel with the exploding epidemic of obesity and type 2 diabetes[79]. In addition, the worldwide increase in the prevalence of MS among children and adolescents[87], constitutes a greater public health concern, as emerging evidence suggested that children who had the MS increase their risk of developing adverse cardiovascular events later in life[88].

In this setting, the purpose of the following section is to describe and compare the MS prevalence rates reported in different studies, carried out during the current decade, in various countries all over the world. A thorough literature search for publications, documenting the prevalence of the MS according to the existing definitions, was performed with an emphasis on the problematical international prevalence comparison. The reported worldwide prevalence rates of the MS are depicted in Tables 10 (a-d). However, it must be noted that determining the prevalence of MS in different regions

varies according to the definition used; globally, it was different across the countries in terms of gender, age groups and ethnicity. In US population, the IDF definition led to a higher MS prevalence estimate (39%) than that based on the R-ATPIII criteria (34.5%)[89]. A spectacular increase in the prevalence was recorded among the same population, between 24% in 1988[89] and 34.5% in 2002[90], by using the NCEP-ATPIII definition. This raise was attributed to the increase in the prevalence of obesity between 1988 and 2000, as well as the aging of the population[91]. In European studies, the prevalence of the MS varied considerably between 18% in Italy[92] and 38% in Turkey[69]. The metabolic syndrome was also frequent in Middle Eastern countries[93] and India[94], although the lowest prevalence rates were recorded in Australia[95], and china[96]. Generally, the IDF criteria gave a higher prevalence rate as compared to the NCEP-ATPIII[79]. This was undoubtedly attributable to the lower WC threshold to define the abdominal obesity criterion. The WHO criteria variably induced a higher prevalence rate when compared to the NCEP-ATPIII definition [79].

Regardless of the definition used, studies were inconsistent regarding the gender-specific MS prevalence. While the MS was higher among men than women in France[97], [98], Germany[85], Ireland[99], Singapore[100], it was higher in Omani[93], Chinese[96] and Indian women[94]. In addition, accumulating evidences demonstrated that the prevalence of the MS was highly age-dependent, so as its individual components[23]. The prevalence increases with age through the sixth decade of life among men and seventh decade among women[101].

Race/ethnicity influenced also the prevalence of the MS. Some ethnic groups have a higher predisposition to central obesity than others: for example, the prevalence of central obesity is higher among South Asians than in Europeans. Asian populations have more metabolic abnormalities with the same obesity than do the Caucasians[96]. Thus, a modification of the WC cut-off values of the NCEP-ATPIII definition has been proposed for Asian populations. By applying the European definition of WC, the prevalence of MS was found generally lower among Asian populations than among European populations, However, when modified Asian WC criteria were used, the prevalence of MS increases and becomes similar (Korean population)[102] to or even higher (urban Indians)[94] than European populations. In USA, NCEP ATPIII-defined MS is more prevalent in Mexican Americans (31.9%) than in Caucasian (23.8%) and African American (21.6%)[30]. Ford et al reported that the MS was more common in Black and Hispanic women than in both counterpart men, which contrasted with the similar gender prevalence for Whites[30].

In fact, the cross-sectional and longitudinal epidemiological studies provided markedly varied prevalence and incidence of MS, because of the lack of internationally agreed-upon criteria to define the syndrome. The NHANES III surveys carried out in USA, aimed at comparing the prevalence of the MS according to the WHO and NCEP-ATPIII definitions demonstrated a substantial discordance for gender and ethnicity[90]. The IDF definition led generally to higher estimates of the prevalence, in all ethnic groups, especially among Mexican American men[89]. An elevated IDF prevalence of the MS was similarly observed in other worldwide studies[69], [92], [95], [103-106]. In 8 European cohorts (DECODE Study), the MS prevalence rate defined according to the WHO, NCEP-ATPIII and EGIR varied widely among the countries; the WHO definition showed particularly a wide gender-specific difference[68]. In Bruneck Italian Study, the prevalence of MS was significantly higher and almost double with the WHO criteria as compared to those of the NCEP (34.1% vs 17.8% respectively)[78].

In sum, the emerging prevalence data from population-based studies suggest that the MS is a very common cardiometabolic disorder worldwide with a wide gender discrepancy. A very consistent finding was that the prevalence of the MS increased dramatically with age and varied considerably across ethnic groups. Racial/ethnic WC component heterogeneity gave rise to substantial racial/ethnic variation in the prevalence of the MS itself. The use of different definitions in diverse populations resulted in wide ranging prevalence rates, thus highlighting the urgent need for a unified definition[107].

The wide variation of published data made direct international comparisons exceedingly difficult, in part, because of important methodological differences with respect to the characteristics of target population, the study design, the sample selection, and the year of conduct and in other part, because of the diversity of definitions[23]. Moreover, each definition relied on at least five different individual criteria with diverse cut-off points. Therefore, a unified definition is fundamental to enable international comparison of the MS prevalence and its relationship with various health outcomes. Only a few international studies reported age-adjusted prevalence rates, to enable meaningful comparison.

Table 10a. Prevalence of the metabolic syndrome in USA

Country, year of publication	Acronym, setting and period of data collection	Study design	Age group and subjects number	Definition	subject's characteristics	Age-adjusted Prevalence of MS
USA, 2002[30]	Third National Health and Nutrition Examination Survey (NHANESIII), 1988-1994	Cross-sectional population-based sample	≥20years (8814 subjects)	NCEP ATPIII	White	23.8%*
					Mexican American	31.9%*
					African American	21.6%*
					Other	20.3%*
USA, 2004[108]	Dearborn , Michigan, 2004	Cross-sectional, random sample	20-75years, (542 subjects)	NCEP ATPIII	Arab Americans population	23% *
				WHO		28% *
USA, 2003[90]	Third National Health and Nutrition Examination Survey (NHANESIII), 1988-1994	Cross-sectional, representative sample	≥20 years, (8608 participants)	NCEP ATPIII	Total	23.9%*
					Men	24.2% *
					Women	23.5%*
				WHO	Total	25.1%*
					Men	27.9%*
					Women	22.6%*
USA, 2005[89]	National Health and Nutrition Examination Survey (NHANES), 1999-2002	Cross-sectional population-based sample	≥20years (3601 subjects)	NCEP ATPIII	Total	34.5%
					Men	33.7%
					Women	35.4%
				IDF	Total	39%
					Men	39.9%
					Women	38.1%

* Non age-adjusted prevalence rate

Table 10b. Prevalence of the metabolic syndrome in Australia

Australia, 2005[95]	Adelaide, south Australia study	Random household sample	≥18 years, (4060 subjects)	NCEP ATPIII	Total	15%
					Men	15.7%
					Women	14.4%
				IDF	Total	22.8%
					Men	26.4%
					Women	19.4%

Table 10c. Prevalence of the metabolic syndrome in European countries

Country, year of publication	Acronym, setting and period of data collection	Study design	Age group and subjects number	Definition	Subject's characteristics	Age-adjusted Prevalence rate
Europe, 2005[68]	The DECODE Study Group, 1991, except in Spain (1996-1997)	Seven cross-sectional European population-based studies	30-77years, (9140 subjects), Non-diabetic Europeans	WHO	Men	26.9%
					Women	19.5%
				EGIR	Men	17.9%
					Women	16.5%
				NCEP ATPIII	Men	22.7%
					Women	23.1%
Germany, 2008[85]	The European Prospective Investigation into Cancer and Nutrition-Potsdam Study (EPIC) Potsdam, 1994-1998	Multi-centre, prospective cohort study	35-65years, (2796 subjects)	Revised NCEP ATPIII	Total	22.5% *
					Men	29.1%*
					Women	18.5%*
				IDF	Total	28.3% *
					Men	33.2%*
					Women	25.2% *
France, 2006[97]	Centre IPC (Investigation Préventives et Cliniques), Paris, 1999-2002	Volunteered for health check-up	62000 subjects, (mean age 53.2+/-9.1years)	Revised NCEP ATPIII	Men	11.8%*
					Women	7.6%*
France, 2003[98]	D.E.S.I.R Study, centre-western France, 1994-1996	Volunteered for health check-up	5446 subjects, 30-64 years	Revised NCEP ATPIII	Men	15%
					Women	10.1%
Norway, 2007[103]	Nord-Trondelag Heart Study(HUNT2), 1995-1997	Cross-sectional population-based sample	20-89 years, (10206 subjects	Revised NCEP ATPIII		25.9%*
				IDF		29.6%*
Finland, 2007[104]	The Cardiovascular risk in Yong Finns Study, 1986-2001	Population-based follow-up study	2182 subjects, 24-39 years	Revised NCEP ATPIII	Total	13%
				EGIR		9.8%
				IDF		14.3%

Ireland, 2003[99]	Primary care setting in the South of Ireland.	Random sample of attended subjects for screening from 17 general practice lists	50–69 years, (1,018 subjects)	WHO	Total	21%*
					Men	24.6%*
					Women	17.8%*
				NCEP-ATPIII	Total	20.7%*
					Men	21.8%*
					Women	21.5%*
Italy, 2003[78]	Bruneck Study, 1990	Prospective population-based survey	40–79 years, 888 subjects	WHO		34.1%*
				NCEP ATPIII		17.8%*
Italy, 2007[92]	FIBAR study	Sample of individuals enrolled in a screening program for diabetes	2,945 subjects, mean age 55.2+/-11.5 years	Revised NCEP ATPIII	Total	16.6%*
				IDF		29.7%*
Spain, 2003[109]	Nutritional Survey of the Canary Islands (ENCA), 1997-1998	Population–based study	18-74 years, 578 adults	NCEP ATPIII	Total	24.4%*
Spain, 2007	Province of Albacete	Cross-sectional, Population–based study	40-70 years, 425 subjects	Adapted NCEP ATPIII	Total	20.9%
Greece, 2007[110]	Greece	Cross-sectional, a representative sample	Adults, 9669 subjects	NCEP-ATP-III		23.3%
				Revised NCEP ATPIII		22.6%
				in IDF		18.3%
Portugal, 2008[111]	VALSIM Study	Primary health care users	18-96 years, 16,856 subjects	NCEP ATPIII	Total	27.5%
					Alentejo region	30.99%
					Algrave region	24.42%
Portugal, 2007[106]	Porto	Representative random sample, Population-based study	18-92 years, 1433 subjects	WHO	adult residents	26.4%
				NCEP ATPIII 2001		24%
				IDF		41.9%
				AHA/NHLBI 2005		37.2%
Turkey, 2007[69]	Turkish Heart Study, 2003	Cross-sectional population-based sample	Age 45± 13 years, (1568 subjects)	WHO	General adult population	19%
				EGIR		20%
				NCEP ATPIII		38%
				IDF		42%

Table 10d. Prevalence of the metabolic syndrome in Asian countries

Country, year of publication	Acronym, setting and period of data collection	Study design	Age group and subjects number	Definition	subject's characteristics	Age-adjusted Prevalence rate
Oman, 2003[93]	Nizwa study, 2001	Cross-sectional population-based sample	≥20years, (1419 subjects)	NCEP ATPIII	Total	21%
					Men	19.5%
					Women	23%
Chile, 2008[105]	Talca city study, year of data collection not mentioned	Probabilistic sample	18-74 years, (1007 subjects)	Revised NCEP ATPIII		29.5%
				IDF		36.4%
China, 2006[96]	The Chinese Multiprovincial Study, 1992	Prospective cohort study	35-64 years, (26972 subjects)	ATPIII according to Asian criteria of waist circumference	Men (≥ 90cm)	14.4%
					Women (≥ 80cm)	20%
				IDF according to Asian criteria of waist circumference	Men (≥ 90cm)	9.8%
					Women (≥ 80cm)	16.6%
South Korea, 2004[102]	Mokdong Study of Diabetes Prevalence, 1997	Random cluster sample	30-80 years, (1804 subjects)	ATPIII based on Asia-Pacific guidelines	Men (≥ 90cm)	29%*
					Women (≥ 80cm)	16.8%*
				ATPIII	Men (≥102 cm)	16%*
					Women ≥88cm)	10.7%*
South Korea, 2006[112]	Korean National Health and Nutrition Examination survey, 1998	Stratified multistage probability sampling design	20-80 years, (6824 subjects)	IDF (with specific waist circumference cut-off points)	Men (≥ 90cm)	13.5%
					Women (≥ 85cm)	15%
India, 2004[94]	Urban Indian population study	Population-based study	>20 years, (1123 subjects)	ATPIII	Total	24.9%
					Men	18.4%
					Women	30.9%

Seychelles (Indian Ocean, African region), 2008[113]	Seychelles Heart Study III, 2004	Cross-sectional, Population-based study	25-64 years, (1218 subjects)	WHO	Men	25%*
					Women	24.6%*
				ATPIII	Men	24%*
					Women	32.2%*
				IDF	Men	25.1%*
					Women	35.4%*
Singapore, 2004[100]	Singapore National Health Survey, 1998	Population-based study	18-69 years, (4723 subjects)	NCEP	Men (all races)	13.1%
					Chinese	10.8%
					Malays	17.3%
					Asian Indians	21.7%
					Women (all races)	11%
					Chinese	8.3%
					Malays	20%
					Asian Indians	19.3%
				NCEP-Asian criteria (Waist circumference 90 cm in men and 80 cm in women)	Men (all races)	20.9%
					Chinese	18.1%
					Malays	24.7%
					Asian Indians	32.4%
					Women (all races)	15.5%
					Chinese	12.5%
					Malays	23.8%
					Asian Indians	25.8%

3. Potential determinants of the metabolic syndrome

At every stage of life, health is determined by complex interactions between multitudes of factors that influence a person's disease or health status. With regards to the MS, the determinants which are centrally involved in its multi-factorial causation can be categorized as: biological or genetic susceptibility, socio-economic, environmental and behavioural factors.

3.1 Biological or genetic susceptibility

Although, twin and family studies showed a high heritability for each of the individual components[114]; the genetic basis of the MS, as a composite phenotype, was not thoroughly investigated. A number of researches indicated a genetic susceptibility of the MS. However, the associations were weak and the replication of findings was poor[115], [116]. While the prevalence of the MS has increased markedly in the last decades, the human genome has not changed. At present, no single gene or cluster of genes has been consistently replicated for the expression of this phenotype (MS) among different populations[117], [118], probably due to the complex interactions between gene and environment.

The 'thrifty genotype' hypothesis, proposed to explain the emergence of insulin resistance and diabetes in populations, shifted from vigorous activity to provide subsistence nutrition to sedentary life style with food abundance. In urban societies, the modern abundant food environment may be responsible for the elevated insulin levels and excessive energy stores in some type 2 diabetic individuals, leading in consequence to insulin resistance and obesity[119].

Genetic background can interact with habitual dietary fat composition, thereby affecting predisposition to the MS, and may also determine the individual's responsiveness to altered dietary fat intake[120]. Recent research indicates that currently ineffective therapeutic dietary recommendations may require a 'personalised nutrition' approach, wherein the genetic profile may determine the responsiveness of patients to specific dietary fatty acid interventions[121]. Complete understanding of the gene-gene, gene-gender and gene-nutrition interactions underlying the MS, will help to determine and then to minimize the principal complications, namely type 2 diabetes and cardiovascular disease[121]. Nevertheless as with most complex traits, it is still premature to propose molecular genetic testing for both diagnosis and treatment[122].

3.2 Socio-economic determinants

Several prospective observational studies showed that low socio-economic position, measured as education level, income, or occupational class was associated with increased risk for type 2 diabetes[123] and coronary heart disease[124], [125]. Clinical features of the MS were more commonly observed among socio-economically disadvantaged individuals[126], in individuals with low education level[127], [128], and in those doing menial jobs[129]. Increasing evidence indicated that the distribution of the MS varies among different geographic and socioeconomic categories of the population, demonstrating notable health inequalities[130], [131], [132].

