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par **Kénora CHAU**

Dysfonction diastolique, rigidité artérielle aortique et hypertension : facteurs anthropométriques et métaboliques associés et prise en charge en population générale

10 décembre 2018

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A ma famille

A mes amis

ABREVIATIONS

Nous ne donnons ici que la signification des abréviations utilisées dans le texte en français. Les abréviations en anglais ont été utilisées et définies dans les publications et les présentations dans des congrès.

ABSI	“A body shape index”
ASE	American Society of Echocardiography
β	Coefficient de régression linéaire
βsa	Coefficient de régression linéaire ajusté sur le sexe, l’âge et la pression artérielle moyenne mesurées le jour où la VOPcf a été mesurée
CIC-P	Centre d’Investigation Clinique Plurithématique
DD	Dysfonction diastolique
DD 2-3	Dysfonction diastolique grades 2 et 3
DEXA	Absorptiométrie biénergétique aux rayons X
EAE	European Association of Echocardiography
FEVG	Fraction d’éjection du ventricule gauche
HDL	Taux de lipoprotéines de haute densité
HTA	Hypertension artérielle
IC 95 %	Intervalle de confiance à 95 %
IMC	Indice de masse corporelle
INSERM	Institut national de la santé et de la recherche médicale
LDL	Taux de lipoprotéines de basse densité
MAPA 24h	Mesure ambulatoire de la pression artérielle sur 24 heures
MG	Médecin généraliste
OR	Odds ratio
ORsa	Odds ratio ajusté sur le sexe et l’âge
ORajusté	Odds ratio ajusté
p	Niveau de signification
PAD	Pression artérielle diastolique
PADc	Pression artérielle diastolique casuelle
PAS	Pression artérielle systolique
PASc	Pression artérielle systolique casuelle
PCR	Protéine C-réactive

PP	Pression pulsée
r	Coefficient de corrélation de Pearson
Ratio TT / IMC	Ratio tour de taille sur taille
Ratio TT / TH	Ratio tour de taille sur tour de hanche
Ratio TT / T	Ratio tour de taille sur taille
STANISLAS	Suivi Temporaire Annuel Non-Invasif de la Santé des Lorrains Assurés Sociaux
TG	Triglycérides
TT	Tour de taille
VOPcf	Vitesse d'onde de pouls carotidofémorale

Table des matières

1. Position des problèmes 8

2. Objectifs 19

3. Association entre l'obésité et des caractéristiques métaboliques 20

4. Association entre l'obésité abdominale et le risque de rigidité artérielle aortique accrue 20 ans plus tard dans une cohorte d'adultes initialement en bonne santé 35

5. Facteurs associés à une hypertension artérielle non-diagnostiquée 46

6. Discussion générale 57

6.1. Association des mesures de l'obésité générale et de l'adiposité abdominale avec la dysfonction diastolique et la rigidité artérielle 57

6.2. Facteurs associés à une hypertension artérielle non-diagnostiquée 61

7. Perspectives 64

8. Conclusion générale 69

9. Production scientifique 71

10. Références 73

Annexe A : Données supplémentaires pour les publications 86

A1. Association entre l'obésité et des caractéristiques métaboliques et le risque de développement à long terme d'une dysfonction diastolique dans une cohorte d'adultes initialement en bonne santé..... 86

A2. Association entre l'obésité abdominale et le risque de rigidité artérielle aortique 20 ans plus tard dans une cohorte d'adultes initialement en bonne santé.....103

A3. Facteurs associés à une hypertension artérielle non-diagnostiquée.....116

Annexe B : Abstracts des présentations orales et affichées 121

Résumé de la thèse en français et abstract en anglais 129

1. Position des problèmes

Le remodelage cardiaque et artériel en réponse à des stimuli physiopathologiques peut se manifester sous différentes formes dont une dysfonction diastolique du ventricule gauche (DD), une rigidité accrue de l'aorte mesurée par une vitesse plus élevée de l'onde de pouls carotido-fémorale (VOPcf) et une hypertension artérielle (HTA). Les maladies cardiovasculaires sont la première cause de mortalité dans le monde et la deuxième cause de mortalité en France juste après les cancers [1]. Malgré quatre décennies de baisse de mortalité et de morbidité grâce à la prévention et aux progrès thérapeutiques, ces maladies ont causé environ 140 000 morts par an [1]. Elles restent l'une des principales causes de morbidité (3,5 millions de personnes traitées en 2012 parmi les assurés du régime général et plus de 11 millions traités pour le risque vasculaire ou le diabète) [1].

