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Elisabete Cristina Macedo Alves

Cardiovascular Risk Profile in Mothers of a Portuguese Birth Cohort

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Dissertação de candidatura ao grau de Doutor apresentada à Faculdade de Medicina da Universidade do Porto

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Ao longo do meu doutoramento, colaborei activamente na definição e operacionalização das hipóteses em todos os artigos, tendo sido responsável pela análise e interpretação dos dados que reportam. Participei na recolha dos dados utilizados em todos os artigos, tendo colaborado na coordenação da avaliação de *follow-up* da coorte. Fui responsável pela redacção da versão inicial dos manuscritos e colaborei activamente na preparação das versões finais de todos os artigos.

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Júri da Prova de Doutoramento

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porque me acompanharam ao longo de todo este percurso
e nunca deixaram de acreditar em mim.

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ABSTRACT

Cardiovascular diseases (CVD) result from a complex interplay of genetic, developmental, environmental and behavioural factors. CVD mortality rates increase with the number of risk factors to which an individual is exposed, supporting that the risk for CVD depends on the interaction among those factors to complete a sufficient causal mechanism. In young women, pregnancy puts a physiological stress on the body that can unmask an underlying propensity for chronic disease. Additionally, pregnancy is often regarded as a good opportunity for health promotion and disease prevention, due to the strong motivation of mothers to protect the health of the unborn baby.

This thesis aims to study the cardiovascular risk profile of mothers of a Portuguese birth cohort (Geração XXI), before and during pregnancy, and 4 years after delivery. To answer this main question, the following 5 specific objectives were defined and pursued, resulting in 5 papers:

1. To estimate the prepregnancy prevalence of five major cardiovascular risk factors (overweight/obesity, smoking, hypertension, dyslipidemia and diabetes mellitus), and to describe their distribution by age, gravidity and indicators of socioeconomic position (SEP).

2. To assess the impact of age, education, family history of cardiovascular disease, prepregnancy BMI and pregnancy weight gain on hypertensive disorders in pregnancy, in primiparous and multiparous mothers.

3. To assess the extent to which gestational hypertensive disorders lead to higher blood pressure in women and their offspring as early as 4 years after birth, and to assess the effect of fetal sex on these consequences.

4. To assess the frequency and determinants of maternal smoking cessation during pregnancy and of the sustainability of smoking cessation 4 years after delivery.

5. To estimate the prevalence of established cardiovascular risk factors (smoking, low fruit and vegetables intake, sedentariness, general overweight/obesity, abdominal obesity, hypertension, dyslipidemia and diabetes mellitus), 4 years after delivery, and to describe their distribution by age, gravidity and indicators of socioeconomic position (SEP).

The birth cohort Geração XXI was assembled between 2005 and 2006 at all 5 public maternity units covering the metropolitan area of Porto, Portugal. Trained interviewers invited the mothers to participate, after delivery. Of the invited mothers, 91.4% accepted to participate. A total of 8647 infants, corresponding to 8495 mothers, were enrolled in the cohort. Data on demographic and socioeconomic characteristics, personal and family medical history, gynaecologic and obstetric history, prenatal care, and lifestyles were collected in a face-to-face interview. Anthropometrics were measured. Clinical records were also reviewed at birth by the same interviewers to retrieve data on prenatal care, pregnancy complications, delivery and neonatal characteristics. Missing data on the questionnaires were recovered through the review of obstetrical records (**PAPER I**), by 2 trained abstractors. Data on personal history of diabetes was highly concordant, while for hypertension it was moderately concordant. In general, the discrepancies found for weight and height indicated higher values in the clinical record than in the questionnaire and lead to discrepancies in prepregnancy body mass index classes of 10.3% of women. Data were very consistent between reviewers, with highest agreement for gestational diabetes and birth weight.

At 4 years of the child's age, between 2009 and 2011, all the mothers with their children were invited to attend the re-evaluation of the cohort, comprising an interview and physical examination. If they refused, they were invited to answer a telephone interview. Overall, 86.2% of the children and 84.2% of the mothers were re-evaluated. In the face-to-face interview, information was collected by trained interviewers, using two structured questionnaires. Mothers' questionnaire comprised data on demographic characteristics, personal and family medical history, gynaecologic and obstetric history, and lifestyles. Children's questionnaire included data on socioeconomic characteristics of the parents, and on child's development, health and habits. A physical examination was also performed on all mothers and children, including anthropometric evaluation and blood pressure measurement, and a fasting venous blood sample was withdrawn. The telephone interview also contained data regarding the health of the mother and the child, although with a restricted number of questions.

In this sample of Portuguese women, before pregnancy, 21.3% were overweight and 8.8% were obese, 26.6% smoked and 11.2% were former smokers (**PAPER II**). The prevalence of hypertension, dyslipidemia and diabetes mellitus was 1.7%, 1.7% and 0.6%, respectively, with an evident tendency to cluster. The prevalence of all cardiovascular risk factors, except smoking, increased with age and body mass index. Education and income were inversely associated with excessive weight. Current smokers were younger, thinner and in a lower socioeconomic position.

Overall, hypertensive disorders affected 4.6% of single pregnancies, and were associated with older age, lower education, family history of cardiovascular disease and excessive weight before and during pregnancy, similarly in primiparae and multiparae (**PAPER III**). Approximately 50% of hypertensive disorders among primiparae and 70% among multiparae were attributable to the joint effect of pregnancies after 34 years of age, education below 12 years, family history of cardiovascular disease, overweight/obesity before pregnancy and excessive weight gain during pregnancy.

Four years after delivery, gestational hypertensive disorders were associated with significant increases of systolic and diastolic blood pressure of the mother (**PAPER IV**). The risk of hypertension in women affected by gestational hypertensive disorders was almost 6 times higher among mothers who delivered a girl, and 3 times higher among those who delivered a boy. Additionally, systolic and diastolic blood pressure at 4 years were significantly higher in boys born of mothers with hypertensive disorders of pregnancy, while no effect was detected among girls.

Although almost half of smokers ceased tobacco consumption during pregnancy, approximately two thirds resumed smoking 4 years after delivery (**PAPER V**). Cigarette smoking cessation during pregnancy was more likely among primigestae, those living with a partner, with higher educational levels, overweight or obese, with adequate prenatal care, who began smoking later and who smoked a lower amount of cigarettes. Those who sustained the smoking cessation were more likely to be older, primigestae, living with a husband/partner at 4 years, with lower tobacco consumption before pregnancy, and to have breastfed for 52 weeks or more, to have gotten pregnant again after the index pregnancy and to have a medical diagnosis of asthma and/or rhinitis in their child.

At follow-up, 25.3% of the participants were smokers, 50.7% consumed less than 3 portions of fruit and vegetables per day, and 81.3% did not practice any leisure-time physical exercise (**PAPER VI**). Moreover, 31.4% were overweight, 21.3% obese and 31.8% had abdominal obesity. Regarding the cardiometabolic comorbidities, 8.7% of the women had hypertension and the prevalence of dyslipidemia and diabetes mellitus was 18.5% and 0.9%, respectively. The presence of at least one risk factor from each of the 3 groups (adverse lifestyles, adiposity and cardiometabolic comorbidities) was observed in 17.0% of women. All risk factors were associated with unemployment, lower education and lower income.

In conclusion, Portuguese young women are at a high level of risk for cardiovascular disease, before and after pregnancy. The clustering of cardiovascular risk factors, as well as the high prevalence of adverse lifestyles and adiposity, show an adverse cardiovascular risk profile of Portuguese mothers since the preconceptional period.

Pregnancy induces profound alterations in maternal health, by revealing previous background risk and/or increasing the propensity to develop cardiovascular diseases. Prepregnancy risk factors explained a high proportion of hypertensive disorders during pregnancy, with excessive weight before and during pregnancy, having a very large contribution, particularly among primiparae. Additionally, 4 years after a single pregnancy complicated by gestational hypertensive disorders in primiparae, the impact on mothers' blood pressure and incident hypertension was large, and this effect was stronger when the foetus was female. Regarding the children, a differential effect by child's sex was observed, supporting the hypothesis of heterogeneous causes of hypertension in pregnancy and that boys live dangerously in the womb.

During pregnancy almost half of the women stopped smoking. However, 4 years after delivery two thirds of these resumed smoking, showing that this behavioural change showed little long-term impact on women's smoking trajectory.

The high risk of cardiovascular disease described in young and apparently healthy women, who achieved at least one successful pregnancy, emphasizes the need to implement coherent and effective strategies of health promotion and disease prevention at early stages of life in order to optimize women's current and future health.

RESUMO

As doenças cardiovasculares resultam de uma complexa interação entre fatores genéticos, de desenvolvimento, ambientais e comportamentais. A taxa de mortalidade por doenças cardiovasculares aumenta com o número de fatores de risco a que um indivíduo está exposto, ilustrando que estes fatores têm efeitos interdependentes para completarem um mecanismo causal suficiente. Em mulheres jovens, a gravidez condiciona uma situação de *stress* fisiológico no organismo, que pode desmascarar uma propensão mais elevada, previamente inaparente, para a ocorrência de doenças crónicas. Adicionalmente, a gravidez é uma boa oportunidade para a promoção de saúde e para a prevenção da doença, devido à forte motivação das mães para proteger a saúde do feto.

Esta tese tem como objetivo estudar o perfil de risco cardiovascular em mães de uma coorte de nascimento Portuguesa (Geração XXI), antes e durante a gravidez, e 4 anos após o parto. Para responder a esta questão geral, foram definidos os seguintes 5 objetivos específicos, os quais resultaram em 5 manuscritos científicos:

1. Estimar a prevalência de cinco fatores de risco cardiovascular *major* (excesso de peso/obesidade, tabagismo, hipertensão arterial, dislipidemia e diabetes mellitus) antes da gravidez, e descrever a sua distribuição de acordo com a idade, o número de gravidezes prévio e indicadores da posição socioeconómica.

2. Avaliar o impacto da idade, da escolaridade, da história familiar de doença cardiovascular, do índice de massa corporal prévio à gravidez e do ganho de peso durante a gravidez na ocorrência de complicações hipertensivas da gravidez, em mulheres primíparas e multíparas.

3. Avaliar em que medida o desenvolvimento de complicações hipertensivas durante a gravidez conduz ao aumento da pressão arterial das mães e das crianças 4 anos após o parto, e avaliar o efeito do sexo da criança nestas consequências.

4. Avaliar a frequência e os determinantes da cessação tabágica durante a gravidez e da manutenção da cessação tabágica 4 anos após o parto.

5. Estimar a prevalência de fatores de risco cardiovascular previamente estabelecidos (tabagismo, baixo consumo de frutas e vegetais, sedentarismo, excesso de peso/obesidade, obesidade abdominal, hipertensão arterial, dislipidemia e diabetes mellitus), 4 anos após o parto, e descrever a sua distribuição de acordo com a idade, o número de gravidezes prévio e indicadores da posição socioeconómica.

A coorte de nascimento Geração XXI foi recrutada entre 2005 e 2006, nos 5 hospitais públicos com maternidade da área metropolitana do Porto, Portugal. Após o parto, inquiridores treinados convidaram as mães a participar. De entre as mães convidadas, 91,4% aceitaram participar. Um total de 8647 crianças e as respetivas 8495 mães foram incluídas na coorte. Através de uma entrevista presencial às mães, foram recolhidas informações sobre as características demográficas e socioeconómicas, história pessoal e familiar de doença, história ginecológica e obstétrica, cuidados pré-natais e estilos de vida. As mães e as crianças realizaram uma avaliação antropométrica. Os mesmos inquiridores treinados reviram também os processos clínicos na altura do parto, para recolher informações relativas aos cuidados pré-natais, à ocorrência de complicações durante a gravidez, e às características do parto e neonatais. Para recuperar informações em falta nos questionários, revimos os processos clínicos obstétricos das mães (**ARTIGO I**), por 2 revisores treinados. A concordância entre os dados do questionário e dos registos obstétricos para a história pessoal de diabetes foi altamente concordante, enquanto para a de hipertensão foi moderadamente concordante. Em geral, as discrepâncias encontradas para o peso e a altura indicavam valores mais elevados nos registos clínicos do que nos questionários, o que resultou em divergências na classe de índice de massa corporal em 10,3% das mulheres. A informação recolhida foi extremamente consistente entre os dois revisores, com máxima concordância para a diabetes gestacional e o peso ao nascimento.

Aos 4 anos de idade das crianças, entre 2009 e 2011, todas as mães e os respetivos filhos foram convidados a participar na reavaliação da coorte, composta por uma entrevista e avaliação física. Caso recusassem, eram convidadas a responder a uma entrevista telefónica. Do total, 86,2% das crianças e 84,2% das mães foram reavaliadas. Durante a entrevista presencial, a informação foi recolhida por inquiridores treinados, utilizando dois questionários estruturados. O questionário da mãe continha informação sobre as suas características demográficas, história pessoal e familiar de doença, história ginecológica e obstétrica, e estilos de vida. O questionário da criança incluía informações relativas às características socioeconómicas parentais, e sobre o desenvolvimento, saúde e hábitos da criança. Foi realizado um exame físico às mães e crianças, incluindo avaliação antropométrica e medição da pressão arterial, e colheita de uma amostra de sangue em jejum. Na entrevista por telefone também se recolheu informações relativas à saúde da mãe e da criança, ainda que com um número mais restrito de questões.

Nesta amostra de mulheres Portuguesas, 21,3% tinham excesso de peso e 8,8% eram obesas, 26,6% fumavam e 11,2% eram ex-fumadoras, antes de engravidar (**ARTIGO II**). A prevalência de hipertensão arterial, dislipidemia e diabetes mellitus era de 1,7%, 1,7% e 0,6%, respectivamente, com uma clara tendência de agregação. A prevalência de todos os fatores de risco cardiovascular, com a exceção do tabagismo, aumentou com a idade e com o índice de massa corporal. A escolaridade e o rendimento associaram-se inversamente com a prevalência de excesso de peso. As fumadoras eram mais novas, com um índice de massa corporal mais adequado e tinham uma posição socioeconómica mais baixa.

Globalmente, as complicações hipertensivas afetaram 4,6% das gravidezes de feto único, e estavam associadas a idade mais avançada, menor escolaridade, história familiar de doença cardiovascular e excesso de peso antes e durante a gravidez, de forma similar em mulheres primíparas e multíparas (**ARTIGO III**). Aproximadamente 50% dos casos de complicações hipertensivas na gravidez em mulheres primíparas e 70% em multíparas foram atribuíveis ao efeito conjunto de idade superior a 34 anos, escolaridade inferior a 12 anos, história familiar de doença cardiovascular, excesso de peso/obesidade e ganho de peso excessivo durante a gravidez.

Quatro anos após o parto, as complicações hipertensivas gestacionais associaram-se a aumentos significativos na pressão arterial sistólica e diastólica da mãe (**ARTIGO IV**). O risco de hipertensão arterial nas mães que desenvolveram uma complicação hipertensiva durante a gravidez, comparativamente com as que tiveram uma gravidez sem hipertensão, foi cerca de 6 vezes superior nas que deram à luz uma criança do sexo feminino e 3 vezes maior nas que deram à luz uma criança do sexo masculino. Adicionalmente, a pressão arterial sistólica e diastólica aos 4 anos de idade foi significativamente superior nos rapazes cujas mães tiveram uma complicação hipertensiva durante a gravidez, enquanto não foi detetado nenhum efeito nas raparigas.

Apesar de quase metade das fumadoras terem parado de fumar durante a gravidez, aproximadamente dois terços destas retomaram o consumo 4 anos após o parto (**ARTIGO V**). A cessação tabágica durante a gravidez foi mais frequente em mulheres primigestas, que viviam com o marido/companheiro, com escolaridade mais elevada, com excesso de peso ou obesas, com cuidados pré-natais adequados, que começaram a fumar mais tardiamente e que fumavam uma menor quantidade de cigarros diária. Aquelas que mantiveram a cessação tabágica eram mais velhas, e mais frequentemente primigestas, viviam com o marido/companheiro 4 anos após o parto, tinham um menor consumo de tabaco antes de engravidar, amamentaram 52 semanas ou mais, voltaram a engravidar após a gravidez índice e os seus filhos tinham mais frequentemente um diagnóstico médico de asma ou rinite.

Na reavaliação da coorte, 25,3% das participantes eram fumadoras, 50,7% consumiam menos de três porções de frutas e vegetais por dia, e 81,3% não praticavam qualquer tipo de exercício físico de lazer (**ARTIGO VI**). Adicionalmente, 31,4% apresentavam excesso de peso, 21,3% eram obesas e 31,8% possuíam obesidade abdominal. Relativamente às comorbilidades cardiometabólicas, 8,7% das mulheres eram hipertensas e, a prevalência de dislipidemia e diabetes mellitus era de 18,5% e 0,9%, respectivamente. A presença de pelo menos um fator de risco de cada um dos três grupos (estilos de vida adversos, adiposidade e comorbilidades cardiometabólicas) foi observada em 17,0% das mulheres. Todos os fatores de risco estavam associados com o desemprego e com níveis de escolaridade e rendimento mais baixos.

Em conclusão, as mulheres jovens Portuguesas apresentam um risco elevado de doença cardiovascular, antes e após a gravidez. A agregação de fatores de risco cardiovascular, assim como as elevadas prevalências de estilos de vida adversos e de adiposidade, mostram um perfil de risco cardiovascular desfavorável em jovens mães, desde o período pré-concepcional.

A gravidez induz profundas alterações na saúde da mãe, desmascarando riscos prévios e/ou uma propensão acrescida para o desenvolvimento de doenças cardiovasculares. As características prévias à gravidez explicam uma elevada proporção de complicações hipertensivas durante a gravidez, com o excesso de peso antes e durante a gravidez a terem uma grande contribuição, particularmente nas mulheres primíparas. Adicionalmente, 4 anos após uma gravidez de feto único, agravada por uma complicação hipertensiva da gravidez, em mulheres primíparas, as mães já possuem valores elevados de pressão arterial e mais frequentemente apresentam hipertensão arterial crónica, sendo este efeito mais acentuado quando o feto é do sexo feminino. Relativamente às crianças, foi observado um efeito diferencial de acordo com o sexo da criança, o que suporta a hipótese da existência de causas heterogéneas para a hipertensão na gravidez e que o desenvolvimento uterino coloca os rapazes em maior risco no futuro.

Durante a gravidez cerca de metade das mulheres parou de fumar. Contudo, 4 anos após o parto dois terços retomaram os hábitos tabágicos, revelando que esta mudança comportamental tem pouco impacto a longo prazo na trajetória tabágica das mulheres.

O elevado risco de doença cardiovascular descrito em mulheres jovens e aparentemente saudáveis, que tiveram pelo menos uma gravidez que resultou num nado-vivo, reforça a necessidade de implementar estratégias coerentes e eficazes de promoção de saúde e de prevenção de doença nas fases precoces da vida adulta, de forma a otimizar a saúde atual e futura das mulheres.

INTRODUCTION

CARDIOVASCULAR DISEASE

Cardiovascular diseases (CVD), defined as diseases of the heart and circulatory system, are the leading cause of death and morbidity worldwide (1), accounting for nearly 30% of deaths (2).

In Europe, CVD are responsible for almost half of deaths (54% in women and 43% in men) (3). Since 1970, a continuous decrease in total cardiovascular mortality rates has been observed in men and women in Western Europe. In fact, between 1970 and 2000, total cardiovascular mortality decreased on average 50% and 60%, corresponding to an average annual decline of 1.8% and 2.0%, in men and women, respectively (4). Two main factors have contributed to this decline: decrease in incidence due to substantial reductions in the prevalence of some major cardiovascular risk factors and decrease in case-fatality due to improvements in treatments, which become more effective and widely used (5). However, despite the decline of age-adjusted cardiovascular death rates during the last decades (4, 6), coronary heart diseases and stroke remain the two most common causes of death in Europe (3).

In Portugal, diseases of the circulatory system accounted for 32.2% of all deaths in 2006; 37.3% in women and 27.6% in men (7). The total CVD mortality rates in Portugal are higher than the European average, with cerebrovascular diseases being the single most important cause of death in Portugal (8).

Beyond their contribution to mortality, CVD also has a large contribution to morbidity outcomes. Morbidity from CVD is more difficult to quantify than mortality, since at present there is no routinely updated source of CVD morbidity data covering the European population (3). Additionally, there are many different measures of morbidity which difficult the comparison of data. The disability adjusted life years (DALYs) lost, which is an aggregate measure of years of life lost due to premature death and years of healthy life lost to disability, is used as an indicator of the burden of the disease. The estimates provided by the World Health Organization (WHO) Global Burden of Disease project indicates that over 34 million DALYs (23% of all DALYs) are lost each year due to CVD, in Europe (9). Regarding more developed European countries, it is estimated that 17% of all DALYs lost are due to CVD, which represent the largest cause of disability after neuropsychiatric disorders. In less developed European countries, CVD were the leading cause of DALYs lost.

Moreover, CVD has major economic costs for Europe (3, 10). In 2006, CVD cost the health care systems of the European Union just under €110 billion, which represents around 10% of the total health care expenditure. However, looking only at the direct costs to the health care systems grossly underestimates the true cost of CVD, since production losses from death and illness in those of working age and from the informal care of people with the disease contribute greatly to the overall financial burden. Production losses due to mortality and morbidity associated with CVD cost almost €41 billion in the European Union, with around two-thirds of this cost due to death and one-third due to illness in those of working age. Overall, CVD is estimated to cost the European Union economy €192 billion a year, of which 57% is due to direct health care costs, 21% to productivity losses and 22% to the informal care of people with CVD (3). Similarly, in Portugal, 10% of the total health care expenditure is spent on CVD, with 69%, 15% and 16% of the overall cost of CVD due to direct health care costs, productivity losses and the informal care of people with CVD, respectively (3).

Due to the extremely high human and economic impact of CVD (3, 6, 10), it is important to descriptively quantify the distribution of cardiovascular risk factors in order to monitor trends over time and guide preventive strategies to reduce the future burden of disease, by identifying groups at higher risk and understanding factors that contribute to the exposure.

CARDIOVASCULAR RISK

CVD reflect a combination of genetic, developmental, environmental and behavioural factors (6, 11). The modifiable nature as well as the considerable impact of lifestyles on the development of CVD (12) emphasize the importance of investing in primary prevention. CVD result of a complex causal chain, with different roots in a multifaceted sequence of events over time, consisting of socioeconomic factors, environmental and community conditions, and individual behaviour. Figure 1 outlines the causal chain of ischaemic heart disease (2). Some elements in the chain, such as high blood pressure or cholesterol, act as a relatively direct cause of the disease, while others risks, located further back in the causal chain, act indirectly through intermediary factors. These risks include physical inactivity, alcohol, smoking or fat intake. Less certainty can be attributed to the causal role of other risk factors, such as education and income. However, modifying these background causes is more likely to have amplifying effects, since such modifications have the potential to yield fundamental and sustained improvements to health.

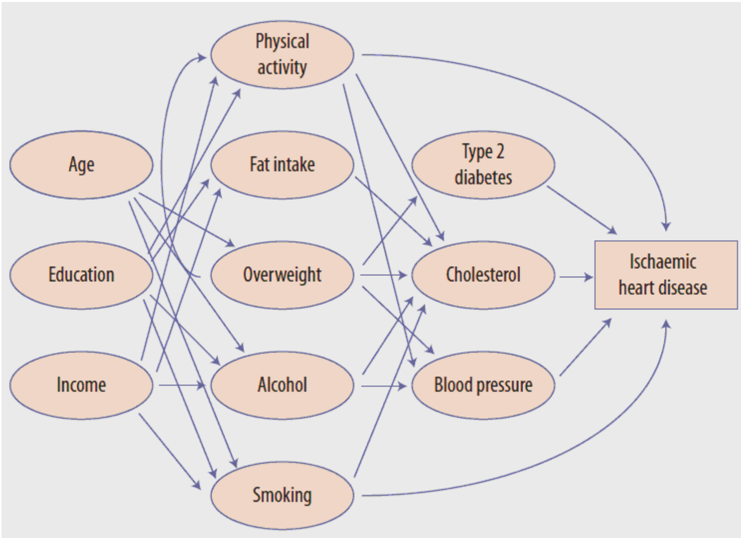

Figure 1. The causal chain. Major causes of ischaemic heart disease are shown. Arrows indicate some (but no all) of the pathways by which these causes interact (2).

Worldwide, hypertension, dyslipidemia, diabetes, obesity, physical inactivity, poor diet with insufficient fruit and vegetables intake, excessive alcohol consumption, smoking and stress are responsible for approximately 90% of all cases of acute myocardial infarction in both sexes (12). According to the up-to-date WHO Report on health risks (2) these risks factors together, except stress, account for 61% of healthy years of life lost due to CVD and 61% of cardiovascular deaths. Among European populations, CVD is mainly attributable to cigarette smoking, high blood pressure, high serum cholesterol, diabetes, overweight/obesity and unhealthy diet (13). They are designated major risk factors for three reasons: their high prevalence in populations, their strong impact on coronary risk; and their preventability and reversibility, primarily by safe improvements in population lifestyles (13). The relation between these risk factors and CVD seem to be independent, strong, continuous and graded, and the modification of these risk factors can result in substantial reduction in mortality (5).

In the Portuguese population, central obesity, defined through the waist-to-hip ratio, was the risk factor with the highest impact in acute myocardial infarction, being responsible for 81.2% of cases in younger men and 88.7% of cases in men aged over 45 years (14) , although the relative contribution of different factors depends largely on the operationalization of their definition. Additionally, fruit and vegetables intake, vitamin and mineral supplement use and leisure-time physical exercise were found to decrease acute myocardial infarction risk, with similar effects between sexes (15).

In the last decades, several studies have shown that CVD mortality rates increase with the number of risk factors to which an individual is exposed (16-18), supporting that the risk for CVD depends on the interaction among those factors to complete a sufficient causal mechanism (19). In fact, these studies reveal that the lower the risk factor profile, the lower the risk for CVD and all-cause mortality. In a prospective population-based cohort of men and women aged 18 to 74 years at baseline, clustering of 3 or more risk factors occurred in about 17% of both sexes and were associated with a 2-fold and an almost 6-fold increased risk of coronary heart disease in men and women, respectively, after 16 years of follow-up (20).

Currently, CVD risk assessment constitutes an important tool in the primary prevention of these diseases. Guidelines advocate the use of cardiovascular risk scores to calculate global risk instead of focusing on single risk factors modification, in order to prevent the occurrence of disease (21). The Framingham Heart Study provided data for the first and most widely used risk prediction tool (22, 23). However, this score overestimated CVD risk in European populations, particularly in those considered at low risk (24-26). In 2003, the Third Joint Task Force of the European Societies on Coronary Prevention recommended the use of the SCORE function in the management of cardiovascular disease prevention in clinical practice (27). Actually, SCORE remains the tool of choice for the prediction of the 10-year risk of fatal CVD (21).

For the most effective prevention of CVD, it is also very important to take into account factors of different nature that could both have direct physiological effects and influence the biological risk factors, referred to, in this context, as “the causes of causes”. Psycho-social factors play an increasingly recognized role in this regard. In particular, socioeconomic position (SEP) has been consistently described as a risk factor for CVD, with those in poorer socioeconomic circumstances presenting poorer health (28). It is argued that SEP influences the capacity to access and interpret health information including the adoption of healthy lifestyles (29, 30). Therefore, health education should be literacy sensitive in order to enhance health knowledge, self-efficacy and motivation to change one’s risk profile.

CARDIOVASCULAR DISEASE IN WOMEN

Gender differences in the cardiovascular system and sex diversity in genetic susceptibility to CVD are highly recognized. At present, there is growing awareness of many fundamental gender dissimilarities in cardiovascular anatomy and pathophysiology (31). These differences become apparent soon after puberty and are more pronounced with age (31, 32).

Women have traditionally been thought of as a low-risk population for CVD. However, as illustrated in Figure 2, CVD are the main cause of death for women in Europe, and are responsible for more than 50% of deaths in women, ranging from 31% of deaths in France to 71% in Bulgaria (3).

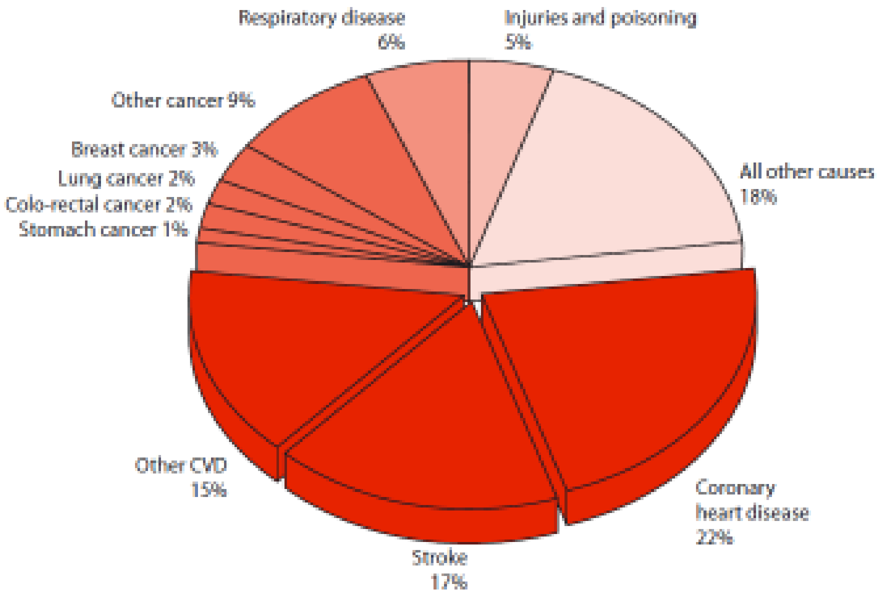

Figure 2. Deaths among women by cause, in Europe (3)

The onset of clinically significant coronary heart disease occurs on average a decade later in women compared with men (33). The more favourable risk profile of CVD among young women may theoretically be explained by the effects of sex hormones. Premenopausal women have lower blood pressure compared with men of similar age, a pattern that is no longer seen after menopause (34). Additionally, the higher risk factor levels at younger ages in men compared to women may also play a role in the course of disease (33).

Nevertheless, young women are also affected and may be at particularly high risk of complications when CVD is present. Recently, an American study focused on coronary heart disease mortality among young adults from 1980 through 2002, postulated that among women aged 35 to 44 years, the mortality rate from coronary heart disease changed little since the late 1980s (35). Particularly noteworthy is that the mortality rate among women, in this age range, has been increasing on average 1.3% (95%CI 0.2-2.5) per year since 1997 (35). Similarly, coronary heart disease mortality rates in Scotland have tended to level off among young adults over the last few years (36). However, according to data derived from the WHO database, different trends have been described for Europe as a whole (37). Since the 1980s, CVD mortality rates at ages 35 to 44 years in both sexes steadily declined in Europe, except in Russia, whose rates were 10 to 15-fold higher than those of most western European countries. Patterns were similar in men and women, though with appreciably lower rates in women. The average annual percent of change in the European Union for coronary heart disease was -3.3% in men and -2.1% in women, while for cerebrovascular disease was -2.5% in both sexes, with steeper declines from the mid-late 1990s onwards.

Despite less common, CVD that occurs at younger ages is associated with a substantial risk of morbidity and mortality in women. It was reported that after myocardial infarction, younger women, but not older women, had higher rates of death during hospitalization than men of similar age (38-40). This may be due to a delay in diagnosis or a lower index of suspicion by health care providers in young women. Several studies reported that women are more likely to present with atypical symptoms including fatigue, weakness, dyspnea, nausea, palpitations, or midback pain (41, 42). In fact, the absence of chest pain or discomfort with acute coronary syndrome is more common in women than in men, particularly among those below 60 years of age (43). Similarly, women with less than 55 years of age are more likely to be discharged from the emergency department with a missed diagnosis of acute coronary syndrome than any other age or gender group (44). A delay in diagnosis or a lower index of suspicion by health care providers may cause treatment delay and less aggressive interventions (45). Additionally, the lack of awareness of risk may be a barrier to prevention of CVD in women. In a survey conducted in the United States, only 16% of women recognized heart disease as the greatest health problem facing women today, and only half identified it as the leading cause of death (46).

Data from the INTERHEART study indicate that nine potentially modifiable risk factors account for 94% of the population attributable risk of myocardial infarction in women (33). Regarding young adulthood, results from a prospective cohort study of women aged 18 to 39 years (17) show that favourable levels of all five major risk factors (smoking, hypertension, diabetes, serum cholesterol and body mass index) were associated with lower long-term CVD and all-cause mortality, after an average follow-up of 31 years. Moreover, the age-adjusted CVD death rate increased with the number of risk factors. In fact, CVD mortality rate per 10000 person-years for women with 2 or more risk factors was approximately 6 times higher than low-risk women. Unfortunately, only about 20% of women younger than 40 years meet these low-risk criteria, presenting favourable levels of for all the risk factors considered (17). Another study reported that in women aged between 18 and 75 years, 19% presented a clustering of three or more metabolic risk factors for coronary heart disease (20).

As illustrated in Figure 3, men and women share most classic cardiovascular risk factors, across various regions of the world (12). Nevertheless, the significance and the relative weighting of these factors are different according to sex (47). As was demonstrated across Europe in the EUROASPIRE III survey, women have a higher prevalence of diabetes and hypertension than men and, especially young women, have taken up smoking habits with its consequences for CVD incidence and prevalence (48). Overall, hypertension and diabetes mellitus imposed a higher risk for myocardial infarction in women compared with men, while exercise and moderate alcohol intake were more protective among women (12, 49). In the INTERHEART study, the population attributable risk for hypertension was 36% in women, while the corresponding figure in men was 19% (33). Regarding diabetes, in a meta-analysis of 37 prospective cohort studies, the risk of fatal coronary heart disease was 50% higher in women with diabetes compared with men (49). The constellation of symptoms termed metabolic syndrome was also found to be most predictive of future myocardial infarction in young women (50).

Across Europe, exposure to modifiable unfavourable lifestyle factors have aggravated, with its consequences for CVD incidence and prevalence (48). With the increase in smoking rates in younger women, reinforcement of healthy lifestyle becomes more important. Smoking has a particularly harmful effect in young women, with a 60% increased risk for myocardial infarction when compared with men (51). A recent prospective cohort study suggests that women with high central obesity are about 20% more likely to develop coronary heart disease compared to their male counterparts (52). Similarly, prospective data from the Women's Health Initiative

Observational Study indicate that both walking and vigorous exercise are associated with substantial reductions in the incidence of cardiovascular events among women, irrespective of race or ethnic group, age, and body-mass index (53). Additionally, coping with stress and emotions as well as depression and anxiety disorders are more associated with elevated CVD risk among women (54, 55).

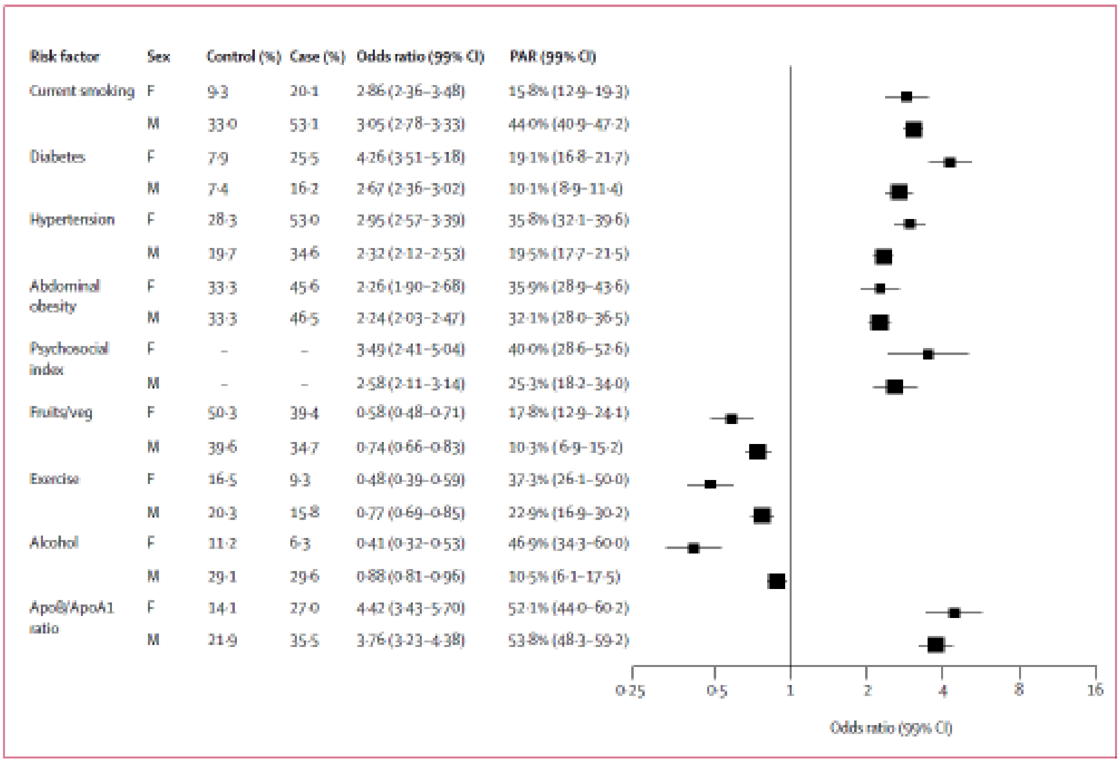

Figure 3. Association of risk factors with acute myocardial infarction in men and women after adjustment for age, sex, and geographic region (12)

As mentioned above, in Europe, the SCORE system is recommended to evaluate CVD risk (27). These guidelines have comparable limitations to the Framingham guidelines for primary prevention in women and tend to underestimate CVD risk in especially the younger age-groups (21). The Reynolds Risk Score was developed specifically for women (56) and the main difference from the Framingham score is the incorporation of parental history of ischemic heart disease and C-reactive protein. This score reclassified 15% of intermediate risk women to high risk in the Women’s Health Study, a nationwide cohort of American women aged 45 years and older. However, it needs validation in other populations and is not applicable to young women.