3.3 Behavioral or lifestyle determinants

Lifestyle choices imposed by modern civilization have been demonstrated to be centrally involved in the multi-factorial causation of severe atherosclerotic disease [132]. There has been an increasing body of evidence demonstrating that unhealthy behaviours were substantially responsible for epidemic prevalence and mortality of CVD, diabetes and metabolic disorders[11], [14], [133], [134]. In contrast, a healthy lifestyle including non-smoking, appropriate diet, satisfactory physical activity level and healthy weight provided substantial cardiovascular and metabolic benefits[135]. Among the major potentially modifiable risk factors for MS and its components are the following:

3.3.1 Smoking

Growing evidence pointed to smoking as an independent risk factor for metabolic syndrome and type 2 diabetes. Smoking is a strong risk factor for atherosclerotic CVD, with a dose dependent relationship[136], [137]. Several population-based studies confirmed that cigarette smoking was independently associated with the MS [138-140], in particular in men[141]. The general belief is that insulin resistance or hyperinsulinemia is the main underlying mechanism. Increased insulin resistance may underlie the clustering of the metabolic and hemodynamic abnormalities that have potent atheroslerotic properties, designated the MS[26]. However, this hypothesis still needs to be tested in prospective studies.

3.3.2 Dietary habits

Although dietary intake has been linked to individual components of the MS[120], [142-144]. the role of diet in its origin is not well understood[145]. Cross-sectional epidemiological studies demonstrated that dietary intake rich in whole-grain foods was linked to a lower prevalence of the MS[146], [147], although other study found no relation[148]. Dairy

intake was inversely associated with the MS both prospectively and in cross-sectional studies [149, 150]. Greater intakes of fruits and vegetables were associated with a lower prevalence of the MS [151]. Intakes of regular and diet soft drinks were also positively associated with the prevalence of the MS, but the diet soda-MS incidence association was not yet hypothesized and needs further prospective studies [152].

Although various individual foods and nutrients were associated with the development or the progression of the MS, only a few studies examined the association with dietary patterns[153]. Prospective findings from Atherosclerosis Risk in Communities (ARIC) study suggested that consumption of a Western dietary pattern, meat, and fried foods promoted the incidence of the MS, whereas diary consumption provided some protection[145].

Recently, dietary pattern analysis has emerged as an alternative and complementary approach to examine the relationship between diet and the risk of chronic diseases. Instead of looking at individual nutrients or foods, pattern analysis examines the effects of overall diet. Conceptually, dietary patterns address the effect of the diet as a whole and thus may provide a broader picture of food and nutrient consumption, and may thus be more predictive of disease risk than individual foods or nutrients[154], [155].

3.3.3 Alcohol consumption

Across the literature, the association between alcohol consumption and the MS is controversial and influenced by several factors, due to broad overlap of alcohol consumption with different components of MS. Protective and detrimental associations were reported between alcohol consumption and the MS, due to variations in drinking patterns and different alcohol effects on the MS components[156]. Mild to moderate alcohol consumption is associated with a lower prevalence of the MS, with a favourable influence on lipids, waist circumference, and fasting insulin. This association was strongest among whites and among beer and wine drinkers[157].

A recent meta-analysis study, carried out by the researcher, aiming to support the evidence available regarding the relationship between alcohol consumption and the MS, as a comprehensive clinical entity, as well as to identify the gender-specific dose-response, showed that alcohol consumption of less than 40 g/day in men and 20 g/day in women significantly reduced the prevalence of MS[158].

3.3.4 Physical activity

In agreement with the notion that physical inactivity is a risk factor of diabetes, obesity, dyslipidemia and hypertension[159-162], the prevalence of the MS was higher in subjects with poor physical activities[78], [163].

Sedentary behaviour is an important potential determinant of the MS. Several studies demonstrated that physical activity was inversely associated with the prevalence of the MS[164-167]. The prevalence of MS was higher among those who spend an increased amount of time in sedentary activity such as watching television or video or using a computer[163]. The adverse effect of excess television watching on obesity and other cardiovascular risk factors is thought to be attributed, in part, to decreased energy expenditure and, in other pat, to increased energy intake. Therefore, an understanding of how sedentary behaviour relates to the MS may provide new opportunities for clinical and public health approaches in its prevention and control.

3.3.5 Psychosocial factors

Accumulating evidence implied that possible psychological mechanisms were underlying the development of the MS. The syndrome appeared to be triggered by adverse psycho-social circumstances[168], certain chronic psychological pathologies[169, 170] and chronic stress[126]. Individuals who had hostile personality and certain behaviour traits, were particularly predisposed to develop the MS[126]. Such factors might interact with others to encourage the development of MS. The stress is exacerbated by lack of social support and/or poor coping skills. As a vicious cycle, the negative psychological behaviours may induce unhealthy lifestyle and/or adverse social circumstances[171]. A large population study demonstrated a higher incidence of the MS among young women, but not in men, with a history of depression after controlling for other associated factors[169]. Features of the MS also appeared more common among women experiencing social anxiety[172]. These findings suggest the possibility of different gender-specific causal pathways to the MS development.

3.4 Environmental factors

Recently, the scientific evidence linking air pollution to heart attacks, strokes and cardiovascular death has been substantially supported, especially for the fine particulate matter (PM). The major source of PM is fossil fuel combustion from industry, traffic, and power generation. Biomass burning, heating, cooking, indoor activities and forest fires may also be relevant sources, particularly in certain regions[173].

Several interrelated pathophysiologic mechanisms underlying the observed short-term and long-term adverse cardiac effects of ambient air pollution have been elucidated[174], for instance, the pivotal role of vascular inflammation in pathogenesis and progression of atherosclerosis and CHD. Systemic inflammatory response to inhaled ambient particles has emerged as an important mediator of the PM-associated acute cardiac effects[175]. However, human data is still scant and conflicting with respect to the pathophysiologic mediators of CVD associated with long-term exposure to fine PM. The researchers hypothesized that long-term exposure is associated with increased systemic inflammation, and that people with MS have a higher degree of inflammatory responses to PM.

3.5 Emergent factors

In recent research, a growing number of other factors, called "emerging or novel risk factors", have been described and linked with features of the MS. Several new bio-markers or candidate cardiovascular risk factors have been proposed as significant predictors of the atherosclerotic disease and its complications. These include inflammatory-, hemostasis or thrombosis-, lipid-related markers, oxidative stress, hormonal factors and infectious agents [176-180].

The novel bio-markers, psychological and environmental factors are outside the scope of the present research work and hence will not be further detailed.

In conclusion, the MS is a multi-factorial disorder and its development is the result of multiple interactions between biological, behavioural and environmental factors. Tackling the potential determinants is therefore of great importance for reducing its burden and for promoting the health of the general population.

Part II

Research method

Chapter 5

ORISCAV-LUX survey

1. Introduction

Today around 60% of worldwide deaths and 43% of the global burden of diseases are attributed to coronary heart disease, stroke and type 2 diabetes mellitus[1]. These diseases are predicted to account for 73% of global deaths and 60% of the global burden by year 2020[2]. In modern industrialized countries, CVD is the leading cause of hospitalisation, disability and death. There is strong evidence that cigarette smoking, obesity, lipid disorders, elevated blood pressure and diabetes mellitus are not only associated with each other[3], [181], [182] but also with cardiovascular morbidity and mortality [183-190]. On the other hand, it has been shown that major changes in the risk of CVD can be reduced by modifications of the lifestyle and social behaviour of individuals[191], [192]. Despite major advances in prevention, diagnosis and treatment measures, CVD is still the main cause of mortality in Europe. It accounts for over 4 million deaths yearly, i.e., nearly half (49%) of all European deaths, but with striking geographical variations[193].

1.1 National context

The Grand-Duchy of Luxembourg is a small country in the heart of Europe landlocked by Belgium, France and Germany, with a population of 493,500 inhabitants (official estimate, 2009) over an area of about 2600 km^2. About 43.7% of the population subjects are well-integrated foreign residents from over 150 different nationalities. In Luxembourg, cardiovascular mortality accounted for about one-third of total mortality in 2006[194]. This outcome made cardiovascular health one of the top priorities of Luxembourg healthcare authorities. Although the Ministry of Health has long been involved in planning and organizing prevention programs and health promotion campaigns to endorse healthy lifestyles, there has been so far no proper population-based study to assess the prevalence and clustering of cardiovascular risk factors (CVRF) among adults. Luxembourg is one of the few European countries without a well-defined structure for permanent and/or periodic observational surveys on cardiovascular health statistics allowing the development of coherent and effective strategies of prevention.

The "Observation of Cardiovascular Risk Factors in Luxembourg" (ORISCAV-LUX) survey, was conducted under the auspices of the Ministry of Health and co-financed by the Ministry of Research. It was designed as a nationwide cardiovascular monitoring survey aimed to establish baseline information on the prevalence of potentially modifiable and preventable CVRF, including obesity, hypertension, diabetes mellitus, lipid disorder, current smoking, physical activity and dietary habits among the general adult population of Luxembourg.

An emphasis on the rational, objectives, study design and conduct, as well as the preliminary salient results with respect to the prevalence of potentially modifiable and treatable cardiovascular risk factors has been published in BMC Public Health Journal (see Appendix).

1.2 Interregional context

According to a recent cross-border study, carried out in the frame of European interregional programme (INTERREG IIIA), aimed to compare the cardiovascular mortality rates in three neighbouring regions, Grand-Duchy of Luxembourg, Wallonia in Belgium, and Lorraine in France, Luxembourg ranked first with elevated cerebrovascular and ischemic coronary disease mortality in both men and women[195].

In convergence with the national needs, the idea of cross-border cardiovascular health monitoring was born in 2005. The outline of a standard protocol was conceived by the inter-regional committee which consisted of 5 partners from the three regions, with various skills in the fields of public health, epidemiology, cardiology, and nutrition.

Thus, the ORISCAV-LUX study is integrated into an inter-regional survey, entitled "Nutrition, Environment and Cardiovascular Health NESCAV". This survey based on a standardised monitoring method and collection tools that enable a relevant comparison between the 3 regions in terms of cardiovascular health and lifestyles-related risk factors in the population of the greater region. The study protocol of NESCAV project has been published in 2010 (see Appendix).

1.3 Inductive approach of research

The ORISCAV-LUX study has dual significance. First, it meets emerging needs for a sustainable health information system through collecting and establishing national baseline statistics for important cardiovascular pathologies and risk factors. Second, it constitutes a worthy database attracting researchers, interested by the topic.

Thus, the ORISCAV-LUX database presents the best opportunity to investigate the epidemiology of the MS in the general population resident in Luxembourg, to study the variation in its frequency, to identify the potential determinants of these variations in order to suggest prevention strategies suitable to the real needs of the groups at risk.

ORISCAV-LUX database is the basis of the present dissertation which constitutes an epidemiological research of descriptive and analytical nature. This research employed an inductive approach or so-called "bottom up" moving from specific observations to broader generalizations and theories (Figure 3). The inductive research is theory-generating. It helps to develop new hypotheses and generate new theories and finally to develop general conclusions.

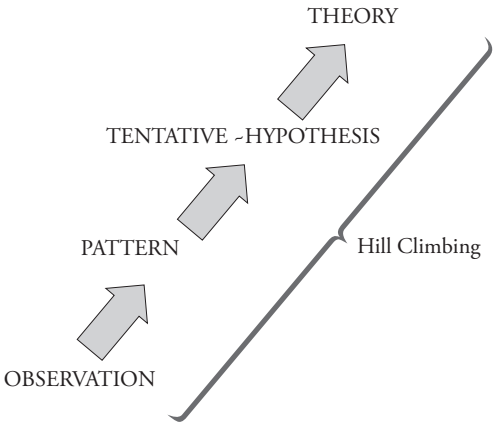

Figure 3. illustration of the "inductive approach" of research

2. Material and Methods

This chapter deals with methodological considerations of ORISCAV-LUX study. Figure 4 illustrates the summary diagram of the study procedure.

2.1 Survey design

The ORISCAV-LUX study was designed as a nationwide stratified, population-based survey, aimed to establish baseline information on the prevalence of potentially modifiable and preventable CVRF, including dietary habits, cigarette smoking, physical activity, obesity, lipid disorder, hypertension, and diabetes mellitus among the general adult population of Luxembourg. From a public health and research perspective, this survey is intended to be repeated at regular intervals to monitor the evolution.

2.2 Target population

The target population including all the individuals residing in Luxembourg aged between 18 to 69 years and fulfilling appropriate physical conditions were eligible to participate in the study. However, pregnant women, people living in institutions, subjects outside the determinated age range, those unable to respond for various reasons (for example: dementia, serious physical or mental illness) and those deceased before recruitment were excluded from the study.

2.3 Sampling plan

The sampling design consists of a representative random sample of the population resident in Luxembourg, stratified according to gender, age (5-year categories) and geographic district (Luxembourg, Diekirch and Grevenmacher). The sample was drawn from the regularly updated national health insurance registry, which covers nearly 98% of the resident population. The distribution of subjects in each stratum was proportional to their distribution in the target population. By power calculation[196], a sample size of 1285 subjects, was found necessary to ensure a statistical precision of at least 2% for the estimation of the prevalence of the risk factors at 95% confidence level. However, in the light of a literature review and previous experience with multiple-stage community-based studies, a high non-participation rate was expected, including refusal, invalid addresses, and non-response. Assuming a response rate of 30% and a proportion of 5% of institutionalized subjects in each stratum, the sample size was augmented to 4496 subjects.

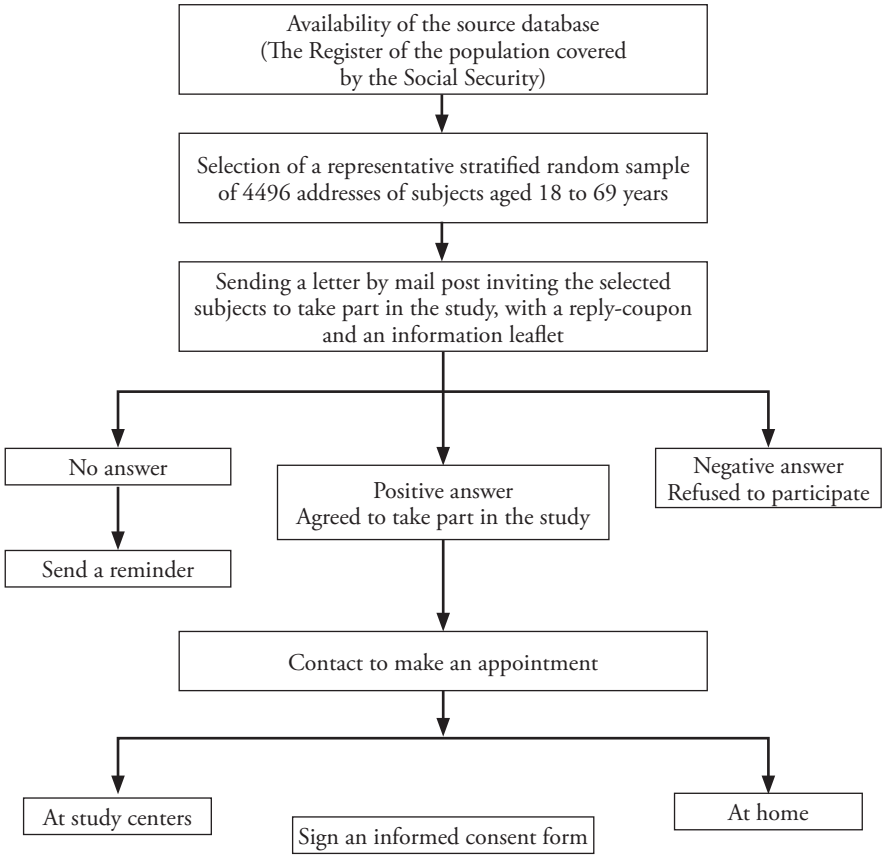

Figure 4. Summary diagram of the study's procedure

2.4 Preparation for research procedure

Various elements related to the operational conduct of the study proceeded rapidly. This concerned:

2.4.1 Ethical considerations

Ethical approval of the study protocol, by the *Comité National d'Ethique de Recherche*, was obtained in July 2006, followed by the authorisation *of Commission Nationale pour la Protection des Données* in September 2007.

2.4.2 Study-related communication and media coverage

Along with study kick-off, a media coverage campaign, targeting the general public and health professionals, was launched at national level. More than 700 posters and leaflets were widely distributed to encourage the resident population to take part in the study. At the same time, the Web site: www.ORISCAV-LUX.lu was created and placed on-line, prior to the start of the field phase.

2.4.3 Instruments translation

All documents, including questionnaire, invitation letter, coupon-answers, and informant leaflets were translated into 4 languages (French, German, Portuguese and English) to ensure the comprehension of, and promote the participation of selected subjects.