Ces problèmes devraient s'accroître avec le vieillissement de la population qui touche les pays développés et les pays émergents [2]. En France, la proportion des personnes de 65 ans ou plus a augmenté de 13,9 % en 1990 à 18,8 % en 2016. La France occupait alors une position intermédiaire parmi les pays en Europe (tableau 1). Le vieillissement de la population s'accompagne d'une augmentation de la sédentarité. En effet, la fréquence de pratique sportive habituelle diminue fortement avec l'âge (tableau 2) [3]. Selon une enquête européenne et l'étude de cohorte Constance, la prévalence de l'obésité augmente fortement avec l'âge dans l'Union européenne et en France jusqu'à 75 ans puis baisse chez les individus plus âgés (tableaux 3 et 4) [4, 5].

D'autre part, l'obésité est une maladie chronique d'évolution pandémique [6]. Dans le monde, la prévalence du surpoids et de l'obésité est de 37 % pour les femmes et de 38 % pour les hommes [6]. En France, selon l'enquête déclarative ObEpi réalisée auprès d'individus de 18 ans ou plus, la prévalence de l'obésité a été estimée en 2012 à 15 %, soit près de 6,9 millions de personnes [7]. L'estimation issue de l'Etude nationale nutrition santé (ENNS) avec des données anthropométriques mesurées dans 73 Centres d'examen de santé de la Sécurité sociale en 2006,

trouvait une prévalence de l'obésité de 16,1 % chez les hommes et de 17,6 % chez les femmes de 18-74 ans [8]. La prévalence de l'obésité a augmenté de 76,4 % entre 1997 et 2012 [7]. Des études ont montré que l'indice de masse corporelle (IMC) pris isolément conduit à une sous-estimation de la présence de facteurs de risque cardio-métaboliques car une certaine proportion de personnes de poids normal ou en surpoids présentaient un ou plusieurs de ces facteurs [9]. Il serait donc opportun d'étudier l'IMC comme une variable quantitative conjointement aux mesures anthropométriques d'adiposité abdominale et biologiques.

Tableau 1. Proportion (%) de personnes de 65 ans dans différents pays en Europe (en 2016)

Pays	%	Pays	%
Italie	22,0	Espagne	18,7
Grèce	21,3	Autriche	18,5
Allemagne	21,1	Slovénie	18,4
Portugal	20,7	Hongrie	18,3
Finlande	20,5	République tchèque	18,3
Bulgarie	20,4	Pays-Bas	18,2
Suède	19,8	Royaume-Uni	17,9
Lettonie	19,6	Roumanie	17,4
Croatie	19,2	Pologne	16,0
Malte	19,0	Chypre	15,1
Lituanie	19,0	Slovaquie	14,4
Estonie	19,0	Luxembourg	14,2
France	**18,8**	Irlande	13,2
Danemark	18,8		

Source : Observatoire des territoires. Le vieillissement de la population et ses enjeux. 2018 [2].

Tableau 2. Fréquence (%) de pratique sportive habituelle selon le sexe et l'âge

	Hommes	Femmes
Age (ans)		
15-24	83	67
25-34	67	56
35-44	64	54
45-54	54	50
55-64	47	51
65 ans ou plus	45	44

Source : Direction de la recherche, des études, de l'évaluation et des statistiques. La santé des femmes en France. Collection Etudes et statistiques. La Documentation Française [3].

Tableau 3. Prévalence (%) de l'obésité selon le sexe et l'âge en France

	Hommes	Femmes
Age (ans)		
30-39	10,4	11,4
40-49	13,8	16,8
50-59	19,2	16,7
60-69	20,8	18,8

Source : Matta J, et al. Prévalence du surpoids, de l'obésité et des facteurs de risque cardio-métaboliques dans la cohorte Constances [5].

Tableau 4. Proportion d'adultes obèses (%) dans l'Union européenne et en France en 2014

	Union européenne	France
Age (ans)		
18-24	5,7	6,7
25-34	9,9	9,3
35-44	14,2	13,0
45-64	19,6	18,0
65-74	22,1	22,5
75 ans ou plus	17,3	18,3

Source : eurostat [4].

Selon les estimations de l'Organisation mondiale de la Santé, la moyenne de l'IMC, chez les hommes comme chez les femmes, a régulièrement augmenté de 1975 à 2016 dans toutes les grandes régions du Globe (tableau 5) [10]. Cette tendance a aussi été observée chez les enfants et les adolescents (<20 ans) [10].