In summary, there is strong international evidence on gender-related specificities of CVD (57). However, few epidemiological studies have assessed the prevalence and clustering of cardiovascular risk factors in women, in a fertile age. Understanding the differences diversities may lead to a better management of CVD and guarantee an improved overall prognosis. Priorities to improve cardiovascular care among women should be discussed within multidisciplinary teams, with a focus on the major threats to cardiovascular health in women.

WOMEN'S REPRODUCTIVE HEALTH

Reproductive health is a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity, addressing the reproductive processes, functions and system at all stages of life (8, 58). Therefore, it implies that people are able to have a responsible, satisfying and safe sex life and that they have the capability to reproduce and the freedom to decide if, when and how often to do so. Implicit in this concept are the right of men and women to be informed and to have access to safe, effective, affordable and acceptable methods of fertility regulation of their choice, and the right of access appropriate health care services that will enable women to go safely through pregnancy and childbirth and provide couples with the best chance of having a healthy infant (8, 58). In this context, preconceptional, prenatal and postnatal care are critical components in the continuum of care of women and newborns (59).

Women's health in Portugal has experienced a huge overall improvement since the late 70s and the implementation of the National Health System, which ensures all citizens nearly free access to primary care centers and public hospitals (60). The dramatic improvements in perinatal health are worth noticing. In 2004, the maternal mortality rate was 7.7 per 100,000 live births, very similar to the Europe mean of 6.6 per 100,000 live births (61). Also, between 1996 and 2008, the infant mortality declined from 6.9 to 3.3 per 1000 live births, the neonatal mortality from 4.2 to 2.1 per 1000 live births and the perinatal mortality from 8.4 to 4.0 per 1000 live births (7). These declines during the last decades are major successes of Portuguese perinatal health (62).

Pregnancy and childbirth are physiological events, but they carry risks that can be reduced by health-care interventions such as the provision of family planning and maternity care and access to safe abortion care (63). In women, preconceptional and prenatal care can provide the opportunities for regular risk assessment and prevention of pregnancy-related co-morbidities. Postpartum care is important for detecting and treating infections and other conditions, including postpartum depression, and for providing advice on family planning. This continued care throughout pregnancy, childbirth and the postpartum period is essential for health promotion at young ages.

PREGNANCY AND CARDIOVASCULAR RISK

Pregnancy is a natural life event, in a woman's life, but implies some psychological and physiological adaptations. It constitutes a stress test for maternal cardiovascular function (64), due to the occurrence of several adaptive changes in the woman's body that facilitate foetal growth. At the same time, it is a good opportunity for health promotion and disease prevention (65), since mothers tend to be strongly motivated to adopt healthier lifestyles in order to protect the health of the unborn baby (65, 66).

Pregnancy: a stress test for maternal cardiovascular function

In healthy pregnancies, hemodynamic changes, hyperlipidaemia, insulin resistance, up-regulation of inflammatory markers and plasma volume expansion take place in women's physiology to meet demands of the rapidly developing foetus (67, 68).

During pregnancy, there is a fall of approximately 10 mmHg in blood pressure until 22 to 24 weeks (69). This reflects the marked reduction in total peripheral vascular resistance, which decreases by 25%, while cardiac output is increased by as much as 50% (68, 70, 71). The fall in blood pressure may obscure the diagnosis of pre-existing mild hypertension, particularly in young women who do not have blood pressure measured regularly before pregnancy. In the third trimester, the blood pressure gradually increases and may normalize to pre-pregnant values by term (69). Immediately after delivery, blood pressure usually falls, but increases again over the first five postnatal days (71). Even women whose blood pressure was normal throughout pregnancy may experience transient hypertension in the early postpartum period, probably reflecting a degree of vasomotor instability (69). Plasma and red cell volumes also expand in normal pregnancy by approximately 40% and 25%, respectively. These changes begin as early as the fourth week of gestation and peak around the 28th week (72, 73). The progressive rise in plasma and blood volume are likely adaptations, via renal sodium retention, to the vasodilatation and fall in blood pressure (74, 75).

Normal pregnancy is a state of insulin resistance, with a doubling in fasting insulin concentrations. This is due to changes in maternal hormonal and metabolic factors related to the placenta, adipose tissue, and the growth hormone axis (76, 77). The increased insulin resistance reaches a maximum in the third trimester, and improves following delivery (78, 79). During pregnancy, there are also changes in lipid profile, with a particular increase of around 300% in triglyceride levels and a 25–50% increase in total cholesterol (80). This gestational hyperlipidaemia fulfils the physiological role of supplying both cholesterol and triglyceride to the rapidly developing foetus (81, 82). Additionally, pregnancy is associated with a generalised maternal inflammatory response (83, 84) and with an overall state of hypercoaguability, due to increases in the levels of several coagulation factors (85). It is likely that this state of hypercoagulability may serve to limit life-threatening bleeding at delivery but there is an increased risk of thromboembolism associated with pregnancy (86).

Altogether, these changes in maternal physiology allow the cardiovascular system to adjust to the physiological demands of the foetus while maintaining maternal cardiovascular integrity (67). However, in some women, this normal adaptive response is greatly exaggerated and can lead to prenatal complications, such as recurrent miscarriage, congenital malformations, gestational hypertensive disorders, gestational diabetes mellitus and venous thromboembolism. Additionally, data linking the maternal vascular, metabolic, and inflammatory complications of pregnancy with an increased risk of vascular disease in later life, have been increasing (64). Moreover, the marked pregnancy-induced hemodynamic alterations put a physiological stress on the body that have a profound effect on future health. Hypertensive disorders in pregnancy have been shown to be predictors for hypertension and CVD events (87, 88), with women with placental complications (89), poor foetal growth or intrauterine death considered to be at the greatest risk (90). Further, an impaired glucose tolerance during pregnancy and gestational diabetes constitute female specific risk factors for the development of diabetes and the metabolic syndrome in relatively young women (91, 92).

Hypertensive disorders in pregnancy are major complications of pregnancy, increasing the risk of adverse obstetric and perinatal outcomes (93-95). They include chronic and gestational hypertension, preeclampsia and eclampsia, with the latter three entities representing generally transient hypertensive conditions with onset during pregnancy (96).

According to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (96), chronic hypertension is defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, diagnosed before pregnancy or before the 20th week of gestation. Gestational hypertension refers to the new onset of hypertension in the absence of proteinuria, in a previously normotensive pregnant woman at or after 20 weeks of gestation. However, if blood pressure elevation persists by 12 weeks postpartum, the woman is considered to have chronic hypertension. Preeclampsia is defined as gestational blood pressure elevation with proteinuria and usually occurs after 20 weeks of gestation. Proteinuria is defined as the urinary excretion of ≥ 300 mg of protein in a 24-hour period. Preeclampsia superimposed on chronic hypertension is diagnosed when a woman with pre-existing hypertension develops new onset proteinuria after 20 weeks of gestation or after a sudden increase in proteinuria or blood pressure in women with hypertension and proteinuria before 20 weeks' gestation. Eclampsia refers to the development of grand mal seizures, not attributable to another cause, in a woman with gestational hypertension or preeclampsia. Because blood pressure usually falls during the first half of pregnancy, pre-existing hypertension may not be recognized if the woman is first seen during that time (96).

Due to the difficulty in establishing a unique cause for preeclampsia, in spite of many attempts to understand its biologic characteristics and characterize its predictors, heterogeneous causes of gestational hypertensive disorders have been proposed (97). These can be categorized into two major causes: one whose genesis is the result of primarily reduced placental perfusion, and another primarily due to pre-existing maternal disorders, frequently not yet spontaneously evident but unmasked by pregnancy. The placental disorder has a currently unidentified pathobiologic origin. The maternal disorder includes cases with obvious underlying morbidity before pregnancy such as hypertension, renal disease, overweight, diabetes and women with predisposing factors for cardiovascular disease that may not be clinically evident (97).

It is not clear whether gestational hypertension and preeclampsia are different diseases with a similar phenotype (hypertension) or if gestational hypertension is an early or mild stage of preeclampsia. However, studies that analysed gestational hypertension and preeclampsia described similar associations with chronic hypertension later in life (98). Studies that analysed preeclampsia and gestational hypertension separately described similar effects, though with stronger associations for preeclampsia (99, 100) which could be interpreted in light of spectrum effects related with the higher severity of this clinical entity.

The etiology and pathogenesis of hypertensive disorders in pregnancy is not completely understood. Abnormal trophoblast invasion of uterine blood vessels, immunological intolerance between fetoplacental and maternal tissues, maladaptation to the cardiovascular changes or inflammatory changes of pregnancy, dietary deficiencies, and genetic abnormalities have been proposed as potential etiologies (101, 102). Moreover, the pathophysiologic abnormalities of preeclampsia are numerous, including placental ischemia, generalized vasospasm, abnormal homeostasis with activation of the coagulation system, vascular endothelial dysfunction, abnormal nitric oxide and lipid metabolism, leukocyte activation, and changes in various cytokines as well as in insulin resistance (101, 103).

Risk factors for hypertensive disorders in pregnancy represent a selection of antecedents that reflect the disease's complexity (104). Among the strongest established risk factors for preeclampsia are nulliparity, multifetal gestation and family or personal history of preeclampsia (105, 106). Advanced maternal age is also an established risk factor for adverse outcomes in pregnancy, with all types of hypertensive disorders in pregnancy more frequent in mothers above 35 years old (107). Additionally, family history of hypertension is associated with a doubling risk of preeclampsia (108). The association between excessive weight before and during pregnancy and the risk of hypertensive disorders in pregnancy (100, 109-112) is also already recognized. Despite some contradictory results, other potential risk factors, such as socioeconomic status (113, 114), seasonality (115) and psychosocial stress (116) have been suggested.

Worldwide, hypertensive disorders in pregnancy affect approximately 10% of all pregnant women (117, 118). An Australian study (95) reported an overall prevalence of 9.8% pregnancies complicated by hypertension, including 0.6% with chronic hypertension, 4.3% with gestational hypertension, 4.2% with preeclampsia and 0.3% with superimposed preeclampsia on chronic hypertension. Also, a prospective cohort study from the United States of America (109), described a prevalence of gestational hypertension and preeclampsia of 7.5% and 3.6%, respectively. Recently, a study performed in Netherlands (100), restricted to low-risk pregnancies, reported prevalences of 2.1% and 4.1% for preeclampsia and gestational hypertension, respectively.

In Portugal, a national survey conducted in 2005 estimated an overall prevalence of hypertensive disorders in pregnancy of approximately 6%, with 1.5% due to chronic hypertension, 2.5% to gestational hypertension, 1.4% to preeclampsia, 0.2% to superimposed preeclampsia and 0.1% to eclampsia (119). Despite the lower rate than described in other countries (95, 100, 109), preterm birth, small for gestational age newborns and foetal death were also more frequent in women with hypertension during pregnancy (119).

These major complications of pregnancy increase the risk of adverse obstetric and perinatal outcomes (93-95). In Africa and Asia, nearly one tenth of all maternal deaths are associated with hypertensive disorders of pregnancy, whereas one quarter of maternal deaths in Latin America have been associated with those complications. In European countries, North America, Australia, New Zealand, and Japan hypertensive disorders during pregnancy are the leading cause of maternal death, being responsible for 16.1% of all deaths (120). Considering only Europe, complications of hypertension accounted for 9.2% of maternal deaths, ranging from 2.3% in Germany to 25% in Spain (61). Although there is less information about morbidity, recent data from large national surveillance studies have confirmed that severe obstetric morbidity occurs at a higher rate than maternal mortality (121-124). In fact, all types of hypertensive disorders during pregnancy are associated with severe obstetric morbidity during delivery hospitalizations such as renal failure, pulmonary edema, adult respiratory distress syndrome, puerperal cerebrovascular disorder, disseminated intravascular coagulation syndrome, cardiac arrest or failure, obstetric embolism, sepsis and antepartum or postpartum haemorrhage (94, 95, 125).

Likewise, infants exposed to hypertension during pregnancy are more likely to suffer death or major morbidity than those without exposure to hypertension (93, 95). Despite the overall decrease in neonatal mortality during the last decades (93), preeclampsia still carries a 2-fold increased risk of neonatal death and this increased risk has remained relatively constant over time (126). Additionally, offspring of women with hypertension during pregnancy are also at increased risk of preterm birth, being small for gestational age, low Apgar scores, intubation, seizures, respiratory distress syndrome, transient tachypnea, sepsis and neonatal intensive care unit admission (95, 125, 127).

A consistent association has been found between preeclampsia and high blood pressure and cardiovascular disease later in women's life (88, 98). Recently, a systematic review and meta-analysis described that, after preeclampsia, women have an almost fourfold increased risk of hypertension and an approximately twofold increased risk of fatal and nonfatal ischaemic heart disease, stroke, and venous thromboembolism in later life. Furthermore, the overall increase mortality risk after preeclampsia was largely driven by an increased risk of death due to cardiovascular disease (87).

Despite some conflicting results, a meta-analysis (128) reported higher systolic and diastolic blood pressure among offspring of women with preeclampsia during pregnancy. Offspring of pregnancies complicated by preeclampsia, between 6 and 19 years old, had an increase of 2.3 and 1.7 mmHg in systolic and diastolic blood pressure, respectively, when compared with offspring from normotensive pregnancies. Also, increased risks of hospitalization have been noted in children born to mothers who had preeclampsia (129). A long-term follow-up study showed that people born after pregnancies complicated by gestational hypertension or preeclampsia are at increased risk of stroke, 60 to 70 years after their birth (130).

The pathophysiological mechanisms underlying the association between gestational hypertensive disorders and later high blood pressure in women and their children remain not completely understood (64, 131). In women, hypertensive disorders of pregnancy and chronic hypertension share pathways initiated by similar risk factors, such as older age and higher body mass index (106, 132, 133). Additionally, abnormal placentation resulting in reduced perfusion may induce *de novo* hypertension in the pregnant women, possibly related with an immunologically mediated mechanism for which enhanced exposure to paternal antigens is protective (97). Any of these complications may in turn induce long-term metabolic and vascular abnormalities that increase the overall risk for cardiovascular disease later in life (134). Intrauterine growth restriction, due to mother's cardiometabolic abnormalities during pregnancy and placental dysfunction, may also increase the risk of vascular dysfunction in the offspring (135-137). In the womb, boys have a different placental growth which puts them at a higher risk of becoming undernourished particularly because their larger size increases nutritional needs. This milieu could increase the vulnerability of boys to consequences of metabolic and vascular derangements of the mother during pregnancy (138).

Pregnancy: opportunity for health promotion and disease prevention

Pregnancy has been widely referred as a good opportunity for prevention and intervention because of mothers' strong motivation to protect the wellbeing of the foetus (65, 139).

It is well established that adverse lifestyles such as smoking, alcohol intake, poor diet and lack of moderate physical activity are associated with increased risks of adverse maternal and foetal outcomes such as ectopic pregnancy, placental abruption, placenta previa, small for gestational age babies, low birth weight and preterm birth (140-146).

The label "teachable moment" has been used to describe naturally occurring life transitions or health events thought to motivate individuals to spontaneously adopt risk-reducing health behaviours. McBride et al (65) proposed a model to describe characteristics of effective teachable moments. These are characterized as times that increase perceptions of personal risk and outcome expectancies, prompt strong affective or emotional responses, and redefine self-concept or social roles. In other words, the cognitive response precedes motivation, skills acquisition and self-efficacy that in turn, increase the likelihood of cease the adverse lifestyle. Additional key factors to consider are predisposing factors such as age, dispositional and cultural characteristics that may influence an individual's cognitive and emotional response (65). Within this model, pregnancy is conceptualized as a powerful "teachable moment".

Pregnancy provides an immediate and personal experience of risk that is related with the health of the mother and baby, which enhances the perceived need of adopting healthy lifestyles (147). According to a study performed in the United Kingdom between 1998 and 2003 (148), there was a significant reduction in smoking, alcohol consumption and intake of caffeinated drinks when women became pregnant, although little change occurred in fruit and vegetable intake. In fact, before pregnancy, 27% of women smoked, 54% of women drank more than 4 units of alcohol per week and 39% had estimated intakes of caffeine in drinks of more than 300mg per day, whereas comparable figures for early pregnancy were 15%, 10% and 16% respectively.

The emotional responses that surround pregnancy may also make it an opportune time to initiate change. Emotional responses are thought to influence an individual's judgment about the significance and meaning of an event (149).Therefore, pregnancy may prompt feelings of concern about the well-being of the foetus, which may motivate women to change their lifestyles. Finally, pregnancy is a time when personal and social roles change as women become mothers in addition to their other roles. Women are adopting the maternal role, which carries expectations for major changes in lifestyle and self-image (147).

Worldwide, smoking is the single most frequent preventable cause of death (150) and smoking cessation reduces the long-term risk of cancer and cardiovascular diseases (151, 152). Cigarette smoking during pregnancy is associated with increased risks for both the mother and the newborn (140-142). Therefore, mothers tend to be strongly motivated to protect the health of the unborn baby and there is important social pressure to quit smoking during pregnancy (66, 139, 153). The EURO-PERISTAT study, that monitored and evaluated perinatal health in Europe, reported prepregnancy smoking prevalence levels in 2004 ranging from 7.9% in Lithuania to 35.9% in France (61). In Portugal, according to a study performed in 25 public maternity units, 30% of women smoked before pregnancy in Portugal (154). In many countries in Europe, more than 10% of women smoke during pregnancy (61). In Portugal, 14.7% of women smoked during the third trimester of pregnancy in 2004 (61).

Previous literature reported smoking cessation rates ranging from 30% to 50% in different countries (155-158). Predictors of smoking cessation among pregnant women have been well investigated, internationally. Women who quit smoking during pregnancy are more likely to report being married or in a stable relationship and having higher educational qualifications (156, 157, 159). However, a study that assessed the reporting of prenatal smoking in birth certificates and in confidential questionnaires found that more educated women are less willing to admit smoking to prenatal care providers, which may lead to overestimation of the association between education and smoking cessation during pregnancy (160). Quitting in pregnancy appears to be more successful in first pregnancies regardless of social background, with the probability decreasing with the number of pregnancies (161). It has been suggested that past pregnancies resulting in the birth of a healthy child despite tobacco consumption might weaken the women’s motivation to change their smoking habits in subsequent pregnancies (162). Also, women receiving adequate prenatal care show a higher rate of smoking cessation (163, 164). Despite the impact of adequate prenatal care on smoking cessation, this may also be due to personal characteristics of women since those more prone to quit smoking are also probably more likely to attend prenatal care (165). Those who initiate smoking earlier or were heavier smokers were more likely to smoke during pregnancy, which may emphasize the physiological and psychological role of nicotine dependence in smoking cessation (166). Additionally, concern about weight gain during and after pregnancy may be a factor that interferes with smokers’ efforts to quit during pregnancy (167), with pregnant smokers reporting the use of smoking as a weight management strategy (168).

Smoking cessation during pregnancy could be a unique opportunity in women life to achieve long-term sustainability of smoking cessation, with clear benefits for their future health. However, despite a high proportion of women quitting their tobacco consumption during pregnancy the rate of relapse or return to previous rates following childbirth is high. In fact, approximately 25% of women who quit smoking during pregnancy will relapse within one month of delivery (157). By three months postpartum, 40% to 50% of women will have returned to smoke and, 70% will have experienced a relapse within one year postpartum (156, 157, 169).

It has been previously described that younger women, divorced or without a partner and with a lower education were more likely to resume smoking (156, 157). Furthermore, breastfeeding may help to prevent or delay postpartum smoking relapse (158), by educating women about the benefits of breastfeeding and by facilitating and encouraging continued breastfeeding throughout the first postpartum year (170). The health of the offspring can also constitute a motivation to stop smoking. A substantial body of evidence supports that involuntary tobacco smoke exposure adversely affects children’s respiratory health by increasing the risk of respiratory infections (171, 172). In uterus exposure to maternal smoking was associated with an almost two-fold increased prevalence of physician-diagnosed asthma (171), while children exposed after birth had more often rhinitis than children of non-smoking parents (172).

In Portugal, smoking remains more frequent among men but its prevalence is increasing in women (173). The prevalence is higher among younger and more educated women placing Portugal at a relatively early stage of the epidemic compared to other Western European countries (174, 175). Therefore, it is expected that, in the near future, the burden of tobacco-related illness will increase substantially (176). In order to guide the development of preventive strategies to reduce the future burden of smoking and promote the health of children and families, it is important not only to describe exposure to smoking in pregnancy and postpartum but also to identify modifiable determinants of such behaviours.

AIMS

This research aims to study the cardiovascular risk profile in mothers of a Portuguese birth cohort (Geração XXI), before and during pregnancy, and 4 years after delivery, including both descriptive and analytic approaches. To answer this main question, the following 5 specific objectives were defined and pursued, resulting in 5 papers:

1. To estimate the prepregnancy prevalence of five major cardiovascular risk factors (overweight/obesity, smoking, hypertension, dyslipidemia and diabetes mellitus), and to describe their distribution by age, gravidity and indicators of socioeconomic position (SEP).

2. To assess the impact of age, education, family history of cardiovascular disease, prepregnancy BMI and pregnancy weight gain on hypertensive disorders in pregnancy, in primiparous and multiparous mothers.

3. To assess the extent to which gestational hypertensive disorders lead to higher blood pressure in women and their offspring as early as 4 years after birth, and to assess the effect of fetal sex on these consequences.

4. To assess the frequency and determinants of maternal smoking cessation during pregnancy and of the sustainability of smoking cessation 4 years after delivery.

5. To estimate the prevalence of established cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus, general overweight/obesity, abdominal obesity, smoking, low fruit and vegetables intake and sedentariness), 4 years after delivery, and to describe their distribution by age, gravidity and indicators of socioeconomic position (SEP).

RESEARCH METHODS

This PhD thesis is based on the cohort Geração XXI, the first prospective Portuguese population-based birth cohort. A general description of the participants and methods in this cohort study is provided below. The selection of participants eligible for each analysis depended on the specific objectives of the investigations and is described in detail in the methods sections of the individual papers.

ASSEMBLING OF THE BIRTH COHORT

The birth cohort Geração XXI was assembled between 2005 and 2006 at all 5 public maternity units covering the metropolitan area of Porto, Portugal: Centro Hospitalar de Vila Nova de Gaia (CHVNG), Centro Hospitalar do Porto - Maternidade de Júlio Dinis (MJD), Hospital de São João (HSJ), Centro Hospitalar do Porto - Hospital de Santo António (HSA), and Unidade Local de Saúde de Matosinhos – Hospital Pedro Hispano (HPH). The maternities corresponded to level III units, with differentiated perinatal support, and all except MJD, were included in a general hospital, with a variety of medical and surgical specialties.

Trained interviewers at the five hospitals were responsible for the study presentation and subsequent invitation of the mothers after delivery. Fathers were also invited to participate. Of the invited mothers 91.4% accepted to participate. A total of 8647 infants, corresponding to 8495 mothers, were enrolled in the cohort.

DATA COLLECTION

Mothers were invited to participate after delivery, during the hospital stay. Data on demographic and socioeconomic characteristics (age, marital status, years of formal education, occupation), personal and family medical history, gynaecologic and obstetric history (age at menarche, number of previous pregnancies and births), prenatal care (number and place of the prenatal care, medication, and symptoms and pregnancy-related co-morbidities), and lifestyles (including smoking, alcohol intake and illicit drug use) were collected within 72 hours after delivery, in a face-to-face interview, conducted by trained interviewers using structured questionnaires. Clinical records were also reviewed at birth by the same interviewers to retrieve data on prenatal care, pregnancy complications (gestational hypertensive disorders, gestational diabetes and placental abnormalities), delivery (type of delivery and medication) and neonatal characteristics (birth weight and gestational age). Fathers were also invited to answer a self-administered questionnaire focused on demographic and social conditions, lifestyles and medical history. Anthropometrics were performed, by the same interviewers, to the mother, the father and their newborn.

After delivery, blood samples were collected from the mother and the umbilical cord. Fathers were also requested to provide a venous blood sample. Plasma and serum samples were distributed in aliquots and a whole blood sample was maintained for each member of the family. All blood samples were put into transitory storage at -20ºC and later stored at -80ºC.

MISSING DATA RECOVERY

Between October 2008 and June 2009, missing data on the questionnaires were recovered through the review of obstetrical records (**PAPER I**). We reviewed the medical records of 3657 women with at least one missing value on personal history of disease, anthropometrics, pregnancy complications, blood glucose or oral glucose tolerance test results during pregnancy, or newborn characteristics at birth, and assessed the agreement of information reported by participants with data from medical records. All the clinical records were reviewed by one trained abstractor, who had been an interviewer at the baseline evaluation of Geração XXI, using standardized criteria. Inter-observer variability was assessed using 400 clinical records randomly selected among the 3657 reviewed. Data were collected independently by 2 trained abstractors, both interviewers at birth.

Data on pregnancy pathological complications and mothers' anthropometrics were successfully recovered. Agreement between questionnaire and records in family history data was fair, particularly for cardiovascular disease [k=0.27; 95%confidence interval (95%CI) 0.23-0.32]. Personal history of diabetes was highly concordant (k=0.82; 95%CI 0.70-0.93), while hypertension was moderately concordant (k=0.60;

95%CI 0.50-0.69). In general, the discrepancies found for weight and height indicated higher values in the clinical record than in the questionnaire and led to discrepancies in prepregnancy body mass index classes of 10.3% of women (weighted k=0.82; 95%CI 0.80-0.83).

Data were very consistent between reviewers, with highest agreement for gestational diabetes (k=1.00) and birth weight (99.5% concordant). The differences observed for women's weight and height were negligible, not affecting the global classification by body mass index categories before pregnancy (weighted k=0.99; 95%CI 0.98-1.00).

RE-EVALUATION OF THE BIRTH COHORT AT 4 YEARS

Between April 2009 and April 2011, an average of 4 years after birth, all the children with their mothers were invited to attend the re-evaluation of the cohort. During this evaluation period, participants were invited to an interview and physical examination. If they were unable to participate, they were invited to answer a telephone interview, covering part of the self-reported data collected in the default interview.

During the follow-up period, 5986 (69.2%) of the children attended a face face-to-face interview, 1472 (17.0%) provided self-reported data by telephone interview, and 1189 (13.7%) were lost to follow-up. Regarding the mothers, 5729 (67.4%) participated in the face face-to-face interview, 1428 (16.8%) provided self-reported data by telephone interview and 1338 (15.8%) were lost to follow-up. Figure 4 presents the maternal participation at follow-up, according to the different strategies implemented. Overall, 86.2% of the children and 84.2% of the mothers were re-evaluated.

The comparison of socio-demographic characteristics between participant and non-participant mothers at follow-up and among mothers who attended a face-to-face interview and who answered a telephone interview are presented in Table 1. Mothers who attended the follow-up re-evaluation were older, more likely to be pregnant for the first time at baseline and married, with a higher educational level, and more frequently employed, than those who did not participate in the re-evaluation. When comparing mothers evaluated by the two strategies of data collection, those who answered a face-to-face interview were older, more educated and more frequently employed.

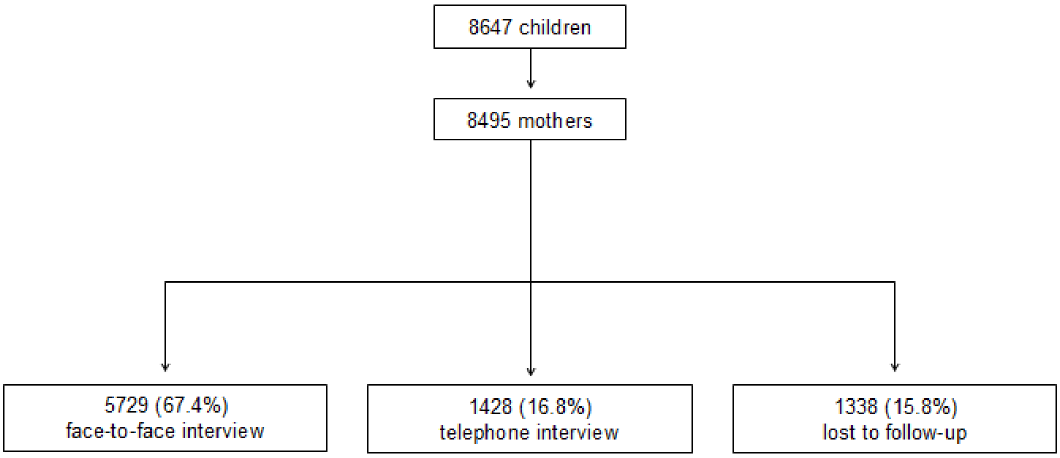

Figure 4. Maternal participation at follow-up, according to the different strategies implemented.

Table 1. Comparison of socio-demographic characteristics between participant and non-participant mothers at follow-up and, among the former, between mothers who attended a face-to-face interview and who answered a telephone interview.

	Non participants	**Face-to-face interview**	**Telephone interview**		
	n(%)	n(%)	n(%)	*p**	*p***
Age (years), n (%)				<0.001	<0.001
< 25	487 (36.7)	1010 (17.7)	356 (25.0)		
25-29	368 (27.7)	1723 (30.2)	441 (31.0)		
30-34	322 (24.3)	1961 (34.3)	406 (28.5)		
≥ 35	150 (11.3)	1019 (17.8)	220 (15.5)		
Gravidity, n (%)				<0.001	0.205
1	607 (45.7)	2778 (48.7)	679 (47.8)		
2	423 (31.9)	1969 (34.5)	475 (33.4)		
≥ 3	298 (22.4)	963 (16.9)	268 (18.9)		
Marital status, n (%)				<0.001	0.058
Married/living with a partner	1196 (90.4)	5389 (94.5)	1320 (93.2)		
Single/ divorced/widow	127 (9.6)	312 (5.5)	96 (6.8)		
Education (years), n (%)				<0.001	<0.001
≤ 4	159 (12.0)	371 (6.5)	133 (9.4)		
5-9	672 (50.9)	2181 (38.4)	634 (44.8)		
10-12	312 (23.6)	1571 (27.7)	370 (26.1)		
> 12	178 (13.5)	1551 (27.3)	279 (19.7)		
Working condition, n (%)				<0.001	<0.001
Employed	760 (57.4)	4238 (74.9)	989 (70.0)		
Unemployed	382 (28.9)	1017 (18.0)	276 (19.5)		
Housewife	122 (9.2)	268 (4.7)	103 (7.3)		
Others	60 (4.5)	132 (2.3)	45 (3.2)		

* Participation *vs.* non participation
** Face-to-face interview *vs.* telephone interview
Note: In each variable, the total may not add to 8495 due to missing data

DATA COLLECTION

In the face-to-face interview, information was collected by trained interviewers, using two structured questionnaires: one concerning the child's health and another regarding the health of the mother. The mothers' questionnaire comprised data on demographic characteristics (marital status and owning one's house), personal and family medical history, gynaecologic and obstetric history (number of pregnancies and births before and after the index pregnancy), and lifestyles (including smoking, alcohol intake, physical activity and diet). The children's questionnaire included data on socioeconomic characteristics of the parents (years of formal education, occupation) and on child's development, health and habits (including sleeping hours, physical activity and diet). Mothers and children also underwent a physical examination, including anthropometric evaluation, blood pressure measurement and a venous blood sample withdrawal. Children were submitted, additionally, to tetrapolar bioimpedance analysis. The venous blood sample was drawn after 12-hour overnight fast and all the samples were analyzed at the central laboratory of Hospital de São João.

The telephone interview also contained data regarding the health of the mother and the children, although with a restricted number of questions. Information was collected by trained interviewers, who also performed face-to-face interviews, using a structured questionnaire. Data on medical and obstetric history (pregnancies and births after the index pregnancy) as well as smoking status and self-reported weight and height were collected for the mothers. Regarding the child, data on socioeconomic characteristics of the parents (years of formal education, occupation), and on child's development, health and habits (including sleeping hours, physical activity and diet) were collected.

QUALITY CONTROL

In both evaluation periods, all interviewers were rigorously trained using a structured protocol addressing all the questionnaires' queries and periodic supervision of their work was undertaken. At baseline, interviewers were responsible for the application of the questionnaires to the mothers, the distribution of self-administered questionnaires to the fathers and the anthropometric evaluations of the parents and newborns, having received specific and intensive training for these tasks. Interviewers were also responsible for managing the blood samples, namely their coded identification and storage. During follow-up reevaluation, interviewers were responsible for the application of the questionnaires to the mothers and for the physical examination both of the mothers and their children.

A multidisciplinary team, including physicians, psychologists, nutritionists and pharmacists, with experience in other national and international projects, were responsible for the staff training and the development of the questionnaires applied at baseline and at follow-up.

STATISTICAL ANALYSES

All statistical analyses were performed using Stata 9.0 (College Station, TX, 2005). Overall, we used classical inferential statistics to answer the objectives of this PhD thesis.

Data were described as counts and proportions for categorical variables, mean and standard deviation (SD) for normally distributed continuous variables, and median and interquartile range (IQR) for non-normally distributed continuous variables. The prevalence of the outcomes is presented with 95% confidence intervals (95% CI), as well as the incidence rates of hypertension, which were reported per 1000 person-years.

According to the specific objectives established, different analytic approaches were used and are described in detail in the methods sections of the papers. The prevalence ratio (PR) is more conservative, consistent, and interpretable than the odds ratio (OR) when prevalences are to be compared between groups (177, 178). For this reason, we privileged the estimate of PR in our models. Therefore, in Papers III and V crude and adjusted prevalence ratios (PR) were computed, using robust Poisson regression. However, PR applies only to dichotomous outcomes, whereas categorical dependent variables with more than two classes request multinomial logistic regression models. Thus, in Papers II and VI, to privilege homogeneity in the analysis among all the outcomes, we used logistic regression to estimate OR for all the risk factors considered, binary for dichotomous outcomes and multinomial for 3-class outcomes. In order to assess the potential for prevention, population attributable fractions were calculated using the command *punaf* (179) in Stata, based on the adjusted PR and putative alternative distributions of exposure (Paper III). In Paper IV, to estimate adjusted mean differences in systolic and diastolic blood pressure, for mothers and offspring, according to gestational hypertensive disorders, multiple linear regression was used. The association between gestational hypertensive disorders and the mother's incidence of hypertension was estimated by crude and adjusted incidence rate ratios (IRR) and respective 95% CI, using Poisson regression.

ETHICAL CONSIDERATIONS

The study protocols for both evaluation periods were approved by the Ethics Committee of Hospital de São João and by the Portuguese Authority of Data Protection.

Procedures were developed in order to guarantee data confidentiality and protection. All participants received an explanation on the purposes and design of the study, and gave written informed consent at baseline and at follow-up evaluation. The children gave it through their legal representative. Verbal consent was explicitly solicited at the beginning of telephone interviews.

PAPER I

Alves E, Lunet N, Correia S, Morais V, Azevedo A, Barros H.

Inter-rater variability in medical record review and agreement with self-reported data collected by questionnaire.

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Original article

Medical record review to recover missing data in a Portuguese birth cohort: agreement with self-reported data collected by questionnaire and inter-rater variability

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A B S T R A C T

Objectives: To assess the yield of medical record review to recover missing data originally collected by questionnaire, to analyze the agreement between these two data sources and to determine interobserver variability in clinical record review.
Methods: We analyzed data from a birth cohort of 8,127 women who were consecutively recruited after giving birth from 2005-2006. Recruitment was conducted at all public maternity units of Porto, Portugal. We reviewed the medical records of 3,657 women with missing data in the baseline questionnaire and assessed agreement between these two sources by using information from participants with data from both sources. Interobserver variability was assessed by using 400 randomly selected clinical records.
Results: Data on pregnancy complications and maternal anthropometric parameters were successfully recovered. Agreement between the questionnaire and records in family history data was fair, particularly for cardiovascular disease [k = 0.27; 95% confidence interval (95%CI): 0.23-0.32]. The highest agreement was observed for personal history of diabetes (k = 0.82; 95%CI 0.70-0.93), while agreement for hypertension was moderate (k = 0.60; 95%CI 0.50-0.69). Discrepancies in prepregnancy body mass index classes were observed in 10.3% women. Data were highly consistent between the two reviewers, with the highest agreement found for gestational diabetes (k = 1.00) and birth weight (99.5% concordance).
Conclusion: Data from the medical records and questionnaire were concordant with regard to pregnancy and well-known risk factors. The low interobserver variability did not threaten the precision of our data.

Revisión de registros médicos para recuperar datos incompletos en una cohorte de nacimiento portuguesa: concordancia con datos recogidos por cuestionario y variabilidad interobservador

Palabras clave:
Métodos epidemiológicos
Registros médicos
Variabilidad interobservador
Antropometría
Estudios de cohortes

R E S U M E N

Objetivo: Evaluar el rendimiento de la revisión de registros médicos para completar datos originalmente recogidos por cuestionario, y analizar la concordancia entre ambas fuentes de datos y la variabilidad interobservador en la revisión de registros médicos.
Métodos: Cohorte de nacimiento con 8.127 mujeres reclutadas de forma consecutiva después del parto en todas las maternidades públicas de Porto, Portugal (2005-2006). Se revisaron los registros médicos de 3.657 mujeres con datos incompletos en el cuestionario inicial, y se evaluó la concordancia entre ambas fuentes. La variabilidad interobservador se evaluó en 400 historias clínicas seleccionadas aleatoriamente.
Resultados: La información sobre complicaciones patológicas del embarazo y la antropometría de las madres se recuperó con éxito. La concordancia entre el cuestionario y los registros con respecto a los antecedentes familiares era débil, especialmente para las enfermedades cardiovasculares (k = 0,27, intervalo de confianza del 95% [IC95%]: 0,23-0,32). La concordancia máxima se observó en los antecedentes personales de diabetes (k = 0,82, IC95%: 0,70-0,93), mientras que para la hipertensión fue moderada (k = 0,60, IC95%: 0,50-0,69). Se observaron discrepancias en las categorías de índice de masa corporal antes del embarazo en el 10,3% de las mujeres. Los datos fueron muy concordantes entre los revisores, con el máximo nivel de concordancia para la diabetes gestacional (k = 1,00), seguida del peso al nacer (99,5% concordantes).
Conclusión: Los registros médicos y la información del cuestionario fueron concordantes para los datos relacionados con el embarazo y los factores de riesgo conocidos. La baja variabilidad interobservador no pone en peligro la precisión de los datos.