2.4.5 Staff training

The study personnel (nurses and administrative agents), was trained prior to the start of the field stage, to perform accurately the assigned tasks. The training covered the following major aspects:

- An introduction to the general context of the study topic, the current state of knowledge of cardiovascular risk factors, and the principal objectives of the ORISCAV-LUX survey;
- Information about the ethical aspect, including the importance of confidentiality, participants' security, and private data protection;
- The technique of how to use the measurement equipments, and to carry out anthropometric and clinical measurements, according to standard operating procedures;
- The attitude of the interviewer in performing the phone calls, establishing a relationship of trust and gaining the co-operation of the respondents;

- Instructions regarding the daily organisation of field data collection and the conducting interviews;
- The procedures for quality control of each participant's file.

Regarding the Food Frequency Questionnaire (FFQ), the project team was trained by the University of Liège, mainly with respect to the theoretical basis, the way of application, and the use of the photographic manual.

2.4.6 Logistical preparation

All necessary equipments were prepared prior to the launch of the field stage, including automatic blood pressure monitors, portable wall stadiometers, electronic medical scales, and tape measures for clinical and anthropometric measurements.

2.4.7 Preparing the data collection centres

In order to ensure a smooth running of the study and facilitate the transportation of participants, 6 centres dispatched all over the national territory were prepared prior to starting the field work.

2.4.8 Creating the data entry template

The data entry template consisting of the major sections; the questionnaires, the clinical, anthropometric and biological data, was developed using Epidatat® software.

2.5 Fieldwork procedures

2.5.1 Subjects recruitment

The subjects' recruitment procedure comprised three steps:

1st step - Invitation Letter

The selected subjects received an official invitation letter, explaining broadly the ORISCAV-LUX study objectives and the tests to be performed. Together with this was an information leaflet, a reply coupon to indicate a willingness to take part and a prepaid envelope holding the address of the study research centre.

2nd step - Phone contact and appointments

The consenting subjects were rapidly contacted by telephone to schedule an appointment at one of the nearest study centres. In case of transportation difficulty, a home visit by the study nurse was organised. A few days prior to the appointment, a confirmation letter was sent to each participant indicating the day, time, and place,

with a map showing the right address, as well as instructions concerning a fasting state for at least 8 hours before attendance, and requests to bring along the prescribed medications.

3rd step - Conduct of the field work
Regardless of the data collection location (at home or at an investigation centre), the trained nurses provided an in-depth explanation of the study, in order to make sure that the participants fully understood the purpose of the study and agreed to undergo the requested clinical, anthropometric and biological tests. Each participant was invited to read and sign an informed consent form before proceeding to data collection. Upon request, the participants received a certificate indicating the day and the period during which they participated.

The blood and urine samples were grouped together at the end of field work morning and forwarded to the laboratory of the Central Hospital of Luxembourg (CHL), in a cold tank within the 2 to 3 hours after collection.

2.5.2 Study duration and recruitment calendar

The subjects' recruitment for the whole study took place over a period of nearly 15 months, from 9 November 2007 to 16 January 2009. Mail was sent to all sampled addresses prior to the start of the data collection. Reminders were sent to those subjects who did not reply to the first invitation letter. Given the considerable sample size, in particular from the Luxembourg district, the post mail was sent out in 3 successive waves of one-month interval between each mailing, taking into account the holiday periods.

The following chart shows the study start, the study end, and the reminder dates for each district

District	1st invitation	1st reminder	2nd reminder
Luxembourg	1st wave: 15th October 2007	2nd April 2008	28th May 2008
	2nd wave: 16th November 2007		
	3rd wave: 2nd January 2008		
Diekirch	5th June 2008	5th September 2008	22nd October 2008
Grevenmacher	5th June 2008	5th September 2008	22nd October 2008

2.5.3 Stages of participation to the ORISCAV-LUX survey

Consistent with the WHO's Step-wise strategy, the participation to the ORISCAV-LUX study involved 3 main stages (Figure 5):

Stage 1 concerned the filling in a self-administered questionnaire with the help of the nurses, to ensure the totality of answers and to reply for any explication.

Stage 2 concerned the measurement of weight, height, waist and hip circumference as well as blood pressure, according to standardised operating procedures.

Stage 3 concerned blood and urine sample collection.

The WHO's STEPS-Wise strategy for monitoring risk factors (2001)

Figure 5. The data collection stages according to the WHO's Step-wise strategy

2.5.4 Survey instruments and parameters

Apart from the nutritional data gathering tool (FFQ), the ORISCAV-LUX questionnaires were chosen by the inter-regional panel, after careful review of the existing internationally tested and validated questionnaires on similar epidemiology studies. The FFQ was developed, tested and validated by the University of Liège. It was adapted to Luxembourg's cultural and linguistic context. The ORISCAV-LUX survey consisted of 2 major topics:

1. General Information Questionnaire

This questionnaire elicited information about the demographic and socioeconomic characteristics of each participant, including the age, gender, country of birth, income, education, profession and marital status, as well as family and personal medical history and medication intake.

2. Life style assessment questionnaires

Several self-administered validated questionnaires, either in complete version or in short version, were used to evaluate certain cardiovascular-related life style behaviors, including:

Tobacco consumption: Data collection based on self-reported current and past smoking, tobacco dependence, history of use, age at initiation, amount used, and knowledge about the incentives for beginning to smoke and related details.

Alcohol use: The "AUDIT" questionnaire (Alcohol Use Disorders Identification test) [197], developed by the WHO, for early detection of harmful alcohol consumption.

Dietary habits: The FFQ is the most common dietary assessment tool used in large epidemiologic studies of diet and health. It aims to assess dietary intake, by asking the participants to report the frequency of consumption and portion size of approximately 134-items over the last three months. Each item is defined by a series of foods or beverages. The Participants reported the frequency of consumption of each food group on the basis of 6 levels of frequencies, ranging from "rarely or never", i.e: < 1 time a day to "2 times or more per day". Standard serving sizes of food or beverage was either specified on the FFQ (e.g. soup spoon), or estimated based on a photographic manual, validated by the SI.VI.MAX study[198]. It was provided for each participant as a reference for the evaluation of consumed portions. Food and beverages from the FFQ were categorized into 9 major food groups: starchy food, fruits, cooked and raw vegetables, meat-poultry-fish-eggs, prepared dishes, diary products, fats, divers' food and, drinks (alcoholic and non-alcoholic). Nutrient intakes were calculated by multiplying the consumption frequency of each food by the nutrient content of specified portion. Nutrient values were obtained from the French SI.VI.MAX Food Composition database[199].

Physical activity : International physical activity Questionnaire (IPAQ), developed by a consensus group of experts in 1998, is a valid and reliable questionnaire[200] measuring health-enhancing physical activity across a variety of daily situations, such as leisure time, work, transportation, and household tasks. In each of the four domains, the frequency (number of days per week) and duration (time per day) spent for at least 10 minutes per session in both moderate and vigorous activity, during the last 7 days before the survey were recorded. Practical examples of culturally relevant activities of moderate and vigorous intensity were given. Similarly, information on walking

and total sitting time, as an indicator of sedentary behaviour was collected. The short form (nine items) of IPAQ questionnaire was applied, as well as a question about the habitual practice of sport and its type.

2.5.5 Clinical measurements

Blood pressure: For blood pressure measurement, subjects were seated in a chair with their arms bared and supported at heart level. Systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg) were measured at least 3 times with a minimum of 5-min interval between each measurement, by using Omrom® MX3 plus automated oscillometric Blood Pressure Monitor (O-HEM-742-E) (Matsusaka, Japan)[201], with an appropriate cuff size adapted to the upper arm perimeter of participant. Measurements were only performed after the participants had been seated for at least 5 minutes after questionnaire completion and at least 30 minutes after blood intake and a refrain from smoking. The average of the last 2 readings was used in the analysis.

Anthropometric measurements: Anthropometric measurements including weight, height, waist and hip circumferences were measured using standardized operating procedure according to the predefined anthropometric standardization reference manual.

Body weight (kg) was recorded with an accuracy of ± 100 g by using a digital column scale (Seca® 701, Hamburg, Germany); with subject barefoot and wearing light clothing. The scale was calibrated regularly.

Standing body height (cm) was recorded to the nearest 0.2 cm with a portable wall stadiometer (Seca, Germany), attached to the scale, with heels together, shoulders in relaxed position and arms hanging freely. Body mass index (BMI) was calculated as body weight in kg divided by the square of height (m). Self-reported height and weight were not acceptable.

Waist circumference (WC, cm) was measured in nearly every case by one nurse throughout the study, at the level midway between 12^{th} rib and the uppermost lateral border of the iliac crest during mild expiration. Care was taken that the tape was placed in a horizontal plane at the appropriate position and the measurement was taken with the tape in close contact with the skin but without indenting the soft tissues. WC was measured to the nearest 0.5 cm with the subject at standing position, using a flexible, non-distensible tape and avoiding pressure exertion on the tissues.

Hip circumference (HC, cm) was taken as the greatest circumference at the level of greater trochanters. The measurement was made to the nearest 0.5 cm. As it was not possible to undress the participants in the field setting, hip measurements were made over very light clothes.

2.5.6 Biological parameters

Several biomarkers were measured, mainly fasting plasma glucose (FPG, mg/dl), triglycerides (TG, mg/dl)), total cholesterol (TC, mg/dl), low-density lipoprotein cholesterol (LDL-C, mg/dl), high-density lipoprotein Cholesterol (HDL-C, mg/dl), as well as to other biomarkers.

2.6 Feedback for the participants

All the results of biological tests were examined and commented by the cardiologists before being sent to each participant. The significant pathological cases were contacted directly by phone and requested to consult their family doctor.

2.7 Quality control measures

Strict control measures were applied to ensure quality throughout the conduct of the study, namely, sample selection, operational data-collection, data processing and reporting. These included well-defined sampling design and prior estimation of sample size to reduce sampling errors; testing and validating the translated questionnaires; introducing multiple cross-checked questions on the same topic to validate the results; training of data collection nurses to perform their duties according to standard operating procedures; monitoring and ascertaining of instruments performance every morning before starting the tests on the subjects; daily assessment of paper forms for answer's relevance and completeness; designing the database in a way that allows to confirm the validity of the participant's identification codes, establishing the completeness of the entered data and performing basic data checks; training of data processing personnel to be able to provide reliable and accurate documentation, as well as periodic summary reports on the latest project progress; independent double data entry followed by matching and checking for data-entry errors, so that problems were appropriately remedied; data cleaning according to experts' consensus; finally, checking of the internal and external consistency of the analyzed data before reporting.

2.8 Measures to increase the participation

Intensive efforts were made to increase the response rate, not only during survey preparation but also during the participants' recruitment phase. At kick-off phase, survey publicity, including flyers and media articles, were disseminated to provide the selected individuals with ample information about the study objectives, relevance to public health policies, ways of participation and participant's rights. A telephone number for inquiries was supplied and the ORISCAV-LUX website was set up. A detailed personal invitation letter with a prepaid reply envelope addressed to the research centre was enclosed with each mailing. The selected subjects were asked to send their approval and phone number for follow-up contact and appointment; otherwise, they were requested to mention the reason for refusal with the purpose of obtaining a prior idea about the reasons of non-participation.

Up to three written invitations (first letter and 2 reminders) were sent at monthly intervals to those who did not respond spontaneously. They were followed by several telephone contacts by skilled personnel, in order to recruit the remaining non-respondents. Those who refused were not contacted again. The field-nurses and phone interviewers were all trained and supplied with detailed manuals. Undecided cases were followed up by the project manager by means of personal phone contact, to allay the subject's hesitations and to give him/her an opportunity to ask further questions about the study. To ensure smooth and well organized data collection, several investigation centres dispatched all over the national territory were prepared to welcome the participants, every morning and occasionally on Saturdays. Home visits were also proposed to those who had transport difficulties related to their health status.

Due to the cultural diversity in Luxembourg, all documents (invitation letter, coupon-answer, consent and questionnaires) were translated into the three most spoken languages: German, Portuguese and English. The translated questionnaires, originally established in French, were independently back-ward translated into French to ensure the validity[202]. Multi-lingual field-nurses and phone interviewers were employed. These measures were taken to increase the potential participation of the minorities. Another method of increasing response rate was providing anonymity to the subject, by using only a research identification number and code-bar for each participant's file. A clear sentence was written over the communicated documents, pointing out the approval of the national ethical committee and the national council for private data protection. In addition, mutual benefit theory was applied, aiming to maximize the participation, by supplying the participants with their biological results complemented by the cardiologist notes. In case of abnormal findings, they were advised to consult their family doctor.

The article[203] titled, Comparison of participants and non-participants to the ORISCAV-LUX population-based study on cardiovascular risk factors in Luxembourg, published in BMC Medical research methodology, provides an insight regarding the strategies applied to increase response rate, sample representativeness, sources of complementary data to investigate the characteristics of non participants. Therefore, these issues will be shortly outlined in the following section.

2.9 Participation rate and survey response

The database received from the IGSS (4,496 subjects) underwent 3 exclusion stages, for the subjects who did not match the inclusion criteria (Figure 6).

- Primary exclusion (before sending the invitation mail) involved 21 addresses belonging to institutionalised subjects.
- Secondary exclusion (after sending the invitation mail) involved 32 cases, related to 21 pregnant women, 5 seriously mental or physical handicapped individuals, 1 prisoner and 5 people who deceased prior to recruitment.
- Tertiary exclusion (prior to analysis of database) involved 2 people being 70 years old at the time of recruitment.

A total of 4452 subjects were potentially eligible to take part in the study. However, further, 213 subjects (4.8%) were no longer residing at their home address as identified by the post office as "return to sender" and were classified as invalid addresses; 502 subjects (11.3%) absolutely refused to participate and were labeled as negative answers; 1545 (34.7%) subjects replied positively and were classified as positive answers; the 2192 (49.2%) individuals who never returned the response-coupon despite 3 invitation letters were considered as "non-respondents". Among initially positive answers, 80 persons eventually refused to continue and were listed as "withdrawal cases"; moreover 31 subjects couldn't come to repeated appointments because of unavailability. The "invalid addresses", "negative answers", "non-respondents", "withdrawal cases" and those how couldn't participate were grouped in a single category called "non-participation", constituting 67.8% of the eligible sample.

Ultimately, a total of 1434 (32.2%) was successfully recruited, hence achieving the prior calculated sample size and the expected response rate. Two participants who reached 70 years of age at the time of recruitment were excluded later from the analysis because they exceeded the recruiting age limit.

A majority of subjects who refused to participate ("negative answers", n= 392; 78.1%) did not indicate the reason. For those who did, the reasons were: lack of time to participate (33 cases), prolonged absence in particular for university students abroad (44 cases), permanent medical control (23 cases), personal reasons (5 cases) and absence of interest in the topic (3 cases).

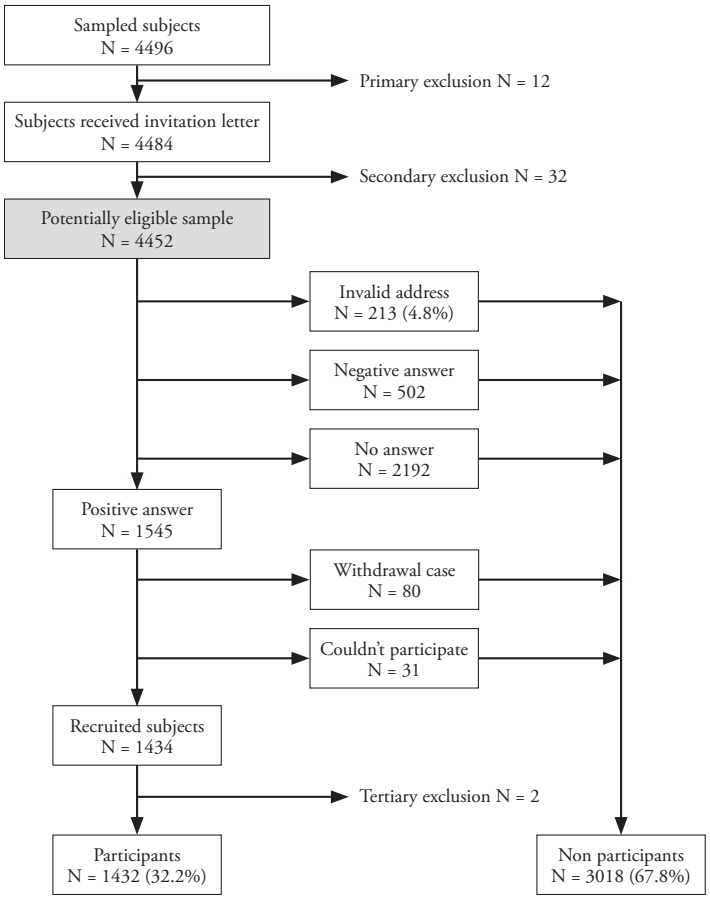

Figure 6. The ORISCAV-LUX subject's recruitment flowchart

2.10 Sample representativeness and non-response bias

As stated above, the response rate (32.2%) corresponded to the expected rate upon which the sample size was calculated. To assess the representativeness, the recruited sample (1,432 participants) was compared to the source population (298,521 individuals) according to the stratification criteria: gender, age category and district of residence.