L'épidémie d'obésité est donc un problème majeur de santé dans différents pays [8, 4, 6, 7, 10, 11-28]. Malgré des différences individuelles en termes de susceptibilité génétique pour l'accumulation de la graisse du corps, la proportion épidémique de l'obésité est partiellement le résultat d'une réduction du niveau d'activité physique quotidienne comme nous avons conçu pour nous-mêmes un environnement sédentaire très confortable [16]. La plupart des personnes sont sédentaires pendant les heures de travail et nous utilisons des moyens de transports pour nous déplacer (voitures, bus, trains, avions, etc.) [16]. Auparavant, les efforts quotidiens constant (pour

obtenir de la nourriture, parfois en quantité limitée) sont devenus plus faciles et les aliments raffinés favorisent la surconsommation passive de calories [16]. Certaines personnes vivent dans un environnement offrant peu de possibilités d'exercer des activités physiques et sportives. Notre environnement favorise donc une faible dépense d'énergie mais facilite la surconsommation de nourriture contribuant ainsi à l'installation de l'épidémie d'obésité dans le monde [16]. La physiopathologie de l'obésité est complexe et certaines personnes sont plus susceptibles d'accumuler l'excès de graisse et de développer des complications métaboliques que les autres [16].

Tableau 5. Moyenne de l'indice de masse corporelle chez les adultes (de 18 ans ou plus) estimée par l'Organisation mondiale de la Santé (estimation standardisée sur l'âge)

	1975	1980	1990	2000	2010	2016
Les 2 sexes confondus						
Afrique	19.7	20.3	21.3	22.2	22.9	23.2
Amérique	23.9	24.3	25.2	26.3	27.2	27.6
Asie du sud-est	18.7	19.2	20.2	20.9	21.7	22.2
Europe	24.4	24.6	25.1	25.6	26.2	26.4
Est Méditerranée	21.9	22.5	23.7	24.7	25.6	26.1
Ouest Pacific	21.0	21.3	21.9	22.4	23.2	23.7
Global	*21.8*	*22.1*	*22.8*	*23.4*	*24.0*	*24.5*
Hommes						
Afrique	19.3	19.8	20.8	21.6	22.2	22.4
Amérique	24.1	24.4	25.2	26.1	27.0	27.4
Asie du sud-est	18.7	19.2	20.1	20.8	21.5	22.0
Europe	24.1	24.4	25.0	25.6	26.4	26.7
Est Méditerranée	21.4	21.9	23.0	23.9	24.8	25.3
Ouest Pacific	20.9	21.2	21.9	22.5	23.3	24.0
Global	*21.6*	*21.9*	*22.6*	*23.2*	*23.9*	*24.3*
Femmes						
Afrique	20.2	20.7	21.8	22.8	23.7	24.1
Amérique	23.8	24.2	25.3	26.4	27.3	27.8
Asie du sud-est	18.7	19.2	20.2	21.1	21.9	22.4
Europe	24.5	24.8	25.2	25.6	26.0	26.1
Est Méditerranée	22.4	23.0	24.3	25.4	26.5	27.0
Ouest Pacific	21.1	21.4	21.9	22.4	23.0	23.4
Global	*22.0*	*22.3*	*23.0*	*23.6*	*24.2*	*24.3*

Source : l'Organisation mondiale de la Santé, 2017 [10].

Le rôle de l'obésité générale et de l'adiposité abdominale sur les risques cardiovasculaires, des dysfonctions et maladies cardiovasculaires (dyslipidémie, dysfonction diastolique, rigidité artérielle aortique, hypertension, fibrillation auriculaire, athérosclérose, etc.), le diabète et la

mortalité a mobilisé un grand nombre de travaux [11- 40]. Le tissu adipeux sous-cutané est souvent considéré comme protecteur alors que le tissu adipeux viscéral comme pathologique [12]. Toutefois, les deux types de tissus ont des potentiels protectifs et pathologiques, avec des fonctions biologiques interdépendantes : l'augmentation du tissu adipeux viscéral est un marqueur de substitution pour le dysfonctionnement du tissu adipeux sous-cutané lequel augmente le tour de taille (TT), reflétant un processus pathologique conduisant à l'accumulation de graisse pathogène d'autres dépôts de graisse et d'infiltration graisseuse des organes du corps non-adipeux [12]. L'obésité centrale ou abdominale est un marqueur clinique pour l'adiposopathie (troubles anatomiques et fonctionnels des adipocytes pathologiques et des tissus adipeux, favorisés par un équilibre calorique positif, chez des individus sensibles) tandis que l'augmentation de l'adiposité viscérale un marqueur de substitution pour le dysfonctionnement global des graisses [12].