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Introduction

Clinical records are an important source of information and medical record review is a commonly used data collection method in epidemiological studies. However, data registered in clinical records are not originally collected for research purposes and may not faithfully reflect all the events that happen during a medical consultation[1,2]. These records are less likely to explicitly include negative self-reports or diagnoses[3] and systematically tend to report incomplete information about lifestyles[4].

Epidemiological studies frequently use personal interviews and self-administered questionnaires as the sole information sources on exposures and outcomes. These methods are regarded as valid tools and provide many advantages for research. Nonetheless, the quality of information obtained through self-report depends substantially on the type of illness[5,6], the participants' characteristics[5,7,8], the method used to administer the questionnaire[9] and the questionnaire's design[10,11].

Information obtained by self-report and medical record review may not be consistent. Several studies have compared self-reported data collected by questionnaires with medical record abstraction for the assessment of history of cardiovascular diseases (CVD)[3,7], pregnancy-related events and birth characteristics[12–14], and show that the agreement between the two data sources depends on the data being collected[15]. Additionally, any data collection method may be affected by interobserver variability, which might influence medical record reviews when multiple abstractors are involved[2,16]. In recent years, little attention has been paid to examining interobserver variability in data abstraction from clinical records, even though these methodological aspects influence the quality of the data and are critical for obtaining reliable results[17,18].

Given the extensive use of these two data collection methods, the practical implications of their use must be understood, especially when both data sources are complementarily used in the same study. In a Portuguese birth cohort, data on several variables from the baseline evaluation were missing for a large number of participants. We planned to complete these data by abstracting them from medical records at delivery. To the best of our knowledge, no previous Portuguese study has evaluated the yield of missing data recovery by medical record review or agreement between questionnaire and clinical records and between multiple raters in medical record review.

The aim of the present study was to assess the success of missing data recovery by medical record review. Additionally, we evaluated the agreement between data recovered from clinical records and data previously obtained through a structured questionnaire administered to mothers of the cohort, as well as interobserver variability in data abstraction from clinical records.

Methods

This study was based on the birth cohort Geração XXI, to which 8,127 mothers were consecutively invited after delivery. These women gave birth to 8,270 infants. Recruitment was conducted between April 2005 and September 2006 at all public maternity units covering the metropolitan area of Porto, Portugal. All the maternity units (Table 1), except Maternidade Júlio Dinis (MJD), are included in a general hospital, with a variety of medical and surgical specialties, and all correspond to level III maternity units, with differentiated perinatal support. At birth, 91.4% of the invited mothers accepted to participate.

Information on family and personal history of disease and the mothers' anthropometric parameters before pregnancy was collected during a face-to-face interview conducted by trained interviewers using structured questionnaires within 72 hours of delivery, during the hospital stay. Data on pregnancy complications, gestational age and neonatal characteristics were abstracted from clinical records by the same interviewers.

Missing data recovery by clinical record review and agreement with questionnaire

Of the 8,127 mothers, 3,771 had at least one missing value in personal history of disease, anthropometric parameters, pregnancy complications, blood glucose or oral glucose tolerance test results during pregnancy, or neonatal characteristics at birth (Fig. 1). This was the sample used in the current study.

There were no significant differences between participants with complete and missing data in age [mean (standard deviation, SD): 29.4 (5.5) vs. 29.6 (5.7) years; $p=0.306$], education [median (interquartile range, IQR): 10 (7-12) vs. 10 (7-12) years; $p=0.122$], gravidity (first pregnancy: 48.7% vs. 47.1%; $p=0.156$) and marital status (married/living with a partner: 93.5% vs. 94.3%; $p=0.165$).

Between October 2008 and June 2009, we reviewed the delivery medical records of 3,657 women to recover missing data. The remaining 114 records were not available for review during the period for which we were authorized to consult them, either because they were being used for subsequent patient care or for administrative purposes (Fig. 1).

The clinical records were reviewed by a trained abstractor (EA), who had been an interviewer at the baseline evaluation of Geração XXI, using standardized criteria (Fig. 1). From each medical record, we abstracted data on all the variables of interest, whether or not they were missing in the questionnaire. Since most women had missing values in one or very few variables, we used those who had data available from both the baseline interview and the medical record review to assess agreement between the two data sources in each variable. Therefore, the sample size was not the same for all the variables (Fig. 1).

Interobserver variability

To assess interobserver variability in data abstraction, among the 3,657 records reviewed, data from a randomly selected subsample of 80 clinical records from each hospital were collected independently by two trained abstractors (EA and VM), both of whom interviewed women after delivery, according to the criteria described in Figure 1. We estimated the required sample size to demonstrate, at a 5% significance level, an excellent level of agreement, corresponding to a kappa coefficient of at least 0.85 on past personal and family history of disease, significantly different from a moderate agreement of $k=0.60$ for conditions with a prevalence as low as 2%[19]. The expected prevalence of each condition was defined according to the observed prevalence in this sample. We also estimated the required sample size for duplicate review to demonstrate that, for a significance level of 5% and a statistical power of 80%, differences in pre-pregnancy weight, weight at the end of pregnancy, height, gestational age at birth and birth weight were smaller than negligible differences of 1 Kg, 1 Kg, 1 cm, 0.2 weeks and 50 g, respectively, for the mean and standard deviation of each variable observed in this sample and a correlation coefficient between groups not lower than 0.90. To respect all these conditions, a minimum of 400 medical records would have to be independently reviewed by two raters. We did not assess interrater variability by maternity unit.

Table 1
Participants' characteristics at baseline by maternity unit.

	Overall	CHVNG	MJD	HSJ	HSA	HPH
N	3,657	1,269	366	478	304	1,240
Age (years), mean (SD)	29.5 (5.7)	29.6 (5.8)	28.6 (6.0)	29.7 (5.5)	30.4 (5.6)	29.5 (5.5)
Marital status, n (%)						
Married/living with a partner	3430 (94.3)	1,192 (94.6)	330 (90.2)	451 (95.2)	285 (94.1)	1,172 (94.9)
Single/ divorced/widowed	208 (5.7)	68 (5.4)	36 (9.8)	23 (4.9)	18 (5.9)	63 (5.1)
Education (years), median (IQR)	10 (7-12)	9 (6-12)	9 (6-12)	12 (7-16)	11 (7-15)	12 (7-15)
Monthly income (€), n (%)						
< 500	249 (7.2)	103 (8.7)	41 (11.7)	19 (4.3)	35 (12.8)	51 (4.2)
500-1,000	1011 (29.3)	434 (36.7)	122 (34.8)	91 (20.8)	77 (28.1)	287 (23.8)
1,001- 1,501	854 (24.8)	286 (24.2)	82 (23.4)	126 (28.8)	61 (22.3)	299 (24.8)
≥ 1,500	927 (26.9)	275 (23.3)	67 (19.1)	172 (39.3)	67 (24.5)	346 (28.7)
Does not know/Prefers not to answer	410 (11.9)	84 (7.1)	39 (11.1)	30 (6.9)	34 (12.4)	223 (18.5)
Family history of diabetes, n (%)	719 (22.5)	265 (23.5)	77 (23.6)	89 (22.1)	6 (26.2)	222 (20.3)
Family history of CVD, n (%)	514 (16.1)	209 (18.5)	55 (16.9)	59 (14.8)	48 (19.0)	143 (13.1)
Hypertension before pregnancy, n (%)	69 (1.9)	25 (2.0)	4 (1.1)	9 (1.9)	16 (5.3)	15 (1.2)
Diabetes mellitus before pregnancy, n (%)	28 (0.8)	7 (0.6)	1 (0.3)	2 (0.4)	15 (4.9)	3 (0.2)
BMI before pregnancy, n (%)						
<24.9 Kg/m^2	1,213 (71.6)	213 (68.9)	152 (71.7)	246 (71.7)	195 (78.0)	407 (70.3)
25.0-29.9 Kg/m^2	342 (20.2)	65 (21.0)	44 (20.7)	68 (19.8)	40 (16.0)	125 (21.6)
≥ 30 Kg/m^2	138 (8.2)	31 (10.0)	16 (7.6)	29 (8.5)	15 (6.0)	47 (8.1)
Gravidity, n (%)						
1	1,717 (47.1)	567 (44.9)	148 (40.6)	233 (48.9)	149 (49.2)	620 (50.3)
2	1,246 (34.2)	441 (34.9)	136 (37.3)	161 (33.8)	92 (30.4)	416 (33.7)
≥ 3	679 (18.6)	256 (20.3)	81 (22.2)	83 (17.4)	62 (20.5)	197 (16.0)
Multiple pregnancy, n (%)	80 (2.2)	28 (2.2)	7 (1.9)	9 (1.9)	16 (5.3)	20 (1.6)
Gestational hypertensive disorders, n (%)[a]	110 (3.6)	61 (5.5)	13 (4.1)	8 (2.2)	19 (8.8)	9 (0.9)
Gestational diabetes, n (%)	219 (7.3)	128 (11.5)	15 (4.7)	18 (5.1)	26 (12.0)	32 (3.2)
Preterm newborn, n (%)[b]	351 (10.4)	100 (8.4)	38 (11.3)	25 (6.0)	54 (22.1)	134 (11.3)
Low birth weight, n (%)[c]	339 (9.7)	105 (8.5)	42 (12.0)	26 (6.0)	41 (15.4)	125 (10.4)

BMI: body mass index; CHVNG: Centro Hospitalar de Vila Nova de Gaia; CVD: cardiovascular disease; HPH: Unidade Local de Saúde de Matosinhos – Hospital Pedro Hispano; HSA: Centro Hospitalar do Porto – Hospital de Santo António; HSJ: Hospital de São João; IQR: interquartile range; MJD: Centro Hospitalar do Porto – Maternidade de Júlio Dinis; SD: standard deviation.

[a] Gestational hypertension and/or pre-eclampsia/eclampsia.
[b] Gestational age <37 weeks.
[c] Birth weight <2,500 g.

Statistical analysis

For the description of the sample's characteristics, data are presented as counts and proportions for categorical variables, mean and standard deviation for normally distributed continuous variables and median and interquartile range for non-normally distributed continuous variables.

To report the yield of missing data recovery, counts of cases with missing values and counts and proportions for which information was recovered are presented.

To assess the agreement between clinical records and questionnaire information, as well as between observers, for continuous variables, we estimated the mean differences and 95% confidence intervals (95%CI) between the questionnaire and clinical records and between independent reviewers. The proportion of concordant observations was calculated assuming concordance within 1 Kg, 1 cm or 0.1 weeks for weight, height and gestational age, respectively. For categorical variables, we calculated the proportion of concordant observations between the questionnaire and clinical record among all variables registered as "No" and all registered as "Yes" in the questionnaire, considering it as the reference because the aim of this study was to replace missing data on the questionnaire by those abstracted from medical records. We made no assumptions on the comparative validity of each method. In both the agreement between data sources and between reviewers, we calculated the observed proportion of agreement and kappa coefficients and 95%CI. The weighted kappa was used for variables with more than two classes.

Missing data recovery and interrater variability were analyzed for all variables, whether self-reported or abstracted from medical records at the baseline evaluation. The agreement between the questionnaire and medical record was evaluated only for variables that were collected by questionnaire at birth (Fig. 1).

Data analysis was performed using Stata 9.0 (College Station, TX, 2005). Sample size estimation for assessment of interrater variability was performed using WinPEPI[20].

Ethics

The study protocol was approved by the Ethics Committee of Hospital de S. João (HSJ). Written informed consent was obtained from all participants at baseline.

Results

Sample characteristics

The mean maternal age at birth was 29.5 years (range: 13 to 45 years). Most women were married or were living with a partner (94.3%) and the median [interquartile range (IQR)] years of education was 10 (7-12). In this sample, 7.2% of the participants had a household monthly income below 500€, while 26.9% had a monthly income above 1,500€. A family history of diabetes and cardiovascular disease (CVD) were reported by 22.5% and 16.1% of the mothers, respectively. The prevalence of

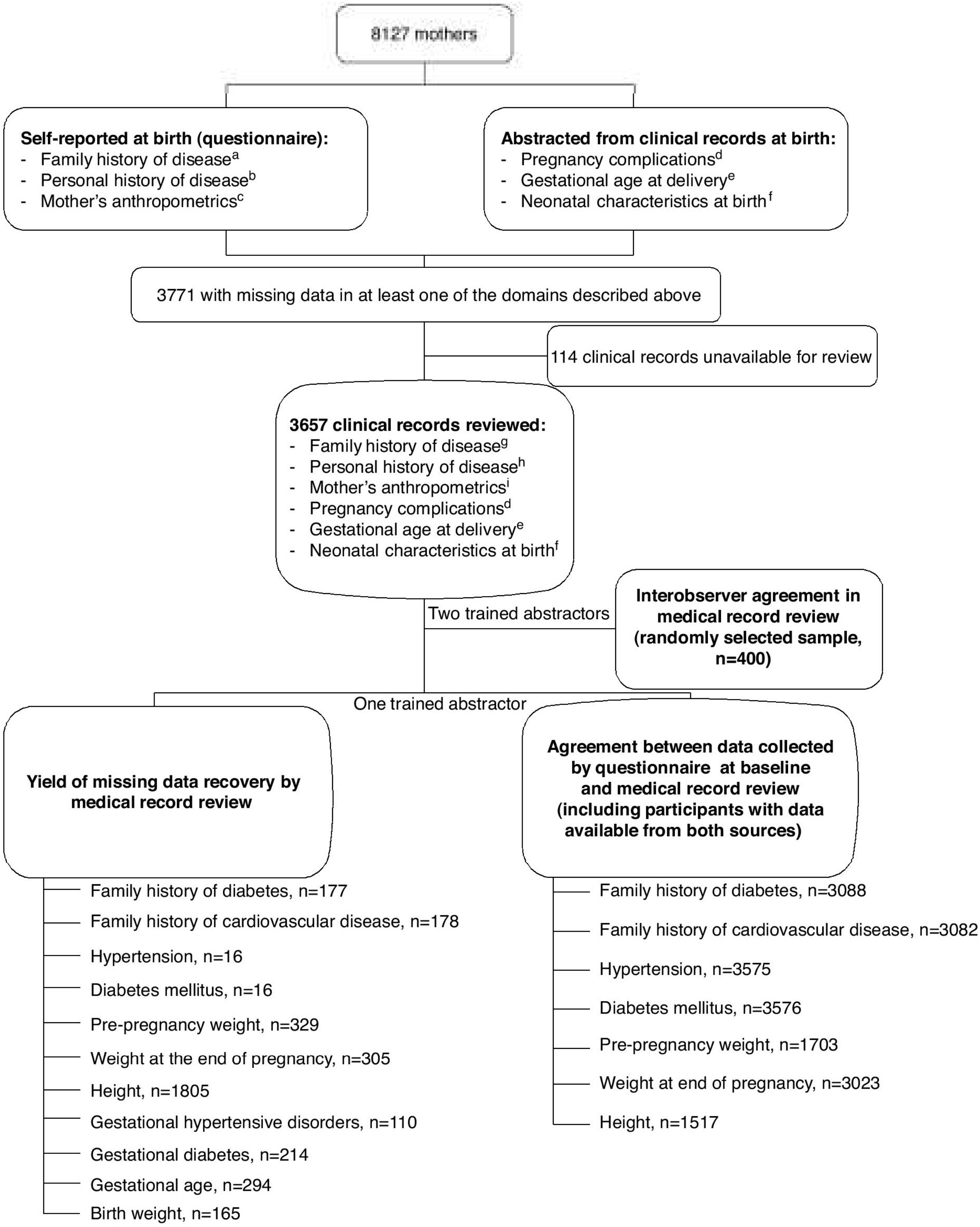

Figure 1. Definition of the samples for missing data recovery, assessment of agreement between data collected by questionnaire and medical record review, and evaluation of interobserver agreement in medical record review.

[a] A family history of diabetes mellitus or cardiovascular disease was considered present when participants reported at least one parent or sibling affected by diabetes or by stroke and/or myocardial infarction, respectively.

[b] A personal history of pre-pregnancy hypertension and diabetes mellitus was considered present when participants recalled having received a medical diagnosis of these conditions.

[c] Usual weight in the 2 years preceding pregnancy and weight immediately before delivery were both obtained through recall information to the nearest 0.1 Kg. Height was measured without shoes by the interviewers to the nearest 0.1 cm. When measurement was not possible, height was reported by the mother as registered in the identity card (35.4% of women with data on height).

[d] Gestational hypertension, eclampsia/pre-eclampsia and gestational diabetes were considered only when explicitly recorded as a diagnosis during the current pregnancy.

[e] Gestational age was considered as that determined by ultrasound or, when this information was not available, as length of amenorrhea, to the nearest 0.1 weeks.

[f] Birth weight, length and head circumference of the newborn were registered to the nearest 1 g and 0.1 cm, respectively.

[g] A family history of CVD and diabetes mellitus was classified using the same criteria as those used in the baseline questionnaire. When the affected relative was not clearly identified as a parent or sibling, the family history was considered positive.

hypertension was 1.9%, while the prevalence of diabetes mellitus was 0.8%. Before pregnancy, 20.2% of the women were overweight and 8.2% were obese. This was the first pregnancy for 47.1% of the women; 9.7% delivered a low birth weight newborn, 10.4% had a preterm delivery and 2.2% of the pregnancies were multiple. Gestational hypertensive disorders and gestational diabetes affected 3.6% and 7.3% of the pregnancies, respectively. When compared with women from the other maternity units, those who delivered at Maternidade de Júlio Dinis (MJD) were younger, more likely to live without a partner, had a lower prevalence of pre-pregnancy diagnosis of hypertension and diabetes and had a higher number of previous pregnancies. Mothers selected at the Hospital de Santo António (HSA) were older, more likely to report a family history of diabetes and CVD, to have a multiple pregnancy and to deliver a premature or low birth weight newborn. These women showed the highest prevalence of hypertension and diabetes before and during pregnancy. At MJD and Centro Hospitalar de Vila Nova de Gaia (CHVNG) women had the lowest educational level and 68.1% of the mothers from Hospital de São João (HSJ) had an income higher than 1,000 €/month. Mothers from Hospital Pedro Hispano (HPH) had the lowest prevalence of gestational hypertensive disorders and gestational diabetes (Table 1).

Yield of missing data recovery

The proportion of participants for whom data was recovered from clinical records is presented in Table 2. Overall, the proportion of missing data recovered ranged from zero to 84.1%, depending on the variables considered. Data on previous diagnosis of hypertension and diabetes mellitus were rarely missing and could never be recovered from medical records. Data on family history of diabetes or CVD and on gestational age and birth weight, when missing at baseline, could seldom be recovered from the medical records. This strategy of recovering missing data was most effective in maternal anthropometric parameters and particularly in pregnancy complications. The highest proportion of data for a family history of both diabetes and CVD was recovered in the HPH. The proportion of participants for whom anthropometric parameters was recovered was lowest at HSJ. At all maternity units, data on pregnancy complications could in general be recovered from medical records, while recovery of missing data on gestational age and birth weight was low (Table 2).

One trained reviewer required around 730 hours to perform the clinical record review, including all the procedures for gaining access to the records plus the review itself, corresponding to approximately 90 working days to complete this task and an average of 11.5 minutes per medical record.

Agreement between clinical records and questionnaire information

Table 3 illustrates the agreement between data collected by the questionnaire and those abstracted from the clinical records. Overall, the agreement in family history was fair, particularly for history of CVD (k = 0.27, 95%CI: 0.23-0.32). At CHVNG the point estimate of the kappa coefficient for family history of disease was higher than in the remaining hospitals, but this difference was not significant. There was no reference to family history of CVD in any of the clinical record reviewed at HSJ. Agreement in personal history of disease was higher than in family history, particularly for diabetes mellitus (k = 0.82, 95%CI: 0.70-0.93), with no significant differences among hospitals. In general, the discrepancies found for weight and height indicated higher values in the clinical record than in the questionnaire. Pre-pregnancy weight reported to the interviewer at birth was 0.6 Kg lower than that registered in the clinical record. The difference between the questionnaire and clinical records in women's weight at the end of pregnancy was much smaller (0.3 Kg). Despite the relatively small differences in means, for about half of the women the discrepancy in weight between the questionnaire and clinical record was greater than 1 Kg. For height, the differences between hospitals were quantitatively negligible (Table 3).

The differences observed in weight and height led to changes in the classification by body mass index categories (<25.0, 25.0 to 29.9, $\geq$30 Kg/m^2) of 10.3% of women and three out of 871 women were misclassified by two body mass index categories (weighted k = 0.82, 95%CI: 0.80-0.83). Nonetheless, the variability was randomly distributed, occurring similarly in both directions.

Interobserver variability

The agreement between data collected by the two reviewers was good or very good. The lowest agreement was observed for personal history of diabetes mellitus (k = 0.66; 95%CI: 0.23-1.00). Data concerning the occurrence of pregnancy complications were highly consistent between the two reviewers, with perfect agreement observed for gestational diabetes (k = 1.00; 95%CI: 1.00-1.00). The differences observed for women's weight and height were negligible, with at least 95% of the data concordant to the nearest 1 Kg or 1 cm, respectively. The mean difference was not significantly different from zero for the three anthropometric variables assessed. The differences in weight and height between reviewers did not affect the global classification by body mass index categories before pregnancy, with only one out of 151 women changing to an adjacent category (weighted k = 0.99, 95%CI: 0.98-1.00). Despite the equality of means, gestational age was registered inconsistently by the two reviewers in almost 20% of the records. The highest agreement was observed for birth weight, with 99.5% concordant observations (Table 4).

Discussion

In this study of pregnant Portuguese women, data on pathological complications of pregnancy and maternal anthropometrics were successfully recovered from medical records when missing from the baseline questionnaire, while the yield of the medical record review was low in recovering past family or personal history of disease.

The overall cost of recovering information from clinical records is an important finding of this study. This procedure required one abstractor over an extended period of time. Clinical records at these maternity units were not electronic and the fact that paper records had to be reviewed likely decreased the yield and increased the time involved. The cost-benefit of perform-

[h] A personal history of hypertension and diabetes was considered present only when explicitly recorded as a diagnosis and not inferred from blood pressure values, serum glucose or drug use.

[i] Pre-pregnancy weight was considered to the nearest 0.1 Kg as self-reported to a health professional, either at early appointments during pregnancy or at birth, while the weight at the end of pregnancy was considered as the weight registered in records at admission for delivery or, when this information was unavailable, at the last medical appointment before birth. Height was considered as registered to the nearest 0.1 cm at admission for delivery or, when this information was unavailable, in the clinical records before birth.

Table 2
Participants with missing information and proportion of recovered data by maternity unit.

	Overall		CHVNG		MJD		HSJ		HSA		HPH	
	Missing data, n	Missing data recovered, n (%)	Missing data, n	Missing data recovered, n (%)	Missing data, n	Missing data recovered, n (%)	Missing data, n	Missing data recovered, n (%)	Missing data, n	Missing data recovered, n (%)	Missing data, n	Missing data recovered, n (%)
Self-reported at birth (questionnaire)												
Family history of diabetes	177	9 (5.1)	59	3 (5.1)	17	1 (5.9)	43	0 (0)	23	0 (0)	35	5 (14.3)
Family history of CVD	178	9 (5.1)	59	3 (5.1)	17	1 (5.9)	44	0 (0)	23	0 (0)	35	5 (14.3)
Hypertension before pregnancy	16	0 (0)	8	0 (0)	1	0 (0)	1	0 (0)	0	0 (0)	6	0 (0)
Diabetes mellitus before pregnancy	16	0 (0)	8	0 (0)	1	0 (0)	1	0 (0)	0	0 (0)	6	0 (0)
Mother's usual prepregnancy weight	329	161 (48.9)	78	42 (53.9)	17	11 (64.7)	17	3 (17.7)	22	12 (54.6)	195	93 (47.7)
Mother's weight at the end of pregnancy	305	55 (18.0)	118	27 (22.9)	40	4 (10.0)	30	2 (6.7)	30	2 (6.7)	87	20 (23.0)
Mother's height	1805	510 (28.3)	951	437 (46.0)	149	24 (16.1)	128	2 (1.6)	44	21 (47.7)	533	26 (4.9)
Abstracted from medical records at birth												
Gestational hypertensive disorders[a]	110	91 (82.7)	61	49 (80.3)	13	11 (84.6)	8	7 (87.5)	19	18 (94.7)	9	6 (66.7)
Gestational diabetes	214	180 (84.1)	127	113 (89.0)	14	9 (64.3)	18	12 (66.7)	23	22 (95.7)	32	24 (75.0)
Gestational age	294	26 (8.8)	85	12 (14.1)	31	5 (16.1)	59	3 (5.1)	60	1 (1.7)	59	5 (8.5)
Birth weight	165	4 (2.4)	27	2 (7.4)	16	0 (0)	45	0 (0)	37	1 (2.7)	40	1 (2.5)

CHVNG: Centro Hospitalar de Vila Nova de Gaia; CVD, cardiovascular disease; HSA: Centro Hospitalar do Porto – Hospital de Santo António; HSJ: Hospital de São João; MJD: Centro Hospitalar do Porto – Maternidade de Júlio Dinis;.
[a] Gestational hypertension and/or pre-eclampsia/eclampsia.

ing this process should be considered case-by-case, taking into account the study aims and the expected yield for distinct variables in each setting. However, this is a time-consuming and expensive solution for correction of methodological errors that should not have occurred in the first place, as when using records to retrieve information that was originally also obtained from medical records.

The agreement between self-reported and medical record data was highly variable. Data directly related to pregnancy and well-known risk factors were concordant. Family history of CVD was underreported in the clinical records of the five hospitals. CHVNG showed the highest estimate of agreement for family history of both diabetes and CVD. This difference can be explained by the clinical record format, which varied between maternity units, including a standardized and pre-formatted section for registration of family history of disease at the CHVNG. In general, there was greater consistency between data sources in family history of diabetes than in family history of CVD. Acknowledgement of family history of diabetes as a major risk factor for the development of gestational diabetes[21] may lead physicians to register these data more systematically and, simultaneously, to increase awareness of these risk factors among pregnant women. A family history of stroke, myocardial infarction and diabetes mellitus can be accurately reported by the participants, when compared with the relatives' self-reports or their death certificates and general practitioners' or hospital notes[22–24].

We showed that the agreement between data collected by questionnaire and those abstracted from medical records is highly dependent on the data recording procedures and practices used and the extent to which these are standardized in each hospital. Our overall results are locale-specific, despite reflecting issues that may be present to a greater or lesser extent in each setting; while the overall yield is likely to be similar in distinct settings, the limited external validity of our results needs to be acknowledged. However, we also present the results by institution and interpret them by taking into account our knowledge of the data collection procedures in each hospital, which provides important information that may be generalized with a smaller number of prior assumptions. Recent mothers are likely to provide more accurate information on personal and family history of diseases than the general population. Therefore, the results of this study cannot be generalized to other types of population.

Few studies have previously focused on the agreement between self-reported data and clinical record review for CVD and risk factors in young women before pregnancy[15,25]. Although the low prevalence and the lack of awareness of hypertension and diabetes diagnosed before pregnancy in young women increase the difficulty of analyzing the agreement[26,27], our results are concordant with previous findings. Ramadhani et al[25] have reported a substantial agreement between medical records and maternal interviews for non-gestational diabetes data (k = 0.75, 95%CI: 0.64-0.86) and similar estimates were found for pre-pregnancy hypertension among pregnant Latin women (k = 0.68, 95%CI: 0.46-0.90)[15].

The accuracy of self-reported weight and height, in comparison with objective measurements, has been extensively reported. Overall, weight and body mass index tend to be underreported and height overreported by women[28,29], and the same pattern has been observed among pregnant women[30–32]. In our study, weight and height were systematically higher in the clinical record than in the questionnaire. The longer time frame considered in the questionnaire could translate into underestimation of weight before pregnancy. The questionnaire data on weight at the end of pregnancy was always self-reported when the cohort was assembled, while in some hospitals weight may have been measured by nurses before delivery. Although we have no possibility of knowing if the weight registered in the clinical records was measured

Table 3
Agreement between data collected by questionnaire at baseline and clinical record review by maternity unit.

	Overall	CHVNG	MJD	HSJ	HSA	HPH
Dichotomous variables	Number of "no" or "yes" responses at the questionnaire interview concordant with the medical record / number of mothers responding "no" or "yes" at the questionnaire interview (%)					
Family history of diabetes, n/n (%)[a]						
No	2210/2390 (92.5)	814/840 (96.9)	216/233 (92.7)	259/313 (82.7)	156/179 (87.2)	765/825 (92.7)
Yes	515/698 (73.8)	193/256 (75.4)	38/74 (51.4)	75/89 (84.3)	48/64 (75.0)	161/215 (74.9)
Agreement (%)	88.2	91.9	82.7	83.1	84.0	89.0
Kappa (95%CI)	0.66 (70.63-0.70)	0.76 (0.71-0.81)	0.48 (0.37-0.60)	0.58 (0.49-0.67)	0.60 (0.49-0.71)	0.67 (0.61-0.73)
Family history of CVD, n/n (%)[a]						
No	2572/2583 (99.6)	886/891 (99.4)	252/253 (99.6)	340/340 (100.0)	198/198 (100.0)	896/901 (99.4)
Yes	95/499 (19.0)	66/204 (32.4)	14/52 (26.9)	0/59 (0.0)	2/45 (4.4)	13/139 (9.4)
Agreement (%)	86.5	86.9	87.2	85.2	82.3	87.4
Kappa (95%CI)	0.27 (0.23-0.32)	0.43 (0.35-0.50)	0.37 (0.23-0.52)	0.00 (0.00-1.00)	0.07 (−0.02-0.16)	0.14 (0.07-0.21)
Hypertension before pregnancy, n/n (%)[a]						
No	3474/3507 (99.1)	1,196/1,217 (98.3)	343/345 (99.4)	466/467 (99.8)	282/283 (99.6)	1,187/1,195 (99.3)
Yes	44/68 (64.7)	16/24 (66.7)	2/4 (50.0)	4/9 (44.4)	9/16 (56.3)	13/15 (86.7)
Agreement (%)	98.4	97.7	98.9	98.7	97.3	99.2
Kappa (95%CI)	0.60 (0.50-0.69)	0.51 (0.36-0.67)	0.49 (0.07-0.92)	0.57 (0.25-0.88)	0.68 (0.47-0.89)	0.72 (0.55-0.89)
Diabetes mellitus before pregnancy, n/n (%)[a]						
No	3547/3548 (100.0)	1235/1236 (99.9)	348/348 (100.0)	474/474 (100.0)	283/283 (100.0)	1207/1207 (100.0)
Yes	20/28 (71.4)	5/7 (71.4)	0/1 (0.0)	1/2 (50.0)	11/15 (73.3)	3/3 (100.0)
Agreement (%)	99.8	99.8	99.7	99.8	98.7	100
Kappa (95%CI)	0.82 (0.70-0.93)	0.77 (0.51-1.00)	0.00 (0.00-1.00)	0.67 (0.05-1.00)	0.84 (0.69-0.99)	1.00 (1.00-1.00)
Continuous variables						
Mother's usual prepregnancy weight (Kg)						
Questionnaire (mean, SD)	62.0 (11.9)	63.7 (12.6)	59.7 (10.0)	61.3 (11.3)	62.2 (11.3)	62.1 (12.4)
Clinical records (mean, SD)	62.6 (12.5)	64.5 (12.9)	60.1 (10.9)	61.5 (12.1)	64.0 (12.4)	62.7 (12.8)
Mean difference (95%CI)	−0.53 (−0.73 to −0.34)	−0.80 (−1.21 to −0.39)	−0.34 (−0.87 to 0.19)	−0.13 (−0.56 to 0.30)	−1.83 (−3.19 to −0.47)	−0.58 (−0.88 to −0.28)
n concordant/n (%)[b]	753/1703 (44.2)	189/407 (46.4)	91/205 (44.4)	187/431 (43.4)	15/59 (25.4)	271/601 (45.1)
Mother's weight at the end of pregnancy (Kg)						
Questionnaire (mean, SD)	75.4 (11.9)	75.8 (11.7)	74.1 (11.5)	75.2 (11.5)	73.1 (11.3)	76.1 (12.5)
Clinical records (mean, SD)	75.6 (12.2)	76.1 (11.9)	74.4 (11.9)	74.8 (12.2)	73.6 (11.5)	76.5 (12.6)
Mean difference (95%CI)	−0.24 (−0.35 to −0.12)	−0.32 (−0.56 to −0.08)	−0.28 (−0.57 to 0.00)	0.41 (0.01 to 0.81)	−0.52 (−1.00 to −0.04)	−0.35 (−0.48 to −0.22)
n concordant/n (%)[b]	1530/3023 (50.6)	400/936 (42.7)	157/294 (53.4)	241/441 (54.6)	156/261 (59.8)	576/1091 (52.8)
Mother's height (cm)						
Questionnaire (mean, SD)	160.9 (6.3)	159.7 (5.8)	160.3 (6.6)	160.8 (6.3)	161.9 (5.8)	161.1 (6.4)
Clinical records (mean, SD)	161.4 (6.3)	160.7 (6.2)	161.0 (6.5)	161.4 (6.3)	161.8 (5.8)	161.5 (6.4)
Mean difference (95%CI)	−0.49 (−0.64 to −0.35)	−1.07 (−1.64 to −0.49)	−0.76 (−1.14 to −0.38)	−0.62 (−0.93 to −0.32)	0.17 (−0.17 to 0.52)	−0.41 (−0.63 to −0.19)
n concordant/n (%)[c]	688/1517 (45.4)	56/146 (38.4)	99/185 (53.5)	150/341 (44.0)	129/192 (67.2)	254/653 (38.9)

95%CI, 95% confidence interval; CHVNG: Centro Hospitalar de Vila Nova de Gaia; CVD: cardiovascular disease; HPH: Unidade Local de Saúde de Matosinhos – Hospital Pedro Hispano; HSA: Centro Hospitalar do Porto – Hospital de Santo António; HSJ: Hospital de São João; MJD: Centro Hospitalar do Porto – Maternidade de Júlio Dinis; SD: standard deviation.

[a] Percentages may not total 100% due to rounding.
[b] Within plus or minus 1 Kg.
[c] Within plus or minus 1 cm.

Table 4
Interobserver agreement in medical record review.

Dichotomous variables	
Family history of diabetes	
Agreement, n (%)	372 (94.4)
Kappa (95% CI)	0.85 (0.79-0.91)
Family history of CVD	
Agreement, n (%)	372 (99.5)
Kappa (95% CI)	0.89 (0.73-1.00)
Hypertension before pregnancy	
Agreement, n (%)	384 (99.5)
Kappa (95% CI)	0.89 (0.73-1.00)
Diabetes mellitus before pregnancy	
Agreement, n (%)	384 (99.5)
Kappa (95% CI)	0.66 (0.23-1.00)
Gestational hypertensive disorders[a]	
Agreement, n (%)	374 (99.2)
Kappa (95% CI)	0.91 (0.80-1.00)
Gestational diabetes	
Agreement, n (%)	388 (100)
Kappa (95% CI)	1.00 (1.00-1.00)
Continuous variables	
Mother's usual prepregnancy weight (Kg)	
Reviewer 1 (mean, SD)	61.8 (11.4)
Reviewer 2 (mean, SD)	61.7 (11.8)
Mean difference (95% CI)	0.048 (−0.16 to 0.26)
n concordant/n (%)[b]	156/165 (94.5)
Mother's weight at the end of pregnancy (Kg)	
Reviewer 1 (mean, SD)	75.5 (12.1)
Reviewer 2 (mean, SD)	75.4 (12.1)
Mean difference (95% CI)	0.043 (−0.05 to 0.14)
n concordant/n (%)[b]	353/371 (95.1)
Mother's height (cm)	
Reviewer 1 (mean, SD)	162.0 (5.7)
Reviewer 2 (mean, SD)	162.1 (5.6)
Mean difference (95% CI)	−0.05 (−0.14 to 0.05)
n concordant/n (%)[c]	302/311 (97.1)
Gestational age (weeks)	
Reviewer 1 (mean, SD)	38.6 (2.2)
Reviewer 2 (mean, SD)	38.6 (2.2)
Mean difference (95% CI)	−0.01 (−0.04 to 0.02)
n concordant/n (%)[d]	324/395 (82.0)
Birth weight (g)	
Reviewer 1 (mean, SD)	3,143 (565)
Reviewer 2 (mean, SD)	3,141 (566)
Mean difference (95% CI)	1.87 (−0.90 to 4.63)
n concordant/n (%)[e]	389/391 (99.5)

95% CI, 95% confidence interval; CVD, cardiovascular disease; SD, standard deviation.
[a] Gestational hypertension and/or pre-eclampsia/eclampsia.
[b] Within plus or minus 1 Kg.
[c] Within plus or minus 1 cm.
[d] Within plus or minus 0.1 week.
[e] Within plus or minus 1 g.

or self-reported, the higher value obtained by the former seems to support our assumption[32]. Pregnant women tend to overreport their height[31]. At birth, most participants were measured, which could explain the differences found.