No significant differences were found for gender and district distribution in the recruited ORISCAV-LUX sample as compared to the source population. By contrast, the youngest age group was under-represented, while adults and elderly were over-represented in the sample. This finding was expected as most of the young adults were not available due to their prolonged absence for studying abroad. In addition, the cardiovascular focus of the ORISCAV-LUX study might not be a priority for young age groups who usually enjoy good health. Conversely, the over-representativeness of the older people might be reasonably due to their perception for the need for clinical check-up, especially when counselling by a cardiologist was provided freely.

The potential non-participation bias of the ORISCAV-LUX data was determined by the degree of similarities between the characteristics of participants and non-participants. Given the absence of discriminating cardiovascular health-related profiles between participants and non-participants, it was concluded that the response rate does not invalidate the results and allows generalizing the findings for the population[203]. More information regarding the sample representativeness in terms of selection criteria (age, gender and district of residence) is detailed in the next chapter.

2.11 Data Weighting

As mentioned above, the ORISCAV-LUX study sample contained a slightly higher proportion of older population and less young adults. Therefore, the potential consequence of age-related non-response bias was handled by adjusting the sample for age, by using the most recent available distribution of the Luxembourg's population (STATEC database). A sampling weight equal to the inverse probability of unit selection was allocated to each subject from the same state. This stratum sampling weight was defined as the ration between the population stratum size and the observed sample stratum. According to research questions, future analyses will be performed after sample weighting to take into account the stratified random sampling design.

3. Personal contribution

The researcher is the ORISCAV-LUX project leader. She supervised the whole progression of study and ensured its conduct, with the help of a team based at the CRP-Santé. The study implementation task included; the planning for participants' recruitment; the co-ordination and preparation of the investigation centres; the organisation of data collection team movements between the various sites of investigation; the acquisition of the required equipments; the training of field and data-entry staff; and the daily follow up of the data collection, entry, validation process and documentation.

Throughout the 15-month field phase, she ensured the quality control process during the different study stages, particularly with regard to the in-office check of the participant's files, in order to make sure that all the answers were correctly and relevantly filled in. Along with the whole team, she was continuously available to reply to the participants for any information relating to the study.

As mentioned at the beginning of this chapter, the ORISCAV-LUX study was the embryo of an interregional partnership. She involved in the conception, tools selection, and drafted the protocol for the Grand Duchy of Luxembourg region.

Chapter 6

Statistical analysis

1. Description of variables

The following paragraphs describe the variables included in the analyses.

1.1 Demographic and socio-economic variables

Age was classified into 5 categories; the range of the first age group was 18 to 29 years, the second group was 30 to 39 years, the third group was 40-49 and so on. Gender was defined as the condition of being female or male. District of residence: the country was divided into three geographic districts (Luxembourg, Diekirch and Grevenmacher). Country of birth: The participants were classified according to their country of birth into 2 major groups: born in European country; and born in a non-European country. The non-Europid group, comprising 5.8% of the total sample was excluded from the analyses.

Level of Education was based on the highest qualification (diploma) achieved. This variable was classified into 3 principal groups: highest tertiary level equivalent to university or more; secondary level equivalent to classical and technical qualification; primary level corresponding to those who did at least first 9 years of mandatory education or more but without academic qualification (devoid of diploma). The variable "years of education" was not chosen due to the national education system particularities which allow repeating the class. Marital status was recorded in 4 categories: single (never married); divorced or separated; widowed; and married or living with partner. Work status was classified in 3 groups as: employed (participants currently engaged in a remunerated occupation); retired and unemployed including sick leaver and disabled. Housewives: this binary indicator concerns merely women. Economic status was ascertained by asking the participants 3 questions to obtain a quantitative assessment of the current economic status "objective economical status" as well as a self perception of wellbeing and satisfaction with the available resources "subjective economical status". The first question was to select one of the 7 categories as best representing total household monthly income; <750 euro/month, 750–1499 euro/month, 1500-2249 euro/month, 2250-2999 euro/month, 3000-4999 euro/month, 5000-10000 euro/month, and > 10000 euro/month. The total household monthly income included the "sum of the earnings from social welfare, pensions, benefits and allowances as well as personal and other working family members' income". The second question concerned the number of adults and children living in the same household. These 2 questions were used to measure the Adult Equivalent Income (AEI) calculated as the ratio of the midpoint of the self-declared family income to the square root of the number

of persons in the household. This indicator is better than the income alone because it takes into account the family size. The official national poverty risk threshold for an AEI was calculated to 1432 euro/month, as published by the national institute of statistics (STATEC). Accordingly, the variable income was classified as follows: above risk of poverty threshold and below risk of poverty threshold. In case of missing data for family income or the family size, these participants were excluded from economic status analyses. The subjective economical status was assessed by using the question "to what extent do your current income and other available resources allow you to provide for your needs?". The answers were classified as: difficult or easy.

Family history of diabetes mellitus, arterial hypertension, myocardial infarction and cerbrovascular accident was considered positive when the participant reported that the parents or close relatives (sister and brother) had history of the selected medical conditions.

1.2 Lifestyle-related variables

Smoking was categorized as current (regular and occasional), former (ex-smoker) and non-smoker. Current smokers were those who reported regular use of at least one cigarette per day as well as the occasional smoking of less than one cigarette per day, at the time of the survey. Considering the "potential residual physiological nicotine effect", former smokers were defined as those who reported previous smoking, but had stopped since at least 12 months before the onset of survey. Subjects with no history of tobacco smoking were considered never smokers. The current dose-related tobacco exposure was estimated from the number of cigarettes smoked per day. Three categories were established: < 10, 10 to 20 and > 20 cigarettes/day.

Alcohol intake was classified as drinker and non-drinker. Never drinkers were those who did not drink alcoholic beverages, while the drinkers were those who self-declared alcohol intake during the past 12 months of the survey.

Physical Activity indicator categorized the population into three levels of physical activity: "low" (physically inactive), "moderate" and "high" levels of physical activity. The "moderate" level indicated meeting any one of the following three criteria: (a) 3 days of vigorous activity of at least 20 minutes/day; (b) 5 or more days of moderate-intensity activity or walking of > 30 minutes/day for > 10 minutes at a time; or (c) 5 or more days of any combination of walking, moderate-intensity or vigorous-intensity activities achieving at least 600 MET-minutes/week. The "High" level indicated

meeting either of two criteria: (a) vigorous-intensity activity on > 3 days/week and accumulating at least 1500 MET-minutes/week; or (b) >5 days of any combination of walking, moderate-intensity, or vigorous-intensity activities achieving at least 3000 MET-minutes/week. The "Low" level of physical activity corresponded to those not meeting neither 'moderate' nor 'high' criteria. These categories were based on scoring criteria defined by the international group of experts who elaborated IPAQ questionnaire. More information is available on the web-site: http://www.ipaq.ki.se.

A Diet Quality Index (DQI) was constructed to provide an overview of the overall diet quality. It comprised 13 components assessed on the basis of the WHO recommendations for the prevention of chronic diseases[204]. The DQI evaluates the intake of dietary elements that must be supplied sufficiently to guarantee a healthy diet. The dietary guidelines stress an adequate intake of key food and nutrients such as fruits and vegetables, complex carbohydrate and protein, but encourage moderation of fat, saturated fatty acids, cholesterol, sodium and sugar. Table 11 describes the construct of the DQI, the nutritional indicators, the intake goals and the scoring criteria for each component. When each component intake goal was achieved, one point is attributed; otherwise zero point indicating poor diet quality. The overall score constitutes 13 points. Components 1 though 4 are based on SFA, PUFA, MUFA and overall fat consumption as a percentage of total daily energy intakes. Component 5 measures ω_6/ω_3 ratio. Component 6 is based on cholesterol intake in mg/day. Component 7, 8 and 9 are based on total carbohydrates, free sugar and total protein respectively as a percentage of total daily energy intakes. Components 10, 11, 12 and 13 measure sodium, fruits/vegetables, total and soluble fibres intakes in g/day.

Table 11. Construct of Diet Quality Index

Components	WHO intake goals (% of total daily energy, unless otherwise stated)
Total fat	15 - 30%
SFA	< 10%
PUFA	6 - 10%
MUFA	10 - 14%
ω_6/ω_3 ratio	< 5.5
Cholesterol	< 300 mg/day
Total carbohydrates	55 - 75%
Simple sugar *	< 10%
Total protein	10 - 15%
Sodium **	< 2 g/day
Fruits and vegetables	≥ 400 g/day
Total fibres	> 25 g/day
Soluble fibres***	> 10 g/day

* The term "Simple sugars" refers to all monosaccharides and disaccharides naturally present in foods (honey, syrups and fruit) and added by the manufacturer, cook or consumer.

** The term "Sodium chloride" refers to salt included in the diet, but not added table salt.

*** Given the absence of NSP (Non starch polysaccharides) in the Food Composition Table, soluble fibres were measured.

1.3 Associated pathologies-related variables

The term "associated pathologies" signifies the classical pathological conditions that are related to cardiovascular risk.

Obesity: Based on the International Obesity Task Force[205], convened by the World Health Organization, a subject with BMI ≥ 30.0 kg/m2 was defined as obese.

Hypertension: Participants were classified as having elevated blood pressure if they reported taking anti-hypertensive medications and/or had SBP ≥140 mmHg and/or DBP ≥ 90 mmHg[206].

Diabetes: Participants were classified as diabetics if they reported taking anti-diabetic medications and/or had FPG ≥ 126 mg/dl[207], [208].

Dyslipidaemia: Subjects with lipid disorder were defined as having at least one of the following anomalies: TC ≥ 190 mg/dl, TG ≥ 150 mg/dl, LDL-C ≥ 115 mg/dl, and HDL-C < 40 mg/dl for men and < 46 mg/dl for women [209], and/or taking hypo-lipid medications.

2. Description of data analyses

The statistical analysis was principally performed using PASW® for Windows® version 18.0 software (formerly SPSS Statistics Inc. Chicago, Illinois), except nutritional data which was analysed by using the SAS 9.2 (© SAS Institute Inc., Cary, NC, USA).

For the descriptive part of ORISCAV-LUX study population, the results were expressed as mean ± SE for quantitative variables and as count and proportion (%) for categorical variables. The Chi-square test was used to analyse the statistical differences among proportions for the characteristics of the study participants. Multiple regression analysis was used to test the effect of age, gender and their interaction on subject's quantitative characteristics.

Overall, gender- and age-specific prevalence rates of the MS (calculated according to the selected criteria of R-ATPIII, as explained in the chapter 8) were calculated among the European adults residing in Luxembourg. The MS was defined as dependent variable, while the age, gender, marital status, education level, work status, smoking habits, alcohol consumption, physical activity, dietary habits, family history of selected medical conditions were considered as independent variables.

After adjustment for age and gender, socio-economic and lifestyle determinants of MS were examined using logistic regression models to estimate the odds and the respective 95% confidence intervals (95% CI) of the MS. The multivariate logistic regression was conducted to identify the variables independently associated with the metabolic syndrome.

The final multivariate logistic regression model was established using a stepwise procedure, considering only the significant variables in the initial model. In the next step, only the variables for which the *P*-value <0.10 were considered. The non significant variables were then discarded from the final model. Same results were obtained when considering 'Housewives' instead of 'Work status' in the initial model.

To account for the stratified random sampling method used to recruit the subjects, weighted statistical methods were applied to produce nationally representative estimates. A sampling weight equal to the inverse probability of unit selection was allocated to each subject from the same stratum. This stratum sampling weight was defined as the ratio between the population stratum size and the observed sample stratum size. Results were considered to be significant at the 5% critical level (P <0.05).

Part III

Results

Chapter 7

Population and sample representativeness

1. Introduction

This chapter summarises the results of the ORISCAV-LUX survey as they are presented in the published papers that are the basis for this thesis (see Appendix). Detailed information is obtainable in the single papers.

The following parts of this chapter reports the representativeness of ORISCAV-LUX sample, and describes the socio-economic, anthropometric, clinical and biochemical characteristics of the studied population. The prevalence rates of cardiovascular risk factors are summarized in the final section.

2. Sample representativeness

To assess the ORISCAV-LUX sample representativeness, the characteristics of 1432 recruited participants were compared to the source population (298,521 individuals) according to the stratification criteria: gender, age category and district of residence. Information about the source population was obtained from the most recent available database published by the national institute of statistics, STATEC 2001.

The ORISCAV-LUX study included 1432 participants, 735 (51.3%) women and 697 (48.7%) men. As seen in Table 12, the ORISCAV-LUX sample was representative of the population for gender and district of residence, but not for age categories. This age difference was significant for both men (P = 0.0004) and women (P = 0.0003). Compared to the source population, the younger age group of 18-29 years was under-represented, whereas adults and elderly were over-represented in the sample.

As above-mentioned in chapter 5, "Data weighting" section, the potential consequence of age-related non-response bias was handled by adjusting the sample for age, by using the most recent available distribution of the Luxembourg's population (STATEC database).

Table 12. Comparison of ORISCAV-LUX participants to the source population by gender, age category and district of residence

Stratification criteria		Source population (N = 298,521) % (n)	Participants (n = 1432) % (n)	*P*-value
Gender				0.19
	Women	49.64 (148,087)	51.33 (735)	
	Men	50.39 (150,434)	48.67 (697)	
Age category (years)				
Women				<0.0001
	18-29	22.38% (33,141)	15.6% (115)	
	30-39	25.57% (37,865)	24.5% (180)	
	40-49	21.91% (32,451)	24.9% (183)	
	50-59	16.41% (24,309)	20.3% (149)	
	60-69	13.72% (20,321)	14.7% (108)	
Men				<0.0001
	18-29	22.34% (33,619)	15.2% (106)	
	30-39	25.72% (38,699)	24.5% (171)	
	40-49	22.47% (33,811)	27.1% (189)	
	50-59	17.08% (25,700)	19.4% (135)	
	60-69	12.37 % (18,605)	13.8% (96)	
District of residence				0.82
	Luxembourg	73.74 (220,116)	72.97 (1045)	
	Diekirch	14.76 (43,956)	15.08 (216)	
	Grevenmacher	11.53 (34,449)	11.94 (171)	

3. Description of the ORISCAV-LUX studied population

3.1 Socio-economic characteristics

The present section outlines the socio-economic characteristics of the 1432 study participants aged 18-69 years, according to gender. Table 13 reports specifically the educational level, country of birth, marital status, employment characteristics, objective economic status based on global family income and family size.

Apart from 83 (6.2%) participants born in non-European countries, most (60.4%) were born in Luxembourg, 12.3% in Portugal and 21.1% in other European countries, but with no gender-specific difference.

There was a significant gender difference regarding the marital status (P=0.0007). Almost 66% subjects were married and 23.6% were single (never married). The proportions of separated and widowed women were higher than that of men; 7% versus 6.5% and 3% versus 1%, respectively.

Although almost half (47%) of the population was at secondary level of education, more than quarter (26%) of the participants had either primary level or university qualifications. There was no significant difference in the level of education between men and women (P= 0.08).

There was a remarkable gender difference with respect to work status. Overall, Approximately 65% of the participants were employed (71% men and 58.9% women). Twelve women (1.5%) reported that they were unemployed at the time of the study against 21 (3.3%) men. The proportions of retired and disabled men were double that of women (14.2% versus 7.9% and 2.2% versus 1.3%) respectively. Among the participants, 176 (22%) women and two men (0.3%) were engaged in home duties. Further 42 (9%) men and 49 (8.8%) women were full time students.