Studies that have examined the accuracy of self-reported height and weight employed to determine body mass index categories have concluded that approximately 80% of women were correctly classified[29,33], which is in accordance with our observations.

The interobserver variability was low and did not threaten data precision. Standardized training of abstractors and rigorous quality assurance were proposed as critical criteria to improve the quality and accuracy of clinical record review[16–18,34,35]. When research involves data collection by distinct observers, the extent to which different observers perceive and record the same information should be evaluated. In the literature, most medical record review studies fail to report on interrater agreement[34]. Our study showed a low interrater variability, and the discrepancies found in family history of diabetes and CVD between the two reviewers can be attributed to a combination of factors, from the different structure of the clinical records and the data registered in them to specific problems in accessing information from the charts. When records are not pre-formatted and standardized, professionals are more likely to underreport or to register data in different locations, increasing the difficulty of the data abstraction procedure, which precludes the generalization of these findings to other settings.

This study provides important information for the planning and interpretation of epidemiological studies on pregnant women, but some limitations should be discussed. Despite the large sample size, the evaluation of conditions such as hypertension and diabetes before pregnancy is limited by their very low prevalence. The absence of reference to a medical condition in the clinical record was considered as the absence of the condition itself. We do not believe that this assumption compromises our conclusions as it is unlikely that physicians did not enquire about such conditions or failed to record them when present. When clinical records did not specify which relative had developed the outcomes studied, we considered the family history of disease as positive, which could lead to a higher proportion of family history in clinical records than in the interview. However, given the unusual occurrence of this situation, we do not expect that this factor had a quantitatively significant influence on the results. In this study, there was no gold-standard and differences between data sources could reflect misclassification in the questionnaires, in the clinical records data or both. We were unable to draw conclusions on which method provides higher validity for the data assessed.

In conclusion, data directly related to pregnancy and well-known risk factors can be safely recovered from medical records when missing from self-reported data. The need to implement structured and standardized methods to abstract data from clinical records cannot be overemphasized to enhance data quality, which can subsequently improve the interpretation and generalization of the results obtained.

Author's contribution

Elisabete Alves collaborated in the acquisition, analysis and interpretation of the data and draft the article. Nuno Lunet collaborated in the analysis and interpretation of the data reviewed and revised the article critically for important intellectual content. Sofia Correia helped to supervise the field activities and reviewed the article. Ana Azevedo designed the study, directed its implementation and reviewed and revised the article critically for important intellectual content. Henrique Barros designed and supervised the birth cohort Geração XXI, on which our study is based, and made a substancial contribution to the revisions made alter the requests of the reviews. All authors approved the final version.

Conflict of interests

The authors declare that they have no conflict of interests.

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RESULTS

PAPER II

Alves E, Correia S, Barros H, Azevedo A.

Prevalence of self-reported cardiovascular risk factors in Portuguese women: a survey after delivery.

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ORIGINAL ARTICLE

Prevalence of self-reported cardiovascular risk factors in Portuguese women: a survey after delivery

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Abstract
Objectives To estimate the pre-pregnancy prevalence of overweight/obesity, smoking, hypertension, dyslipidemia and diabetes mellitus, in women who delivered a live born.
Methods In a birth cohort study, puerperae were consecutively recruited at five public maternities of Porto, Portugal (2005–2006). We included 7,381 women with complete data for the current analysis. Socioeconomic characteristics, smoking habits, pre-pregnancy weight and chronic diseases diagnosis were self-reported and height was measured.
Results Before pregnancy, 21.3% of women were overweight and 8.8% were obese, 26.6% smoked and 11.2% were former smokers. The prevalence of hypertension, dyslipidemia and diabetes mellitus was 1.7, 1.7 and 0.6%, respectively, with an evident tendency to cluster. The prevalence of all cardiovascular risk factors, except smoking, increased with age and body mass index. Education and income were inversely associated with excessive weight. Current smokers were younger, thinner and in a lower socioeconomic position, whereas former smokers were older and in a higher socioeconomic position.
Conclusion Despite the low prevalence of hypertension, dyslipidemia and diabetes, their tendency to cluster and the increased prevalence among overweight/obese women highlight the high level of risk of this young female population.

Keywords Cardiovascular risk factors · Cohort studies · Pregnancy · Prevalence

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Introduction

Pregnancy is often regarded as a good opportunity for health promotion and disease prevention (McBride et al. 2003). In healthy pregnancies, adaptive changes take place in women's physiology to meet demands of the rapidly developing foetus, including insulin resistance and hyperlipidemia (Catalano 2010). In addition, the hyperdynamic circulatory character of pregnancy may be regarded as a stress test for maternal cardiovascular function.

In Portugal, diseases of the circulatory system accounted for 32.2% of all deaths in 2006 (INE 2009). The clustering of cardiovascular risk factors, such as hypertension, dyslipidemia, diabetes mellitus, obesity and smoking is well documented (Daviglus et al. 2004; Lloyd-Jones et al. 2006; Wilson et al. 1999) and the modification of these risk factors can result in substantial reduction in mortality (Ford et al. 2007).

Despite the similar prevalence of cardiovascular risk factors in women and men, the lack of awareness of risk may be a barrier to prevention of CVD in women. In a survey conducted in the USA, only 16% of women recognized heart disease as the greatest health problem facing women today, and only half identified it as the leading cause of death (Mosca et al. 2010). Recently, a stronger emphasis on women's health status and risk behavior patterns before pregnancy is advocated

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(Moos 2004) to increase the awareness and the potential for prevention at younger ages.

In the last 30 years, Portugal experienced a significant development regarding economic modernization and social structure (Costa et al. 2000), which resulted in lifestyle changes that may have an impact on cardiovascular risk. Therefore, it is important to descriptively quantify the distribution of cardiovascular risk factors to monitor trends over time and guide preventive strategies to reduce the future burden of disease.

In this study, our objective was to estimate the pre-pregnancy prevalence of five major cardiovascular risk factors (overweight/obesity, smoking, hypertension, dyslipidemia and diabetes mellitus), in mothers of a Portuguese birth cohort, and to describe their distribution by age, gravidity and indicators of socioeconomic position (SEP).

Methods

This study is based on the birth cohort Geração XXI. A total of 8,495 mothers, who gave birth to 8,647 live born infants, were enrolled into the cohort. The present study is based on the 8,182 mothers consecutively invited after delivery. We excluded 313 who were recruited and evaluated during pregnancy, since pre-pregnancy characteristics were self-reported in the first trimester and their report is expected to change over time during pregnancy. The recruitment took place between April 2005 and September 2006 at all five public maternity units covering six municipalities of the metropolitan area of Porto, Portugal. All the maternities, except one, are included in a general hospital, with a variety of medical and surgical specialties, and all correspond to level III maternity units, with differentiated perinatal support. At birth, 91.4% of the invited mothers accepted to participate.

Data on demographic and socioeconomic characteristics, lifestyles, obstetric history, anthropometrics and personal history of disease were collected within 72 h after delivery, during the hospital stay, in a face-to-face interview conducted by trained interviewers using structured questionnaires. Educational level of the mother, household income, working condition, social class and marital status were used as indicators of SEP. Social class, at the individual level, was defined according to the ACM (Almeida, Costa and Machado) social class typology (Almeida et al. 2006; Costa et al. 2000), based on two main socio-professional indicators: occupation and employment status (employer, self-employed/family workers or employee). Self-reported occupations were classified by major professional groups, according to the National Classification of Occupations (version 1994) (IEFP 2001). Working condition was defined as employed, unemployed, housewife and others (student or retired). Gravidity was recorded as the number of pregnancies for each participant, including the current one. Personal history of hypertension, dyslipidemia and diabetes mellitus was considered present when participants recalled a medical diagnosis of these conditions previously to the current pregnancy. Pre-pregnancy weight was obtained through recall information to the nearest 0.1 kg. At baseline, height was measured (without shoes) by the interviewers to the nearest 0.1 cm. When measurement was not possible, height was reported by the mother as registered in the identity card (30.8% of women with data on height). The participants' body mass index (BMI) was categorized according to the standard World Health Organization definition as underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) and obese (≥ 30 kg/m^2) (Expert Panel 1998). Smoking habits included information on the daily number of smoked cigarettes before and during pregnancy, and age at smoking initiation. Current smokers included both daily (at least one cigarette per day in the 3 months previous to pregnancy) and occasional smokers (less than a cigarette per day). Women were considered former smokers when they had previously smoked but not in the last 3 months before pregnancy.

Missing data on the questionnaires were recovered through the review of delivery medical records. The agreement between data collected by questionnaire and abstracted from medical records was good for personal history of hypertension, weight and height and very good for personal history of diabetes mellitus, and there was very low inter-rater variability between two independent abstractors (Alves et al. 2010).

After exclusion of the participants who presented at least one missing value on personal history of hypertension, dyslipidemia, diabetes mellitus, BMI and smoking status, 7,381 women were included in our analysis. There were no significant differences between participants with complete and missing data regarding age [mean (standard deviation (SD)): 29.0 (5.6) vs. 28.9 (5.7) years, $p = 0.793$], gravidity (first pregnancy: 48.3 vs. 45.8%, $p = 0.413$), marital status (married/living with a partner: 94.0 vs. 92.9%, $p = 0.245$) and education (education >9 years: 48.9 vs. 50.1%, $p = 0.671$).

Statistical analysis was performed using Stata 9.0 (College Station, TX, 2005). Sample characteristics are presented as counts and proportions for categorical variables, mean and standard deviation (SD) for normally distributed continuous variables, and median and interquartile range (IQR) for non-normally distributed continuous variables. The prevalence of the outcomes is presented with 95% confidence intervals (95% CI). Unconditional binary logistic regression models were fitted to compute age-adjusted odds ratios (OR) and 95% confidence intervals for hypertension, dyslipidemia and diabetes mellitus, and multinomial logistic regression models for BMI and smoking status, taking BMI < 25 kg/m^2 and never smokers as reference classes, respectively.

The study protocol was approved by the Ethics Committee of Hospital de S. João. Written informed consent was obtained from all participants.

Results

The socio-demographic characteristics of the study participants are summarized in Table 1. The mothers' mean age at birth was 29.0 years (range 14–47 years) and the index pregnancy was the first for 48.3%. Most women were married or living with a partner (94.0%) and the median (IQR) educational level was 10 (7–12) years. Approximately 72% were employed and 6.4% of the participants had a household monthly income bellow 500€, while 28.5% had a monthly income above 1,500€ (Table 1).

Table 1 Socio-demographic characteristics of the participants (Porto, Portugal, 2005–2006)

	n (%)[a]
Age (years)	
<25	1,586 (21.5)
25–29	2,236 (30.3)
30–34	2,345 (31.8)
≥35	1,209 (16.4)
Mean (SD)	29.0 (5.6)
Gravidity	
1	3,563 (48.3)
2	2,493 (33.8)
≥3	1,324 (17.9)
Marital status	
Married/cohabiting	6,911 (94.0)
Single/divorced/widow	445 (6.0)
Education	
≤4	541 (7.4)
5–9	3,055 (41.5)
10–12	1,972 (26.8)
>12	1,790 (24.3)
Median (IQR)	10 (7–12)
Working condition	
Employed	5,274 (71.7)
Unemployed	1,457 (19.8)
Housewife	412 (5.6)
Other	217 (3.0)
Income (€/month)	
<500	460 (6.4)
500–1,000	2,107 (29.5)
1,001–1,500	1,821 (25.5)
>1,500	2,034 (28.5)
Does not know/prefers not to answer	716 (10.0)

In each variable, the total may not add to 7,381 due to missing data

SD standard deviation, *IQR* interquartile range

[a] Except if otherwise specified

In this sample of Portuguese women who delivered a live born, 21.3% (95% CI 20.3–22.2) were overweight and 8.8% (95% CI 8.2–9.5) were obese before pregnancy, 26.6% (95% CI 25.6–27.6) reported to have smoked in the 3 months prior to pregnancy and 11.2% (95% CI 10.5–12.0) to be former smokers (Table 2). The prevalence of self-reported pre-pregnancy hypertension, dyslipidemia and diabetes mellitus was 1.7% (95% CI 1.4–2.0), 1.7% (95% CI 1.4–2.0) and 0.6% (95% CI 0.4–0.8), respectively (Table 3). Overall, 3.7% (95% CI 3.3–4.2) of participants had at least one of these cardiometabolic risk factors and in 0.2% (95% CI 0.1–0.4) two or three were simultaneously present, a fourfold higher prevalence than that expected under independence.

Overall, body mass index was associated with age, gravidity and SEP, with stronger effects on obesity than overweight. Age was progressively and significantly associated with overweight and obesity (≥35 vs. <25 years: OR 1.85; 95% CI 1.54–2.23 and OR 2.49; 95% CI 1.90–3.28, respectively) and a similar association was observed with gravidity independently of age (age-adjusted OR 1.43; 95% CI 1.21–1.68 and OR 2.44; 95% CI 1.96–3.05 for overweight and obesity, respectively, in women with more than 1 previous pregnancy in comparison with primigestae). Married women or those living with a partner were more likely to be overweight, as well as housewives and unemployed, when compared with employed women, independently of age. A significant inverse association was observed for education and household monthly income, while self-employed women and those in lower individual social class were more likely to be overweight or obese (Table 2).

Participants aged above 25 years were approximately half as likely to have smoked before pregnancy as younger ones. Participants with more than 1 previous pregnancy (age-adjusted OR 1.46; 95% CI 1.25–1.70), not living with a partner (age-adjusted OR 2.22; 95% CI 1.80–2.73), unemployed (age-adjusted OR 1.77; 95% CI 1.55–2.03) and no paid jobs (age-adjusted OR 1.56; 95% CI 1.15–2.13) were more frequently smokers in the 3 months prior to pregnancy. Household monthly income (age-adjusted OR 0.49; 95% CI 0.39–0.62, for income ≥1,500€ when compared with income <500€) and BMI (age-adjusted OR 0.41; 95% CI 0.30–0.56, for BMI ≥30 kg/m^2, when compared with BMI < 18.5 kg/m^2) were inversely associated with smoking. The prevalence of former smokers increased with age (≥35 years vs. <25 years: OR 1.34; 95% CI 1.05–1.72) and educational level (≥13 years

Table 2 Prevalence of overweight, obesity and smoking status before pregnancy, and age-adjusted odds ratios estimated by multinomial logistic regression for the association with gravidity, socio-economic characteristics and BMI before pregnancy, in mothers of a Portuguese birth cohort (Porto, 2005–2006)

	BMI (Kg/m^2)[a]				Smoking status[b]			
	Overweight		Obesity		Current		Former	
	n (%)	Age-adjusted OR (95% CI)[c]	*n* (%)	Age-adjusted OR (95% CI)[c]	*n* (%)	Age-adjusted OR (95% CI)[c]	*n* (%)	Age-adjusted OR (95% CI)[c]
Age (years)								
<25	273 (17.2)	1[d]	95 (6.0)	1[d]	621 (39.2)	1[d]	134 (8.5)	1[d]
25–29	457 (20.4)	1.29 (1.09–1.52)	197 (8.8)	1.60 (1.24–2.06)	511 (22.9)	0.47 (0.40–0.54)	261 (11.7)	1.11 (0.88–1.38)
30–34	527 (22.5)	1.47 (1.24–1.73)	214 (9.1)	1.71 (1.33–2.20)	549 (23.4)	0.48 (0.42–0.55)	269 (11.5)	1.09 (0.87–1.37)
≥35	312 (25.8)	1.85 (1.54–2.23)	146 (12.1)	2.49 (1.90–3.28)	282 (23.3)	0.50 (0.42–0.59)	165 (13.7)	1.34 (1.05–1.72)
Gravidity								
1	666 (18.7)	1[d]	233 (6.5)	1[d]	957 (26.9)	1[d]	388 (10.9)	1[d]
2	579 (23.2)	1.27 (1.12–1.45)	225 (9.0)	1.42 (1.17–1.73)	612 (24.6)	1.02 (0.90–1.16)	287 (11.5)	0.99 (0.83–1.18)
≥3	325 (24.6)	1.43 (1.21–1.68)	194 (14.7)	2.44 (1.96–3.05)	393 (29.7)	1.46 (1.25–1.70)	155 (11.7)	1.06 (0.85–1.32)
Marital status								
Married/living with a partner	1,498 (21.7)	1[d]	632 (9.1)	1[d]	1,737 (25.1)	1[d]	799 (11.6)	1[d]
Single/divorced/widow	67 (15.1)	0.69 (0.52–0.90)	18 (4.0)	0.47 (0.29–0.76)	220 (49.4)	2.22 (1.80–2.73)	30 (6.7)	0.89 (0.60–1.32)
Education (years)								
≤4	174 (32.2)	1[d]	100 (18.5)	1[d]	131 (24.2)	1[d]	36 (6.7)	1[d]
5–9	710 (23.2)	0.66 (0.53–0.81)	330 (10.8)	0.56 (0.43–0.73)	954 (31.2)	1.32 (1.06–1.65)	294 (9.6)	1.82 (1.26–2.63)
10–12	419 (21.3)	0.51 (0.41–0.64)	139 (7.1)	0.30 (0.23–0.41)	547 (27.7)	1.27 (1.01–1.60)	240 (12.2)	2.25 (1.55–3.27)
>12	263 (14.7)	0.27 (0.22–0.35)	82 (4.6)	0.15 (0.11–0.20)	322 (18.0)	0.81 (0.64–1.03)	256 (14.3)	2.30 (1.59–3.34)
Social class (individual)								
Entrepreneurs and executives	110 (19.8)	1[d]	41 (7.4)	1[d]	139 (25.0)	1[d]	81 (14.5)	1[d]
Professionals and managers	210 (15.4)	0.69 (0.54–0.90)	57 (4.2)	0.50 (0.33–0.76)	238 (17.5)	0.63 (0.49–0.80)	187 (13.7)	0.83 (0.62–1.11)
Self-employed	40 (26.9)	1.68 (1.10–2.58)	16 (10.7)	1.86 (1.00–3.48)	38 (25.5)	0.90 (0.59–1.38)	17 (11.4)	0.77 (0.43–1.36)
Routine employees	751 (22.7)	1.36 (1.08–1.71)	292 (8.8)	1.49 (1.05–2.11)	1,016 (30.7)	1.14 (0.92–1.41)	356 (10.8)	0.79 (0.61–1.04)
Industrial workers	219 (26.4)	1.80 (1.38–2.34)	118 (14.2)	2.74 (1.87–4.01)	170 (20.5)	0.62 (0.48–0.81)	65 (7.8)	0.47 (0.33–0.68)
Working condition								
Employed	1,116 (21.2)	1[d]	425 (8.1)	1[d]	1220 (23.1)	1[d]	608 (11.5)	1[d]
Unemployed	327 (22.4)	1.24 (1.07–1.44)	153 (10.5)	1.62 (1.32–1.98)	544 (37.3)	1.77 (1.55–2.03)	158 (10.8)	1.25 (1.02–1.52)
Housewife	97 (23.5)	1.35 (1.05–1.72)	63 (15.3)	2.36 (1.76–3.19)	111 (26.9)	1.05 (0.83–1.33)	30 (7.3)	0.64 (0.43–0.94)
Others	26 (12.0)	0.62 (0.40–0.95)	11 (5.1)	0.82 (0.43–1.54)	82 (37.8)	1.56 (1.15–2.13)	31 (14.3)	1.95 (1.27–2.99)

Table 2 continued

	BMI (Kg/m^2)[a]				Smoking status[b]			
	Overweight		Obesity		Current		Former	
	n (%)	Age-adjusted OR (95% CI)[c]	*n* (%)	Age-adjusted OR (95% CI)[c]	*n* (%)	Age-adjusted OR (95% CI)[c]	*n* (%)	Age-adjusted OR (95% CI)[c]
Household monthly income (€)								
<500	111 (24.1)	1[d]	53 (11.5)	1[d]	189 (41.1)	1[d]	40 (8.7)	1[d]
500–1,000	491 (23.3)	0.88 (0.69–1.12)	241 (11.4)	0.87 (0.63–1.21)	604 (28.7)	0.63 (0.50–0.78)	203 (9.6)	0.89 (0.62–1.28)
1,001–1,500	406 (22.3)	0.76 (0.59–0.98)	179 (9.8)	0.67 (0.47–0.94)	461 (25.3)	0.58 (0.46–0.73)	201 (11.0)	0.98 (0.68–1.43)
>1,500	367 (18.0)	0.50 (0.39–0.65)	117 (5.8)	0.31 (0.22–0.44)	425 (20.9)	0.49 (0.39–0.62)	277 (13.6)	1.16 (0.80–1.67)
Does not know/prefers not to answer	151 (21.1)	0.73 (0.55–0.98)	45 (6.3)	0.45 (0.29–0.69)	238 (33.2)	0.75 (0.58–0.97)	81 (11.3)	1.17 (0.77–1.76)
BMI before pregnancy (kg/m^2)								
<18.5	–	–	–	–	122 (38.9)	1[d]	37 (11.8)	1[d]
18.5–24.9	–	–	–	–	1,342 (27.7)	0.63 (0.49–0.80)	540 (11.2)	0.74 (0.51–1.07)
25.0–29.9	–	–	–	–	371 (23.6)	0.52 (0.40–0.68)	184 (11.7)	0.72 (0.49–1.07)
≥30	–	–	–	–	128 (19.6)	0.41 (0.30–0.56)	69 (10.6)	0.60 (0.39–0.93)

95% *CI* 95% confidence interval, *BMI* body mass index, *OR* odds ratio

[a] Reference class: BMI < 25 kg/m^2

[b] Reference class: never smokers

[c] Except for age

[d] Reference class

Table 3 Prevalence of hypertension, dyslipidemia, diabetes mellitus and the aggregation of the three before pregnancy, and age-adjusted odds ratios estimated by unconditional logistic regression for the association with gravidity, socio-economic characteristics and BMI before pregnancy, in mothers of a Portuguese birth cohort (Porto, 2005–2006)

	Hypertension		Dyslipidemia		Diabetes mellitus		≥1 cardiometabolic comorbidities	
	n (%)	Age-adjusted OR (95% CI)[a]	*n* (%)	Age-adjusted OR (95% CI)[a]	*n* (%)	Age-adjusted OR (95% CI)[a]	*n* (%)	Age-adjusted OR (95% CI)[a]
Age (years)								
<25	18 (1.1)	1[b]	12 (0.8)	1[b]	5 (0.3)	1[b]	32 (2.0)	1[b]
25–29	24 (1.1)	0.95 (0.51–1.75)	38 (1.7)	2.27 (1.18–4.35)	11 (0.5)	1.56 (0.54–4.51)	72 (3.2)	1.62 (1.06–2.46)
30–34	38 (1.6)	1.43 (0.82–2.52)	48 (2.1)	2.74 (1.45–5.18)	16 (0.7)	2.17 (0.79–5.94)	95 (4.1)	2.05 (1.37–3.08)
≥35	46 (3.8)	3.45 (1.99–5.97)	28 (2.3)	3.11 (1.57–6.14)	10 (0.8)	2.64 (0.90–7.74)	76 (6.3)	3.26 (2.14–4.96)
Gravidity								
1	56 (1.6)	1[b]	71 (2.0)	1[b]	22 (0.6)	1[b]	141 (4.0)	1[b]
2	37 (1.5)	0.70 (0.45–1.09)	34 (1.4)	0.55 (0.36–0.84)	15 (0.6)	0.78 (0.40–1.55)	79 (3.2)	0.62 (0.46–0.83)
≥3	34 (2.6)	1.00 (0.62–1.61)	21 (1.6)	0.57 (0.34–0.96)	5 (0.4)	0.42 (0.15–1.18)	56 (4.2)	0.72 (0.51–1.01)
Marital status								
Married/living with a partner	121 (1.8)	1[b]	119 (1.7)	1[b]	39 (0.6)	1[b]	262 (3.8)	1[b]
Single/divorced/widow	4 (0.9)	0.62 (0.22–1.71)	7 (1.6)	1.35 (0.61–2.99)	2 (0.5)	1.07 (0.25–4.63)	11 (2.5)	0.87 (0.46–1.62)
Education (years)								
≤4	17 (3.1)	1[b]	8 (1.5)	1[b]	6 (1.1)	1[b]	25 (4.6)	1[b]
5–9	65 (2.1)	1.02 (0.58–1.79)	61 (2.0)	1.76 (0.83–3.75)	17 (0.6)	0.62 (0.24–1.63)	134 (4.4)	1.31 (0.84–2.05)
10–12	29 (1.5)	0.66 (0.35–1.23)	25 (1.3)	1.00 (0.44–2.25)	7 (0.4)	0.37 (0.12–1.13)	59 (3.0)	0.80 (0.49–1.31)
>12	16 (0.9)	0.33 (0.16–0.66)	31 (1.7)	1.15 (0.52–2.53)	12 (0.7)	0.60 (0.22–1.64)	57 (3.2)	0.72 (0.44–1.17)
Social class (individual)								
Entrepreneurs and executives	8 (1.4)	1[b]	14 (2.5)	1[b]	5 (0.9)	1[b]	23 (4.1)	1[b]
Professionals and managers	13 (1.0)	0.66 (0.27–1.60)	21 (1.5)	0.59 (0.30–1.18)	9 (0.7)	0.72 (0.24–2.16)	41 (3.0)	0.71 (0.42–1.19)
Self-employed	3 (2.0)	1.49 (0.39–5.73)	3 (2.0)	0.85 (0.24–3.01)	0 (0.0)	–	6 (4.0)	1.03 (0.41–2.59)
Routine employees	59 (1.8)	1.45 (0.69–3.08)	46 (1.4)	0.62 (0.34–1.14)	11 (0.3)	0.40 (0.14–1.16)	113 (3.4)	0.93 (0.59–1.48)
Industrial workers	21 (2.5)	2.07 (0.90–4.73)	18 (2.2)	0.96 (0.47–1.95)	8 (1.0)	1.14 (0.37–3.55)	42 (5.1)	1.39 (0.83–2.35)
Working condition								
Employed	82 (1.6)	1[b]	87 (1.7)	1[b]	27 (0.5)	1[b]	185 (3.5)	1[b]
Unemployed	29 (2.0)	1.53 (0.98–2.37)	24 (1.7)	1.23 (0.77–1.95)	11 (0.8)	1.79 (0.87–3.66)	59 (4.1)	1.41 (1.04–1.92)
Housewife	13 (3.2)	2.04 (1.12–3.72)	11 (2.7)	1.80 (0.95–3.41)	3 (0.7)	1.52 (0.46–5.07)	24 (5.8)	1.80 (1.16–2.80)
Others	3 (1.4)	1.35 (0.41–4.50)	3 (1.4)	1.54 (0.46–5.10)	1 (0.5)	1.53 (0.19–12.1)	7 (3.2)	1.57 (0.71–3.48)
Household monthly income (€)								
<500	8 (1.7)	1[b]	3 (0.7)	1[b]	6 (1.3)	1[b]	16 (3.5)	1[b]
500–1,000	49 (2.3)	1.28 (0.60–2.74)	41 (1.9)	2.66 (0.82–8.64)	14 (0.7)	0.44 (0.17–1.16)	95 (4.5)	1.19 (0.69–2.05)

Table 3 continued

	Hypertension		Dyslipidemia		Diabetes mellitus		≥1 cardiometabolic comorbidities	
	n (%)	Age-adjusted OR (95% CI)[a]	*n* (%)	Age-adjusted OR (95% CI)[a]	*n* (%)	Age-adjusted OR (95% CI)[a]	*n* (%)	Age-adjusted OR (95% CI)[a]
1,001–1,500	33 (1.8)	0.97 (0.44–2.14)	31 (1.7)	2.13 (0.64–7.03)	8 (0.4)	0.26 (0.09–0.77)	67 (3.7)	0.90 (0.51–1.58)
>1,500	28 (1.4)	0.60 (0.27–1.36)	35 (1.7)	1.92 (0.58–6.33)	9 (0.4)	0.23 (0.08–0.67)	71 (3.5)	0.74 (0.42–1.30)
Does not know/prefers not to answer	5 (0.7)	0.37 (0.12–1.14)	9 (1.3)	1.81 (0.49–6.74)	2 (0.3)	0.19 (0.04–0.97)	14 (2.0)	0.52 (0.25–1.07)
BMI before pregnancy (kg/m^2)								
<25.0	49 (1.0)	1[b]	75 (1.5)	1[b]	22 (0.4)	1[b]	140 (2.7)	1[b]
25.0–29.9	44 (2.8)	2.86 (1.89–4.33)	30 (1.9)	1.25 (0.81–1.92)	10 (0.6)	1.42 (0.67–3.02)	79 (5.0)	1.80 (1.36–2.39)
≥30	34 (5.2)	5.33 (3.39–8.37)	21 (3.2)	2.09 (1.28–3.42)	10 (1.5)	3.40 (1.59–7.23)	57 (8.7)	3.18 (2.31–4.40)

95% *CI* 95% confidence interval, *BMI* body mass index, *OR* odds ratio

[a] Except for age

[b] Reference class

vs. ≤4 years: age-adjusted OR 2.30; 95% CI 1.59–3.34). Women in the lowest social class were less frequently former smokers than women in the highest. When compared with employed puerperae, unemployed and student or retired were more likely to be former smokers, while housewives were less likely to had stopped smoking before pregnancy, independently of age. Obese women were less frequently former smokers than underweight women (age-adjusted OR 0.60; 95% CI 0.39–0.93) (Table 2).

The prevalence of the three cardiometabolic comorbidities—hypertension, dyslipidemia and diabetes mellitus—considered individually or in aggregation, increased significantly with age (≥35 years vs. <25 years: OR for the presence of at least one of the factors = 3.26; 95% CI 2.14–4.96) and BMI (≥30 vs. <25.0 kg/m^2: age-adjusted OR 3.18; 95% CI 2.31–4.40). An inverse association was observed with gravidity, independently of age, with a more relevant individual effect for dyslipidemia (>1 previous pregnancies vs. primigestae: age-adjusted OR 0.57; 95% CI 0.34–0.96). Overall, unemployed women and housewives were more frequently hypertensive, dyslipidemic or diabetic, when compared with employed women. There was a non-significant trend for an inverse association of these cardiometabolic comorbidities with education and income (Table 3).

When restricting our analysis to primigestae, the prevalence of smoking, hypertension, dyslipidemia and diabetes mellitus remained unchanged. Although we observed a lower prevalence of overweight and obesity in primigestae (18.7%; 95% CI 17.4–20.0%, and 6.5%; 95% CI 5.7–7.4%, respectively), the direction and strength of the associations with age, socio-economic characteristics and BMI before pregnancy were essentially unchanged in comparison with those observed for the entire cohort.

Discussion

In this study of Portuguese puerperae, the prevalence of hypertension, dyslipidemia and diabetes mellitus before pregnancy was lower than 2% and although the prevalence of multiple cardiometabolic comorbidities was very low, their tendency to cluster was evident. Approximately a third of the women were overweight or obese and more than a quarter smoked before pregnancy. The prevalence of cardiovascular risk factors, except smoking, increased with age and BMI, and was higher in married women or living with a partner. Education and income were inversely associated with overweight. Current smokers were younger, thinner and had a lower socioeconomic position, whereas former smokers were older and had a higher socioeconomic position.

Prevalence estimates of overweight and obesity in childbearing age women before pregnancy vary across countries. In our study, the prevalence of overweight and obesity was lower than that previously described in other industrialized nations (Chu et al. 2009; Khashan and Kenny 2009; Stepan et al. 2006). A recent study from the United States (Chu et al. 2009) reported overweight and obesity rates before pregnancy of 23.0 and 18.7%, respectively. Regarding European countries, the figures were very similar between the UK (Khashan and Kenny 2009) and Germany (Stepan et al. 2006), with prevalence estimates of 28.4 and 31.0%, respectively, for overweight and 17.9 and 18.8%, respectively, for obesity. Beyond the true variation in overweight and obesity rates between populations, at least part of these differences is explained by variable methods of data collection within each study. In the American study (Chu et al. 2009), pre-pregnancy BMI was calculated based on self-reported weight and height, while in the British study (Khashan and Kenny 2009) it was calculated using measurements during the first antenatal visit, and in the German study (Stepan et al. 2006) was abstracted from a computerized perinatal database. In Portugal, the prevalence of overweight and obesity in women aged between 18 and 39 years, according to a national survey conducted in 2003–2005, in which weight and height were measured, was 30.2 and 8.5%, respectively (do Carmo et al. 2008). Relying on self-reported weight and height, the 2005/2006 Portuguese National Health Survey described prevalences of overweight and obesity very similar to ours (19.6 and 9.4%, respectively), for women aged 18–44 years old (INS 2009).

As previously described (McLaren 2007), we found an inverse association between socioeconomic characteristics and weight, probably related to less access to healthy foods (Drewnowski and Darmon 2005) and lower participation in leisure-time physical activity (Giles-Corti and Donovan 2002) among lower social classes. In addition, since education may increase the ability to obtain and understand health-related information and women in high social strata are more likely to perceive themselves as overweight or obese (Paeratakul et al. 2002; Wardle and Griffith 2001), they may have stronger expectations of a slim physical appearance and, therefore, a higher motivation for weight regulation (Gutierrez-Fisac et al. 2002; Halkjaer et al. 2003). In fact, socioeconomic differences in healthy lifestyles are associated with differences in attitudes to health, with a relevant social value placed on weight, especially for women in high socioeconomic strata (Ball et al. 2003; Wardle and Griffith 2001).

The EURO-PERISTAT study, that monitored and evaluated perinatal health in Europe, reported pre-pregnancy smoking prevalence levels ranging from 7.9% in Lithuania to 35.9% in France (EURO-PERISTAT 2008). No data for pre-pregnancy smoking in Portugal were available at that time but the prevalence of current smoking in the general population women aged between 15 and 44 years old, according to data from the National Health Survey, was 18.4% (INS 2009). The higher prevalence of smoking in our sample could reflect its urban nature. In addition, participants aged 15–24 years were more frequently smokers than that observed in the same age range (39.2 vs. 16.0%) of the general population. Women who get pregnant at younger ages are less educated and with lower income and are, probably, more likely to smoke. Moreover, in the National Health Survey (INS 2009), the prevalence may have been underestimated since the questionnaire could be answered by a proxy in case the index subject was absent and proxies might not be aware of the smoking status of these women, especially in younger ones.

Portugal was placed at stage 2 of the smoking epidemic, with a higher prevalence of smoking in women with higher educational levels (Machado et al. 2009; Santos and Barros 2004). Our results revealed a lower proportion of smokers among women at the highest category of education, which could reflect both an evolution across the tobacco epidemic stages and the effect of pregnancy planning. Given that the more educated women more frequently planned their pregnancy, it is possible that these women had stopped smoking before pregnancy, because they intended to get pregnant. The higher proportion of ex-smokers with more than 12 years of education supports this interpretation. Surprisingly, in our study obese women were less likely to be former smokers. As described for education, we believe that a large proportion of these women stopped smoking in the 3 months before pregnancy only due to pregnancy planning and, therefore, will return to their usual consumption after birth (Carmichael and Ahluwalia 2000).

Recently, a national survey on hypertension in pregnancy reported a prevalence of chronic hypertension very similar to ours (1.5%; 95% CI 1.2–1.8%) (Povoa et al. 2008). Our low prevalence of diabetes mellitus is in accordance with a population-based study from the United States (Rosenberg et al. 2005), in which data were collected from the New York City birth register that contained a specific category for chronic diabetes (including types 1 and 2), reporting a prevalence of 0.3% before pregnancy. Similarly, a population-based study from the UK reported a prevalence of 0.47%, considering women with diabetes diagnosed at least 6 months prior to pregnancy (Bell et al. 2008). We were not able to find data regarding dyslipidemia before pregnancy available in the literature. Even in studies considering the general population, the heterogeneity of definitions of dyslipidemia impairs a comparison with our results. In the Bogalusa Heart Study, performed in a cohort of young adults (younger than 45 years), the self-reported prevalence of dyslipidemia in white females was 5.8% (Frontini et al. 2003). The lower prevalence described in our study may be explained by the specific characteristics of our sample, since we studied a sample of women who successfully led a pregnancy to a live born, which may imply that these women were on average healthier than the general population of the same age group. This assumption is supported by data from the Portuguese National Health Survey that reported a prevalence of 7.2 and 2.7% for hypertension and diabetes mellitus, respectively, in women aged between 15 and 44 years old (INS 2009) However, when comparing these data, we must take into consideration that in our study we only considered the presence of these comorbidities after a medical diagnosis, while in the National Health Survey the report of those conditions did not imply such diagnosis. Therefore, participants may have reported to have hypertension or diabetes mellitus even not fulfilling objective criteria for a medical diagnosis.

We intended to estimate the prevalence of overweight, obesity, smoking, hypertension, dyslipidemia and diabetes mellitus before pregnancy to establish a baseline overview with which to compare these women's cardiovascular profile during a prospective follow up. Since multigestae were included and a previous pregnancy can affect both the prevalence of the studied features and their associations with socio-demographic determinants, we compared the prevalence of the five cardiovascular risk factors between these two groups of women. Although we found a lower prevalence of overweight and obesity in women who had never been pregnant before, restriction of our analysis to primigestae did not change the prevalence estimates of the other cardiovascular risk factors or the relations of each risk factor with determinants considered.

The tendency for the three cardiometabolic comorbidities to cluster was evident in these women of childbearing age. It has been recognized that these cardiovascular risk factors are associated with each other and their effects tend to be synergistic rather than additive (Wilson et al. 1999). In our study, the prevalence of having at least two of these cardiometabolic comorbidities was 0.2%, which is 4 times higher than the prevalence expected by the individual contribution of each risk factor. The aggregation found between these risk factors in our sample suggests that the pathogenic process is initiated early in life. The prevalence of overweight, obesity and smoking was very high. As expected, overweight and obesity were major contributing factors for the development of the three cardiometabolic comorbidities considered, independently of age.

This is the first study that presents the prevalence of several cardiovascular risk factors in young Portuguese women that achieved a successful pregnancy. However, some limitations should be pointed. Despite the large sample size, the precision of estimates of the prevalence of hypertension, dyslipidemia and diabetes before pregnancy is low due to their very low prevalence. Besides, the absence of objective measurements of blood pressure, fasting blood lipids and glucose can lead to an underestimation of the prevalence of these cardiometabolic comorbidities. According to a previous study, in 2003 the awareness of hypertension in Portuguese women aged below 35 years was only 21.9%, which can be explained by the fact that younger women had measured their blood pressure fewer times in the past (Macedo et al. 2005). Similar awareness estimates in young women were found for dyslipidemia and diabetes mellitus in other populations (Scuteri et al. 2009). Also, pre-pregnancy weight and smoking were both self-reported after delivery. Overall, weight tends to be underreported by women (Brunner Huber 2007), which may lead to an underestimation of the overweight and obesity prevalence, and social desirability may lead to biased recall of smoking in new mothers. However, since 99.3% of the participants had more than three prenatal visits, they were probably more aware of their health status. Therefore, we believe that our estimates truly reflect the prevalence of the five cardiovascular risk factors in women of childbearing age.

Our findings reveal that women in a lower socioeconomic position have a higher pre-pregnancy prevalence of cardiovascular risk factors, suggesting a higher risk of developing cardiovascular disease in the future. Therefore, women from the lowest educational and income strata should be the main target group for educational intervention regarding these risk factors. In this context and since low health literacy is associated with a range of adverse health outcomes (Dewalt et al. 2004), health education should be literacy sensitive to enhance health knowledge and self-efficacy to promote the adoption of healthier lifestyles (Osborn et al. 2011).

To the best of our knowledge, there are no published studies on educational programs regarding overall cardiovascular risk in women after delivery. However, data from a systematic review (Hoedjes et al. 2010) revealed that individual and group counseling, use of diaries or other correspondence materials were shown to be effective interventions for prevention in weight loss, smoking cessation and prevention of smoking relapse in the postpartum. These results support that women of childbearing age would benefit from the development of specific educational programs, after giving birth.

In conclusion, the clustering of hypertension, dyslipidemia and diabetes mellitus, as well as the high prevalence of overweight, obesity and smoking, shows an adverse cardiovascular risk profile of Portuguese young mothers and highlight the importance of implementing preventive interventions at early stages of life to modulate cardiovascular risk.

Ethical standards The study protocol was approved by the Ethics Committee of Hospital de S. João and written informed consent was obtained from all participants, in compliance with the current laws of Portugal.

Conflict of interest The authors declare that they have no conflict of interest.

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PAPER III

Alves E, Azevedo A, Rodrigues T, Santos AC, Barros H.
Impact of risk factors on hypertensive disorders in pregnancy, in primiparae and multiparae.
[submitted]

Impact of risk factors on hypertensive disorders in pregnancy, in primiparae and multiparae

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ABSTRACT

Purpose: To assess the impact of age, education, family history of cardiovascular disease, prepregnancy overweight/obesity and weight gain during pregnancy on hypertensive disorders, among primiparae and multiparae.

Methods: In a birth cohort study, puerperae were consecutively recruited at all public maternities of Porto, Portugal (2005-2006). We included 6952 women with singletons and complete data on key variables. Hypertensive disorders included chronic hypertension, gestational hypertension or preeclampsia/eclampsia. Prevalence ratios were computed using Poisson regression and population attributable fractions were calculated.

Results: Overall, hypertensive disorders affected 4.6% of single pregnancies, and were associated with older age, lower education, family history of cardiovascular disease and excessive weight before and during pregnancy, similarly in primiparae and multiparae. Approximately 50% of cases among primiparae and 70% among multiparae were attributable to the joint effect of pregnancies after 34 years of age, education below 12 years, family history of cardiovascular disease and excessive weight before and during pregnancy.

Conclusions: The risk factors explained a high proportion of hypertensive disorders during pregnancy. Excessive weight before and during pregnancy had a very large contribution. The substantial joint effect of the risk factors suggests that interventions focusing on these risk factors should be part of pre-conceptional and prenatal care.

Keywords: Cohort studies; Hypertension, Pregnancy-Induced; Risk factors

INTRODUCTION

Hypertensive disorders complicating pregnancy include chronic and gestational hypertension, preeclampsia and eclampsia, with the latter three entities representing generally transient hypertensive conditions with onset during pregnancy (1). These major complications of pregnancy increase the risk of adverse obstetric and perinatal outcomes (2, 3, 4) and are associated with high blood pressure and cardiovascular disease later in women's life (5, 6), with approximately half of those with preeclampsia developing chronic hypertension (7).

In Portugal, a national survey conducted in 2005 estimated an overall prevalence of hypertensive disorders in pregnancy of approximately 6% (8). Although this rate was lower than in other countries (4, 9, 10), preterm birth, small for gestational age newborns and fetal death were more frequent in women with hypertensive pregnancies (8).

Maternal socio-demographic and metabolic factors, as well as family history of hypertension, have been reported as determinants of hypertension in pregnancy, but the etiology of hypertensive disorders of pregnancy is not completely understood (11, 12, 13). Primiparity is consistently associated with preeclampsia (12) while other risk factors, usually related with chronic hypertension in the general population, could be expected to have a stronger effect in multiparae. Also, the interdependence of these risk factors, resulting in their clustering (14), raises the question of the added predictive value of considering several factors simultaneously. We are unaware of studies considering the joint impact of several risk factors on the risk of hypertension during pregnancy.

Thus, we assessed the impact of age, education, family history of cardiovascular disease, prepregnancy BMI and pregnancy weight gain on hypertensive disorders in pregnancy, in primiparous and multiparous mothers of a Portuguese birth cohort. In order to assess the potential for prevention, we estimated the population attributable fractions for each risk factor, individually and in aggregation with each other.

METHODS

This study is based on the baseline information obtained at the assembling of the birth cohort Geração XXI. A total of 8495 mothers, who gave birth to 8647 live born infants, were enrolled. We excluded a subgroup of 313 who were recruited and evaluated during pregnancy to address specific objectives (15), since self-report of prepregnancy clinical characteristics is expected to change over time during pregnancy. In the present study, from the 8182 mothers consecutively invited at delivery we only included 8045 who delivered singleton babies. The recruitment took place between April 2005 and September 2006 at all 5 public maternity units covering the metropolitan area of Porto, Portugal. All the maternities corresponded to level III units, with differentiated perinatal support, and were included in a general hospital, with a variety of medical and surgical specialties, except one. Of the invited mothers 91.4% accepted to participate.

Data on demographic and socioeconomic characteristics, lifestyles, obstetric history and anthropometrics were collected within 72 hours after delivery, during the hospital stay, in a face-to-face interview conducted by trained interviewers using structured questionnaires. Clinical records were also reviewed at birth to retrieve data on complications of pregnancy. Parity was recorded as the number of deliveries, including the index one. Family history of cardiovascular disease was considered when participants reported to have at least one parent or sibling affected by stroke and/or myocardial infarction. Current smokers included both daily and occasional smokers. Women were considered former smokers if they had previously smoked but not in the 3 months before pregnancy. Prepregnancy weight was recalled and recorded to the nearest 0.1 Kg. At baseline, height was measured (without shoes) to the nearest 0.1 cm. When measurement was not possible, height was reported by the mother as registered in the identity card (30.8% of women with data on height). BMI was categorized according to the standard WHO definition as underweight, normal weight, overweight and obese (16). Weight gain during pregnancy was calculated as the difference between the mother's reported weight immediately before delivery and prepregnancy weight, and categorized as bellow, above or as recommended, taking into account the prepregnancy BMI, according to the IOM guidelines (17).

Hypertensive disorders in pregnancy included the presence of chronic hypertension, gestational hypertension or preeclampsia/eclampsia. Personal history of hypertension was considered present when participants recalled a medical diagnosis of this condition before the current pregnancy, while gestational hypertension or preeclampsia/eclampsia were considered only when explicitly recorded on obstetrical records as a diagnosis during the current pregnancy. When gestational hypertension and preeclampsia/eclampsia were simultaneously recorded in the medical record, the diagnosis of preeclampsia/eclampsia was considered.

Missing data on the questionnaires were recovered through the review of obstetrical records. The agreement between data collected by questionnaire and abstracted from obstetrical records was good for personal history of hypertension, weight and height, and there was very low inter-rater variability between two independent abstractors (18).

After excluding participants who presented at least one missing value on key variables, 6952 women were considered in the current analysis. There were no significant differences between participants with complete and missing data regarding age [mean (standard deviation (SD)): 29.0(5.6) vs. 29.1(5.8) years, p=0.570], BMI (overweight or obese: 30.0% vs. 33.1%, p=0.208) and parity (primiparous: 56.5% vs. 57.4%, p=0.588), while women with no missing data on key variables had a higher educational level [median (interquartile range (IQR)): 10(7-12) vs. 9(6-12) years, p<0.001].

Statistical analysis was performed using the statistical software Stata 11.0 (College Station, TX, 2005). The associations between explanatory variables and gestational hypertensive disorders were estimated by crude and adjusted prevalence ratios (PR) and respective 95%CI, using robust Poisson regression. Separate models were built for primiparae and multiparae, considering the hypothesis of different effects of risk factors in the two groups. The final model was fitted adjusting for age at delivery and social, clinical, obstetric and behavioral characteristics which were a priori considered potential confounders of the association. The population attributable fractions were calculated using the command *punaf* (19) in Stata, based on the adjusted PR and putative alternative distributions of exposure. We considered several scenarios of prevention defined according to the potential of change at the individual level: (1)prevention of pregnancies in women after 34 years of age (shift to 30-34 years old); (2)prevention of pregnancies in women with education below 12 years (shift to ≥12 years); (3)prevention of pregnancies in women with family history of cardiovascular disease; (4)prevention of pregnancies in overweight/obese women (shift to normal weight); (5)prevention of pregnancies in women with weight gain during pregnancy above recommended (shift to weight gain as recommended); (6)prevention of pregnancies in women after 34 years old (shift to 30-34 years old), with overweight/obesity (shift to normal weight) and weight gain during pregnancy above recommended (shift to weight gain as recommended); (7)prevention of pregnancies in women after 34 years old (shift to 30-34 years old), with education below 12 years (shift to ≥12 years), family history of cardiovascular disease, overweight/obesity (shift to normal weight) and weight gain during pregnancy above recommended (shift to weight gain as recommended). We emphasize that not all risk factors are regarded as modifiable in the individual, but rather the occurrence of pregnancies in women with those characteristics.

The study protocol was approved by the Ethics Committee of Hospital de São João. Written informed consent was obtained from all participants.

RESULTS

The characteristics of the study participants are summarized in Table 1. Overall, the mothers' mean age at the child's birth was 29 years (range: 14 to 47 years). Most women were married or living with a partner (93.9%) and the median (IQR) educational level was 10 (7-12) years. Almost 72% were employed and 6.4% of the participants had a household monthly income below 500€. Family history of cardiovascular disease was reported by 16.3% of the mothers and, three months before pregnancy, 26.7% of the women smoked and 11.4% were ex-smokers. Before pregnancy, 21.2% were overweight and 8.8% were obese. During the index pregnancy, 37.7% of the women gained more weight than recommended for their prepregnancy BMI, while 25.8% gained less than recommended. This was the first delivery for 56.5% of women and 51.0% delivered a male newborn. In this sample, multiparae were older, more frequently married, with a lower socioeconomic position and with a higher prevalence of family history of cardiovascular disease. They were also more frequently overweight and obese but gained less weight during pregnancy than recommended.

In this sample of Portuguese women who delivered a singleton live born, 342 (4.6%; 95%CI: 4.1–5.1) presented a hypertensive disorder during pregnancy. The prevalence was slightly higher in primiparae than multiparae (5.0%; 95%CI: 4.3–5.7 vs. 4.1%; 95%CI: 3.5–4.9). This increased prevalence among primiparous was mainly due to preeclampsia/eclampsia (1.6% vs. 0.8% in multiparous). Primiparae and multiparae had a similar prevalence of chronic (1.6% vs. 1.9%) and gestational hypertension (1.9% vs. 1.7%). Among all 86 cases of preeclampsia/eclampsia, 6 (7.0%) were superimposed on chronic hypertension, 3 in primiparous and 3 in multiparous.

Overall, the occurrence of hypertensive disorders during pregnancy differed according to socio-demographic, familial and metabolic factors, both in primiparae and multiparae (Table 2). Women older than 34 years were more likely to have a hypertensive disorder than those younger than 25 years, with non-significantly stronger effects in multiparae than primiparae (PR=2.98 vs. PR=1.82; p for interaction=0.268). Hypertension was more frequent among participants with less than 5 years of education, with a slightly stronger association for primiparae than multiparae (PR=2.04 vs. PR=1.53; p for interaction=0.820). In both primiparae and multiparae, family history of cardiovascular disease was associated with a 1.5-fold increased prevalence of hypertensive disorders during pregnancy, overweight and obesity with an almost 2-fold and 4-fold increased prevalence, respectively, and weight gain during pregnancy above recommended with a 1.4-fold increase in prevalence. A significant 32% decrease in prevalence was observed for delivery of a female newborn among primiparae (Table 2).

Among primiparae, previous BMI and weight gain during pregnancy were the most relevant independent contributors of hypertension complicating pregnancy. Overweight and obesity explained almost a third of hypertensive disorders in pregnancy, while gaining more weight than recommended throughout pregnancy independently contributed 17.0%. The joint effect of age above 34 years old, overweight, obesity, and excessive weight gain during pregnancy explained, altogether, 44.2% of cases. An additional 7.7% (PAF=51.9%) were explained by the contribution of education and family history of cardiovascular disease.

In general, the assessed risk factors had a higher impact on the hypertensive disorders in pregnancy in multiparae, particularly for age, education and family history of cardiovascular disease. Independently, age and overweight/obesity before pregnancy had the largest contribution to hypertensive cases (29.2% and 36.5%, respectively). Overall, the combination of all risk factors considered was responsible for over two thirds of the hypertensive disorders in pregnancy among multiparae (PAF= 69.9%).

DISCUSSION

In this study of Portuguese puerperae, 5% of primiparae and 4% of multiparae had a hypertensive disorder in pregnancy. Approximately 50% of cases among primiparae and 70% among multiparae were attributable to the joint effect of pregnancies after 34 years of age, low education, family history of cardiovascular disease, prepregnancy overweight/obesity and excessive weight gain during pregnancy. The associations between the risk factors and hypertensive disorders during pregnancy were not different between primiparae and multiparae, but overall the impact was higher among multiparous reflecting the higher prevalence of risk factors among those women.

This is the first study that approaches the impact of several risk factors on hypertensive disorders in pregnancy in a large population-based cohort study. However, some limitations should be pointed. In our study, the prevalence of hypertensive disorders during pregnancy was lower than reported in other industrialized nations (4, 9, 10), and also slightly lower than the 5.6% previously described in a national survey for the Portuguese population (8) Since the authors reported no significant differences in prevalence across the country (8) we expected to find a similar prevalence. Despite the high proportion of participation in our cohort, it is possible that the refusals occurred mainly in cases with higher maternal and/or perinatal complications in the post-partum. Since hypertensive disorders are associated with increased risks of adverse outcomes (2, 3, 4) their prevalence may have been underestimated. The absence of objective measurements of blood pressure could also lead to this underestimation. However, 99.3% of the women had more than three prenatal visits and 85% attended the first appointment before 12 weeks of gestation (results not shown); thus, it is unlikely that a diagnosis of hypertension was missed. Additionally, considering a combined endpoint of hypertensive disorders during pregnancy is an advantage, because even if some cases of chronic hypertension were misclassified as gestational, due to the low awareness of hypertension in young ages (20) they were still identified as a hypertensive disorder in our sample.

The higher proportion of missing data among those with lower education, which is also associated with the outcome, raises the possibility of a selection bias. In this case, we may be underestimating the prevalence and, consequently, the association of hypertensive disorders in pregnancy among less educated women. Also, since pre-pregnancy weight was self-reported after delivery and weight tends to be underreported by women (21), the prevalence of overweight and obesity may be underestimated; if this information bias affected hypertensive women less than non-hypertensives, the differential effect could have contributed to an overestimation of the association. However, it is unlikely that such effect would explain an almost 4-fold increase in prevalence.

We observed a positive association between delivering a male newborn and hypertensive disorders during pregnancy among primiparae. Heterogeneous causes of gestational hypertensive disorders have been proposed, comprising both a background increased vascular risk possibly with a yet unidentified higher blood pressure beforehand and hypertension induced by disturbed perfusion of the placenta (22). In light of this causal model, the role of an immune response to paternal antigens in a de novo and transient hypertensive state could be expected to occur more often with male babies. The lack of association in multiparae may be explained by the sex of previous children, which was not assessed.

In contrast, the associations between all other risk factors and hypertensive disorders during pregnancy were not different between primiparae and multiparae. Although most previous research has focused on preeclampsia (23), the similarities in risk factors according to parity support that gestational hypertension and preeclampsia/eclampsia represent different stages of one pathological process, as previously proposed (24). Studies that analyzed these two entities separately described similar effects, though with stronger associations for preeclampsia (10, 25) which could be interpreted in light of spectrum effects related with the higher severity of this clinical entity. When analyzing chronic hypertension as the sole outcome, we found no significant differences regarding the associations with the risk factors considered in comparison with their association with gestational hypertension and preeclampsia/eclampsia (data not shown). It could be hypothesized that, even if a specific pregnancy-induced hypertension due to disturbed circulation in the placenta exists, as discussed above, the risk would be higher in women with more classical risk factors for high blood pressure.

Overall, 30.6% and 36.5% of hypertensive cases were attributable to overweight or obesity, among primiparae and multiparae, respectively. Our study confirms the association between excessive weight before and during pregnancy and the risk of hypertensive disorders in pregnancy (9, 10, 23, 26, 27). In a Danish study, overweight independently contributed 9.2% and obesity 11.0% for the occurrence of preeclampsia in primiparae (26). Similarly, among multiparae, overweight and obesity were responsible for 8.3% and 10.9% cases of preeclampsia, respectively. In a population of Latin women, those who gained more weight than recommended had a 3-fold increased risk of gestational hypertension and a 4-fold increased risk of preeclampsia (27). In our obstetric population, overweight, obesity and weight gain during pregnancy above recommended were common and had a considerable independent impact on hypertension in pregnancy. These metabolic conditions constitute main modifiable risk factors at the individual level, with a vast potential for prevention before and during pregnancy. Information regarding lifestyles, such as physical exercise and diet were not available in our cohort. However, BMI is a good surrogate for these lifestyles and is much more objective and easy to quantify reliably.

Socio-demographic and metabolic factors, as well as family history of cardiovascular disease were positively associated with hypertensive disorders during pregnancy in both primiparae and multiparae. Maternal age is an established risk factor for adverse outcomes in pregnancy, with all types of hypertensive disorders more frequent in mothers above 35 years old (28). Family history of hypertension is associated with a doubling risk of preeclampsia (29). Similarly, a first-degree family history of vascular risk increases the likelihood of developing preeclampsia and gestational hypertension (30). Despite some contradictory results, probably due to differences in exposure or outcome definition, prospective data from a large Dutch population-based cohort showed that women with low educational level were more likely to develop gestational hypertension (31) and preeclampsia (32) than women with higher educational level. The association between education and pregnancy hypertension may represent an early manifestation of the socioeconomic differences in cardiovascular morbidity and mortality in women (33). Despite similar associations, the impact of low education and family history of cardiovascular disease was approximately double in multiparous, while the effect of age increased from 5 to 29%, due to the higher proportion of pregnancies after 35 years of age in multiparae. We recognize that, regarding these risk factors, the potential for change is mainly theoretical or only effective at the global community level. However, a stricter control of overall risk could be attained if health education was sensitive to literacy (34).

In conclusion, the five risk factors explained a high proportion of hypertensive disorders during pregnancy. Despite the relatively low prevalence of these conditions, the severity of short- and long-term consequences for both mother and child emphasizes the importance of control of this outcome. Excessive weight before and during pregnancy, the most modifiable of all factors considered, had a very large contribution, particularly among primiparae. The substantial joint effect of the risk factors emphasizes the need to improve patient education and suggests that interventions focusing on these risk factors should be part of pre-conceptional and prenatal care in order to prevent maternal and perinatal complications.

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Table 1. Characteristics of the participants, according to parity.

	Overall	Parity		
		Primiparae	**Multiparae**	
	n (%)	n (%)	n (%)	p
Age (years)				
<25	1504 (21.6)	1164 (29.6)	340 (11.3)	
25-29	2119 (30.5)	1423 (36.2)	696 (23.0)	
30-34	2210 (31.8)	1059 (27.0)	1151 (38.1)	
≥35	1119 (16.1)	283 (7.2)	836 (27.6)	<0.001
Marital status				
Married/cohabiting	6512 (94.0)	3575 (91.3)	2937 (97.5)	
Single/divorced/widow	416 (6.0)	339 (8.7)	77 (2.6)	<0.001
Education (years)				
<5	493 (7.1)	110 (2.8)	383 (12.7)	
5-9	2883 (41.5)	1491 (38.0)	1392 (46.0)	
10-11	528 (7.6)	337 (8.6)	191 (6.3)	
≥12	3048 (43.8)	1991 (50.7)	1057 (35.0)	<0.001
Employment status				
Employed	4973 (71.7)	2904 (74.1)	2069 (68.6)	
Unemployed	1374 (19.8)	737 (18.8)	3637 (21.1)	
Housewife	385 (5.6)	104 (2.6)	281 (9.3)	
Other (student/retired)	205 (3.0)	175 (4.5)	30 (1.0)	<0.001
Income (€/month)				
<500	435 (6.4)	210 (5.5)	225 (7.6)	
500-1000	2002 (29.4)	1086 (28.2)	916 (30.8)	
1001-1500	1767 (25.9)	1052 (27.4)	715 (24.1)	
≥1501	1943 (28.5)	1101 (28.6)	842 (28.3)	
Does not know/ Prefers not to answer	669 (9.8)	395 (10.3)	274 (9.2)	<0.001
Family history of cardiovascular disease§				
No	5820 (83.7)	3408 (86.7)	2412 (79.8)	
Yes	1132 (16.3)	7521 (13.3)	611 (20.2)	0.001
Newborn's sex				
Male	3548 (51.0)	2030 (51.7)	1518 (50.2)	
Female	3404 (49.0)	1899 (48.3)	1505 (49.8)	0.230
Smoking status				
Never smoker	4303 (61.9)	2433 (61.9)	1870 (61.9)	
Current smoker	1855 (26.7)	1066 (27.1)	789 (26.1)	
Ex-smoker	794 (11.4)	430 (10.9)	364 (12.0)	0.289
Prepregnancy BMI (Kg/m^2)				
<25.0	4867 (70.0)	2943 (74.9)	1924 (63.6)	
25.0-29.9	1475 (21.2)	717 (18.2)	758 (25.1)	
≥30	610 (8.8)	269 (6.9)	341 (11.3)	<0.001
Weight gain during pregnancy¥				
As recommended	2536 (36.5)	1425 (36.3)	1111 (36.8)	
Bellow recommended	1796 (25.8)	916 (23.3)	880 (29.1)	
Above recommended	2620 (37.7)	1588 (40.4)	1032 (34.1)	<0.001

BMI, body mass index

§ Reporting at least one parent or sibling affected by stroke and/or myocardial infarction

¥ According to the Institute of Medicine recommendations (2009)

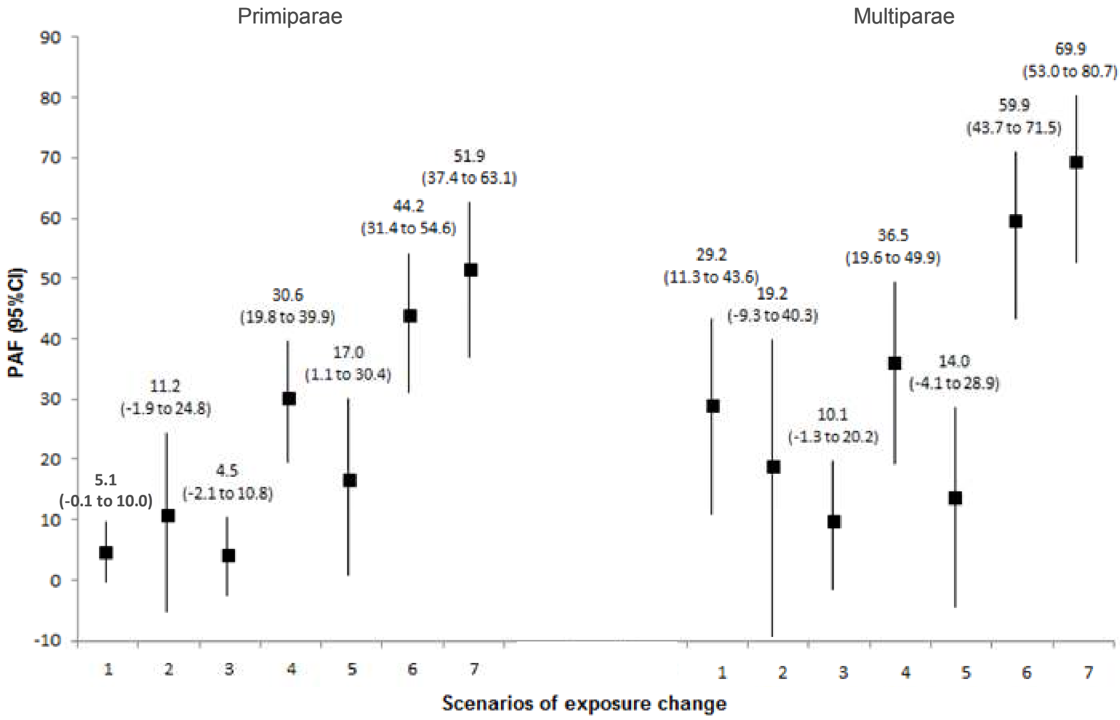
Note: In each variable, the total may not add to 6952 due to missing data

Table 2. Crude and adjusted prevalence ratios for the association between baseline characteristics of women, pregnancy and newborn, and pregnancy complicated by hypertension, among primiparous and multiparous women.

	Primiparae			Multiparae			
	n (%)	**Crude PR (95%CI)**	**Adjusted PR* (95%CI)**	**n (%)**	**Crude PR (95%CI)**	**Adjusted PR* (95%CI)**	***p* for interaction**
Age (years)							
<25	45 (3.9)	1	1	6 (1.8)	1	1	
25-29	73 (5.1)	1.33 (0.92-1.91)	1.23 (0.83-1.82)	21 (3.0)	1.71 (0.70-4.20)	1.51 (0.61-3.78)	
30-34	55 (5.2)	1.34 (0.91-1.97)	1.25 (0.82-1.91)	43 (3.7)	2.12 (0.91-4.93)	1.92 (0.81-4.59)	
≥ 35	22 (7.8)	2.01 (1.23-3.29)	1.82 (1.07-3.10)	55 (6.6)	3.73 (1.62-8.58)	2.98 (1.26-7.08)	0.268
Education (years)							
≥12	87 (4.4)	1	1	33 (3.1)	1	1	
10-11	15 (4.6)	1.02 (0.60-1.74)	1.05 (0.60-1.83)	7 (3.7)	1.17 (0.53-2.62)	1.15 (0.50-2.62)	
5-9	80 (5.4)	1.23 (0.91-1.65)	1.22 (0.88-1.70)	59 (4.2)	1.36 (0.89-2.06)	1.31 (0.85-2.04)	
<5	13 (11.8)	2.70 (1.56-4.69)	2.04 (1.12-3.70)	26 (6.8)	2.17 (1.32-3.59)	1.53 (0.90-2.61)	0.820
Family history of cardiovascular disease							
No	159 (4.7)	1	1	86 (3.6)	1	1	
Yes	36 (6.9)	1.48 (1.04-2.10)	1.33 (0.92-1.91)	39 (6.4)	1.79 (1.24-2.59)	1.48 (1.00-2.17)	0.589
Newborn's sex							
Male	118 (5.8)	1	1	65 (4.3)	1	1	
Female	77 (4.1)	0.70 (0.53-0.92)	0.68 (0.51-0.91)	60 (4.0)	0.93 (0.66-1.31)	0.92 (0.55-1.49)	0.185
Smoking status							
Never smoker	127 (5.2)	1	1	88 (4.7)	1	1	
Current smoker	41 (3.9)	0.74 (0.52-1.04)	0.77 (0.53-1.10)	26 (3.3)	0.70 (0.46-1.08)	0.82 (0.53-1.29)	
Ex-smoker	27 (6.3)	1.20 (0.80-1.80)	1.21 (0.80-1.84)	11 (8.8)	0.64 (0.35-1.19)	0.71 (0.37-1.33)	0.327
Prepregnancy BMI (Kg/m^2)							
<25.0	97 (3.3)	1	1	46 (2.4)	1	1	
25.0-29.9	54 (7.5)	2.29 (1.65-3.16)	1.94 (1.37-2.76)	40 (5.3)	2.21 (1.46-3.34)	1.78 (1.14-2.77)	
≥30	44 (16.4)	4.96 (3.55-6.93)	4.16 (2.87-6.03)	39 (11.4)	4.78 (3.17-7.21)	3.61 (2.29-5.69)	0.704
Weight gain during pregnancy[¥]							
As recommended	53 (3.7)	1	1	38 (3.4)	1	1	
Bellow recommended	36 (3.9)	1.06 (0.70-1.60)	1.07 (0.70-1.63)	27 (3.1)	0.90 (0.55-1.46)	0.91 (0.55-1.49)	
Above recommended	106 (6.7)	1.79 (1.30-2.48)	1.46 (1.04-2.05)	60 (5.8)	1.70 (1.14-2.53)	1.41 (0.93-2.14)	0.841

95%CI, 95% confidence interval; BMI, body mass index; PR, prevalence ratio
* Adjusted for all the variables in the table
¥According to the Institute of Medicine recommendations (2009)

Figure 1. Population attributable fractions (PAF) for pregnancy complicated by hypertension, according to several scenarios of exposure change for prevention, among primiparous and multiparous women. All estimates are based on adjusted prevalence ratios from the models presented in Table 2.



(1) prevention of pregnancies in women after 34 years of age (shift to 30-34 years old);
(2) prevention of pregnancies in women with education below 12 years (shift to ≥12 years);
(3) prevention of pregnancies in women with family history of cardiovascular disease;
(4) prevention of pregnancies in overweight or obese women (shift to normal weight);
(5) prevention of pregnancies in women with weight gain during pregnancy above recommended (shift to weight gain as recommended);
(6) prevention of pregnancies in women after 34 years old (shift to 30-34 years old), with overweight or obesity (shift to normal weight) and weight gain during pregnancy above recommended (shift to weight gain as recommended).
(7) prevention of pregnancies in women after 34 years old (shift to 30-34 years old), with education below 12 years (shift to ≥12 years), family history of cardiovascular disease, overweight or obesity (shift to normal weight) and weight gain during pregnancy above recommended (shift to weight gain as recommended).

PAPER IV

Alves E, Azevedo A, Rodrigues T, Correia S, Santos AC, Barros H.

Fetal sex modifies the effect of gestational hypertensive disorders on blood pressure of mothers and children at 4 years.

[submitted]

Fetal sex modifies the effect of gestational hypertensive disorders on blood pressure of mothers and children at 4 years

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ABSTRACT

A putative association between gestational hypertensive disorders and higher blood pressure in mothers and offspring later in life is of concern. The aim of this study was to assess to which extent gestational hypertensive disorders lead to higher blood pressure in women and their offspring 4 years after birth, and to assess the effect of fetal sex on these consequences. A birth cohort was assembled at public maternities of Porto, Portugal in 2005-2006 and reevaluated an average of 4 years after delivery. In the current analysis, 2877 primiparous women with singletons and no previous chronic hypertension and 2460 children were included. Gestational hypertensive disorders included gestational hypertension and preeclampsia/eclampsia. At follow-up, systolic and diastolic blood pressure were measured. Overall, the 4-year risk of hypertension in women affected by gestational hypertensive disorders was almost 6 times higher among mothers who delivered a girl, and 3 times higher among those who delivered a boy. Systolic and diastolic blood pressure at 4 years were 2.3 and 3.1 mmHg significantly higher in boys born of mothers with hypertensive disorders of pregnancy, while no effect was detected among girls. The differential effects observed by child's sex support the hypothesis of heterogeneous causes of hypertension in pregnancy and that boys live dangerously in the womb. The high incidence of chronic hypertension in women and the higher blood pressure in their offspring as early as 4 years after birth emphasizes the short period after delivery as critical to develop and promote preventive strategies.

Key words: Blood Pressure; Child; Cohort Studies; Hypertension, Pregnancy-Induced; Incidence.

INTRODUCTION

Gestational hypertension, preeclampsia and eclampsia are major complications of pregnancy, associated with increased risks of adverse maternal and perinatal outcomes.[1-3] Although these complications are considered transient, an association between gestational hypertensive disorders and hypertension, fatal and non-fatal ischaemic heart disease, stroke, and venous thromboembolism in mothers[4, 5] and higher blood pressure in offspring later in life[6] has been documented.

The pathophysiological mechanisms underlying the association between gestational hypertensive disorders and high blood pressure in women and their children remain incompletely understood.[7, 8] In women, hypertensive disorders of pregnancy and chronic hypertension share pathways initiated by similar risk factors, such as older age and higher body mass index.[9-11] Additionally, abnormal placentation resulting in reduced perfusion may induce de novo hypertension in the pregnant women, possibly related with an immunologically mediated mechanism for which enhanced exposure to paternal antigens is protective.[12] Any of these complications may in turn induce long-term metabolic and vascular abnormalities that increase the overall risk for cardiovascular disease later in life.[13] Intrauterine growth restriction, due to mother's cardiometabolic abnormalities during pregnancy and placental dysfunction, may also increase the risk of vascular dysfunction in the offspring.[14-16] A meta-analysis reported higher systolic and diastolic blood pressure in the offspring after preeclampsia, but most studies involved small samples and focused on school aged children and adolescents.[6]

In the womb, boys have a different placental growth which puts them at a higher risk of becoming undernourished particularly because their larger size increases nutritional needs. This milieu could increase the vulnerability of boys to consequences of metabolic and vascular derangements of the mother during pregnancy.[17]

Most studies that reported an increased risk of later hypertension and cardiovascular outcomes after preeclampsia were retrospective and focus on the occurrence of the outcomes a long time after pregnancy,[4] limiting the ability to study the time frame for development of such outcomes. An association with chronic hypertension shortly after delivery would argue in favour of the continuous nature of the pathological process, once long term effects are know.

The aim of this study was to assess the extent to which gestational hypertensive disorders lead to higher blood pressure in women and their offspring as early as 4 years after birth, and to assess the effect of fetal sex on these consequences in a prospectively followed birth cohort.

METHODS

Study design

This study is based on the birth cohort Geração XXI, assembled between 2005 and 2006 at 5 public maternity units covering the metropolitan area of Porto, Portugal. All the maternities corresponded to units with differentiated perinatal support, and were included in a general hospital, except one. Of the invited mothers 91.4% accepted to participate. A total of 8495 mothers, who gave birth to 8647 infants, were enrolled in the cohort. At 4 years of the child's age, the cohort was re-evaluated. Mothers were invited to participate in a parallel study on women's cardiovascular health, and 67.3% attended a face-to-face interview and physical examination at the study site. An additional 16.7% provided data by telephone interview, but were not included in the current analysis due to the lack of blood pressure measurement.

We excluded 313 participants who had been recruited and evaluated during the first trimester of pregnancy to address specific objectives[18] because the diagnosis and management could be expected to be different in these cases who had prenatal care at the hospital and 3461 multiparous women. Among the primiparae, we excluded 91 with multiple gestations, 85 with chronic hypertension before pregnancy and 39 with missing data on gestational hypertensive disorders. From the remaining, 3070 participated in the follow-up evaluation at the study site. After exclusion of 139 women who were pregnant at the follow-up visit and 54 with missing data on key variables, 2877 women were available for the current analysis. From those, 99 had a diagnosis of gestational hypertensive disorders during the index pregnancy.

Blood pressure measurement in children only started in September 2009. Thus, data on blood pressure among children was available for 2460 consecutively recruited cohort members. Among these, 86 were born from mothers who developed gestational hypertensive disorders (Figure 1).

Among the 4506 eligible mothers, those who attended the follow-up re-evaluation were older [mean (standard deviation (SD)): 28.4 (5.4) vs. 26.4 (5.0) years, p<0.001], had a higher socioeconomic position (schooling >12 years: 31.6% vs. 20.3%, p<0.001 and income >1500€/month: 31.6% vs. 20.3%, p<0.001), and were more likely to live with a partner (92.5% vs. 88.6%, p<0.001) than those who did not participate in the re-evaluation, but there were no significant differences between the two groups regarding the prevalence of gestational hypertensive disorders (3.4% vs. 3.3%, p=0.811). The proportion of low birth weight (8.4% vs. 7.2%, p=0.450) and preterm newborns (11.0% vs. 10.2%, p=0.457) was not significantly different among children who participated and those who missed the follow-up reevaluation, and there were no differences regarding the sex of the child (male sex: 51.3% vs. 52.2%, p=0.566).