More than 77% of the participants were above the risk of poverty thresholds. No gender difference was observed.

Table 13. Description of socio-economic characteristics according to gender in the ORISCAV-LUX study (N=1432 subjects)

	Men N=697	Women N=735	Overall N=1432	*P*-value
Country of birth				0.41
European country	143 (19.6)	168 (22.6)	311 (21.1)	
No European country	40 (6.1)	43 (6.3)	83 (6.2)	
Portugal	93 (13.4)	76 (11.1)	169 (12.3)	
Luxembourg	421 (60.9)	448 (60.0)	869 (60.4)	
Marital status				0.0007
Married	495 (66.8)	502 (65.6)	997 (66.2)	
Never married	140 (25.6)	131 (21.6)	271 (23.6)	
Separated	53 (6.5)	76 (9.6)	129 (8.0)	
Widowed	9 (1.1)	26 (3.1)	35 (2.1)	
Education level				0.08
Primary level	163 (23.6)	217 (29.0)	380 (26.3)	
Secondary level	340 (49.2)	327 (44.9)	667 (47.1)	
University level	188 (27.2)	183 (26.1)	371 (26.7)	
Work status				<0.0001
Employed	503 (71.0)	422 (58.6)	925 (64.8)	
Student	42 (9.0)	49 (8.8)	91 (8.9)	
Unemployed	21 (3.3)	12 (1.5)	33 (2.4)	
Retired	112 (14.2)	64 (7.9)	176 (11.1)	
Housewives	2 (0.3)	176 (22.0)	178 (11.1)	
Sick leave or disabled	17 (2.2)	11 (1.3)	28 (1.7)	
Objective economical status				0.94
Below risk of poverty threshold	134 (22.7)	134 (22.5)	268 (22.6)	
Above risk of poverty threshold	490 (77.3	480 (77.5)	970 (77.4)	

Results are expressed as number of subjects and (percentage). Comparison between genders was performed using chi-square test.

3.2 Anthropometric, clinical and biochemical characteristics

The anthropometric, clinical and biochemical characteristics of the participants are displayed in Table 14 by age category and gender. As expected, mean values of BMI, WC, SBP, DBP, FPG, TC, LDL-C, and TG increased significantly with age; HDL-C levels, however, remained quite stable across age categories ($P = 0.64$). A significant gender-specific difference was observed for BMI, WC, SBP, FPG, HDL-C, LDL-C and TG, systematically higher in men than in women ($P < 0.0001$), except for TC ($P = 0.94$). For DBP, a significant age-gender interaction was found ($P = 0.0005$), in the sense that DBP increased more markedly with age in men than in women.

3.3 Nutritional intake

Table 15 describes the proportion of the participants who were adherent to the nutritional recommendations, according to gender. Globally, more than three quarter (78, 74%) of the participants were complied with the goal of limited free sugar to less than 10% of total energy intake, irrespective to their gender. Only 57% of the studied population were conforming to the recommended quantity of fruits and vegetables consumption, with gender-specific difference (50% for men versus 64% for women; $P < 0.0001$).

Compliance for carbohydrate (5%) and soluble fibre (3.5%) was particularly poor regardless of gender.

Although the overall adherence to limited intake of saturated fat (12%), men were significantly more conform to this dietary recommendation than women (15% versus 10%; $P = 0.0050$, respectively).

Table 14. Description of anthropometric, clinical and biochemical characteristics by age category and gender in the ORISCAV-LUX study (N=1432 subjects)

Characteristic		18-29 y	30-39 y	40-49 y	50-59 y	60-69 y	*P*-value*	*P*-value**
Number of subjects (men/women)		221 (106/115)	351 (171/180)	372 (189/183)	284 (135/149)	204 (96/108)		
BMI (kg/m^2)	Men	24.1 ± 0.3	26.6 ± 0.3	27.7 ± 0.3	28.6 ± 0.4	29.1 ± 0.5	<0.0001	<0.0001
	Women	22.9 ± 0.4	25.3 ± 0.3	25.9 ± 0.4	26.6 ± 0.4	29.1 ± 0.6		
WC (cm)	Men	83.5 ± 1.0	91.6 ± 0.8	96.7 ± 1.0	99.4± 1.0	102.0 ± 1.3	<0.0001	<0.0001
	Women	76.6 ± 1.0	83.1 ± 0.9	84.3 ± 0.9	87.7 ± 1.0	93.8 ± 1.4		
SBP (mmHg)	Men	124.3 ± 1.1	127.5 ± 1.0	134.0 ± 1.1	139.5 ± 1.3	149.7 ± 1.9	<0.0001	<0.0001
	Women	114.8 ± 0.8	116.9 ± 0.9	124.0 ± 1.1	131.8 ± 1.3	142.8 ± 2.0		
DBP (mmHg)	Men	74.1± 0.7	81.9 ± 0.8	87.1 ± 0.8	88.2 ± 0.8	88.5 ± 1.2	<0.0001$	0.26$
	Women	74.8 ± 0.8	77.1 ± 0.8	81.2 ± 0.8	83.7 ± 0.8	84.3 ± 1.1		
FPG (mg/dl)	Men	89.6 ± 1.0	91.9 ±0.7	97.7 ± 0.9	106.2 ± 2.3	108.5 ± 2.7	<0.0001	<0.0001
	Women	84.4 ± 0.6	86.8 ± 0.6	92.2 ± 0.9	96.3 ± 1.8	99.9 ± 2.4		
TC (mg/dl)	Men	170.5 ± 3.4	198.3 ± 2.9	214.5 ± 2.9	210.1 ± 3.2	198.9 ± 4.2	<0.0001	0.94
	Women	177.7 ± 3.3	189.9 ± 2.9	199.1± 2.5	220.3 ±2.7	217.1 ± 4.5		
HDL-C (mg/dl)	Men	53.9 ± 1.2	53.2 ± 0.9	53.1 ± 1.1	53.9 ± 1.2	54.7 ± 1.5	0.64	<0.0001
	Women	68.4 ± 1.4	67.9 ± 1.2	67.6 ± 1.2	69.1 ± 1.5	69.4 ± 2.0		
LDL-C (mg/dl)	Men	104.1± 2.9	126.1 ± 2.3	140.1 ± 2.6	137.0 ± 2.8	127.8 ± 3.9	<0.0001	<0.0001
	Women	98.2 ± 2.8	109.9 ± 2.3	119.5 ± 2.2	135.5 ± 2.5	132.4 ± 4.0		
TG (mg/dl)	Men	95.4 ± 6.5	138.9 ± 11.2	149.3 ± 7.5	140.5 ± 6.5	134.4 ± 6.0	<0.0001	<0.0001
	Women	85.8 ± 3.8	97.8 ± 11.5	89.6 ± 3.6	105.7 ± 5.1	107.7 ± 5.6		

Results are expressed as Mean ± SE. * *P*-value for age, ** *P*-value for gender, $ adjusted for age and sex interaction when necessary

Table 15. Description of participant's adherence to nutritional goals according to gender in the ORISCAV-LUX study (N=1296 subjects)

	Men N=630	Women N=662	Overall N=1292	*P*-value
Total lipids	103 (15.86)	51 (7.96)	154 (11.95)	<0.0001
Saturated fatty acid	96 (14.81)	64 (9.51)	160 (12.19)	0.005
Poly-unsaturated fatty acid	243 (38.71)	290 (43.13)	533 (40.89)	0.12
Monounsaturated fatty acid	173 (27.14)	146 (22.01)	319 (24.61)	0.04
ω_6/ω_3 ratio	5 (0.39)	8 (0.56)	13 (0.96)	0.50
Total carbohydrates	36 (5.93)	26 (4.08)	62 (5.02)	0.15
Simple sugar	22 (3.17)	15 (2.15)	37 (2.66)	0.79
Total proteins	235 (37.5)	243 (36.93)	478 (37.22)	0.84
Cholesterol	232 (36.07)	359 (53.87)	591 (44.88)	<0.0001
Sodium	56 (8.44)	116 (16.79)	172 (12.57)	<0.0001
Fruits and vegetables	320 (49.76)	433 (63.84)	753 (56.73)	<0.0001
Total fibers	275 (44)	272 (41.02)	547 (42.52)	0.30
Soluble fibers	19 (2.87)	27 (4.09)	46 (3.47)	0.24

Results are expressed as number of subjects and (percentage).

3.4 Prevalence of cardiovascular risk factors

From prevention viewpoint, it is interesting to investigate the potentially modifiable and treatable risk factors or so often called the lifestyle-related risk factors, in particular, current smoking, physical inactivity, and obesity, as well as associated pathologies, such as diabetes, hypertension and lipid disorders. The latter factors constitute essentially the criteria to identify the MS.

Table 16 displays the overall, age- and gender-specific prevalence of lifestyle-related risk factors. By decreasing prevalence, the most predominant cardiovascular risk factors were lipid disorder (69.9%), hypertension (34.5%), current smoking (22.3%), obesity (20.9%), physical inactivity, and diabetes (4.4%), respectively. The prevalence of hypertension, obesity, diabetes mellitus and lipid disorders increased remarkably with advancing age ($P < 0.0001$). By contrast, the prevalence of current smoking decreased significantly with age ($P < 0.0001$). Further, the prevalence was significantly higher in men than in women for hypertension (41.9% vs 27.1%), obesity (23.0% vs 18.7%), lipid disorders (74.3% vs 65.5%), current smoking (24.9% vs 19.7%) and physical inactivity (20.7% vs 14.9%), but not for diabetes (5.2% vs 3.5%, $P = 0.08$). No age-gender interaction was found for any of the CVRF.

Table 16. Prevalence of cardiovascular risk factors (N=1432 subjects)

CVRF		18-69y n (%)	18-29y n (%)	30-39y n (%)	40-49y n (%)	50-59y n (%)	60-69y n (%)	*P*-value*	*P*-value**
Obesity	Total	325 (20.9)	14 (6.5)	63 (17.3)	90 (23.7)	77 (27.7)	81 (39.0)	<0.0001	0.03
	Men	175 (23.0)	7 (6.3)	35 (20.3)	50 (26.6)	45 (32.9)	38 38.6)		
	Women	150 (18.7)	7 (6.7)	28 (14.2)	40 (20.6)	32 (22.2)	43 (39.4)		
Hypertension	Total	540 (34.5)	17 (7.8)	72 (21.0)	146 (38.7)	150 (53.6)	155 (75.6)	<0.0001	<0.0001
	Men	322 (41.9)	10 (9.3)	50 (28.7)	95 (50.2)	86 (63.0)	81 (84.1)		
	Women	218 (27.1)	7 (6.3)	22 (13.1)	51 (26.7)	64 (43.5)	74 (67.8)		
Diabetes	Total	69 (4.4)	1 (0.5)	2 (0.6)	12 (3.1)	20 (7.1)	34 (16.7)	<0.0001	0.08
	Men	39 (5.2)	1 (1.1)	1 (0.7)	7 (3.8)	12 (8.8)	18 (18.8)		
	Women	30 (3.5%)	0 (-)	1 (0.5)	5 (2.4)	8 (5.3)	16 (14.7)		
Lipid disorder	Total	1033 (69.9)	92 (42.5)	212 (61.5)	283 (76.3)	256 (90.8)	190 (94.1)	<0.0001	<0.0001
	Men	533 (74.3)	44 (42.7)	119 (70.9)	159 (84.5)	120 (89.7)	91 (96.5)		
	Women	500 (65.5)	48 (42.3)	93 (52.0)	124 (67.8)	136 (92.0)	99 (92.0)		
Current smoking	Total	307 (22.3)	74 (33.7)	71 (20.0)	77 (20.7)	61 (21.4)	24 (10.9)	<0.0001	0.03
	Men	165 (24.9)	41 (38.6)	39 (22.7)	46 (24.5)	30 (22.4)	9 (8.6)		
	Women	142 (19.7)	33 (28.7)	32 (17.3)	31 (16.7)	31 (20.3)	15 (13.0)		
Physical inactivity	Total	246 (17.8)	37 (17.5)	48 (14.3)	64 (18.1)	59 (22.3)	38 (18.7)	0.60	0.023
	Men	139 (20.7)	21 (21.1)	24 (15.0)	40 (22.5)	33 (25.4)	21 (21.7)		
	Women	107 (14.9)	16 (13.9)	24 (13.5)	24 (13.7)	26 (19.0)	17 (16.0)		

Results are expressed as number of cases (%). * P value for age, ** P-value for gender.

Chapter 8

Prevalence of the metabolic syndrome

1. Introduction

As mentioned previously in the literature review (chapter 1), the use of different definitions of the MS had an impact on the estimated prevalence rates in different populations and confused the interpretation of the epidemiological results[210]. Numerous studies compared the degree of agreement between the WHO, NCEP-ATP, R-ATPIII, and IDF definitions yielded a mixture of viewpoints concerning the most appropriate criteria to define the MS. In addition, the recent guidelines released by the Joint Interim Statement 2009 stressed the need to adopt ethnic-specific values of waist circumference; an important component of the MS.

Therefore, the foremost concern was the selection of appropriate definition to estimate the prevalence of MS in the adult population residing in Luxembourg. For this purpose, prior research was undertaken to achieve this objective. This work has been published in BMC Public Health Journal in December 2010 (see Appendix).

2. Selection of definition

In 2009, several major international organisations have released a Joint Interim Statement (JIS) in an attempt to harmonize the criteria to define the MS. It was agreed that four diagnostic components (reduced HDL, elevated blood pressure, TG and FPG) remained identical to those provided by the R-ATPIII and IDF. Although abdominal obesity was not deemed as a compulsory criterion, the cut-off points for WC were ethnic and country-specific defined[47].

The WC thresholds were thus still ill-defined, particularly for the Europid; the IDF recommends a WC ≥ 94 cm for men and ≥ 80 cm for women and the European Cardiovascular Societies suggest a WC ≥ 102 cm for men and ≥ 88 cm for women. Given the dual references for Europid-specific WC cut-off points to define abdominal obesity, the research work purposed to estimate the prevalence of the MS among the dominating European population (comprising 94.2% of the total studied population), according to both the low and high WC thresholds.

In this text, the JIS definition considered the low values designated as (94/80 thresholds), because by applying the high values (102/88 thresholds), the definition criteria were exactly consistent with the R-ATPIII definition. Interestingly, the findings demonstrated that the 10-year predicted risk of CHD by Framingham risk score (FRS)

was not significantly different for both thresholds, suggesting that the two cut-off values did not affect the MS prevalence estimates. As yet, there is no comparative study showing the inter-definition agreement with the JIS criteria. Therefore, the research aimed also to assess the concordance with the other operating definitions sharing substantially the same criteria. The results of inter-definition comparison demonstrated an "almost perfect" level of agreement between the JIS and R-ATPIII-defined MS ($\kappa = 0.91$). This indicates that these definitions and/or WC-thresholds can be used interchangeably without having a large impact on either preventive strategies or health care resources. Similar results were documented by a German-American study aimed to harmonize the MS definition by comparing the R-ATPIII and IDF criteria in both populations[211].

Against this background, and to facilitate the international comparison, we selected the 102/88 thresholds (i.e. strictly the similar criteria as R-ATPIII [43]) to define the MS in our study population. To avoid confusion, the term "R-ATPIII" will be used alternatively hereafter to signify the JIS-102/88 definition.

The participants were identified as having the MS if they had three or more of the following criteria: 1) raised concentration of TG ≥ 150 mg/dl or specific treatment for this lipid anomaly; 2) reduced concentration of HDL-C < 40 mg/dl for men and < 50 mg/dl for women or specific treatment for this lipid anomaly; 3) SBP was ≥ 130 mmHg, or DBP ≥ 85 mmHg or treatment of previously diagnosed hypertension; 4) FPG level ≥100 mg/dl or use of medication for hyperglycaemia; 5) elevated WC ≥ 102 cm for men and ≥ 88cm for women.

3. Europid study population

As previously stated, a total of 1432 subjects took part in the ORISCAV-LUX survey. However, after eliminating the non-Europeans, only 1349 participants were available for the analysis of the research work presented in this dissertation. All further analyses will concern this group of Europid. The predominantly white homogeneous nature of the sample (94.2% were of European origin) ensured the control over ethnicity factor, hence permitting generalization of the results over the source population.