Baseline evaluation

At baseline, data on demographic and socioeconomic characteristics, lifestyles, reproductive history and anthropometrics were collected within 72 hours after delivery, during the hospital stay, in a face-to-face interview conducted by trained interviewers using structured questionnaires. Clinical records were also reviewed at birth to retrieve data on complications of pregnancy, birth weight and gestational age of the newborn. Personal history of hypertension was considered present when participants recalled a medical diagnosis of this condition and/or reported antihypertensive drug therapy prescribed specifically for hypertension, before the current pregnancy.

Prepregnancy weight was recalled and recorded to the nearest 0.1 Kg and height was measured by the interviewers to the nearest 0.1 cm. When measurement was not possible, height was self-reported as registered in the identity card. The participants' body mass index (BMI) was categorized according to the standard World Health Organization definition.[19] Weight gain during pregnancy was calculated as the difference between the mother's reported weight before delivery and prepregnancy weight, and was categorized according to the Institute of Medicine recommendation.[20]

Gestational hypertensive disorders were defined by the presence of gestational hypertension or preeclampsia/eclampsia, always considered only when explicitly recorded on obstetrical records as a diagnosis during the index pregnancy. Gestational hypertension was only considered in the absence of a previous diagnosis of chronic hypertension.

Newborn’s birth weight was registered to the nearest 1g and gestational age to the nearest 0.1 weeks. Classes of the sex specific adequate birth weight for gestational age were defined according to the Canadian fetal growth standard.[21]

Missing data on the questionnaires at baseline were recovered through the review of obstetrical records. The agreement between data collected by questionnaire and abstracted from medical records was good for personal history of hypertension, weight and height, and there was very low inter-rater variability between two independent abstractors.[22]

Follow-up evaluation

At the cohort’s follow-up, after a median [interquartile range (IQR)] follow-up time of 50 (48-54) months, data were collected by trained interviewers using structured questionnaires, regarding the health of the mother and her child. For the sake of simplicity, 4 years of age will be assumed hereafter. Socioeconomic characteristics, personal and family history of disease, lifestyles and obstetric history of the mother were self-reported. Family history of hypertension was considered present when the women reported to have at least one parent or sibling affected by this condition. Current smokers included both daily and occasional smokers. Ex-smokers did not smoke for at least 6 months.

Anthropometrics of mothers and children were measured with the participants wearing light clothing and no footwear. Weight was measured using a digital scale to the nearest 0.1 kg and height measured to the nearest 0.1 cm. The mothers’ BMI was categorized according to the standard World Health Organization definition.[19] Regarding the children, height and BMI was classified according to the age specific percentiles estimated by the United States Center for Disease Control and Prevention.[23]

Blood pressure was measured on a single occasion by non-physician trained interviewers. For the mother, two measurements of blood pressure separated by at least 5 minutes were taken with an automatic upper arm blood pressure monitor (OMRON M6 comfort (HEM-7000-E)) after 10-minute rest, on the dominant upper arm resting at the heart level. The mean was calculated and when the difference was larger than 5 mmHg for systolic or diastolic blood pressure a third measurement was taken and the mean of the 2 closest values was considered. Arterial hypertension was defined as systolic and/or diastolic blood pressure ≥140/90 mmHg and/or self-reported antihypertensive drug therapy prescribed specifically for hypertension. Blood pressure of the child was measured with an aneroid sphygmomanometer (Erka Vario DeskModel), with a proper size cuff. Korotkoff phases I and V were used to indicate systolic and diastolic blood pressure. Blood pressure was measured twice, in a seated position with the antecubital fossa supported at heart level, after 5 minutes of rest. The two measurements of blood pressure were separated by at least 5 minutes and when the difference was larger than 5 mmHg for systolic or diastolic blood pressure a third measurement was taken and the mean of the 2 closest values was considered. Systolic and diastolic blood pressure were classified according to the criteria of the American Academy of Pediatrics24 and hypertension was considered as systolic and/or diastolic blood pressure ≥95th percentile for sex, age and height.[21]

Statistical analysis

Statistical analysis was performed using the software Stata 9.0 (College Station, TX, 2005). To estimate adjusted mean differences in systolic and diastolic blood pressure, for mothers and offspring, according to gestational hypertensive disorders, multiple linear regression was used. Women under anti-hypertensive drug therapy were excluded from this analysis (n=49). No child was under anti-hypertensive drug therapy. The association between gestational hypertensive disorders and the mother's incidence of hypertension 4 years after giving birth was estimated by crude and adjusted incidence rate ratios (IRR) and respective 95% confidence intervals (95% CI), using Poisson regression. Both for children and mothers, separate analyses were performed for girls and boys, since an interaction term between fetal sex and gestational hypertensive disorders was statistically significant at the 5% level.

Ethics

The study protocol was approved by the Ethics Committee of Hospital de São João and by the Portuguese Authority of Data Protection. Written informed consent was obtained from all the mothers and children, who gave it through their legal representative.

RESULTS

Characteristics of the study sample

There were no significant differences in socio-demographic characteristics, the number of subsequent births and the smoking status 4 years after delivery between participants with and without gestational hypertensive disorders (Table 1). Mothers who developed those conditions during pregnancy were more likely to report a family history of hypertension, more often gained more weight during pregnancy than recommended and remained more likely to be overweight and obese 4 years after giving birth. The proportion of women who delivered a small for gestational age newborn was higher among those who developed gestational hypertension or preeclampsia/eclampsia during the index pregnancy.

Outcomes of the mother

In this sample of Portuguese primiparae, approximately 4 years after delivery, the mean (SD) systolic and diastolic blood pressure were significantly higher in mothers with gestational hypertensive disorders who delivered a girl (120.7 (15.7) vs. 106.4 (11.1) mmHg; $p<0.001$, and 84.7 (12.5) vs. 73.1 (10.8) mmHg; $p<0.001$, respectively), and among those who delivered a boy (113.5 (12.5) vs. 105.6 (10.8) mmHg; $p<0.001$, and 79.5 (9.6) vs. 72.9 (9.0) mmHg; $p<0.001$, respectively). The 4-year crude incidence rate of hypertension per 1000 person-years was much higher in women with gestational hypertension or preeclampsia/eclampsia during pregnancy who gave birth to a female (114.6 vs. 12.2, $p<0.001$) or to a male newborn (52.7 vs. 11.6, $p<0.001$) than normotensive women (Figure 2). After adjustment for age, family history of hypertension, BMI at follow-up and smoking status, gestational hypertensive disorders were significantly associated with an increase of systolic blood pressure of 11 and 6 mmHg for women who delivered a female and a male newborn, respectively (p for interaction=0.018). Similarly, gestational hypertension or preeclampsia/eclampsia were significantly associated with an approximately 8 and 5 mmHg higher diastolic blood pressure in mothers of girls and in mothers of boys, respectively (p for interaction=0.033). Four years after delivery, gestational hypertensive disorders were significantly associated with an almost 6-fold increase in the incidence of hypertension among mothers who delivered a girl, and with a 3-fold increase in those who delivered a boy (p for interaction=0.265) (Table 2).

Outcomes of the offspring

An average of 4 years after birth, the incidence rate of hypertension per 1000 person-years was higher for both girls (50.0; vs. 32.0, p=0.218) and boys (39.1 vs. 28.0, p=0.334) born of women with gestational hypertension or preeclampsia/eclampsia, when compared with those born of normotensive women (Figure 2). After adjustment for classes of birth weight for gestational age, current age and height, gestational hypertensive disorders were associated with a non-significant increase of approximately 2 mmHg on systolic and 0.5 mmHg on diastolic blood pressure, at age 4 among girls. Among boys, gestational hypertensive disorders remained significantly associated with a 2 and 3 mmHg higher systolic and diastolic blood pressure after adjustment (Table 3).

DISCUSSION

In this sample of Portuguese primiparous women, the development of gestational hypertensive disorders was significantly associated with higher systolic and diastolic blood pressure, an average of 4 years after giving birth. Overall, the 4-year risk of hypertension in women who developed those conditions during pregnancy was almost 6 times higher among mothers who delivered a girl, and 3 times higher among those who delivered a boy. Systolic and diastolic blood pressure at 4 years were higher in boys born of mothers with hypertensive disorders of pregnancy, while no effect was detected among girls.

The increase of more than 5 mmHg in both systolic and diastolic blood pressure, among mothers with gestational hypertensive disorders during the index pregnancy, represents a substantial shift to the right in blood pressure distribution. Similar estimates were found in a case-control study, with a mean increase of 7.3mmHg and 4.7mmHg in systolic and diastolic blood pressure, after a average period of 7.8 years from the index pregnancy.[25] In the long term, at least preeclampsia is associated with a 4-fold increased risk of a later diagnosis of hypertension, with over 50% of women with preeclampsia developing chronic hypertension after 14 years.4 Recently, a prospective study in which women were interviewed by telephone 6 to 13 months after delivery reported a strong and positive association between preeclampsia and self-reported chronic hypertension.[26] Our study adds the prospective follow-up with objective measurement of blood pressure of mothers of a population-based birth cohort, showing that as soon as 4 years after delivery, the risk of chronic hypertension was already significantly higher in women with gestational hypertensive disorders. Taken together and considering the overlap of determinants of chronic and gestational hypertensive disorders, these findings question the transient nature of this hypertension. Evidence of sub-clinical maternal endothelial dysfunction after a pregnancy affected by preeclampsia but before the onset of clinical cardiovascular disease supports that a continuous uninterrupted pathological process develops.[13, 27] Heterogenous causes of gestational hypertensive disorders have been proposed, comprising both a background increased vascular risk possibly with a yet unidentified higher blood pressure beforehand and hypertension induced by disturbed perfusion of the placenta.[12] In light of this causal model, the role of an immune response to paternal antigens in a de novo and transient hypertensive state could be expected to occur more often with male babies, resulting in a smaller effect of hypertension in pregnancy on later blood pressure of the mother when the fetus is male, while hypertension in pregnancy with a female fetus might more often only represent the revelation of a previous higher vascular risk.

Despite controversial,[28] aggregation of gestational hypertension and preeclampsia/eclampsia into a composite endpoint is an advantage, assuming the two entities could represent different stages of one pathological process and reducing the possibility of misclassification between more specific outcomes. Moreover, studies that analyzed gestational hypertension and preeclampsia described similar associations with chronic hypertension later in life.[29]

It has been argued that women with uncomplicated pregnancies have a lower rate of later cardiovascular disease than the general population and are therefore not an appropriate reference category.[12] Thus, we compared the 4-year incidence of hypertension of our unexposed study participants with that from a general population to assess a putative differential selection in exposed and unexposed. In a representative sample of the adult population of Porto, assembled from 1999 to 2003,[30] the 4-year crude incidence rate of hypertension in women aged below 40 years (median age similar to the one of our cohort) was 22.3 per 1000 person-years (data not shown). This rate is considerably higher than that of women with uncomplicated pregnancies in our current sample, confirming the expected healthier average profile of women who achieved successful uncomplicated pregnancies, but it is still much lower than the one estimated for those with gestational hypertensive disorders. We restricted our analysis to primiparae in order to remove the possible effect of a gestational hypertensive disorder occurring in a previous pregnancy. Additionally, achieving an additional successful pregnancy is expected to be associated with a lower likelihood of hypertension, which would introduce selection bias.

In a meta-analysis considering 10 studies6 of offspring between 6 and 19 years old, those born from women with preeclampsia had an increase of 2.3 mmHg and 1.7mmHg in systolic and diastolic blood pressure when compared with offspring from normotensive pregnancies.[6] Our study shows that this increase in systolic and diastolic blood pressure is already observed in preschool children. Regarding systolic blood pressure, a higher mean was described among 3 to 6-year-old children of mothers with elevated blood pressure during pregnancy than that of children whose mothers did not have hypertension in pregnancy.[31] Despite the lack of significance, the point estimates of systolic and diastolic blood pressure remained higher in the offspring female of mothers with gestational hypertensive disorders. We found a statistical significant increase of 2.3 and 3.1 mmHg in systolic and diastolic blood pressure of boys born from mothers who developed gestational hypertension or preeclampsia/eclampsia. This association was not explained after adjustment for systolic and diastolic blood pressure of the mother (data not shown). A stronger association between gestational hypertensive disorders and diastolic blood pressure in boys had already been described at 6 years of age, suggesting a possible sex-specific effect of preeclampsia.[32] In fact, male sex has been described as an independent risk factor for adverse pregnancy outcome.[33] In the womb, boys grow more rapidly and invest less in placental growth, which puts them at greater risk of becoming undernourished. During fetal development the kidney has low priority because the placenta performs most of its functions. In case of impaired capacity of the placenta to transport nutrients, boys exchange more easily renal development than girls to protect more important organs, which will lead to a lifelong reduction in the number of nephrons.[17] Sex differences are observed in the placenta at multiple levels, from epigenetic modification of DNA, through gene expression to functional changes in the way in which the placenta responds to hormones and transports nutrients. It is clear that these changes become established in the placenta via mechanisms such as DNA methylation, and are not simply due to direct effects of fetal sex hormones.[34]

A major strength of this study is the prospective assessment, relying on objective and standardized measurements, of hypertension risk in a short period of time after birth, at a point when women and children may be in a time window for more effective prevention. However, some limitations should be acknowledged. Despite the large size of the cohort, the number of women with gestational hypertensive disorders was relatively small. However, it was enough to demonstrate a differential effect by sex of the child. The absence of objective measurements of the mother's blood pressure before and during pregnancy, together with the low awareness of chronic hypertension in young women[35] can lead to an erroneous diagnosis of gestational hypertension or preeclampsia/eclampsia and, consequently, an overestimation of the prevalence of these pathologies. In this case, this would lead to an overestimation of the incidence of chronic hypertension, 4 years after delivery. However, since 75% of the pregnancies were planned and 85% of women had the first prenatal visit before 12 weeks of pregnancy (data not shown), it is unlikely that a diagnosis of chronic hypertension before pregnancy was underreported or undetected. Also, it is possible that the refusals of participation at baseline occurred mainly in cases with higher maternal and/or perinatal complications in the post-partum period, namely when the newborn was admitted to a neonatal intensive care unit. Since hypertensive disorders in pregnancy are associated with increased risks of adverse maternal and fetal outcomes,[1-3] the cases with worst outcomes may have been lost. Despite the high proportion of participation at follow-up, mothers who attended the follow-up re-evaluation were older, more educated and more likely to live with a partner. However, we found similar proportions of preeclampsia and gestational hypertension between women who participated and those lost to follow-up, suggesting that the associations examined should not be markedly different in those lost to follow-up.

In the present study, hypertension in children was defined as systolic and/or diastolic blood pressure above the 95th percentile measured in only one moment, while the American

Academy of Pediatrics'[24] recommends the measurement of blood pressure in 3 or more occasions. It was previously described that the proportion of children with elevated blood pressure based on one visit was 4 to 5 times higher than based on three measurements taken at few-week intervals.[36, 37] Therefore, we may be overestimating children's usual blood pressure as well as the incidence rate of hypertension in both exposed and unexposed groups. However, we do not expect that this overestimation occurred differentially by gestational hypertensive disorders during pregnancy and, in the worst scenario, this would result in underestimating the reported associations.

PERSPECTIVES

Four years after a single pregnancy complicated by gestational hypertensive disorders in primiparae, mothers already have higher blood pressure and more frequently have chronic hypertension, and this effect is stronger when the fetus was female. The effects on offspring's blood pressure are evident only among male sex children, supporting the thesis that boys live dangerously in the womb. Such short-term outcomes reinforce the importance of effective preventive strategies to control cardiovascular risk beginning immediately after birth, possibly by extending post-partum care and integrating it with children's health care plan.

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Table1. Characteristics of primiparae with single pregnancies and no previous chronic hypertension, and their children, according to sex of the offspring and the occurrence of gestational hypertensive disorders.

	Girls			Boys		
	GHD[a]	Normotensive	*p*	GHD[a]	Normotensive	*p*
Mothers	**n=39**	**n=1359**		**n=60**	**n=1419**	
Age at baseline (years), mean (SD)	29.2 (5.9)	28.4 (5.1)	0.391	28.9 (4.9)	28.4 (5.0)	0.405
Education (years), median (IQR)	10 (7-12)	12 (9-16)	0.082	12 (9-16)	12 (9-16)	0.061
Family history of hypertension, n (%)	27 (69.2)	674 (49.6)	0.016	38 (63.3)	687 (48.4)	0.024
Smoking at 4 years, n (%)			0.231			0.195
Never smoker	24 (61.5)	819 (60.3)		42 (70.0)	835 (59.0)	
Current smoker	6 (15.4)	335 (24.6)		10 (16.7)	371 (26.2)	
Ex-smoker	9 (23.1)	205 (15.1)		8 (13.3)	211 (14.9)	
Weight gain during pregnancy[b], n (%)			0.151			0.152
Below recommended	7 (21.2)	327 (26.9)		10 (19.6)	338 (26.5)	
As recommended	9 (27.3)	461 (37.9)		17 (33.3)	503 (39.5)	
Above recommended	17 (51.5)	427 (35.1)		24 (47.1)	434 (34.0)	
BMI at 4 years (kg/m^2), n (%)			<0.001			0.002
<24.9	5 (12.8)	721 (53.1)		19 (31.7)	747 (52.6)	
25.0-29.9	15 (38.5)	393 (28.9)		22 (36.7)	428 (30.2)	
≥30.0	19 (48.7)	245 (18.0)		19 (31.7)	244 (17.2)	
At least one birth after the index birth, n (%)	9 (23.1)	272 (20.0)	0.638	9 (15.0)	309 (21.8)	0.210
Children	**n=35**	**n=1151**		**n=51**	**n=1223**	
Birth weight for gestational age[c], n (%)			0.010			0.369
Small (<10th percentile)	10 (28.6)	180 (15.6)		12 (23.5)	197 (16.1)	
Adequate (10th - 90 percentile)	22 (62.9)	940 (81.7)		38 (74.5)	1004 (82.1)	
Large (≥90th percentile)	3 (8.6)	31 (2.7)		1 (2.0)	22 (1.8)	
Age at follow-up (months), median (IQR)	51 (50-55)	53 (50-59)	0.190	53 (50-58)	51 (50-55)	0.377

BMI, body mass index; GHD, gestational hypertensive disorders; IQR, interquartile range; SD, standard deviation
[a] Gestational hypertension and/or preeclampsia/eclampsia
[b] According to the Institute of Medicine classification (2009)
[c] According to Canadian fetal growth standard

Table 2. Mean difference (β) of systolic and diastolic blood pressure (mmHg), and incidence rate ratio (IRR) of hypertension, an average of 4 years after delivery, for mothers who delivered girls (n=1398) and boys (n=1479), according to gestational hypertensive disorders. Women under antihypertensive drug therapy were excluded from the analysis of mean blood pressure.

	Systolic blood pressure β (95% CI)		**Diastolic blood pressure β (95% CI)**		**Hypertension IRR (95% CI)**	
	Crude	Adjusted[a]	Crude	Adjusted[a]	Crude	Adjusted[a]
Mothers who delivered girls						
Gestational hypertensive disorders (yes vs. no)	14.89 (10.93 to 18.85)	12.34 (8.57 to 16.11)	11.55 (8.61 to 14.49)	8.52 (5.73 to 11.30)	12.07 (8.82 to 15.32)	9.89 (6.78 to 12.89)
Mothers who delivered boys						
Gestational hypertensive disorders (yes vs. no)	7.71 (4.85 to 10.57)	6.16 (3.37 to 8.94)	6.54 (4.22 to 8.86)	4.80 (2.58 to 7.02)	6.20 (3.82 to 8.58)	4.62 (2.35 to 6.89)

95%CI, 95% confidence interval; β, linear regression coefficient; IRR, incidence rate ratio

[a] Adjusted for mothers' age at birth, family history of hypertension, body mass index (BMI) at follow-up and smoking status at follow-up

Table 3. Mean difference (β) of systolic and diastolic blood pressure (mmHg) for girls (n=1186) and boys (n=1274), at 4 years, according to gestational hypertensive disorders.

	Systolic blood pressure β (95% CI)		Diastolic blood pressure β (95% CI)	
	Crude	Adjusted[a]	Crude	Adjusted[a]
Girls				
Gestational hypertensive disorders (yes *vs.* no)	2.36 (-0.45 to 5.17)	1.93 (-0.71 to 4.56)	0.56 (-2.19 to 3.32)	0.48 (-2.20 to 3.17)
Boys				
Gestational hypertensive disorders (yes *vs.* no)	2.60 (0.28 to 4.92)	2.29 (0.10 to 4.48)	3.10 (0.83 to 5.38)	3.11 (0.87 to 5.34)

95%CI, 95% confidence interval; β, linear regression coefficient.

[a] Adjusted for childs' percentile of birth weight for gestational age classes (according to the Canadian fetal growth standard), age (continuous) and height percentile classes at follow-up (according to the CDC criteria)

Figure 1. Flowchart for study sample definition.

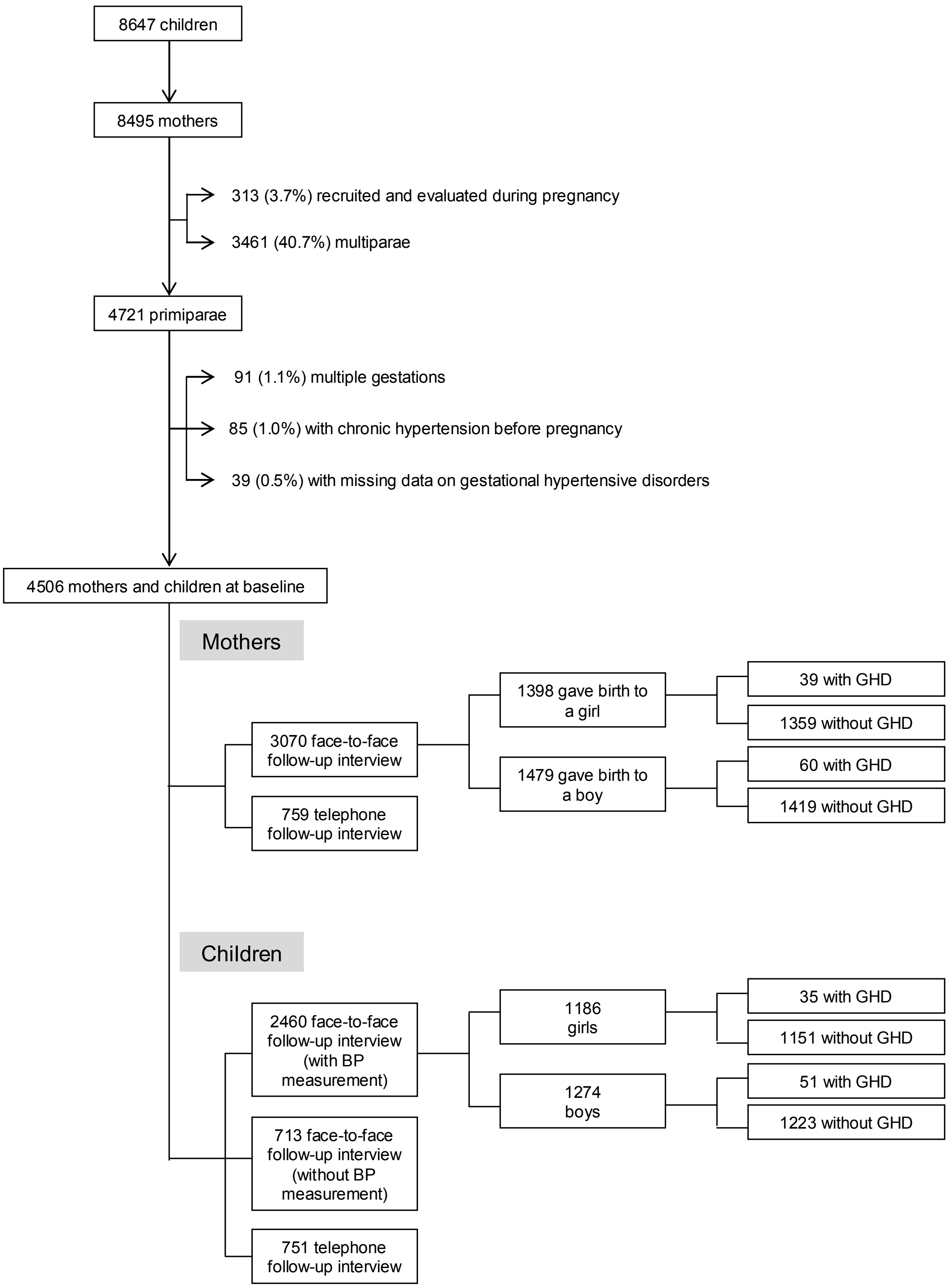
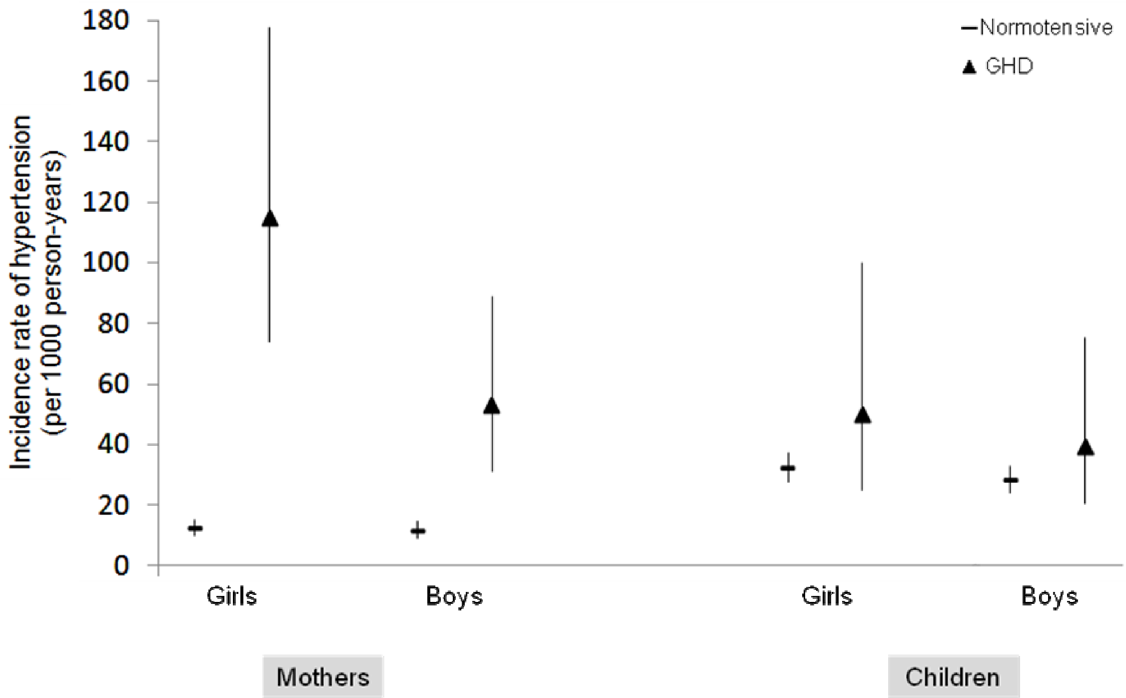


Figure 2. Incidence rates of hypertension among mothers and children, according to the occurrence of gestational hypertensive disorders (GHD) in the index pregnancy and child's sex. The symbols represent the incidence rate point estimates and vertical lines the 95% confidence intervals. Hypertension was defined as blood pressure ≥140/90 mmHg and/or or reported antihypertensive drug therapy prescribed specifically for hypertension in women and as systolic and/or diastolic blood pressure ≥95th percentile for sex, age and height in children.



PAPER V

Alves E, Azevedo A, Correia S, Barros H.
Pregnancy and afterwards: opportunities to modify the course of the smoking epidemic in a female population at high risk.
[submitted]

Pregnancy and afterwards: opportunities to modify the course of the smoking epidemic in a female population at high risk

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ABSTRACT

INTRODUCTION: Pregnancy is a privileged opportunity in women's life to promote tobacco cessation but information is lacking regarding the long term effect of pregnancy related behavioural changes. We assessed the smoking cessation during pregnancy and its sustainability 4 years after delivery.

METHODS: A birth cohort was assembled at public maternities of Porto, Portugal in 2005-2006 and reevaluated an average of 4 years after delivery. In the current analysis, 5420 mothers were included. Smoking status at baseline and at follow-up was ascertained by interview. Adjusted prevalence ratios (PR) and 95% confidence intervals (95%CI) were computed using robust Poisson regression.

RESULTS: During pregnancy, almost half of smokers stopped and approximately 40% reduced consumption. Cigarette smoking cessation during pregnancy was more likely among primigestae, those living with a partner, with higher educational levels, overweight or obese, with adequate prenatal care, who began smoking later and who smoked less. Four years after delivery, only a third of the women who ceased smoking during pregnancy remained non-smokers. They were more likely older, primigestae, living with a partner at 4 years, with lower tobacco consumption before pregnancy, who breastfed ≥52 weeks, got pregnant again after the index pregnancy and whose child had a medical diagnosis of asthma and/or rhinitis.

CONCLUSIONS: Most smokers stopped or decreased consumption during pregnancy, but this behavioural change showed little long-term impact on their smoking trajectory.

Keywords: Cohort studies; Pregnancy; Recurrence; Smoking Cessation.

INTRODUCTION

Worldwide, smoking is the single most frequent preventable cause of death (WHO, 2011) and smoking cessation reduces the long-term risk of cancer and cardiovascular diseases (Kenfield, Stampfer, Rosner, & Colditz, 2008; Teo et al., 2006).

Cigarette smoking during pregnancy is associated with increased risks of adverse maternal and fetal outcomes such as ectopic pregnancy, placental abruption, placenta previa (Castles, Adams, Melvin, Kelsch, & Boulton, 1999), small for gestational age babies (Rodrigues & Barros, 2007), low birth weight and preterm birth (Jaddoe et al., 2008). Mothers tend to be strongly motivated to protect the health of the unborn baby and there is important social pressure to quit smoking during pregnancy (Edwards & Sims-Jones, 1998; Ripley-Moffitt et al., 2008). However, it is not clear whether, or to what extent, smoking cessation during pregnancy persists long after pregnancy, since studies have focused on the sustainability of smoking cessation only in the initial postpartum period, shortly after birth (Carmichael & Ahluwalia, 2000; Colman & Joyce, 2003; Polanska, Hanke, Sobala, Lowe, & Jaakkola, 2011).

In Portugal, smoking remains more frequent among men but its prevalence is increasing in women (Fraga et al., 2005). The prevalence is higher among younger and more educated women placing Portugal at a relatively early stage of the epidemic compared to other Western European countries (Precioso et al., 2009; Santos & Barros, 2004). Therefore, it is expected that, in the near future, the burden of tobacco-related illness will increase substantially (Lopez, Collishaw, & Piha, 1994). In order to guide the development of preventive strategies to reduce the future burden of smoking and promote the health of children and families, it is important not only to describe exposure to smoking in pregnancy and postpartum but also to identify modifiable determinants of such behaviours.

In this study, our objective was to assess the frequency and determinants of maternal smoking cessation during pregnancy and of the sustainability of smoking cessation 4 years after delivery.

METHODS

Study design and sample characteristics

This study is based on the birth cohort Geração XXI, which has been described previously (Alves, Correia, Barros, & Azevedo, 2012). Briefly, the cohort was assembled between 2005 and 2006 at 5 public maternity units covering the metropolitan area of Porto, Portugal. A total of 8495 mothers (91.4% of those invited), who gave birth to 8647 infants, were enrolled in the cohort. An average of 4 years after delivery, the cohort was re-evaluated and the mothers were invited to participate in a parallel study on women's cardiovascular health.

We excluded 313 mothers who had been recruited and evaluated from the first trimester of pregnancy to address specific objectives (Pinto et al., 2010), since smoking habits before and during pregnancy report is expected to change over time during pregnancy. From the remaining 8182 participants, 6881 participated in the follow-up evaluation. After exclusion of women with missing or inconsistent data in any variable used in the current analyses, 5420 women were available (Figure 1).

Mothers who attended the follow-up re-evaluation were older [mean (standard deviation (SD)): 29.3 (5.4) vs. 27.1 (5.9) years, $p<0.001$], more educated (education >9 years: 53.4% vs. 37.2%, $p<0.001$), with higher income (income >1000€/month: 61.6% vs. 37.2%, $p<0.001$), less frequently smokers before pregnancy (24.8% vs. 34.7%, $p<0.001$) and more likely to stop smoking during pregnancy (45.8% vs. 35.8%, $p<0.001$)) than those who did not participate in the re-evaluation.

Baseline evaluation

At baseline, data on demographic and socioeconomic characteristics, lifestyles, obstetric history and anthropometrics were collected within 72 hours after delivery, during the hospital stay, in a face-to-face interview conducted by trained interviewers using structured questionnaires. Clinical records were also reviewed at birth to retrieve data on complications of pregnancy, birth weight and gestational age of the newborn.

Pregnant current smokers included both daily (at least one cigarette per day) and occasional smokers (less than a cigarette per day) in the 3 months prior to pregnancy. Women were considered former smokers if they ever smoked but not during the 3 months before pregnancy. Smoking cessation during pregnancy was defined as quitting during the first or second trimester of pregnancy. Reduction of consumption was considered when women reported to smoke a lower daily number of cigarettes in the third trimester than in the three months before pregnancy.

Prepregnancy weight was recorded to the nearest 0.1 Kg as recalled. At baseline, height was measured to the nearest 0.1 cm. When measurement was not possible, height was reported by the mother as registered in the identity card (30.8% of women with data on height). The body mass index (BMI) was categorized according to the standard World Health Organization definition as underweight (<18.5 kg/m2), normal (18.5-24.9 kg/m2), overweight (25.0–29.9 kg/m2) and obese (≥30 kg/m2) (Expert Panel, 1998). Pregnancy complications included the diagnosis of any infectious, placental, hemorrhagic and cardiovascular events during pregnancy. Adequacy of prenatal care was determined by the Adequacy of Prenatal Care Utilization (APNCU) Index (Kotelchuck, 1994), based on the combination of the month of initiation of prenatal care, the observed and expected number of prenatal visits and the gestational age at birth. According to the APNCU index, having less than 50% of the recommended number of prenatal visits for a given gestational age or initiation of prenatal care after the first trimester was defined as inadequate care.

Part of the data missing on the questionnaires at baseline was recovered through the review of delivery medical records. The agreement between data collected by questionnaire and abstracted from medical records was good for weight and height, and there was very low inter-rater variability between 2 independent abstractors (Alves et al., 2010).

Follow-up

At the fourth anniversary of the children from the cohort a follow-up was performed and data were collected using structured questionnaires, regarding the health of the mother and her child. All mothers and children were invited to participate in a face-to-face interview but, if they refused, a telephone interview was performed. From the 5420 mothers included in our sample, 4343 (80.1%) attended a face-to-face interview and physical examination at the study site and 1077 (19.9%) provided self-reported data by telephone interview. There were no significant differences between participants evaluated by face-to-face and telephone interview regarding smoking characteristics at baseline (smokers before pregnancy: 22.5% vs. 24.3%, p=0.416; respectively), changes in consumption during pregnancy (reduced consumption: 42.0% vs. 40.5% and smoking cessation: 47.8% vs. 45.8%, p=0.564) and smoking habits at follow-up (smokers: 24.5% vs. 26.3%, p=0.191, respectively).

Smoking habits were self-reported and included information on the daily number of smoked cigarettes, 4 years after giving birth. An ex-smoker was a woman who formerly smoked but not for at least 6 months. Current smokers included both daily (at least one cigarette per day) and occasional smokers (less than a cigarette per day) at the time of the survey. Women who sustained their smoking cessation were defined as those who reported not to smoke 4 years after delivery, among those who had stopped smoking during pregnancy. Thirty women were excluded due to contradictory data regarding baseline and follow-up smoking habits.

Socioeconomic characteristics, personal and family history of disease, lifestyles and obstetric history of the mother were self-reported. The duration of breastfeeding was recorded in weeks, as the period of time that a child received maternal milk exclusively or together with complementary foods. Offspring's history of asthma or rhinitis was considered present when mothers recalled a medical diagnosis of these conditions.

Statistical analysis

Statistical analysis was performed using the statistical software Stata 9.0 (College Station, TX, 2005). Sample characteristics are presented as counts and proportions and were compared using the chi-square test. Crude and adjusted prevalence ratios (PR) and 95% confidence intervals (95%CI) were estimated by robust Poisson regression in order to assess the maternal determinants of smoking cessation during pregnancy and of sustainability of cessation 4 years after delivery. Determinants were selected taking into account those previously described in the literature, such as socioeconomic characteristics, lifestyles, gynaecologic and obstetric history, prenatal care, complications of the index pregnancy and delivery. In the final model all the determinants which were statistically significant were included as well as those who based on previous knowledge could possibly confound the associations.

Ethics

The study protocol was approved by the Ethics Committee of Hospital de São João and by the Portuguese Authority of Data Protection. Written informed consent was obtained from all the mothers and children, the latter through their legal representative, in case of face-to-face interview. Verbal consent was explicitly solicited at the beginning of telephone interviews.

RESULTS

Characteristics of study sample according to smoking before pregnancy

In this sample of Portuguese women who delivered a live born, 22.9% (95%CI: 21.8-24.0) reported smoking in the three months prior to pregnancy and 11.4% (95%CI: 10.6-12.3) to be former smokers (Figure 1).

Mothers who smoked during the three months prior to pregnancy, were younger, less educated, with a lower household income and were more frequently unemployed or housewives (Table 1). These women were less likely to be overweight or obese before pregnancy but more likely to have inadequate prenatal care during the index pregnancy. Prepregnancy smokers less often lived with a partner at follow-up, or returned to work, within 1 year after delivery and never breastfed or breastfed their child for a short period of time. Overall, 29.8% of the smoking mothers initiate their tobacco consumption before 15 years and 29.6% after 18 years old. Among the mothers who smoked before pregnancy, 45.5% smoked more than 10 cigarettes per day.