The demographic and socio-economic characteristics of the European studied population are comparable to those of the general ORISCAV-LUX sample.

4. Prevalence of metabolic syndrome

Table 17 illustrates the age- and gender-specific prevalence of MS and its components among Europid adults resident in Luxembourg, according to R-ATPIII criteria. The overall prevalence was 25%, with significant gender difference (18.5% for women versus 30.8% for men, $P < 0.0001$). Of all elements of MS, hypertension was the most commonly abnormal criterion (52.5%) in the study population.

For both genders, the MS prevalence rate increased remarkably with age, ranging from <1% among the young women of 18 to 29 years old, to reach a peak of 60% in men of 60-69 age range. All other components of the MS followed a similar pattern. No age-gender interaction was found for the MS or for the individual components.

Table 17. Prevalence of the metabolic syndrome and its components among Europid adults aged 18-69 years in the ORISCAV-LUX study (N=1349 subjects)

	n	MS (n = 1319)	Abdominal obesity (n = 1348)	Raised TG (n = 1320)	Low HDL-C (n = 1320)	High BP (n = 1348)	Hyperglycaemia (n = 1317)
Total	1349	24.7 (22.7 - 26.8)	30.6 (28.4 -33.0)	25.6 (23.5 - 27.9)	18.8 (16.8 - 20.9)	52.5 (50.1 - 54.8)	21.7 (19.8 - 23.8)
Gender							
Women	692	18.5 (16.1 - 21.2)	35.1 (31.8 - 38.4)	14.7 (12.4 - 17.4)	16.2 (13.7 – 19.1)	42.2 (39.1 - 45.4)	14.4 (12.2 - 16.9)
Men	657	30.8 (27.6 - 34.0)	26.3 (23.3 - 29.6)	36.5 (33.0 - 40.2)	21.3 (18.5 - 24.6)	62.5 (59.0 - 65.9)	29 (25.9 - 32.4)
P-value		<0.0001	0.0002	<0.0001	0.014	<0.0001	<0.0001
Age (years)							
Women							
18-29	108	0.90 (0.1 – 6.4)	11.2 (6.5 – 18.6)	4.2 (1.6 – 10.2)	6.9 (3.3 – 14.0)	11.1 (6.3 – 18.7)	0.00 (-)
30-39	165	7.8 (4.5 – 13.1)	30.2 (23.6 - 37.8)	8.8 (5.3 – 14.4)	9.5 (5.7 – 15.5)	27.0 (20.4 – 34.7)	5.2 (2.7- 9.9)
40-49	175	16.3 (11.4 – 22.6)	34.5 (27.6 – 42.1)	10.0 (6.2 – 15.7)	13.8 (9.2 – 20.2)	42.6 (35.6 – 49.8)	18.3 (13.2 - 24.9)
50-59	140	34.2 (26.8 - 42.4)	48.2 (40.3 - 56.2)	20.2 (14.3 – 27.7)	20.3 (14.3 – 28.1)	66.7 (58.6 – 73.9)	31.0 (24.0 – 39.0)
60-69	104	49.8 (40.0 - 59.7)	66.7 (57.4 - 75.8)	42.6 (32.2 - 52.6)	41.8 (32.5 - 51.7)	89.0 (80.6 – 94.0)	27.5 (19.8 – 36.7)
P-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Men							
18-29	98	7.5 (3.6 – 15.0)	8.1 (4.1 – 15.4)	15.1 (9.1 – 24.2)	10.9 (5.8 – 19.6)	36.0 (27.5 - 45.6)	9.5 (5.0 – 17.4)
30-39	156	17.1 (12.0 - 23.9)	18.0 (12.8 – 24.7)	29.6 (22.9 – 37.3)	11.8 (7.6 - 17.9)	50.9 (43.2 - 58.6)	16.4 (11.3 – 23.2)
40-49	180	34.4 (27.6 - 41.8)	32.9 (26.4 – 40.1)	42.1 (34.9 - 49.7)	21.2 (15.8 - 27.7)	67.2 (60.1 – 73.7)	33.7 (27.2 – 41.0)
50-59	129	52.1 (43.2 - 60.8)	40.1 (31.9 – 49.0)	50.1 (41.5 - 58.7)	31.2 (23.9 - 39.7)	83.7 (76.1 – 89.2)	45.4 (36.9 - 54.1)
60-69	94	60.4 (50.0 - 70.0)	43.1 (33.9 - 52.7)	56.7 (46.4 - 66.5)	43.7 (33.7 - 54.2)	93.1 (85.5 – 96.8)	54.5 (44.0 - 64.6)
P-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<.0001

Data are expressed as percentages (95% CI). Non-fasting subjects were eliminated from the analysis.

Chapter 9

Determinants of the metabolic syndrome

1. Introduction

The present chapter outlines the association of MS with socio-economic, family history and lifestyle characteristics of the European studied population, using a range of statistical analyses.

1.1 Prevalence of metabolic syndrome and socio-economic factors

As demonstrated previously, the prevalence of MS increased remarkably with age with significant gender-specific difference. Therefore, the effect of each socioeconomic characteristic was studied after the adjustment for age and gender. The interaction of each variable with age and with gender was also considered. Table 18 displays the age and gender adjusted odd ratio for the MS according to socioeconomic characteristics. Except for marital status, there were a significant association between the prevalence of the MS and selected socioeconomic characteristics, presented by the level of education ($P < 0.0001$), working status ($P = 0.037$), subjective ($P = 0.024$) and objective economic status ($P = 0.003$). There was a significant work status-age interaction.

Regardless of age and gender, those with primary and secondary level of education were at more than 2-fold and 1.5-fold odd risk of the MS than those with university qualification (adjusted Odd ratio: 2.34 and 1.51), respectively.

The prevalence of MS was significantly lower among the employed participants (19.5%) than among the retired (54%) and the non-employed, including sick leavers and disabled (37.7%) ($P = 0.037$) with age-interaction effect. Considering housewife status as a separated risk factor, non-working women were significantly associated with higher prevalence of MS ($P < 0.0001$) and double fold of risk (OR = 2.40, 95% CI [1.51 - 3.80]) compared with working women, even after age adjustment.

As regards the objective economic status, the MS was significantly more prevalent among the subjects lived above the risk of poverty threshold than those lived below it ($P = 0.003$). After age and gender adjustment, the subjects below poverty threshold were at risk (OR = 1.75, 95% CI [1.21-2.53]) compared to those above.

The prevalence of the MS was lower among the subjects reported living easily with their available resources than those reported difficult economic status (24.3% vs 25.9%, respectively). The latter group was at risk of the MS (age and gender adjusted Odd ratio = 1.5, 95% CI [1.06-2.28]).

Table 18. The prevalence of metabolic syndrome according to socio-economic characteristics of the Europid population participated to ORISCAV-LUX study (N= 1439 subjects)

	Metabolic syndrome		Adjusted OR	*P*-value
	n	%	(IC95%)*	
Marital status				0.67
Married /living with partner (n = 924)	275	28.7	1	
Single (never married) (n = 244)	32	10.3	0.89 (0.55 - 1.45)	
Divorced/separated (n = 119)	33	26.4	0.78 (0.48 - 1.25)	
Widowed (n = 32)	15	47.8	1.23 (0.58 - 2.60)	
Level of education				
Tertiary (university level) (n = 341)	62	16.3	1	<0.0001
Primary (n = 340)	123	34.0	2.34 (1.57 - 3.48)	
Secondary (n =625)	165	24.2	1.51 (1.04 - 2.17)	
Work status				0.037§
Employed (n = 856)	180	19.5	1	
Retired (n = 170)	92	54	4.15 (1.15 - 15.02)	
Sick leaver / disabled / unemployed (n = 50)	20	37.7	1.77 (0.85 - 3.72)	
Housewives†				<0.0001
No (n = 520)	78	13.1	1	
Yes (n = 160)	61	38	2.40 (1.51 - 3.80)	
Subjective economical status				0.024
Easy (n = 1006)	264	24.3	1	
Difficult (n = 241)	69	25.9	1.56 (1.06 - 2.28)	
Objective economical status				0.003
Above risk of poverty threshold (n = 911)	231	23.6	1	
Below risk of poverty threshold (n = 228)	73	29.2	1.75 (1.21-2.53)	

* Odd ratio adjusted for age and gender. The interaction of each variable with gender is presented as $ and with the age as § when necessary. † Only women

1.2 Prevalence of metabolic syndrome and lifestyle factors

The associations between lifestyle factors, such as smoking status, number of cigarette smoked per day, alcohol consumption, physical activity and the prevalence of MS are presented in table 19.

After adjustment for age and gender, current cigarette smokers showed greater odds of having the syndrome (1.49; 95%CI [1.05-2.10]) than the non-smokers. Likewise, smoking more than 20 cigarettes per day showed significant inverse association with the MS. The odds ratios for having the MS in the moderately active and inactive subjects were 1.37 (95% CI: 0.99-1.89) and 1.53 (95% CI: 1.04-2.27) respectively. No association was seen between alcohol intake and the MS.

Table 19. The prevalence of metabolic syndrome according to lifestyle characteristics of the Europid population participated to ORISCAV-LUX study (N= 1439 subjects)

	Metabolic syndrome		Adjusted OR	*P*-value
	n	%	(IC95%)*	
Smoking status				0.078
Non-smokers (n = 703)	165	21.4	1	
Former smokers (n = 310)	107	33.4	1.12 (0.79 - 1.59)	
Current smokers (n =306)	83	23.8	1.49 (1.05 – 2.10)	
Number of cigarettes per day				
<10 cigarettes/day (n =1150)	302	24.1	1	0.034
11-20 cigarettes/day (n =122)	33	23.3	1.41 (0.89-2.22)	
> 20 cigarettes/day (n =47)	20	42.5	2.23 (1.11-4.48)	
Alcohol consumption				0.25
Non-drinker (n=185)	57	28	1	
Drinker (n=1134)	298	24.2	0.80 (0.54-1.17)	
Physical activity				0.044
Active (n = 685)	162	21.8	1	
Moderately active (n= 359)	103	26.3	1.37 (0.99 - 1.89)	
Inactive (n = 216)	73	31.1	1.53 (1.04 - 2.27)	

* Odd ratio adjusted for age and gender. The interaction of each variable with the age and with gender is presented as $ when necessary.

1.3 Prevalence of metabolic syndrome and family history

The associations of the MS prevalence rates and the participants' family history of four selected medical conditions (diabetes mellitus, arterial hypertension, myocardial infarction and cerebrovascular accident) are studied in table 20. Only family history of diabetes and arterial hypertension was associated with significantly greater odds of having the MS (2.40; 95%CI [1.72-3.36] and 1.61; 95%CI [1.17-2.22] respectively.

Table 20. The prevalence of metabolic syndrome according to family history of selected medical conditions of the Europid population participated to ORISCAV-LUX study (N= 1439 subjects)

Family history of selected medical conditions	Metabolic syndrome		Adjusted OR	*P*-value
	n	%	(IC95%)*	
Hypertension				0.004
No (n = 677)	161	21.5	1	
Yes (n = 438)	134	28.4	1.61 (1.17 - 2.22)	
Diabetes				<0.0001
No (n = 979)	225	20.8	1	
Yes (n = 273)	106	36.5	2.40 (1.72 - 3.36)	
Myocardial infarction				0.42
No (n = 965)	247	23.2	1	
Yes (n = 285)	93	31.5	1.15 (0.82- 1.63)	
Cerebro-vascular accident				0.87
No (n =1035)	255	22.5	1	
Yes (n = 219)	82	35.6	1.03 (0.72 - 1.48)	

* Odd ratio adjusted for age and gender. ** The referent category is the absence of history of each of the selected medical conditions. The interaction of each variable with gender is presented as $ and with the age as § when necessary.

1.4 Prevalence of metabolic syndrome and dietary factors

The prevalence of MS according to food components in the diet is demonstrated in table 21. A significant association was found between the prevalence of MS and the adherence of the participants to the recommendations with respect to saturated fatty acid ($P = 0.017$), simple sugar ($P = 0.0004$) and total protein ($P = 0.006$). Particularly, protein consumption, lower than 10% or higher than 15% of total energy intake, showed high odd of having the MS (1.56; 95%CI [1.14-2.15]).

The Diet Quality Index (DQI) measures diet quality using thirteen dietary components. It provides an idea about the dietary guidance for healthy eating. After age and gender adjustment, no association was observed between the prevalence of MS and the DQI of the ORISCAV-LUX Europid population.

Table 21. The prevalence of metabolic syndrome according to food components in thediet of the Europid population participated to ORISCAV-LUX study (N= 1229 subjects)

Component	Reference	Compliance	Metabolic syndrome		Adjusted OR	*P*-value
			n	%	(IC95%)*	
Total fat	15 - 30%	Yes (n = 144)	52	32.5	1	0.43
		No (n = 1060)	272	23.7	0.84 (0.55 – 1.29)	
SFA	< 10%	Yes (n =147)	58	37.5	1	0.02
		No (n = 1057)	266	22.9	0.60 (0.39 – 0.91)	
PUFA	6 - 10%	Yes (n = 500)	130	23.4	1	0.30
		No (n = 704)	194	25.6	1.17 (0.87 – 1.56)	
MUFA	10 - 14%	Yes (n = 300)	91	27.7	1	0.86
		No (n = 904)	233	23.7	1.03 (0.73 – 1.45)	
ω_6/ω_3 ratio	< 5.5	Yes (n = 11)	2	16.5	1	
		No (n = 1193)	322	24.8	4.91 (0.82 - 29.45)	0.081
Cholesterol	< 300mg/d	Yes (n = 551)	140	23.6	1	0.53
		No(n = 653)	184	25.7	1.10 (0.81 -1.49)	
Total carbohydrates	55 - 75%	Yes (n = 59)	14	21.5	1	0.25§
		No (n = 1145)	310	24.9	1.45 (0.77 - 2.71)	
Simple sugar	< 10%	Yes (n = 33)	19	56.8	1	0.0004
		No (n = 1171)	305	23.9	0.27 (0.13 - 0.56)	
Total protein	10 - 15%	Yes (n = 446)	99	20.6	1	0.006
		No (n = 758)	225	27.2	1.56 (1.14 - 2.15)	
Sodium	< 2g/day	Yes (n = 153)	45	27.1	1	0.73
		No (n = 1051)	279	24.4	0.93 (0.62 - 1.34)	
Fruits and vegetables	≥ 400g/day	Yes (n = 727)	205	26.5	1	0.80
		No (n = 477)	119	22.2	0.96 (0.70 - 1.31)	
Total fibres	> 25g/day	Yes (n = 510)	143	26.1	1	0.90§
		No (n = 694)	181	23.7	1.02 (0.76 - 1.37)	
Soluble fibre	> 10g/day	Yes (n = 45)	16	33.4	1	0.74
		No (n = 1159)	308	24.4	0.89 (0.45 - 1.76)	
DQI	Mean (SE) =3.01 (0.05)				0.98 (0.90 - 1.07)	0.64

* Odd ratio adjusted for age and gender. ** The referent category is the absence of history of each of the selected medical conditions.The interaction of each variable with gender presented as $ and with the age as § when necessary.

Chapter 10

Metabolic syndrome modelling

1. Introduction

After age and gender adjustment, only significant variables, for which the *P*-value <0.10 after the initial model, were examined in association with the prevalence of MS using multiple logistic regression analyses. The final modelling of the MS was studied in table 22. It demonstrated that the age, male gender, primary level of education, physical inactivity, family history of diabetes and hypertension and inadequate total protein and simple sugar consumption were significant determinants of the MS, after full adjustment for other socioeconomic, family history and lifestyle factors. A sensitivity approach was applied to this final model by testing the significance effect of the rejected variables one by one. No more variable was added.

Table 22. Final multivariate logistic regression model of the Europid population participated to ORISCAV-LUX study

Indicators	Categories	Fully adjusted OR (IC95%)	*P*-value
Age		1.09 (1.07 – 1.11)	<0.0001
Sex	Women	1	<0.0001
	Men	3.08 (2.13 – 4.47)	
Level education	Tertiary (university level)	1	0.03
	Primary	1.34 (0.86 – 2.09)	
	Secondary	1.93 (1.18 – 3.15)	
Physical activity	Active	1	0.015
	Moderately active	1.49 (1.00 – 2.21)	
	Inactive	1.94 (1.18 – 3.17)	
Diabetes	No	1	<0.0001
	Yes	2.46 (1.62 – 3.73)	
Hypertension	No	1	0.05
	Yes	1.44 (1 – 2.08)	
Simple sugar	Yes	1	0.004
	No	0.25 (0.01 – 0.63)	
Total protein	Yes	1	0.014
	No	1.59 (1.01 – 2.31)	

Part IV

Discussion and conclusion

1. Discussion

During the last decade, the MS has emerged as a major public health problem worldwide, owing to its association with high risk of type 2 diabetes mellitus and cardiovascular disease. Different definitions and diagnostic criteria were proposed by several scientific associations resulted in wide-ranged prevalence rates [107].

Epidemiological baseline prevalence estimate is useful for assessing the scope and the distribution of the public health problem posed by the MS. It facilitates the identification of groups in greatest need of health care and the development of appropriate intervention strategies. The prevalence of MS has been reported in a large number of population-based studies. However, the wide variation of published data make relevant international comparisons exceedingly difficult, because of important methodological differences with respect to the socio-demographic characteristics of target population, the study design, the sample selection, and the year of conduct. Generally, the emerging prevalence data from European population-based studies suggests that the MS is a very common cardiometabolic disorder with a prevalence rate varies considerably between 18% in Italy[92] and 38% in Turkey[69]. This work describes for the first time in Luxembourg the gender and age variation of the prevalence of MS and of its components in a representative sample of presumably healthy 18-69 years old adults. Almost one-fourth (24.7%) of the adults Europid population residing in Luxembourg are affected by the MS, as estimated by the most commonly used (R-ATPIII) definition. Globally this prevalence rate is comparable to that estimated in most European countries, but lower than that in USA (34.5%)[90], and higher than that in Australia (15%) and China (17%).

As elucidated earlier in the literature review (chapter 4), the prevalence of MS was different across the countries in terms of gender, age groups, ethnicity and criteria used. Agreed with a distinctive finding of wide gender discrepancy, the prevalence of MS in European residents in Luxembourg was significantly higher in men than in women (30.8 vs. 18.5; $P<0.0001$, respectively). Across literature, the Asiatic women were more prone to develop the MS than European counterpart; while the MS was higher among men than women in France[97, 98], Germany[85], and Ireland[99], it was higher in Omani[93], Chinese[96] and Indian women[94].

Another key finding, in consistence with other studies, was the remarkable increase of the MS prevalence rate with age in both genders [103]. This effect can be explained largely by age-related rises of blood pressure and glucose level [91]. However, the significantly

higher prevalence of MS and its components in our male population is of particular concern, especially for the younger age groups, indicating their potential prolonged exposure to the pro-atherosclerotic risk factors associated with the MS.

The prevalence of MS and respective odd ratio was significantly high in the participants having family history of diabetes and arterial hypertension, irrespective to their age and gender. This variation remained significant even after multivariate adjustment for potential socioeconomic and lifestyle factors, indicating that this group of participants is more susceptible to develop the MS. A family history of diabetes or hypertension is a marker of genetic predisposition to components of MS. This finding was reported in other studies [212]. It may imply that family history is associated with the development of MS. Globally, the number of people suffering from diabetes and hypertension is rapidly increasing, hence calling the health care authorities for action to achieve a successful primary prevention.

The principal finding of the present research is that education level is inversely associated with the risk of MS. After adjustment for age, gender and other socio-economic and lifestyle factors, the relationship remained statistically significant. These data suggest that there are clear educational differences in the prevalence of MS in European adult population residing in Luxembourg. Adjusting for family history, behavioural and other socioeconomic factors cannot narrow these differences. This finding is consistent with previous studies[128], [213], [214] that reported pronounced inverse associations between educational level and features of MS particularly in women[127], [215]. The reasons for this association might be related to the influence of education in predicting food choices[216], [217] and healthy behaviours[218], both of which are related to the MS. Better education facilitates the understanding and acquisition of healthy lifestyle which may explain the greater protection against the MS in educated people. Moreover, it is likely that highly educated individuals are provided with better level of social, psychological and economic support [219]. In a wealthy country as Luxembourg, higher education generally leads to a better income, better standard of living, and higher likelihood to follow through on healthcare provider's recommendations and healthy behaviours, such as not smoking, healthy nutritional choices and exercises.

The prevalence of the MS also differed significantly by objective household income independently of age and gender; however these associations were attenuated and did not remain statistically significant in multivariate analyses. Social inequalities in the MS have been shown in several studies using different indicators of socioeconomic position. An independent association was observed in the United States [220], [215]. In

France, the association between the MS and household income was demonstrated only for women [217]. Likewise, lower socioeconomic status was associated with higher risk of the MS in Korean women but not men[221]. A recent study did not report an independent association between childhood or adulthood social class and the MS in elderly British men[222].

Socioeconomic indicators such as income, occupation and wealth are limited in their ability to capture the complex forces that dominate social structure[223]. The subjective economical status, reflecting the resources perception, is an indirect parameter that might aggregates several indicators of socio-economic position. It reflects a "cognitive rating" of multiple dimensions of socio-economic circumstances, e.g., earning, personal wealth (or financial security), prestige, occupational grade and educational attainments. After adjustment for age and gender, an inverse association was observed between the MS and subjective economical status, suggesting that self-perceived economical constraints may increase the MS risk. To our knowledge, ORISCAV-LUX study is the first population-based study that examines the subjective perception of individual economical status, along with the objective income, though these associations were attenuated and did not remain statistically significant in multivariate analyses. Marital status is a social variable rarely explored in population-based studies. It was not associated with significant increase in the prevalence of MS after age and gender adjustment, suggesting that this indicator has no impact on MS prevalence in our population. The prevalence of MS was significantly different according to working status. Sick leavers, disabled and retired were more likely to be affected by the MS than the employed group, independently of their age and gender. Among women, being a housewife was associated with increased prevalence of MS independently of age. However, the association of MS prevalence with working, subjective or objective socioeconomic status was attenuated after adjusting for other potential confounding factors, suggesting that family history, behavioural and other socioeconomic (education) factors have accounted for the MS prevalence variation in the fully adjusted model.

In fact, education, working status, subjective and objective economic positions are highly interrelated, which make it difficult to determine the specific contribution of each variable. The analyses indicated that high education level, being employed and living easily with objective financial resources were significant indicators associated with low prevalence of the MS, independently to age or gender. However, the positive independent relationship between MS and socioeconomic factors of interest was disappeared when adjusting for family history and lifestyle factors, except the education attainment; this

indicator remained independently significant, thus representing the more important socioeconomic discriminating factor. The reason why socioeconomic determinants may lead to lower risk of the MS are likely multifactorial and the mechanisms are not totally elucidated. One potential mechanism is through health-impairing attributes of habit and lifestyle[224]. Simple education and limited economical resources jointly bring people to choose low-cost, unhealthy energy-dense foods composed of fat, refined grain and added sugar. This type of food favours the development of insulin resistance, hypertriglyceridemia and body weight gain [217],[216]. The absence of wealth feeling and difficult resources perception may affect not only, the appropriate food choice, but also the ability to practice paid-leisure activities. Another frequently cited correlate to low socioeconomic status is the stress that may induce a psychological defeat reaction, which would activate the hypothalamus-pituitary-adrenal axis and promote in consequence the cardiovascular risk[221]. The psychosocial stress may be occasioned by challenges of daily living, poor social network, uncertainties of future prospect related to social or material disadvantage[225]. As a vicious cycle, people in lowest income category are likely unemployed and/or unqualified (have no diploma) and are bothered by their limited resources, resulting in reduced physical activity and/or stress [217]. This in sequence may favour weight gain and insulin resistance, the major precursor to the MS. In spite of the cross-sectional nature of these analyses, the direction of the association between education and MS is understandable, thus the hypotheses of reverse causality are less likely to address. However, pre-existing ill health may influence the household income due to unemployment, work leave and in consequence poor self-resources perception. Only prospective data can prove or refute this hypothesis.

Cigarette smoking is primary cause of preventable death in western societies and is associated with cardiovascular disease and cancer, the two leading causes of mortality in Luxembourg. Smoking is known to be independently associated with CV risk, and seems to have an adverse effect on several components of the MS, as high fasting glucose and high blood pressure[226], [220], [137]. In this research work, a positive dose-response relation between smoking exposure (more than 20 cigarettes per day) and MS was seen independently of age and gender. However, this association was disappeared when adjusting for other confounders. Our results are consistent with recent findings showing a positive and dose-dependent relationship between the numbers of cigarettes smoked daily and the risk of MS[138], [139], [140]. Although many pharmacological actions of cigarette smoking and nicotine have been demonstrated, the precise mechanism of how cigarette smoking increases the risk of MS remains uncertain. Smokers have abnormalities in lipoprotein metabolism and insulin resistance [227]. A negative effect of smoking exposure on insulin sensitivity has been related to increase in the circulating

levels of insulin-antagonistic hormones (i.e., catecholamine, cortisol, and growth hormone)[139]. These population-based data support the hypothesis that cigarette smoking may provoke the metabolic abnormalities and may increase the risk of MS. However, further studies are needed to explain the underlying mechanisms and the causal effects of smoking on MS.

Regarding alcohol consumption, literature review showed inconsistent findings. This controversy could be related to the complex mechanistic relation between alcohol consumption and each component of MS. While mild to moderate alcohol consumption has a favourable influence on lipids metabolism, abdominal obesity and glucose regulation[228], on the other hand, heavy alcohol consumption causes hypertension[229], and hypertriglyceridemia[230]. A U-shaped relationship was reported between the MS and alcohol drinking[231], [232]. A recent meta-analysis demonstrates that "responsible drinking" place the individual at lower risk of having the MS[158]. In ORISCAV-LUX study, no significant association was seen. However, this finding should be interpreted with caution for several reasons. First, the data on alcohol consumption are based on self-declaration with the possibility of misclassification of exposure due to under-reporting. Second, in such a population-based study aiming to observe the cardiovascular risk factors, the "social desirability" might push the participants to under-report their real alcohol consumption, despite the general alcohol acceptance and nearly similar socio-cultural European population habits regarding this issue. The overall self-reported alcohol drinking during the last 12 months (5.4g/day, i.e., correspond to a half standard glass/day) was sensibly under-estimated. Third, due to the very limited cases in the high drinking category, the population was classified into 2 principal groups (drinkers versus non-drinkers). This may lead to underpowered inference about the effect of harmful drinking on MS. The quality of research on alcohol relies primarily on the accuracy of assessment tool. The epidemiological community-based studies have shown that the reliability of self-reported alcohol consumption is good[233], [234]. In our study, the inter-reliability between the 2 questionnaires measured by Cohen's kappa coefficient was almost sufficient (κ= 0.61), however, it is highly recommended to validate self-reported alcohol consumption by using serum Υ-glutamyl transferase and Carbohydrate Deficient Transferrin (CDT)[235].

In the ORISCAV-LUX study, the prevalence of MS was significantly different according to the level of physical activity. The inactive subjects have double fold odd of having MS compared to physically active subjects. A borderline association persists after full multivariate adjustment for age, gender, smoking, family history of selected clinically related conditions, dietary factors and socioeconomic variables. According

to IPAQ tool, the studied population was categorized into three levels of physical activity: "low" or physically inactive, "moderate" or moderately active and "high" level of physical activity or "active". Interestingly, the "moderate" level corresponds to the national and international physical activity guidelines, i.e., performing 30 minutes of moderate-intensity activity 5 days a week, or 20 minutes of vigorous activity 3 days a week, or a combination of both. Basically, the guidelines are based mainly on leisure-time activity, whereas the IPAQ assesses four domains (work, leisure-time, transport and household tasks); the "high" activity level is developed to reflect an amount greater than the standard recommended levels, i.e., a threshold approximately twice the MET-minutes of the "moderate" level[236]. This finding is of significant importance because it indicates that even the subjects complied with current recommended level of physical activity still at high odd of having the MS. Only the highly active subjects seem predominantly protected. This finding implies the need to recommend more active lifestyle for those prone to have the MS. The major limitation of IPAQ includes difficulties with participants in distinguishing moderate and vigorous activities[236]. The inactive subjects probably tend to report moderate physical activities rather than absence of activity. The self-reported measures can over-estimate physical activity[162]. Poor precision in questionnaire-based measures of moderate activities is likely to result in underestimation of the association between moderately active and the disease outcome[167]. Therefore, bias related to self-misclassification cannot be excluded and may explain the attenuated moderate activity-MS association. In spite of the abovementioned methodological weakness, the self-report measures remain the most feasible and affordable instruments for global surveillance of physical activity. Objective measures, such as pedometers or accelerometers may be beneficial to validate the current available self-reported assessment tools[236]. In addition, the advantage of the IPAQ tool is that the physical activity is expressed in MET-minutes per week rather than energy expenditure (Kcal), resulting in physical activity estimate independent of body weight. Energy expenditure prevents direct comparison between participants with different body sizes and would confound the analyses between physical activity and MS. In agreement with our findings, previous studies showed that the MS was inversely associated with physical activity[163], [166], [237]. However, comparison between studies is difficult, as different definitions of MS and dissimilar physical activity evaluation tools were applied. In contrast to the number of studies that investigated the association of exercise with the development of diabetes or cardiovascular disease, data considering specifically the MS are spare in the literature. For the best of our knowledge, this is the first population-based study that examines the association between the MS and the classification of the population, in terms of their physical activities according to an international physical activity tool (IPAQ). The Whitehall II study of English civil

servants (aged 45-68 years), based on the Minnesota leisure-time physical activity questionnaire, documented that the moderate and vigorous physical leisure-time activity were both associated with reduced risk of MS independently of age, smoking and high alcohol intake[167]. This study did not investigate the confounding effect of dietary factors. In a study of young adults, the sedentary behaviours measured by the number of hours of inactivity and of watching television or playing video or computer games were positively associated with the presence of at least three metabolic risk factors[165]. The adverse effect of inactivity is thought to be attributable to reduce energy expenditure, which affects all five components of the MS. It is inversely associated with body weight, blood pressure and triglycerides[163]. Physical activity was significantly associated with high HDL-C level[238]. Due to cross-sectional nature of these analyses, the direction of the association between physical activity and MS is uncertain. Hence, further extension of these observations to fully prospective investigation is warranted to assess whether inactivity do increase the risk of MS, or possibly those who reported low level of activity may have reduced their activities as a result of having the MS.