Cigarette smoking cessation during pregnancy

Overall, 47.4% of the women ceased smoking and 41.7% reduced their tobacco consumption during pregnancy, on average by 8.9 cigarettes per day, from 15.4 to 6.5 cigarettes.

In this sample of women who achieved a successful pregnancy, those who did not live with a partner at delivery and those with at least 1 additional previous pregnancy, are 20% less likely to cease smoking during pregnancy. Educational level and prepregnancy BMI were progressively and significantly associated with smoking cessation during pregnancy. Those with an educational level above 12 years had a 40% higher probability of quitting smoking, in comparison with mothers with educational level below 10 years, while obese women had a 30% increased probability of quitting smoking, in comparison with normal weight. Inadequacy of prenatal care was associated with a lower probability of quitting smoking in a graded mode, up to 45% reduction. The later the women initiated smoking the higher the likelihood of stopping, with up to 30% increase in probability for women who started smoking after 18 years of age. Heavier smokers (more than 10 cigarettes per day in the three months prior to pregnancy) had an almost 50% lower probability of smoking cessation.

Sustainability of smoking cessation 4 years after delivery

Four years after delivery, 32.1% of former smokers remained smoke-free and 19.0% sustained a reduction in the amount smoked. On average, smokers at both time points smoked 2.5 cigarettes per day less at 4 years than during the 3 months before pregnancy.

The sustainability of smoking cessation 4 years after pregnancy increased with age (≥35 vs. <25 years: PR=2.21; 95%CI: 1.43-3.41) and duration of breastfeeding (≥53 weeks vs. never or ≤4 weeks: PR=1.53; 95%CI: 1.07-2.19). Women who got divorced during the follow-up period were over two-fold less likely to maintain the smoking cessation. Multiparous women at the index pregnancy were 30% less likely to sustain smoking cessation at 4 years whereas those who achieved subsequent pregnancies were 50% more likely to maintain abstinence within this period. Mothers who smoked more than 10 cigarettes per day in the three months prior to pregnancy had a 30% lower probability of sustain the smoking cessation. A diagnosis of asthma or rhinitis in the offspring was positively associated with the sustainability 4 years after delivery (PR=1.56; 95%CI: 1.08-2.25).

DISCUSSION

In this study of Portuguese women who delivered of a live born, the prevalence of smoking was 23% before pregnancy but almost half stopped during the index pregnancy. Factors associated with smoking cessation during pregnancy were parity, marital status, education, BMI, prenatal care, smoking initiation age and the amount of cigarettes smoked per day. Four years after delivery two thirds resumed smoking. Older women, primigestae, with lower tobacco consumption, married or living with a partner at follow-up, who got pregnant again after the index pregnancy and breastfed more than 52 weeks and whose child had a medical diagnosis of asthma and/or rhinitis were more likely to maintain the cigarette smoking cessation.

The EURO-PERISTAT study, that monitored and evaluated perinatal health in Europe, reported prepregnancy smoking prevalence levels in 2004 ranging from 7.9% in Lithuania to 35.9% in France (EURO-PERISTAT, 2008). According to a study performed in 25 public maternity units, 30% of women smoked before pregnancy in Portugal (Rodrigues & Barros, 2008). The lower prevalence described in our study may be explained by the higher educational level of the mothers included in the Geração XXI cohort. Since more educated women more frequently planned their pregnancy, it is possible that these women had stopped smoking before pregnancy, because they intended to get pregnant. In Portugal, the prevalence of smoking is higher among more educated women (Fraga et al., 2005), and the higher prevalence described in this study may be due to the specific characteristics of the women included. In the latest National Health Survey, in 2005-2006, the prevalence of smoking among women from the general population aged between 15 to 44 years was 18.4% (INS, 2009), possibly underestimated since the questionnaire could be answered by a proxy in case the index subject was absent and proxies might not be aware of the smoking status of these women, especially in younger ones.

In many countries in Europe, more than 10% of women smoke during pregnancy (EURO-PERISTAT, 2008). In our study, 12.0% reported to smoke during pregnancy, which means that almost half of the women stopped smoking during pregnancy. This estimate is in accordance with previous literature reporting smoking cessation rates ranging from 30% to 50% (Colman & Joyce, 2003; Correia et al., 2007; DiSantis, Collins, & McCoy, 2010; Fingerhut, Kleinman, & Kendrick, 1990).

Overall, maternal socio-demographic characteristics, as well as the mother's reproductive history and prenatal care, are associated with smoking during pregnancy (Al-Sahab, Saqib, Hauser, & Tamim, 2010; Colman & Joyce, 2003; Lu, Tong, & Oldenburg, 2001; Mohsin & Bauman, 2005; Severson, Andrews, Lichtenstein, Wall, & Zoref, 1995). Predictors of smoking cessation among pregnant women have been well investigated, internationally. Women who quit smoking during pregnancy are more likely to report being married or in a stable relationship and having higher educational qualifications (Al-Sahab et al., 2010; Colman & Joyce, 2003; Fingerhut et al., 1990). However, a study that assessed the reporting of prenatal smoking in birth certificates and in confidential questionnaires found that more educated women are less willing to admit smoking to prenatal care providers, which may lead to overestimation of the association between education and smoking cessation during pregnancy (Dietz, Adams, Kendrick, & Mathis, 1998). Quitting in pregnancy appears to be more successful in first pregnancies regardless of social background, with the probability decreasing with the number of pregnancies (Graham, Hawkins, & Law, 2010). It has been suggested that past pregnancies resulting in the birth of a healthy child despite tobacco consumption might weaken the women’s motivation to change their smoking habits in subsequent pregnancies (Chaaya, Awwad, Campbell, Sibai, & Kaddour, 2003).

Women receiving adequate prenatal care show a higher rate of smoking cessation (Bachir & Chaaya, 2008; Mohsin & Bauman, 2005). In fact, those smokers who quitted while pregnant were more likely to have initiated prenatal care in the first trimester and to have an adequate number of prenatal visits. Despite the impact of adequate prenatal care on smoking cessation, this may also be due to personal characteristics of women since those more prone to quit smoking are also probably more prone to attend prenatal care (Barros, Tavares, & Rodrigues, 1996). According to a study that assessed women's knowledge and sources of information about adverse effects of smoking during pregnancy in Portugal, in 2003-2004, 45% of the mothers were misinformed or had no information about the adverse effects of smoking during pregnancy. Additionally, the doctors' role as a source of information was surpassed by the media, which was the main source of information (Correia et al., 2007).

Women who initiate smoking earlier or were heavier smokers were more likely to smoke during pregnancy, emphasizing the physiological and psychological role of nicotine dependence in smoking cessation (Ebbert, Montori, Erwin, & Stead, 2009). Concern about weight gain during and after pregnancy may be a factor that interferes with smokers' efforts to quit during pregnancy (Berg, Park, Chang, & Rigotti, 2008), with pregnant smokers reporting the use of smoking as a weight management strategy (Pomerleau, Brouwer, & Jones, 2000). In our study there was no association with weight gain during pregnancy (data not shown) but we found a positive association between prepregnancy overweight and obesity and smoking cessation during pregnancy. Therefore, it is possible that women with a normal prepregnancy BMI had a higher concern with postpartum weight gain and therefore, were less likely to try to quit smoking during pregnancy than those with a BMI above 25Kg/m2.

Besides the high proportion of women who stopped smoking during pregnancy, most of the remaining smokers reported to have reduced their tobacco consumption. The reduction in consumption during pregnancy to an average of 6.5 cigarettes per day found in our study is in accordance to previous findings that reported an average daily consumption of 7 cigarettes during the third trimester (Al-Sahab et al., 2010) among Canadian women. Despite the undeniable benefit of reducing the number of cigarettes on health, the main aim of prevention is smoking cessation and for this reason, this article focuses, essentially, on smoking cessation during pregnancy and its determinants and long-term sustainability. Also, the potential for misclassification regarding dose is higher than for smoking versus not. Still, we considered important to also present data about reduction in a descriptive perspective, since it highlights women's concern with their unborn baby protection and can promote a long term reduction in the consumption of cigarettes, which will have a positive impact on the future health of the mother (Edwards & Sims-Jones, 1998; Ripley-Moffitt et al., 2008). Unfortunately, the tendency observed among those women who reduce their consumption is the same as for cessation, since 80% of mothers who reduced the number of cigarettes during pregnancy returns to its regular consumption, 4 years after delivery.

Despite a high proportion of women quitting or reducing their tobacco consumption during pregnancy the rate of relapse or return to previous rates following childbirth is high. In fact, approximately 25% of women who quit smoking during pregnancy will relapse within one month of delivery (Fingerhut et al., 1990). By three months postpartum, 40% to 50% of women will have returned to smoke and, 70% will have experienced a relapse within one year postpartum (Colman & Joyce, 2003; Fingerhut et al., 1990; Polanska et al., 2011). In our study, 4 years after giving birth, 68% of women returned to smoke among those who had quitted during pregnancy.

As described previously, younger women, divorced or without a partner and with a lower education were more likely to resume smoking (Colman & Joyce, 2003; Fingerhut et al., 1990). These results are consistent with a large body of evidence on inequalities in smoking. Women with lower levels of education may have limited access to smoking cessation programs, and the programs available may not be adequate for them (Cluss, Levine, & Landsittel, 2011; Gilman, Breslau, Subramanian, Hitsman, & Koenen, 2008). Despite the positive association between the number of previous pregnancies and resumption of tobacco consumption, having a subsequent pregnancy revealed to be associated with the sustainability of smoking cessation. Breastfeeding may help prevent or delay postpartum smoking relapse (DiSantis et al., 2010). Therefore, educating women about the benefits of breastfeeding and facilitating its continuity throughout the first postpartum year may be an effective strategy to reduce smoking resuming (Kendzor et al., 2010). Accordingly, in our sample, the longer the women breastfed, the longer they sustained their smoking cessation.

A substantial body of evidence supports that involuntary tobacco smoke exposure adversely affects children's respiratory health by increasing the risk of respiratory infections (Gilliland, Li, & Peters, 2001; Johansson, Ludvigsson, & Hermansson, 2008). In uterus exposure to maternal smoking was associated with an almost two-fold increased prevalence of physician-diagnosed asthma (Gilliland et al., 2001). Additionally, children exposed after birth had more often rhinitis than children of non-smoking parents (Johansson et al., 2008). The higher smoking cessation sustainability among mothers of children with a diagnosis of asthma or rhinitis may reflect a concern of the mother with the health of the child, beyond the period of pregnancy.

This is the first study that approaches the prevalence of smoking before, during and after pregnancy in a large population-based cohort study of Portuguese women who achieved a successful pregnancy. However, some limitations should be pointed. Firstly, we did not validate the self-reported information on tobacco smoking. Though self-reported data are most often used for this purpose and in general are reliable (Patrick et al., 1994) and yield a favourable cost-effectiveness balance for collection of such data in large samples (Gorber, Schofield-Hurwitz, Hardt, Levasseur, & Tremblay, 2009), reliance on self-reported smoking status, especially during pregnancy, may result in exposure misclassification due to social desirability and an increased concern of the negative effects of smoking in the foetus (Bottorff, Johnson, Irwin, & Ratner, 2000; Shipton et al., 2009). Also, the definition of ex-smokers as those who did not smoke in the 3 months before pregnancy may have underestimated the prevalence of regular smoking before pregnancy and, consequently, the pregnancy smoking cessation, since it is possible that women had stopped smoking more than 3 months before pregnancy already because they intended to get pregnant. However, since the estimated prevalence of smoking in our sample is not lower than reported for the Portuguese general population (INS, 2009), large underestimation is unlikely. Additional limitations were the lack of information regarding other potentially important risk factors (Severson et al., 1995). In particular, despite collected at baseline, data regarding partner's smoking status before, during and after pregnancy were available only for a subsample and adjustment for this factor would differentially condition the sample, thereby reducing generalizability and introducing bias.

There was a high proportion of participation at follow-up but losses may have introduced bias once they occurred differentially by smoking characteristics before and during pregnancy. This differential effect could have contributed to an underestimation of prepregnancy smoking and an overestimation of the prevalence of smoking cessation during pregnancy and sustainability of cessation 4 years after delivery. Besides, the lower proportion of participation at follow-up among younger and less educated women also raises the possibility of a selection bias. In this case, we may be overestimating the smoking cessation during pregnancy and the sustainability of that cessation among these women and, consequently, the association described.

The present study revealed that although many women stopped smoking during pregnancy, this change does not appear to have a lasting impact on their smoking trajectory. To remain abstinent, it is necessary that the motivation not to smoke remain higher than the motivation to smoke on all occasions when smoking could occur. In this context, long-term abstinence is achieved through a process of identity change, from 'smoker' towards 'non-smoker' (Vangeli & West, 2012). The high proportion of women who ceased tobacco consumption during pregnancy demonstrated that women are aware of the harmful impact of smoking on reproductive and infant health during pregnancy (Ingall & Cropley, 2009). Nevertheless, the also high relapse rate suggests that mothers are less aware of the adverse effects of second hand smoke exposure on their offspring. Therefore, successful educational interventions should be focused on the detrimental effects of passive exposure to smoking on the child's health after birth and not just during pregnancy. This may promote the long-term sustainability of smoking cessation after delivery, which would benefit the health of the whole family.

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Table 1. Characteristics of the participants at baseline and at follow-up, according to smoking status before pregnancy (n=5420).

	Smoking status			
	Never smoker n (%)	**Ex-smoker** n (%)	**Current smoker** n (%)	*p*
Age (years)				
<25	589 (16.6)	83 (13.4)	351 (28.3)	
25-29	1140 (32.0)	189 (30.5)	338 (27.2)	
30-34	1234 (34.7)	217 (35.0)	358 (28.9)	
≥35	596 (16.7)	131 (21.1)	194 (15.6)	<0.001
Marital status (baseline - follow-up)				
Married/cohabiting - married/cohabiting	3175 (89.2)	550 (88.7)	944 (76.1)	
Married/cohabiting - divorced/widow	241 (6.8)	50 (8.1)	170 (13.7)	
Single/divorced - single/divorced	81 (2.3)	11 (1.8)	74 (6.0)	
Single/divorced - married/cohabiting	62 (1.7)	9 (1.4)	53 (4.3)	<0.001
Education (years)				
≤9	1630 (45.8)	222 (35.8)	659 (53.1)	
10-12	921 (25.9)	192 (31.0)	360 (29.0)	
≥13	1008 (28.3)	206 (33.2)	222 (17.9)	<0.001
Employment status				
Employed	2728 (76.8)	481 (77.6)	813 (65.7)	
Unemployed	560 (15.8)	103 (16.6)	314 (25.4)	
Housewife	203 (5.7)	16 (2.6)	62 (5.0)	
Other (student/retired)	62 (1.8)	20 (3.2)	49 (4.0)	<0.001
Household income (€/month)				
<500	158 (4.6)	21 (3.5)	99 (8.1)	
500-1000	1016 (29.3)	153 (25.4)	375 (30.5)	
1001-1500	918 (26.5)	161 (26.7)	329 (26.7)	
≥1501	1096 (31.6)	212 (35.2)	296 (24.1)	
Does not know/ Prefers not to answer	277 (8.0)	55 (9.1)	131 (10.6)	<0.001
Return to work				
Did not have a paid job before pregnancy	204 (7.1)	36 (7.2)	91 (9.3)	
Did not return to work within 1 year	353 (12.3)	50 (10.1)	140 (14.3)	
Returned to work within 1 year	2314 (80.6)	411 (82.7)	749 (76.4)	0.019
Primigestae	1789 (50.3)	308 (49.7)	606 (48.8)	0.681
At least 1 subsequent pregnancy	758 (21.3)	148 (23.9)	291 (23.5)	0.152
Prepregnancy BMI (kg/m^2)				
<25.0	2415 (67.9)	432 (69.7)	918 (74.0)	
25.0-29.9	796 (22.4)	137 (22.1)	237 (19.1)	
≥30.0	348 (9.8)	51 (8.2)	86 (6.9)	0.001
Pregnancy complications[b]	1047 (31.6)	167 (29.5)	370 (32.3)	0.496
Adequacy of prenatal care[c]				
Adequate Plus	280 (7.9)	63 (10.2)	125 (10.1)	
Adequate	1610 (45.2)	317 (13.0)	521(42.0)	
Intermediate	1538 (43.2)	223 (36.0)	533 (42.9)	
Inadequate	131 (3.7)	17 (2.7)	62 (5.0)	<0.001
Breastfeeding (weeks)				
Never or ≤4	791 (22.2)	135 (21.8)	355 (28.6)	
5-16	865 (24.3)	168 (27.1)	332 (26.7)	
17-52	1198 (33.7)	209 (33.7)	326 (26.3)	
≥53	705 (19.8)	108 (17.4)	228 (18.4)	<0.001
Offspring's asthma or rhinitis	260 (7.3)	54 (8.7)	96 (7.7)	0.459

BMI, body mass index
[a] According to the Institute of Medicine classification (2009)
[b] Including infectious, placental, hemorrhagic and cardiovascular complications during pregnancy
[c] According to the Adequacy of Prenatal Care Utilization Index (APNCU)
Note: In each variable, the total may not add to 5420 due to missing data

Table 2. Crude and adjusted prevalence ratios to assess the determinants of smoking cessation during pregnancy (588 women) among 1241 prepregnancy smokers

	n (%)	Crude PR (95%CI)	Adjusted PR* (95%CI)
Age (years)			
<25	168 (47.0)	1	1
25-29	163 (48.2)	1.03 (0.88-1.20)	0.91 (0.77-1.06)
30-34	168 (46.9)	1.00 (0.85-1.17)	0.82 (0.70-0.97)
≥35	92 (47.4)	1.01 (0.84-1.21)	0.88 (0.72-1.06)
Marital status at baseline			
Married/cohabiting	542 (48.7)	1	1
Single/divorced/widow	46 (36.2)	0.74 (0.59-0.94)	0.81 (0.64-1.01)
Education (years)			
≤9	268 (40.7)	1	1
10-12	185 (51.4)	1.26 (1.10-1.45)	1.19 (1.05-1.36)
≥13	135 (60.8)	1.50 (1.30-1.72)	1.41 (1.21-1.64)
Gravidity			
1	328 (54.1)	1	1
≥2	260 (40.9)	0.76 (0.67-0.85)	0.81 (0.72-0.92)
Prepregnancy BMI (Kg/m^2)			
<25.0	414 (45.1)	1	1
25.0-29.9	126 (53.2)	1.18 (1.03-1.35)	1.23 (1.08-1.41)
≥30	48 (55.8)	1.24 (1.01-1.51)	1.29 (1.08-1.54)
Adequacy of prenatal care[a]			
Adequate Plus	63 (50.4)	1	1
Adequate	273 (52.4)	1.04 (0.86-1.26)	1.01 (0.85-1.21)
Intermediate	236 (44.3)	0.88 (0.72-1.07)	0.90 (0.75-1.09)
Inadequate	16 (25.8)	0.51 (0.32-0.81)	0.55 (0.34-0.87)
Smoking initiation age (years)			
≤14	143 (37.0)	1	1
15-18	249 (49.7)	1.35 (1.15-1.57)	1.26 (1.09-1.47)
≥19	196 (55.5)	1.50 (1.28-1.76)	1.29 (1.10-1.52)
Number of cigarettes smoked before pregnancy per day			
≤10	407 (60.2)	1	1
>10	181 (32.0)	0.53 (0.46-0.61)	0.55 (0.48-0.62)

95%CI, 95% confidence interval; BMI, body mass index; PR, prevalence ratio
* Adjusted for all the variables in the table
[a] According to the Adequacy of Prenatal Care Utilization Index (APNCU)

Table 3. Crude and adjusted prevalence ratios to assess the determinants of smoking cessation sustainability 4 years after delivery (189 women) among 588 who stopped smoking during pregnancy

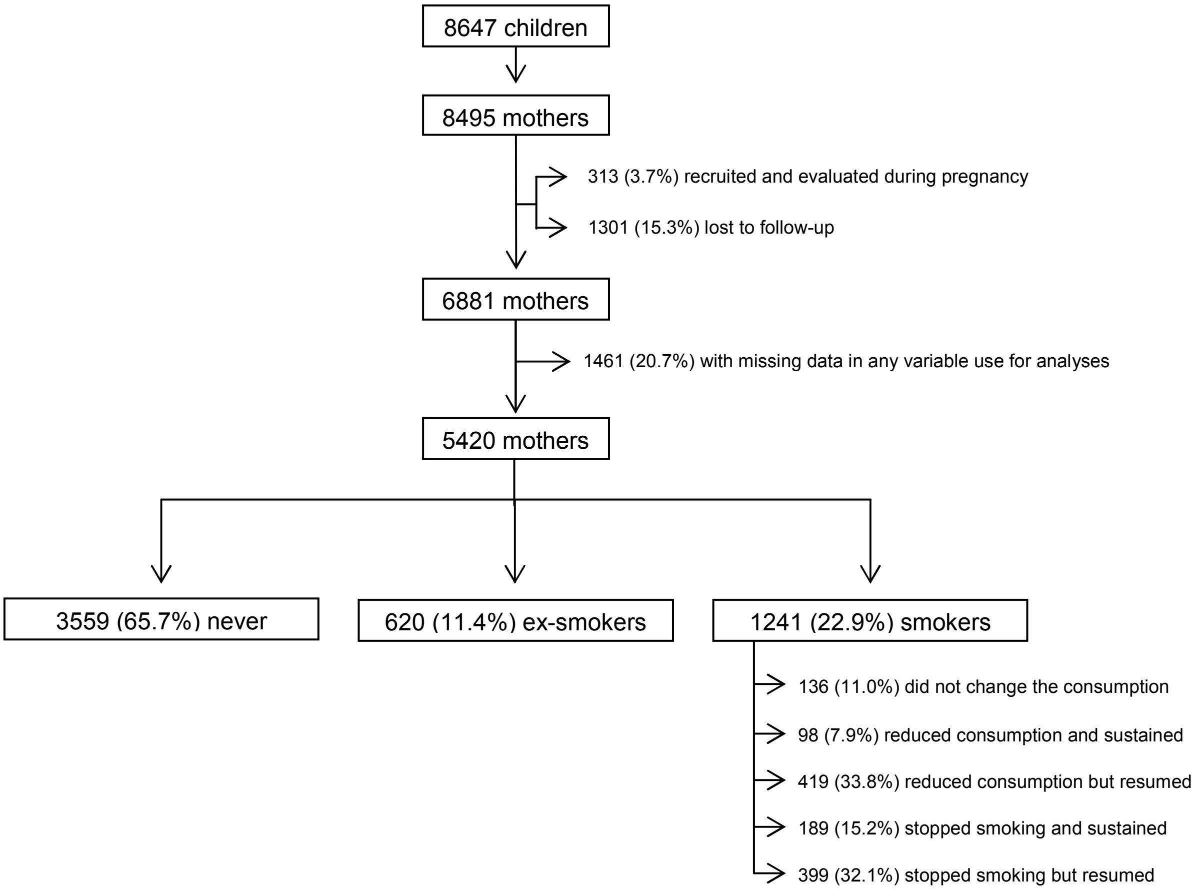
	n (%)	Crude PR (95%CI)	Adjusted PR* (95%CI)
Age (years)			
<25	42 (25.5)	1	1
25-29	47 (28.8)	1.13 (0.79-1.62)	1.27 (0.86-1.87)
30-34	66 (39.3)	1.54 (1.12-2.13)	1.76 (1.21-2.55)
≥35	34 (37.0)	1.45 (1.00-2.11)	2.11 (1.37-3.25)
Marital status (baseline - follow-up)			
Married/cohabiting - married/cohabiting	166 (35.0)	1	1
Married/cohabiting - divorced/widow	10 (14.9)	0.43 (0.24-0.77)	0.45 (0.25-0.81)
Single/divorced - single/divorced	6 (24.0)	0.69 (0.34-1.40)	0.74 (0.35-1.55)
Single/divorced - married/cohabiting	7 (33.3)	0.95 (0.51-1.77)	1.28 (0.67-2.43)
Education (years)			
≤9	79 (29.5)	1	1
10-12	61 (33.0)	1.12 (0.85-1.48)	0.98 (0.74-1.30)
≥13	49 (36.3)	1.23 (0.92-1.65)	0.92 (0.67-1.27)
Gravidity at baseline			
1	114 (34.8)	1	1
≥2	75 (28.9)	0.83 (0.65-1.06)	0.70 (0.54-0.91)
Subsequent pregnancies			
0	128 (29.0)	1	1
≥1	61 (41.8)	1.44 (1.13-1.84)	1.51 (1.17-1.93)
Number of cigarettes smoked before pregnancy per day			
≤10	146 (35.9)	1	1
>10	43 (23.8)	0.66 (0.49-0.89)	0.69 (0.52-0.92)
Breastfeeding (weeks)			
Never or ≤4	35 (25.0)	1	1
5-16	46 (30.5)	1.21 (0.84-1.77)	1.13 (0.78-1.62)
17-52	64 (35.2)	1.41 (0.99-1.99)	1.28 (0.92-1.80)
≥53	44 (38.3)	1.53 (1.06-2.21)	1.49 (1.04-2.12)
Offspring's asthma or rhinitis			
No	172 (31.3)	1	1
Yes	17 (43.6)	1.39 (0.95-2.03)	1.56 (1.08-2.25)

95%CI, 95% confidence interval; PR, prevalence ratio

* Adjusted for all the variables in the table

[a] According to the Adequacy of Prenatal Care Utilization Index (APNCU)

Figure 1. Definition of the study sample, prevalence of smoking status before pregnancy and changes in tobacco consumption during pregnancy and 4 years after delivery.



PAPER VI

Alves E, Henriques A, Azevedo A, Barros H.

Cardiovascular risk profile of mothers of a Portuguese birth cohort: a survey 4 years after delivery.

[submitted]

Cardiovascular risk profile of mothers of a Portuguese birth cohort: a survey 4 years after delivery

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ABSTRACT

Background: Cardiovascular risk at young ages is increasing, even in societies that shown important decreases in cardiovascular mortality for decades. Pregnancy may unmask or induce cardiovascular disorders, and should be a good opportunity to promote healthier lifestyles.

Purpose: To estimate the prevalence of smoking, low fruits and vegetables consumption, sedentariness, overweight/obesity, abdominal obesity, hypertension, dyslipidemia and diabetes mellitus, in mothers of a Portuguese birth cohort, 4 years after child's birth.

Methods: A birth cohort was assembled at public maternities of Porto, in 2005-2006, and reevaluated at 4 years. In the current analysis, 5435 women were included. Socioeconomic characteristics, smoking, diet and exercise were self-reported. Anthropometrics and blood pressure were measured. A subgroup of 2483 randomly selected women provided blood for lipids and glucose.

Results: Overall, 25.3% of the participants smoked, 50.7% consumed less than 3 portions of fruits or vegetables per day, 81.3% did not practice physical exercise, 31.4% were overweight, 21.3% obese and 31.8% had abdominal obesity. The prevalence of hypertension, dyslipidemia and diabetes mellitus was 8.7%, 18.5% and 0.9%, respectively. The presence of at least one risk factor from each of the 3 groups (adverse lifestyles, adiposity and cardiometabolic comorbidities) was observed in 17.0% of women. All risk factors were associated with unemployment, lower education and lower income.

Conclusions: The prevalence of unfavorable lifestyles and adiposity was very high, and the clustering of risk factors emphasizes the adverse cardiovascular risk profile at a young age. The potential for prevention is vast.

Keywords: Cohort studies; Prevalence; Risk factors; Women's Health

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of death and morbidity worldwide (1). Although women have traditionally been thought of as a low-risk population for CVD, this is the main cause of death in women in Europe, responsible for almost half of the deaths (2). In Portugal, diseases of the circulatory system accounted for 37.3% of all deaths among women in 2006 (3).

CVD reflect a complex interplay of genetic, developmental, environmental and behavioural factors (4, 5). In European populations, CVD is mainly attributable to classical risk factors, namely cigarette smoking, high blood pressure, high serum cholesterol, diabetes, overweight/obesity and adverse diet (6). The relation between these risk factors and CVD is independent, strong, continuous and graded, and the modification of these risk factors can result in substantial reduction in mortality (7). In the last decades, several studies have reported that CVD mortality rates increase with the number of risk factors present in an individual, suggesting that the lower the risk factor profile, the lower the risk for CVD and all-cause mortality (8, 9, 10, 11). Despite the difficulty in assessing the impact of cardiovascular risk factors measured in young adulthood on mortality, due to low short-term death rates, results from a prospective cohort study of women aged below 40 years (9) showed that favourable levels of major risk factors were associated with lower long-term CVD and all-cause mortality.

According to the World Health Organization (12), health risks are in transition: populations are ageing and, at the same time, patterns of physical activity and diet, alcohol and tobacco consumption are changing. The modifiable pattern, as well as the considerable impact of lifestyles on the development of CVD (13), emphasize the importance of primary prevention.

Pregnancy puts a physiological stress on the body that can unmask an underlying propensity for chronic disease (14). Additionally, pregnancy is often regarded as a good opportunity for health promotion and disease prevention (15), due to the strong motivation of the mothers to protect the health of the unborn baby.

In this study, our objective was to estimate the prevalence of eight established cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus, general overweight/obesity, abdominal obesity, smoking, low fruits and vegetables consumption and sedentariness), in mothers of a Portuguese birth cohort, 4 years after delivery, and to describe their distribution by age, gravidity and indicators of socioeconomic position (SEP).

METHODS

This study is based on the birth cohort Geração XXI, which has been described previously (16). Briefly, the cohort was assembled between 2005 and 2006 at 5 public maternity units covering the metropolitan area of Porto, Portugal. Of the invited mothers, 91.4% accepted to participate. A total of 8495 mothers, who gave birth to 8647 infants, were enrolled in the cohort. At 4 years of the child's age, between 2009 and 2011, the cohort was re-evaluated. Mothers were invited to participate in a parallel study on women's cardiovascular health, and 67.4% attended a face-to-face interview and physical examination at the study site. Among those, 47.7% provided a fasting blood sample. An additional 16.8% provided self-reported data by telephone interview, but were not included in the current analysis due to the lack of physical examination data.

Among the 5729 mothers who attended the face-to-face interview, we excluded 174 women who were pregnant at the follow-up visit and 120 participants who presented at least one missing value on variables used in this study. The remaining 5435 women were included in the current analysis, among whom 2483 (45.7%) had biochemical laboratorial data.

At the cohort's reevaluation, an average of 4 years after delivery, data were collected in a face-to-face interview conducted by trained interviewers using structured questionnaires, regarding the health of the mother and her child. Socioeconomic characteristics, personal and family history of disease, lifestyles and obstetric history of the mother were self-reported. Current smokers included both daily (at least one cigarette per day at the time of the survey) and occasional smokers (less than a cigarette per day), and ex-smokers did not smoke for at least 6 months. A food frequency questionnaire was used to assess the frequency of consumption of fruits, soup and "vegetables on the dish", without considering the specific items in each of these 3 groups or portion sizes. Low fruits and vegetables consumption was defined as the combination of items from any of these groups summing less than 3 per day. Leisure physical exercise was considered as the practice of any leisure-time physical activity, of mild, moderate or vigorous intensity, not taking into account the time spent on exercise.

All the mothers undertook a physical examination at the study site. Participants were measured wearing light clothing and no footwear. Weight was measured using a digital scale to the nearest 0.1 kg and height measured to the nearest 0.1 cm. The mothers' body mass index (BMI) was categorized according to the standard World Health Organization definition as underweight (<18.5 kg/m2), normal (18.5-24.9 kg/m2), overweight (25.0–29.9 kg/m2) and obese (≥30 kg/m2) (17). Waist circumference was measured midway between the lowest rib and the superior border of the iliac crest. Abdominal obesity was defined as waist circumference >88 cm according to American Heart Association (18). Blood pressure was measured on a single occasion by non-physician trained interviewers. Two measurements of blood pressure separated by at least 5 minutes were taken with an automatic upper arm blood pressure monitor (OMRON M6 comfort (HEM-7000-E)) after 10-minute rest, on the dominant upper arm resting at the heart level. The mean was calculated and when the difference was larger than 5 mmHg for systolic or diastolic blood pressure a third measurement was taken and the mean of the 2 closest values was considered. Arterial hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or or self-reported antihypertensive drug therapy prescribed specifically for hypertension (19).

For the subgroup of women who collected a blood sample, dyslipidemia was considered when one of these conditions were verified: total cholesterol ≥ 240 mg/dL, high-density lipoprotein (HDL) ≤ 40 mg/dL, low-density lipoprotein (LDL) ≥ 160 mg/dL, triglycerides ≥ 200 mg/dL (20) or self-reported antidyslipidemic drug therapy . Diabetes mellitus was defined, according to the World Health Organization criteria, as fasting plasma glucose concentration ≥ 126 mg/dL (21), or self-reported antidiabetic drug therapy prescribed specifically for diabetes.

Overall, the socio-demographic characteristics of the participants were similar between all the women included for the current analysis and those with a fasting blood sample collection (Table 1). Almost half of the mothers were 35 or more years old and the index pregnancy was the only pregnancy of approximately 37%. Most of the mothers were married or lived with a partner, approximately 27% had 13 or more years of education and more than 75% were employed. Less than 5% of women had a household monthly income below 500€ and more than 40% above 1500€ (Table 1).

Statistical analysis was performed using the statistical software Stata 9.0 (College Station, TX, 2005). Sample characteristics are presented as counts and proportions and the prevalence of the outcomes is presented with 95% confidence intervals (95% CI). To assess the clustering of cardiovascular risk factors, these were grouped into unfavourable lifestyles (smoking, low fruits and vegetables consumption, and sendentariness), adiposity (overweight/obesity and abdominal obesity) and cardiometabolic risk factors (hypertension, dyslipidemia and diabetes mellitus), and possible combinations of at least one factor from each group were analyzed, only for the subsample with information available for all risk factors. Unconditional binary logistic regression models were fitted to compute age-adjusted odds ratios (OR) and 95% confidence intervals for hypertension, dyslipidemia, diabetes mellitus, abdominal obesity, fruits and vegetables consumption and physical activity, and multinomial logistic regression models for BMI and smoking status, taking BMI <25 Kg/m2 and never smokers as reference classes, respectively.

The study protocol was approved by the Ethics Committee of Hospital de São João and by the Portuguese Authority of Data Protection. Written informed consent was obtained from all the participants.

RESULTS

An average of 4 years after delivery, a quarter (25.3%; 95%CI: 24.1-26.5) of the participants were smokers, while approximately half (50.7%; 95%CI: 49.4-52.0) consumed less than 3 portions of fruits and vegetables per day and 81.3% (95%CI: 80.2-82.3) did not practice any leisure-time physical exercise. At that time, 31.4% (95%CI: 30.2-32.7) were overweight, 21.3% (95%CI: 20.2-22.4) were obese and 31.8% (95%CI: 30.6-33.1) had abdominal obesity. Regarding the cardiometabolic comorbidities, 8.7% (95%CI: 7.9-9.5) of the women had hypertension and, among the subsample with available data from the fasting blood sample collection, the prevalence of dyslipidemia and diabetes mellitus was 18.5% (95%CI: 17.0-20.1) and 0.9% (95%CI: 0.6-1.3), respectively (Figure 1). Overall, the presence of at least one risk factor from each of 3 groups (unfavorable lifestyles, adiposity and cardiometabolic comorbidities) was observed in 17.0% of women. Moreover, more than 30% presented both adverse lifestyles and adiposity, almost 6% unfavorable lifestyles and cardiometabolic risk factors, and only 1.4% had excessive weight and/or abdominal obesity and at least one cardiometabolic risk factor (Figure 2).

Above 30 years of age, the prevalence of smoking, low intake of fruits and vegetables and sedentariness was approximately half that of younger women. Women with 3 or more pregnancies were 31% and 38% more likely to smoke and to be sedentary, whereas those not living with a partner were almost 3-fold more frequently smokers. In general, adverse lifestyles were inversely associated with education and income, independently of age. When compared with employed women, the unemployed were 40% more likely to smoke and 53% more likely to consume less than 3 portions of fruits and vegetables per day, while housewives were 37% less likely to smoke. Four years after delivery, smokers were 28% less likely to be obese, while those who did not practice any physical exercise were 27% more likely to be obese.

The prevalence of former smoking increased with age and educational level, and was lower among housewives (Table 2).

In this study, women aged above 40 years were 62% more frequently overweight and just above 30% more likely to have overall and abdominal obesity, compared to women aged less than 30 years. Gravidity was also associated with both outcomes, independently of age. A significant inverse association was observed for education and household monthly income with a clear dose-response effect for both variables. Married women or those living with a partner were more likely to have excessive weight or abdominal obesity, as well as housewives and unemployed, when compared with employed women (Table 3).

The prevalence of the three cardiometabolic comorbidities – hypertension, dyslipidemia and diabetes mellitus – increased significantly with age and BMI. Women aged over 40 years were more likely to have hypertension (6.82-fold), dyslipidemia (1.55-fold) and diabetes (4.57-fold), while obesity was associated with a 4-fold increase in the prevalence of hypertension and a 3-fold increase in the prevalence of dyslipidemia or diabetes, independently of age. Overall, an inverse association was observed with income for the three cardiometabolic comorbidities, and a similar association was observed with education, with a more relevant effect for hypertension (>12 years vs. ≤4 years: age-adjusted OR=0.51; 95%CI: 0.35-0.73). Unemployed women were more frequently hypertensive, dyslipidemic or diabetic, when compared with employed women. Marital status was only associated with diabetes mellitus, with a 3-fold increase in the prevalence of diabetes among women who lived without a partner (Table 4).