In addition to the abovementioned behavioural habits, diet and particularly the intake of specific nutrients may have different effects on the development of MS. During the last decades, an emerging scientific evidence indicated that diets which include fish, nuts, low-fat dairy products and rich in fruits, vegetable and whole grain have protective health effect [238]. In the present study, the association of MS with individual dietary component was investigated. In addition, a composite measure of diet quality (DQI) was created to evaluate the overall healthfulness of dietary intake, in terms of adherence to the dietary guidelines. Unexpectedly, the non-complied subjects regarding saturated fat and simple sugar showed significantly low odds of having the MS, regardless of their age and gender. The SFA-MS association was disappeared after full adjustment to potential confounders. The persistence of low odd ratio of having the MS among those who complied with simple sugar intake guidelines, in the full adjusted model, can be explained by the cross-sectional nature of the study that precludes comment on causality. The plausible explanation of this finding is that having dyslipidemia or diabetes may significantly encouraged the participants to limit their intake of saturated fat or simple sugar, hence shift the odd ratio toward the left side of referent category. In line with this explanation, the study results have demonstrated that the participants having diabetes and lipid disorder were better adherent to the recommendations than those without these pathologies, notably those under treatment. In addition, a significant proportion of those having the MS were currently on one or more diets, for example to lower their cholesterol, sugar intake, blood pressure or lose weight (data not shown). The MS has been identified as a target for dietary therapy to reduce CVD. Current guidelines

have emphasized on the importance of increasing carbohydrate intake and reducing total and saturated fat, because of their reduced-energy density effect. However, there is now substantial evidence that low-fat and high carbohydrate diets decrease HDL-C concentrations[239], [240], and increase triglycerides[241]. Emphasis on the need to reduce total fat in the diet of apparently healthy people could lead to increase carbohydrate consumption, which may have adverse effects on blood lipids and consequently increase risk of the MS. Previous studies reported an inconsistent relationship between the MS and dietary fat or carbohydrate intake[242], [243]. In elderly men, greater risk of the MS was associated with low-fat intake[241]. Recent findings from the NHANES study stated that high-carbohydrate intake was associated with a greater risk of MS[220]. These conflicting results could be attributed to the heterogeneity of study designs, limited accuracy of dietary assessment and source of dietary carbohydrates considered for the analyses[242]. The quality of dietary fat is of great interest, as there is considerable evidence in experimental animals that saturated fat in the diet may lead to insulin resistance. In man, intervention studies on changes in dietary fat quality and insulin sensitivity have so far been inconclusive[244]. Alike, the detrimental effect of saturated fat or the beneficial effect of polyunsaturated fat is controversial[242]. High MUFA diet significantly improves insulin sensitivity compared to a high SFA diet; however, this beneficial effect disappears in individuals whose total fat intake exceeds 38% of total energy[244]. Evaluating the effect of dietary fat on insulin sensitivity-related pathologies is a complex issue. The more appropriate study design to study this effect, independently of all possible confounders, is the intervention trail[244]. Unfortunately, such studies are rarely available in the literature. The principal and innovative finding of ORISCAV-LUX study is the persistent independent association between MS and total protein intake, even after adjustment for age, gender, education, socioeconomic factors, smoking, physical activity, family history and other dietary factors. There have been no similar findings from previous studies on this issue. Therefore, it is unclear whether this relation is unique to our studied population. The reason for this nutrient-specific finding requires replication and further investigation. The role of dietary protein in the development of coronary heart disease (CHD) has been less widely studied in epidemiologic investigations than have the effects of dietary fats, carbohydrates, and alcohol[245]. The potential underlying mechanism is that high dietary protein intake associated with an increased prevalence of diabetes [246], and has detrimental effects on glucose homeostasis by promoting insulin resistance and increasing gluconeogenesis[247]. Considering diet quality index, no association was seen with increased odd of MS after adjusting for potential confounding factors, suggesting that the overall quality of diet had no significant impact on the prevalence MS among our studied population. However, external validation of the created DQI is necessary before final conclusion on this issue.

In addition to the impact of age and gender, the final multivariate model suggests that the majority of studied population would not be diagnosed with the MS if they are well qualified, had no family history of diabetes or hypertension and had appropriate lifestyle behaviors, such as being physically active and have adequate protein intake. Considering the BMI in this model, only diabetic family history remains independently associated with high prevalence of the MS, suggesting that the BMI is the most sensitive marker among the associated factors for the MS. This finding is consistent with results from US and Korean adults, in which the BMI was shown to be a strong predictor for the MS[220], [248].

2. Conclusion

The MS has emerged as an important public health problem in Luxembourg. Almost one-fourth of the adult population are affected by this pathology. People with the MS are at increased risk for developing diabetes and CVD[27], [16]. Because of the high prevalence and the associated morbidity and mortality, a thorough understanding of its potential determinants and risk factors is a key element to designing primary and secondary prevention programs.

In agreement with previous studies[232], [248], [249], the MS was positively associated with many modifiable lifestyle factors, particularly, daily smoking of more than 20 cigarettes, physical inactivity and high-protein diet, independently of age and gender. The association with tobacco consumption was however attenuated when adjusting for other socioeconomic and lifestyle factors. No association was seen with alcohol intake, or with dietary fat intake, consistent with findings from US[220] and UK studies[241].

The ORISCAV-LUX study has contributed to advance the knowledge of epidemiological profile of MS, an important cardiometabolic risk factor of adult population residing in Luxembourg. The results suggest that male gender, age, low education, family history of diabetes and hypertension as well as specific behavioural factors, such as physical inactivity and inadequate protein intake account for the disparities observed in the MS prevalence rates among our studied population. The multiple factors contributing to MS highlights the potential interactions that occur at both individual and behavioural level to produce the condition. The MS does not develop overnight, but rather a progressive overlapping of dietary, behavioural and inherited risk factors. These findings support the need for comprehensive approach in clinical and community settings to promote healthier habits.

3. Study limitations

Although ORISCAV-LUX study is characterized by several strong points, certain shortcomings should still be recognized. Primarily, the cross-sectional design has inherent drawbacks; it limits the possibility to determining the criteria which better predict adverse cardiometabolic outcomes and thus precludes causal inferences. Basically, it can generate hypothesis for future research. Secondly, the analyses were based on Europid population; our results may therefore not apply to other ethnic groups. Third, as in most epidemiological studies, the potential for incomplete adjustment for latent confounders exists. The relationship is possibly confounded by other factors, such as psychosocial which are probably co-related to MS and to studied socioeconomic indicators. Finally, the evaluation of tobacco consumption, alcohol use, physical activity and food habits was based on self-reported information. Although the participants completed the auto-administered questionnaire with the help and supervision of well-trained staff, we cannot exclude the possibility of under- or over-reporting. This might lead to a selective misclassification of high-risk individuals which would blur the potential association, especially for alcohol use and physical activity. An objective confirmation of self-reported alcohol use by using serum ϒ-glutamyl transferase and recently by Carbohydrate Deficient Transferrin (CDT) is recommended[235]. While there is evidence indicating that self-reported information by the IPAQ on physical activity is suitable for epidemiological studies[236], valid assessment techniques of physical activity are still vital, such as the use of pedometers to provide more objective measures of the activity of participants. This technique is extremely expensive and not practically available for population-based studies.

Similarly, although FFQ has been largely used in cross-sectional surveys, it could be considered limited by its lack of quantitative accuracy; under-reporting of energy intake may be a problem when obese subjects are under investigation[242]. Future research and new epidemiologic practice may take advantage of recently available technologies to improve nutritional assessment. There are many opportunities for technological solutions to assist both in capturing and analyzing information on current, actual food use (Collect Real-time Food-Use Information Using Computer-Aided Technologies). Study participants could use a digital phone with an embedded camera to transmit pictures and descriptions of foods eaten on a meal-by-meal basis. A computer-administered 24-hour recall could be delivered over the internet or on a pocket PC[250].

The strengths of the ORISCAV-LUX study reside firstly in the population sample; the small size of the country made it possible to organize data collection at a national level. Secondly, the ORISCAV-LUX study is based on recent nationwide, representative sample of Luxembourg adult residents. An ample study of non-participants showed that the demographic and clinical characteristics of the ORISCAV-LUX participants were comparable with those of the non-participants[203]. Furthermore, the predominantly white homogeneous nature of the sample (94.2% Europid) ensured the control over ethnicity factor, hence permitting the generalizing of the results.

Additionally, the conception of the survey was consistent with the WHO stepwise approach[251], which recommends measuring chronic diseases risk factors by using standardized tools and objective measurements to facilitate national and international comparability. To avoid inaccurate retrieving of essential components of the MS from self-administered information, extensive direct measurements, obtained from the ORISCAV-LUX study participants, provided more reliable and objective measures (for example, hypertension, obesity, diabetes).

Intensive efforts were accomplished to ensure quality control throughout the conduct of the study. Noteworthy, the high reproducibility observed in duplicate measurements indicated good quality control of physical examination, in particular for the waist circumference; the fundamental criteria to identify the MS.

Finally, the ORISCAV-LUX study has dual significance; public health surveillance and research development. It is the first population-representative direct health measurements survey ever conducted in Luxembourg.

Despite the above-mentioned limitations, this data is useful and valid source of information for health professional and public health decision-makers. The findings constitute a basis for developing health education and health promotion programs regarding cardiometabolic risk prevention and control.

4. Application of findings with respect to the prevention

Valid and reliable health statistics are essential for planning and implementing health policy in all settings. Over the last decade, the need for better evidence has become manifest in the public health sector. The aim of evidence-based decision making (EBDM) is to ensure that decisions about health and health care are based on the best available knowledge.

Diabetes and cardiovascular disease prevention have become a crucial contemporary public health challenge. Although the ORISCAV-LUX study findings suggest that lifestyle changes in diet and physical activity should be recommended as the first-line intervention for the prevention of MS, the multi-factorial aetiology of the MS implies multi-facetted intervention program. A holistic population health approach, including physical, social, mental and environmental health, is needed to promote healthy diet, exercise, weight control, complete smoking cessation, stress management and avoidance of environmental pollution [252]. Although environmental biomarkers were not considered in the scope of this research work, important part of this information is currently available. Further research is required to generate the supplementary information needed, for instance, with regards to mental and social well-being, quality of life, life satisfaction, working and education conditions, and other factors known to influence cardiovascular health.

5. Perspectives

In view of previous reflections, the following paragraphs give suggestions for future research. Basically, my own future research would concern the follow up of ORISCAV-LUX database analyses as regards the global cardio-metabolic disorders. Large amounts of information are still available, and are worthwhile exploring in greater depth. In particular, the importance of physical activity and dietary patterns associated with MS development. In this perspective, a peer-review protocol has been projected and approved by the National Research Funds to obtain a 2-year financial support. It aims to study profoundly the diet-metabolic syndrome relationships, by using appropriate approaches, based on dietary patterns and/or food components.

Luxembourg is characterized by its multicultural nature. Among Europeans, the Portuguese represent the largest segment of the population. The after-thesis research will explore the cross-cultural differences between Luxembourgish and Portuguese people, in how nutritional factors or dietary patterns may influence the prevalence of the metabolic syndrome.

The preliminary ORISCAV-LUX findings showed that the prevalence of hypertension and lipid disorders differed significantly between countries of birth (Luxembourg, Portugal, Europe and others). Characterising groups at risk in the general population is important to tailoring public health action accordingly. This issue needs further research to support the hypothesis that the risk of CVD is influenced by the country of birth and that immigrants tend to have better health[253].

In the context of ORISCAV-LUX study, other potential determinants of the MS including mental health and psychological factors were not investigated. Therefore, supplementary information about depression, perceived stress, social network, conditions of housing and cohabitation merit study in the future.

Increasing evidence suggests that hormonal dys-regulation plays a pivotal role in causing the MS. It is hypothesized that alteration in hormone levels, for example: age-related changes in androgens, high levels of testosterone, dehydroepiandrosterone sulfate (DHEA-S) and cortisol, low levels of sex hormone-binding globulin (SHBG) and insulin-like growth factor (IGF-I) would affect the development of the MS and in consequence would contribute to an increased risk of cardiovascular disease. Relevant hormones may form potential targets for intervention.

The NESCAV cross-border survey should allow interregional comparison and add-value to the present findings. For example, investigating the most appropriate Europid waist circumference cut-off points to define central obesity, based on a large interregional cohort population of European origin, would be most welcome in the future.

Future research should focus on identifying the early-life determinants of the MS. Less investigated determinants include genetic predisposition, healthy child development and adverse peri-natal environment. Interestingly, short and long-term prospective investigations are needed to study the range of factors implicated in childhood and adult MS development, both from an individual and a population perspective.

Interventional trails, in which all potential risk indicators can be measured prospectively, is needed to test the direct effects of dietary modification and physical activity intervention on the prevention of MS. Moreover, longitudinal designed studies with standard adiposity measures and dietary intake data are needed to understand the interplay between body weight, fat distribution, and dietary habits to the genetic predisposition of the MS, which is a common cardiovascular disease risk factor in western countries.

Finally, from a public health and research perspective, the examination of cardiovascular risk factors needs to be repeated and maintained at regular intervals to monitor the evolution over time.

Publications which have come out of the thesis work

A. Alkerwi et M-L.Lair, Le syndrome métabolique: nécessité d'une précision scientifique, La semaine médicale luxembourgeoise, N° 358, 29 Août 2008.

Marie-Lise Lair und Ala'a Alkerwi, Studie ORISCAV : Wie gesund sind die Luxembourg?, InSight Santé Sécu, Ausgabe 2/2008

This thesis is based on the following peer-reviewed papers

1. Alkerwi Ala'a, Boutsen Michel, Vaillant Michel, Barre Jessica, Lair Marie-Lise, Albert Adelin, Guillaume Michèle, Dramaix Michèle., *Alcohol consumption and the prevalence of metabolic syndrome: A meta-analysis of observational studies,* Atherosclerosis, 2009 vol. 204, no2, pp. 624-635.

2. Ala'a Alkerwi, Nicolas Sauvageot, Anne-Françoise Donneau, Marie-Lise Lair, Sophie Couffignal, Jean Beissel, Charles Delagardelle,Yolande Wagener, Adelin Albert, Michèle Guillaume, *First nationwide survey on cardiovascular risk factors in Grand-Duchy of Luxembourg (ORISCAV-LUX)*, BMC Public Health 2010, 10:468.

3. Ala'a Alkerwi, Nicolas Sauvageot, Sophie Couffignal, Adelin Albert, Marie-Lise Lair, Michèle Guillaume, *Comparison of participants and non-participants to the ORISCAV-LUX population-based study on cardiovascular risk factors in Luxembourg***,** Medical Research Methodology 2010, 10:80.

4. Ala'a Alkerwi, Michèle Guillaume, Faiez Zannad, Ulrich Laufs, Marie-Lise Lair, the NESCAV project group, *Nutrition, environment and cardiovascular health (NESCAV): protocol of an inter-regional cross-sectional study,* BMC Public Health 2010, 10:698.

5. Ala'a Alkerwi, Anne-Françoise Donneau, Nicolas Sauvageot, Marie-Lise Lair, André Scheen, Adelin Albert, Michèle Guillaume, *Prevalence of the metabolic syndrome in Luxembourg according to the Joint Interim Statement definition estimated from the ORISCAV-LUX study*, BMC Public Health 2011, 11:4.

During the course of the thesis, a number of oral or poster presentations were made:

1. A. Alkerwi, M. Boutsen, M-L Lair, A. Albert, M. Guillaume, M. Dramaix, *Alcohol consumption and the prevalence of metabolic syndrome: A meta-analysis of observational studies.* Third International Congress on Prediabetes and the Metabolic Syndrome, Nice, France, 1-4th April 2009 (Poster published in Abstract Book 2009).

2. Alkerwi A. and Guillaume M., *Glance on preliminary nutritional data ORISCAV-LUX Survey.* The first Luxembourgish Food and Nutrition Conference (NULUX)" « Phytochemicals and Micronutrients in Chronic Disease Prevention", 22nd April 2009 (Oral presentation).

3. *A. Alkerwi, M-L. Lair, S. Couffignal, N. sauvageot, L. Counet, S. Hatert, A-F, Donneau, A. Abert, M. Guillaume, Etude épidémiologique des comportements alimentaires au service de la promotion de la santé*. The International Congres « XX Congrès de l'ALASS » « *L'avenir des systèmes de santé : impact sur les systèmes de santé de la recherche et de l'innovation dans les sciences de la vie*», Luxembourg, 10-12th September 2009 (Oral presentation).

4. A. Alkerwi and Nicolas Sauvageot, *Les facteurs de risque cardiovasculaires au Luxembourg Résultats préliminaires*, Scientific day NESCAV, Nancy, France, 28th October 2009 (Oral presentation).

5. A. Alkerwi, M-L Lair, M. Guillaume, Focus *on the epidemiology of the metabolic syndrome and several of its potential determinants among the apparently healthy adults in Luxembourg*, The BIT's 2nd Annual International Congress of Cardiology, Shanghai, China, 7-9th December 2010 (Oral presentation).

6. A. Alkerwi, Anne-Françoise Donneau, Nicolas Sauvageot, Marie-Lise Lair, André Scheen, Adelin Albert, Michèle Guillaume, *Prevalence of the metabolic syndrome in Luxembourg according to the Joint Interim Statement definition estimated from the ORISCAV-LUX study*, The « PhD day 2010 », organized by the "Ecole Doctorale Santé Publique Santé et Société -SPSS, 18th Novembre 2010 (Oral presentation)

7. Ala'a Alkerwi, Anne-Françoise Donneau, Nicolas Sauvageot, Marie-Lise Lair, André Scheen, Adelin Albert, Michèle Guillaume, *Prevalence of the metabolic syndrome in Luxembourg according to the Joint Interim Statement definition estimated from the ORISCAV-LUX study*, The 2nd International Congress on Abdominal Obesity, Buenos Aires, Argentina, 24-27 February 2011 (Poster published in Abstract Book 2011).

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