DISCUSSION

In this study of Portuguese women who delivered a live born, almost 90% of the participants presented at least one unfavorable lifestyle, more than half had a marker of adiposity and a quarter presented one or more cardiometabolic comorbidities. Overall, 17% of the women presented the aggregation of factors from all three groups. Smoking, low fruit and vegetables intake and sedentary lifestyle were more common in younger women, while adiposity and cardiometabolic risk factors were more frequent in older women. The prevalence of all hypertension, dyslipidemia, diabetes mellitus and sedentariness increased with BMI. Unemployment, education and income were inversely associated with all risk factors, except smoking.

This is the first study that presents the prevalence of several cardiovascular risk factors in a large sample of young Portuguese women, embedded in the context of their reproductive life. The objective measurements of weight, height, blood pressure, fasting blood lipids and glucose are obvious advantages when considering prevalence.

In 2006, the global prevalence of smoking in female adults in Europe was 27%, while in Portugal, the prevalence in the female population over 15 years of age was only 11.8% (22). According to data from the 2005/2006 Portuguese National Health Survey, the prevalence of current smoking for women aged between 15 to 54 years old, was 17.0% (23). The higher prevalence of smoking in our sample could reflect its urban nature. Moreover, in the National Health Survey (23), the prevalence may have been underestimated since the questionnaire could be answered by a proxy in case the index subject was absent and proxies might not be aware of the smoking status of these women. In our sample, more than half of the women consumed fruits and vegetables less than 3 times per day, which was previously associated with higher cardiovascular incidence and mortality, after adjustment for established cardiovascular disease risk factors (24). In 1997, among fifteen countries of the European Union, Portugal presented the highest rate of sedentary lifestyles, with 90.0% of women aged above 15 years having low energy expenditure (25). Additionally, in a study performed in 2000, among European university female, aged between 18 and 30 years old, 36.7% of women were considered physically active, which was defined as the practice of any exercise in the 2 weeks before the survey (26). In the present study, less than 20% of women reported to practice any kind of physical exercise. The high prevalences of adverse lifestyles in this cohort of mothers highlight the need for prevention early in life. The implications for the health of the family and particularly of their children, both through the shared environment and their responsibility as role models, are a major indirect consequence of these unfavorable behaviors.

In Portugal, the prevalence of overweight and obesity in women aged between 18 and 49 years in a national survey conducted in 2003-2005, was 34.0% and 10.6%, respectively. This same study reported a prevalence of abdominal obesity among women aged between 20 to 29 years and between 30 to 39 years of 11.2% and 19.9%, respectively (27). We observed a considerably higher prevalence of both overall and abdominal obesity. There is evidence that adiposity is increasing in Portugal, with a systematic review reporting an increase in overweight prevalence of 3.2% and obesity prevalence of 7.4% among women, between 1995 and 2005 (28). Moreover, these women had been pregnant 4 years before, and approximately 20% had a subsequent pregnancy meanwhile (data not shown). Thus, the observed body size may reflect changes induced by this experience with incomplete recovery (29).

In 2003, the prevalence of hypertension in Portuguese women aged below 35 years was 12.4%, which is higher than the one described in the present study, where the mean age was 35 years (30). In a systematic review that assessed trends in hypertension prevalence in Portugal, between 1990 and 2005, the authors estimated a prevalence of 23.2% for women at average age 35 years, in 2005 (31). Regarding dyslipidemia, the heterogeneity of definitions among different studies is a universally recognized difficulty for their comparison. No Portuguese study could be identified using similar enough methodology and criteria. In the United States, the prevalence of high blood cholesterol or low HDL was 25.9% in women aged between 20 and 39 years (32), which is higher than the one described in the present study. Data from a recent study that aimed to determine the prevalence of type 2 diabetes, in the Portuguese population described a prevalence of 0.6% among women aged between 20 and 39 years (33). Although slightly lower than the prevalence described in the current study, taking into account that the authors did not include type 1 diabetes and that approximately 15% of the mothers included in the cohort are above 40 years of age, we believe that the 0.9% prevalence described is probably lower than the true prevalence of diabetes mellitus in general Portuguese women within this age range. This assumption is supported by data from the Portuguese National Health Survey, that described a self-reported prevalence of 2.7% for diabetes mellitus in women aged between 15 and 44 years old (23). Overall, the prevalence of the cardiometabolic comorbidities seems to be lower than previously described in the general population. This may be explained by the specific characteristics of our sample, since we studied a sample of women who successfully led at least one pregnancy to a live born, which may imply that these women were on average healthier than the general population of the same age group. In contrast, this is not true for the metabolic and lifestyle risk factors.

The high prevalence of young women with at least one cardiovascular risk factor, as well as their clustering, highlights the adverse cardiovascular profile of these women. Results from a prospective cohort study (9) showed that only about 20% of American women younger than 40 years of age presented favourable levels of five major risk factors (smoking, hypertension, diabetes, serum cholesterol and body mass index). Another study found that, in women aged between 18 and 75 years, 19% presented a clustering of three or more metabolic risk factors for coronary heart disease (11). In this study of Portuguese women who delivered a live born the proportion of women without any of the 8 cardiovascular risk factors considered is less than 5%, shortly after delivery. Additionally, the clustering of cardiovascular risk factors is already evident, with 17% of women presenting at least one risk factor from each group of risk considered: unfavorable lifestyles, adiposity and cardiometabolic comorbidities. Our intention in approaching several risk factors in the same population is related with the need to appreciate global cardiovascular risk, more than the fragmented view of individual risk factors. Tools for absolute risk estimation have been recommended for this purpose, even to support therapeutic decisions (34). In Europe, the SCORE system is recommended to evaluate CVD risk (35). These guidelines have several limitations and tend to underestimate CVD risk in the younger age-groups (36). Therefore, we believe that the aggregation of risk factors is more informative of risk at younger ages than a risk score.

A previous work from our research group presented the self-reported prevalence of 5 risk factors, in this sample of Portuguese women, before pregnancy (16). Overall, 21.3% were overweight, 8.8% were obese and 26.6% smoked. The prevalence of hypertension, dyslipidemia and diabetes mellitus was 1.7%, 1.7% and 0.6%, respectively, with an evident tendency to cluster. Only 4 years after delivery, the prevalence of these risk factors, except smoking, increased drastically. Although part of this increase may be due to underreport of weight by women (37) and to the lack of awareness of clinical diagnoses in young ages (30, 38), it is unlikely that this would totally explain such a huge increase in prevalence.

In the present study, indicators of socio-economic position were inversely associated with all risk factors. This reveals the existence of inequalities in health with those from lower social classes having an unfavorable cardiovascular risk profile. In the last 30 years, Portugal experienced a significant development regarding economic modernization and social structure (39), which resulted in lifestyle changes that may have an impact on cardiovascular risk. The economic improvements may contribute to a higher frequency of adverse lifestyles, such as sedentary behaviours and unhealthy eating habits, especially among the lower social classes (40, 41). Therefore, women from the lowest educational and income strata should be the main target group for educational intervention regarding cardiovascular risk factors. In this context and since low health literacy is associated with a range of adverse health outcomes (42), health education should be literacy sensitive in order to enhance health knowledge and self-efficacy to promote the adoption of healthier lifestyles (43).

In conclusion, the prevalence of unfavorable lifestyles and adiposity was very high among women who achieved a successful pregnancy, as early as 4 years after delivery, and the clustering of risk factors emphasizes the unfavourable cardiovascular risk profile at a young age. However, the potential for prevention is vast especially when considering the modifiable nature of the most important risk factors. Thus, these data emphasize the need for prevention early in life, by lifestyle approaches, which should be considered a national public policy priority.

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Table 1. Participant's characteristics in the overall study sample and those with fasting blood sample.

	All women n=5435	**With fasting blood sample** n=2483
Age (years), n (%)		
< 25	240 (4.4)	115 (4.6)
25-29	829 (15.2)	407 (16.4)
30-34	1780 (32.8)	819 (33.0)
35-39	1784 (32.8)	795 (32.0)
≥ 40	802 (14.8)	347 (14.0)
Gravidity, n (%)		
1	2007 (36.9)	926 (37.3)
2	2172 (40.0)	1014 (40.9)
≥ 3	1256 (23.1)	543 (21.9)
Marital status, n (%)		
Married/living with a partner	4843 (89.1)	2177 (87.7)
Single/divorced/widow	592 (10.9)	306 (12.3)
Education (years), n (%)		
≤ 4	345 (6.4)	177 (7.1)
5-9	2088 (38.4)	968 (39.0)
10-12	1516 (27.9)	671 (27.0)
> 12	1486 (27.3)	667 (26.9)
Working condition, n (%)		
Employed	4117 (75.8)	1869 (75.3)
Unemployed	928 (17.1)	446 (18.0)
Housewife	254 (4.7)	106 (4.3)
Others	136 (2.5)	62 (2.5)
Household monthly income (€), n (%)		
< 500	224 (4.1)	125 (5.0)
500-1000	1296 (23.9)	641 (25.8)
1001-1500	1523 (28.0)	648 (26.1)
> 1500	2304 (42.4)	1030 (41.5)
Does not know/ Prefers not to answer	88 (1.6)	39 (1.6)

Table 2. Prevalence of smoking, low fruits and vegetables consumption and sedentariness, 4 years after delivery, and age-adjusted odds ratios for the association with gravidity, socio-economic characteristics and BMI, in mothers of a Portuguese birth cohort (n=5435).

	Smoking Status[a]				Fruits and vegetables consumption		Leisure physical exercise	
	Current		Former		<3 portions/day		Sedentariness	
	n (%)	Age-adjusted OR (95%CI)[b]	n (%)	Age-adjusted OR (95%CI)[b]	n (%)	Age-adjusted OR (95%CI)[b]	n (%)	Age-adjusted OR (95%CI)[b]
Age (years)								
< 30	409 (38.3)	1[c]	136 (12.7)	1[c]	687 (64.3)	1[c]	939 (87.8)	1[c]
30-34	424 (23.8)	0.49 (0.41-0.58)	238 (13.4)	0.82 (0.65-1.04)	910 (51.1)	0.58 (0.50-0.68)	1414 (79.4)	0.53 (0.43-0.66)
35-39	371 (20.8)	0.43 (0.36-0.51)	303 (17.0)	1.05 (0.84-1.32)	827 (46.4)	0.48 (0.41-0.56)	1397 (78.3)	0.50 (0.40-0.62)
≥ 40	172 (21.5)	0.47 (0.38-0.58)	164 (20.5)	1.36 (1.05-1.76)	331 (41.3)	0.39 (0.32-0.47)	666 (83.0)	0.68 (0.52-0.88)
Gravidity								
1	507 (25.3)	1[c]	295 (14.7)	1[c]	1076 (53.6)	1[c]	1605 (80.0)	1[c]
2	531 (24.5)	1.10 (0.95-1.27)	347 (16.0)	1.04 (0.87-1.24)	1061 (48.9)	0.93 (0.81-1.05)	1759 (81.0)	1.14 (0.97-1.33)
≥ 3	338 (26.9)	1.31 (1.10-1.56)	199 (15.9)	1.01 (0.82-1.25)	618 (49.2)	1.01 (0.87-1.17)	1052 (83.8)	1.38 (1.14-1.68)
Marital status								
Married/living with a partner	1100 (22.7)	1[c]	772 (15.9)	1[c]	2420 (50.0)	1[c]	3940 (81.4)	1[c]
Single/ divorced/widow	276 (46.6)	2.71 (2.24-3.27)	69 (11.7)	1.08 (0.82-1.43)	335 (56.6)	1.16 (0.97-1.38)	476 (80.4)	0.84 (0.68-1.05)
Education (years)								
≤ 4	75 (21.7)	1[c]	43 (12.5)	1[e]	205 (59.4)	1[e]	319 (92.5)	1[e]
5-9	650 (31.1)	1.51 (1.13-2.00)	269 (12.9)	1.33 (0.93-1.91)	1213 (58.1)	0.80 (0.63-1.02)	1833 (87.8)	0.57 (0.37-0.87)
10-12	377 (24.9)	1.23 (0.92-1.65)	260 (17.2)	1.76 (1.23-2.52)	789 (52.0)	0.65 (0.51-0.82)	1201 (79.2)	0.31 (0.21-0.48)
> 12	274 (18.4)	0.96 (0.71-1.29)	269 (18.1)	1.63 (1.14-2.33)	548 (36.9)	0.39 (0.31-0.50)	1063 (71.5)	0.22 (0.14-0.33)
Working condition								
Employed	985 (23.9)	1[c]	653 (15.9)	1[c]	2003 (48.7)	1[c]	3308 (80.4)	1[c]
Unemployed	299 (32.2)	1.40 (1.19-1.66)	139 (15.0)	1.07 (0.87-1.31)	563 (60.7)	1.53 (1.32-1.78)	773 (83.3)	1.13 (0.94-1.38)
Housewife	48 (18.9)	0.63 (0.45-0.88)	28 (11.0)	0.57 (0.38-0.85)	122 (48.0)	0.96 (0.74-1.24)	217 (85.4)	1.35 (0.94-1.93)
Others	44 (32.4)	1.35 (0.91-1.99)	21 (15.4)	1.14 (0.69-1.87)	67 (49.3)	0.90 (0.63-1.27)	118 (86.8)	1.45 (0.87-2.40)
Household monthly income (€)								
< 500	94 (42.0)	1[c]	26 (11.6)	1[c]	136 (60.7)	1[c]	201 (89.7)	1[c]
500-1000	390 (30.1)	0.61 (0.45-0.83)	160 (12.4)	0.88 (0.55-1.40)	738 (56.9)	0.89 (0.66-1.19)	1129 (87.1)	0.81 (0.51-1.29)
1001-1500	368 (24.2)	0.50 (0.37-0.68)	239 (15.7)	1.09 (0.69-1.72)	859 (56.4)	0.90 (0.67-1.21)	1303 (85.6)	0.74 (0.47-1.17)
> 1500	495 (21.5)	0.48 (0.36-0.66)	403 (17.5)	1.19 (0.76-1.86)	974 (42.3)	0.55 (0.41-0.73)	1711 (74.3)	0.38 (0.24-0.59)
Does not know/ Prefers not to answer	29 (33.0)	0.77 (0.44-1.33)	13 (14.8)	1.09 (0.51-2.32)	48 (54.6)	0.86 (0.52-1.42)	72 (81.8)	0.53 (0.27-1.07)
Body mass index (kg/m^2)								
<24.9	735 (28.6)	1[c]	384 (15.0)	1[c]	1329 (51.7)	1[c]	2071 (80.6)	1[c]
25.0-29.9	378 (22.1)	0.72 (0.62-0.84)	276 (16.2)	0.97 (0.81-1.15)	844 (49.4)	0.94 (0.83-1.07)	1370 (80.2)	0.98 (0.84-1.14)
≥30	263 (22.7)	0.72 (0.61-0.85)	181 (15.6)	0.95 (0.78-1.15)	582 (50.3)	0.95 (0.83-1.09)	975 (84.3)	1.27 (1.06-1.54)

95%CI, 95% confidence interval; BMI, body mass index, OR, odds ratio
[a] Reference class of outome: never smokers
[b] Except for age
[c] Reference class

Table 3. Prevalence of overweight, obesity and abdominal obesity, 4 years after delivery, and age-adjusted odds ratios for the association with gravidity and socio-economic characteristics, in mothers of a Portuguese birth cohort (n=5435).

	BMI[a]				Abdominal obesity	
	Overweight		Obesity			
	n (%)	Age-adjusted OR (95%CI)[b]	n (%)	Age-adjusted OR (95%CI)[b]	n (%)	Age-adjusted OR (95%CI)[b]
Age (years)						
< 30	299 (28.0)	1[c]	240 (22.5)	1[c]	329 (30.9)	1[c]
30-34	542 (30.5)	1.12 (0.94-1.34)	380 (21.4)	0.98 (0.81-1.19)	546 (30.7)	1.00 (0.84-1.17)
35-39	576 (32.3)	1.18 (0.99-1.41)	346 (19.4)	0.89 (0.73-1.08)	555 (31.1)	1.02 (0.86-1.20)
≥ 40	292 (36.4)	1.62 (1.31-2.01)	191 (23.8)	1.32 (1.04-1.67)	298 (37.2)	1.33 (1.10-1.62)
Gravidity						
1	598 (29.8)	1[c]	382 (19.0)	1[c]	565 (28.2)	1[c]
2	697 (32.1)	1.12 (0.97-1.29)	447 (20.6)	1.18 (1.00-1.39)	694 (32.0)	1.19 (1.04-1.36)
≥ 3	414 (33.0)	1.28 (1.07-1.51)	328 (26.1)	1.71 (1.41-2.06)	469 (37.3)	1.47 (1.26-1.72)
Marital status						
Married/living with a partner	1539 (31.8)	1[c]	1052 (21.7)	1[c]	1588 (32.8)	1[c]
Single/ divorced/widow	170 (28.7)	0.81 (0.66-0.99)	105 (17.7)	0.70 (0.55-0.88)	140 (23.7)	0.63 (0.52-0.78)
Education (years)						
≤ 4	132 (38.3)	1[c]	123 (35.7)	1[c]	169(49.0)	1[c]
5-9	684 (32.8)	0.63 (0.47-0.84)	565 (27.1)	0.54 (0.40-0.73)	817 (39.1)	0.73 (0.58-0.93)
10-12	483 (31.9)	0.48 (0.36-0.65)	284 (18.8)	0.30 (0.22-0.40)	437 (28.8)	0.45 (0.36-0.58)
> 12	410 (27.6)	0.32 (0.23-0.42)	185 (12.5)	0.15 (0.11-0.21)	305 (20.5)	0.27 (0.21-0.35)
Working condition						
Employed	1282 (31.2)	1[c]	778 (18.9)	1[c]	1185 (28.8)	1[c]
Unemployed	296 (31.9)	1.33 (1.12-1.58)	267 (28.8)	1.94 (1.62-2.33)	376 (40.5)	1.70 (1.47-1.98)
Housewife	90 (35.4)	1.60 (1.18-2.17)	75 (29.5)	2.19 (1.59-3.02)	115 (45.3)	2.02 (1.56-2.61)
Others	41 (30.2)	1.19 (0.79-1.79)	37 (27.2)	1.70 (1.12-2.60)	52 (38.2)	1.57 (1.10-2.34)
Household monthly income (€)						
< 500	75 (33.5)	1[c]	62 (27.7)	1[c]	91 (40.6)	1[c]
500-1000	422 (32.6)	0.96 (0.68-1.34)	370 (28.6)	1.02 (0.72-1.46)	523 (40.4)	0.98 (0.73-1.31)
1001-1500	494 (32.4)	0.83 (0.60-1.16)	366 (24.0)	0.75 (0.53-1.07)	537 (35.3)	0.77 (0.58-1.03)
> 1500	693 (30.1)	0.58 (0.42-0.80)	340 (14.8)	0.35 (0.24-0.50)	546 (23.7)	0.42 (0.32-0.56)
Does not know/ Prefers not to answer	25 (28.4)	0.61 (0.34-1.10)	19 (22.5)	0.57 (0.31-1.08)	31 (35.2)	0.75 (0.45-1.26)

95%CI, 95% confidence interval; BMI, body mass index, OR, odds ratio

[a] Reference class of outcome: BMI <25 Kg/m^2

[b] Except for age

[c] Reference class

Table 4. Prevalence of hypertension, dyslipidemia and diabetes mellitus, 4 years after delivery, and age-adjusted odds ratios for the association with gravidity, socio-economic characteristics and BMI, in mothers of a Portuguese birth cohort.

	Hypertension n=5435		**Dyslipidemia** n=2483		**Diabetes mellitus** n=2483	
	n (%)	**Age-adjusted OR (95%CI)[a]**	**n (%)**	**Age-adjusted OR (95%CI)[a]**	**n (%)**	**Age-adjusted OR (95%CI)[a]**
Age (years)						
< 30	33 (3.1)	1[b]	81 (15.5)	1[b]	2 (0.4)	1[b]
30-34	117 (6.6)	2.21 (1.49-3.28)	146 (17.8)	1.18 (0.88-1.59)	2 (0.2)	0.64 (0.09-4.53)
35-39	179 (10.0)	3.50 (2.40-5.12)	156 (19.6)	1.33 (0.99-1.78)	12 (1.5)	3.98 (0.89-17.88)
≥ 40	143 (17.8)	6.82 (4.62-10.09)	77 (22.2)	1.55 (1.10-2.20)	6 (1.7)	4.57 (0.92-22.80)
Gravidity						
1	152 (7.6)	1[b]	157 (17.0)	1[b]	6 (0.7)	1[b]
2	187 (8.6)	0.90 (0.72-1.14)	187 (18.4)	1.06 (0.83-1.34)	10 (1.0)	1.14 (0.41-3.21)
≥ 3	133 (10.6)	0.95 (0.73-1.23)	116 (21.4)	1.24 (0.94-1.63)	6 (1.1)	1.12 (0.35-3.63)
Marital status						
Married/living with a partner	432 (8.9)	1[b]	409 (18.8)	1[b]	16 (0.7)	1[b]
Single/ divorced/widow	40 (6.8)	0.88 (0.62-1.23)	51 (16.7)	0.90 (0.65-1.25)	6 (2.0)	3.39 (1.29-8.91)
Education (years)						
≤ 4	51 (14.8)	1[b]	32 (18.1)	1[b]	2 (1.1)	1[b]
5-9	180 (8.6)	0.78 (0.56-1.11)	195 (20.1)	1.26 (0.83-1.92)	13 (1.3)	1.66 (0.36-7.59)
10-12	129(8.5)	0.75 (0.52-1.07)	126 (18.8)	1.14 (0.74-1.76)	3 (0.5)	0.57 (0.09-3.47)
> 12	112 (7.5)	0.51 (0.35-0.73)	107 (16.0)	0.86 (0.55-1.33)	4 (0.6)	0.54 (0.10-2.99)
Working condition						
Employed	337 (8.2)	1[b]	329 (17.6)	1[b]	14 (0.8)	1[b]
Unemployed	93 (10.0)	1.37(1.07-1.75)	102 (22.9)	1.42 (1.10-1.83)	6 (1.4)	1.79 (0.68-4.72)
Housewife	30 (11.8)	1.43 (0.95-2.14)	21 (19.8)	1.17 (0.71-1.92)	1 (0.9)	1.16 (0.15-9.00)
Others	12 (8.8)	1.34 (0.72-2.47)	8 (12.9)	0.72 (0.34-1.53)	1 (1.6)	2.63 (0.33-20.63)
Household monthly income (€)						
< 500	24 (10.7)	1[b]	24 (19.2)	1[b]	2 (1.6)	1[b]
500-1000	130(10.0)	0.89 (0.56-1.44)	126 (19.7)	1.03 (0.63-1.68)	10 (1.6)	0.94 (0.20-4.41)
1001-1500	127 (8.3)	0.68 (0.43-1.10)	127 (19.6)	1.00 (0.61-1.63)	6 (0.9)	0.54 (0.11-2.78)
> 1500	186 (8.1)	0.57 (0.36-0.91)	175 (17.0)	0.80 (0.49-1.29)	3 (0.3)	0.14 (0.02-0.88)
Does not know/ Prefers not to answer	5 (5.7)	0.39 (0.14-1.06)	8 (20.5)	1.02 (0.41-2.50)	1 (2.6)	1.21 (0.11-14.00)
Body mass index (kg/m^2)						
<24.9	116 (4.5)	1[c]	135 (11.6)	1[b]	6 (0.5)	1[b]
25.0-29.9	158 (9.3)	2.02 (1.57-2.59)	165 (21.1)	2.00 (1.56-2.56)	6 (0.8)	1.40 (0.45-4.38)
≥30	198 (17.1)	4.38 (3.43-5.59)	160 (29.9)	3.24 (2.50-4.20)	10 (1.9)	3.60 (1.30-9.99)

95%CI, 95% confidence interval; BMI, body mass index; OR, odds ratio
[a] Except for age
[b] Reference class

Figure 1. Prevalence and 95% confidence intervals of individual risk factors.

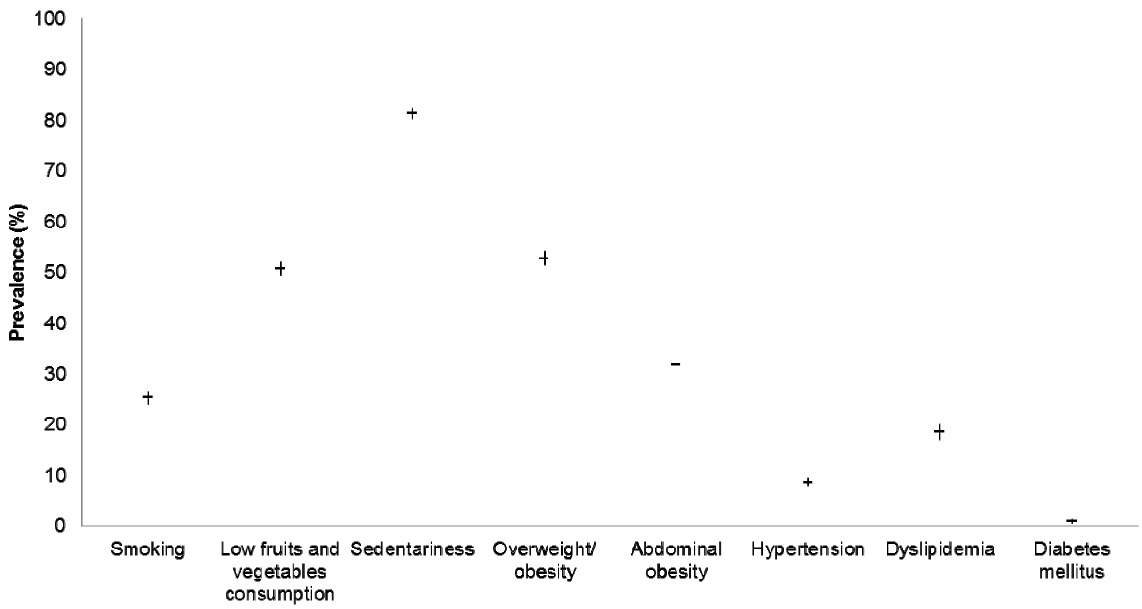
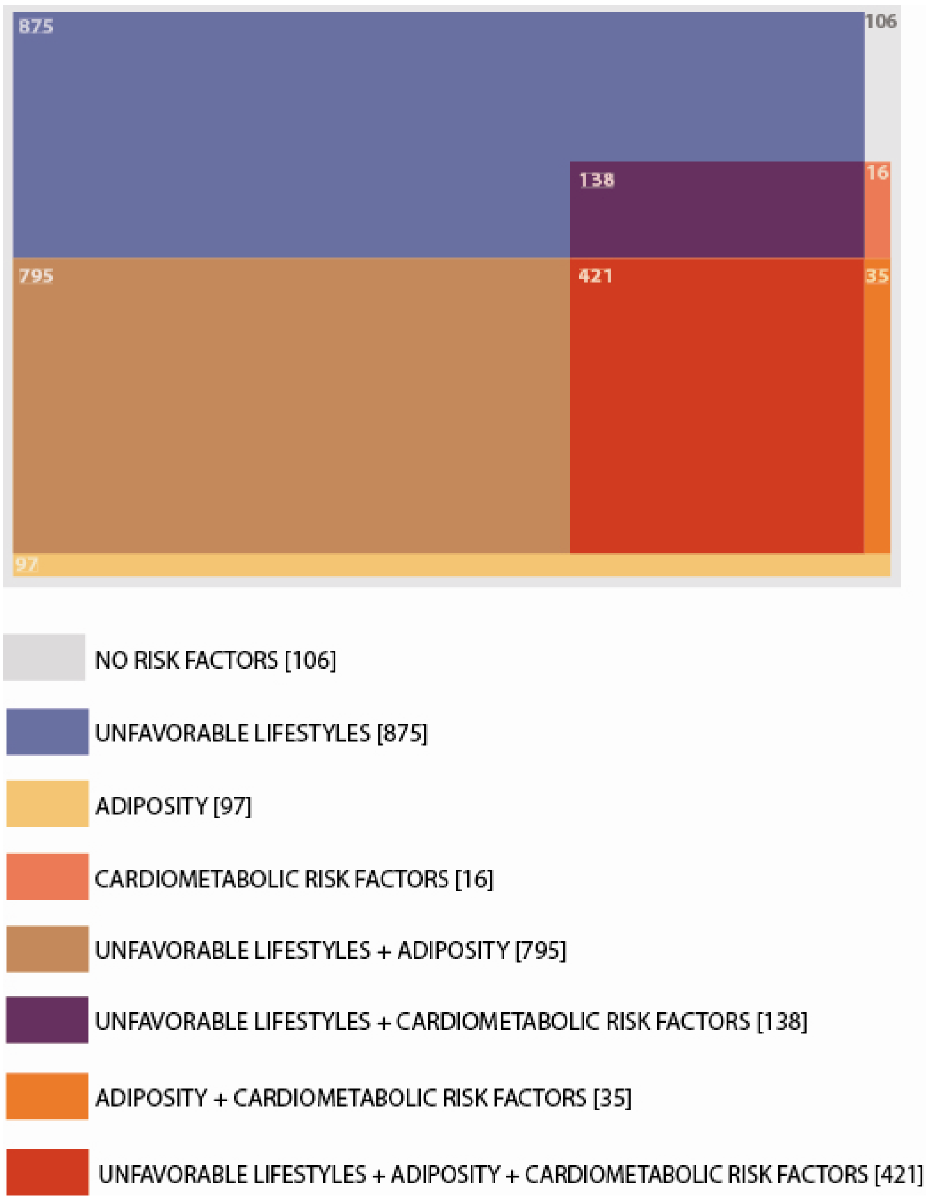


Figure 2. Number of women with no risk factors or at least one risk factor from each of 3 groups considered: unfavorable lifestyles, adiposity and cardiometabolic comorbidities. The area of the individual rectangles and overlap areas are proportional to the number of women in the respective level of exposure. Only the subsample with information available for all risk factors was considered (n=2483).



GENERAL DISCUSSION

In this dissertation, the cardiovascular risk profile of mothers of a Portuguese birth cohort was assessed referring to before and 4 years after pregnancy, including both descriptive and analytic approaches to cover the quantification of the burden of risk factors, factors contributing to such exposure, consequences to mother and child, and the effect of pregnancy itself on the change of risk. Overall, the results suggest a high level of risk among this young female population with successful reproduction, and unfortunately do not support long-term effects of lifestyle changes during pregnancy.

Before pregnancy, approximately a third of the women were overweight or obese and more than a quarter smoked. Although the prevalence of self-reported cardiometabolic comorbidities (hypertension, dyslipidemia and diabetes mellitus) was lower than 2%, their tendency to cluster was evident. As early as 4 years after delivery, almost 90% of the participants had at least one the three unfavourable lifestyles: smoking, low intake of fruit and vegetables, and sedentariness. At this time, more than half were overweight, obese or had abdominal obesity and a quarter presented hypertension, dyslipidemia or diabetes mellitus. Overall, 17% of the women presented at least one risk factor from each of the 3 groups: adverse lifestyles, adiposity and cardiometabolic comorbidities.

It has been recognized that cardiovascular risk factors are associated with each other and their effects tend to be synergistic rather than additive (20). Thus, the assessment of multiple risk factors is crucial to identify a high risk population. The aggregation found between these risk factors, even before pregnancy, among young and apparently healthy women, suggests that the pathogenic process is initiated early in life. Results from a prospective cohort study of women aged 18 to 39 years (17) showed that favourable levels of major risk factors were associated with lower long-term CVD and all-cause mortality. Unfortunately, only about 20% of the women met the lowest criteria of having no unfavourable risk factors. In our cohort, the prevalence of women without any cardiovascular risk factors was even lower. Overall, a high prevalence of potentially modifiable cardiovascular risk factors was described among women who were able to successfully lead a pregnancy to a live born. 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 (180, 181), contributing to a marked reduction in mortality, morbidity, and maintaining quality of life (182, 183). Therefore, early detection of individuals with modifiable and treatable cardiovascular risk factors may result in saving lives, and reducing the burden of disease and healthcare costs.

Pregnancy induces profound alterations in maternal haemodynamics and metabolism, which may reveal previous background risk and/or induce long-term metabolic and vascular abnormalities that increase the propensity to develop cardiovascular diseases (67, 68).

In fact, the presence of risk factors before pregnancy was also associated with pregnancy-related complications. In the cohort Geração XXI, 5% of primiparous and 4% of multiparous women had a hypertensive disorder in pregnancy and a high proportion of cases were explained by the joint effect of previously recognized prepregnancy risk factors. This emphasizes the importance of preconception and prenatal health, widely recognized as critical components of maternal and child health promotion, during women's reproductive life (184, 185). However, in Portugal, a study performed in the north of the country showed that, although 99% of pregnant women received prenatal surveillance, only 27% had preconceptional care (186). Therefore, it is important to invest in pregnancy planning, with the objective of optimizing women's wellness and subsequent pregnancy outcomes.

Additionally, the development of gestational hypertensive disorders was significantly associated with higher systolic and diastolic blood pressure an average of 4 years after birth, both in mothers and their male offspring. Despite the relatively low prevalence of hypertensive disorders in pregnancy, the severity of short-term consequences observed emphasizes the period after delivery as critical to develop and promote preventive strategies. In Portugal, a puerperium visit is recommended but there are no specific guidelines regarding further care after a pregnancy (187). Since children are regularly followed by their family physician, until enter in adulthood (188), this contact with the health care may constitute an opportunity to manage cardiovascular risk and other relevant health issues in the mothers, shortly after pregnancy. In this context, integration of the mother's care during the routine appointments of the child might constitute an effective strategy to assess and manage maternal health, with a higher likelihood of attendance and adherence. Obviously, this model would have to be tested to confirm its feasibility and success, which is out of scope of this work.

Beyond the harmful effects on the health of the developing foetus, a compelling reason to promote smoking cessation during pregnancy is the prospect that the short-term abstinence would become lifelong cessation. However, although almost half of smokers stopped during pregnancy, 4 years after delivery, two thirds resumed smoking. This high rate of relapse questions the true impact of smoking cessation during pregnancy on women's smoking trajectory. Quitting smoking during pregnancy is a different behaviour than quitting at any another time in a woman's life. Because the intention to quit is often motivated by the health of the baby and not the woman's own health (66), the process and motivation for smoking cessation is different compared to quitting smoking at other times. Postpartum relapse may reflect the extent to which initial cessation was extrinsically motivated by social pressure and concerns with the child health (189). Although there are still negative health consequences of secondhand smoke on children, parents may feel that they can have a higher control of the child exposure to smoke after delivery than during pregnancy. Additionally, depression, anxiety and the stress of caring for a newborn (190), as well as the lack of perceived social support to remain abstinent, may also precipitate relapse (191). To remain abstinent, it is necessary that the motivation not to smoke remain higher than the motivation to smoke on all occasions when smoking could occur. In this context, long-term abstinence is achieved through a process of identity change, from 'smoker' towards 'non-smoker' (192). Therefore, successful educational interventions should be implemented from preconceptional care to postpartum, in a continuum process of promotion of smoking cessation.

Following Western European countries movement, the fertility rate has been decreasing over the last 20 years, from 2.1 to 1.37 children per woman, between 1980 and 2008. Simultaneously, a drop in the fertility rate in the age groups below 30 was observed, opposed to an increase in higher age groups (7). These changes in the pattern of fertility may also play a role among the implications of pregnancy for the future health of the women, since older age is a risk factor for cardiovascular risk factors and for the development of cardiometabolic comorbidities during pregnancy.

Overall, indicators of socio-economic position were inversely associated with a favourable cardiovascular profile, before, during and after pregnancy. This suggests the existence of inequalities in health with those from lower social classes having a higher risk of developing cardiovascular disease in the future. In the last 30 years, Portugal experienced a significant development regarding economic modernization and social structure (193), which resulted in lifestyle changes that may have an impact on cardiovascular risk. The economic improvements may contribute to a higher frequency of adverse lifestyles, especially among the lower social classes (29, 30). In this context and since low health literacy is associated with a range of adverse health outcomes (194), health education should be literacy sensitive in order to enhance health knowledge and self-efficacy to promote the adoption of healthier lifestyles at a long term (195). However, it was reported that, during pregnancy, more educated women are less willing to admit smoking to prenatal care providers (160), which can lead to misclassification of the exposure. Therefore, it is possible that, at least during pregnancy, the association between socio-economic position and adverse lifestyles has been overestimated, due to social desirability.

This is the first study to assess the cardiovascular risk profile of young Portuguese women, before, during and shortly after a successful pregnancy. However, some limitations should be discussed. The cohort Geração XXI is a birth cohort and maternal data was collected in this context. Therefore, mothers were invited to participate after delivery and data regarding prepregnancy characteristics were self-reported. Consequently, the prevalence of the risk factors before pregnancy may be underestimated due to the underreport of weight by women (196) and the lack of awareness of disease in young ages (197, 198). As early as 4 years after delivery, we described a drastic increase on the prevalence all the risk factors, except smoking. Although part of this increase may be explained by the self-report of the risk factors at baseline, it is unlikely that this would explain totally the increase in prevalence.

In the last decades, a stronger emphasis on women's health status and risk behaviour patterns before pregnancy is advocated (199) in order to increase the awareness and the potential for prevention at younger ages. In fact, the high prevalence of several cardiovascular risk factors, as well as their clustering, not only after but also before pregnancy, reveals an unfavourable cardiovascular risk profile of these women. Therefore, the main results of this thesis emphasize the need to implement coherent and effective strategies of health promotion and disease prevention at early stages of life in order to optimize women's current and future health.

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