Plusieurs organisations recommandent d'utiliser des mesures d'adiposité abdominale conjointement avec l'IMC pour étudier le risque pour les problèmes de santé liés à l'obésité [13, 15]. De nombreuses études ont montré que les mesures anthropométriques de l'adiposité abdominale (telles que le TT) sont fortement et positivement associées à la mortalité toute cause confondue, la mortalité cardiovasculaire et celle due au cancer indépendamment de l'IMC [17]. La mortalité est une mesure globale des effets des facteurs de risques et de leurs conséquences durant la vie entière. Les dysfonctionnements et maladies cardiovasculaires sont des mesures des effets de ces facteurs jusqu'au moment de l'étude ; leur sévérité et la morbidité associée pourraient beaucoup différer entre les populations étudiées, ce qui pourrait conduire des études à des résultats discordants.

Dans le contexte du vieillissement de la population et de l'augmentation de l'IMC et de la prévalence de l'obésité, il serait important d'étudier l'association de l'obésité générale et abdominale et des caractéristiques métaboliques avec le risque de développement à long terme de la DD et de la VOPcf. Il faut noter que la mortalité cardiovasculaire représentait 31 % en 2002

alors qu'au moins 80 % des décès prématurés par maladies cardiaques, accident vasculaire cérébral et diabète de type 2 pourraient être évités (grâce à une alimentation saine, une activité physique régulière et en évitant le tabac) [41]. Pour l'hypertension artérielle, il serait important d'identifier les facteurs associés à une hypertension artérielle non-diagnostiquée (sans que les individus concernés en soient conscients, retardant ainsi sa détection et sa prise en charge). Un retard dans le repérage du risque cardiovasculaire et dans la dispensation des soins sont imputés à la méconnaissance du risque, aux difficultés de reconnaissance des symptômes parfois atypiques, ainsi qu'aux difficultés liées aux traitements et au parcours de soins [1]. La connaissance des critères permettant de repérer le plus efficacement possible les sujets ayant une hypertension artérielle non-diagnostiquée et des facteurs de risque cardiovasculaire associés permettrait leur détection et leur prise en charge précoces.

Une approche pour étudier l'impact de l'obésité et des caractéristiques métaboliques sur le risque de développement à long terme de la DD et de la rigidité artérielle durant ces dernières décennies en Lorraine, serait une étude de cohorte incluant initialement un échantillon représentatif de la population générale en bonne santé (sans maladies aigües et chroniques et donc sans hypertension artérielle) et de la suivre sur une longue période. La cohorte STANISLAS donne une opportunité unique pour aborder ces problèmes. En effet, c'est une cohorte, de grande taille, représentative de la population lorraine comprenant initialement, en 1994-1995, des personnes (enfants et adultes) en bonne santé, suivies environ 20 ans. La dernière visite a eu lieu entre 2011 et 2016. Cette approche nous permet d'étudier la genèse (ou les nouveaux cas survenus pendant le suivi) de DD.

La dysfonction diastolique du ventricule gauche

Une DD détectée par l'échocardiographie est fréquente dans différentes populations. Sa prévalence varie entre 11 % et 35 % selon la méthodologie et la cohorte utilisées [34, 42]. Une

DD, quelle que soit sa sévérité favorise le développement d'une fibrillation atriale et d'une insuffisance cardiaque et est associée à la mortalité toutes causes confondues et même à un risque de mortalité à court terme (3 à 5 ans) cinq fois plus élevé chez des patients asymptomatiques [42, 43, 44, 45].

Des études ont montré que la DD est associée avec l'obésité (mesurée par l'IMC, le TT, le ratio tour de taille sur tour de hanche (TT/TH)), la pression artérielle systolique (PAS), la pression artérielle diastolique (PAD), et le syndrome métabolique [29, 33, 34, 46, 47]. Ce dernier est défini par une valeur plus élevée du TT, des triglycérides, de PAS/PAD ou un traitement antihypertenseur, une valeur plus basse du high-density lipoprotein cholesterol (HDL) et un taux élevé de glycémie veineuse. Certains phénotypes métaboliques, en particulier les perturbations métaboliques liées à l'obésité abdominale, sont associés à une élévation des cytokines circulantes, une inflammation chronique et une augmentation du stress oxydatif [20]. Ils pourraient augmenter le risque de DD. Une inflammation systémique serait un déterminant important de l'apparition d'anomalies diastoliques [48], un faible niveau d'inflammation lié à l'obésité viscérale pourrait être un prédicteur important de DD.

Actuellement, le paradigme de DD reste une question ouverte [48] et le rôle pronostique de différents paramètres métaboliques sur la DD reste méconnu dans la population générale. Les études existantes ayant examiné l'impact de l'obésité et du syndrome métabolique sur la DD étaient principalement des études transversales [29, 33, 46], ciblant des groupes d'âge spécifique, des personnes âgées ou des sujets malades. D'autre part, la durée de suivi des sujets dans les études longitudinales était courte [49-51] et la plupart des études focalisaient sur certains éléments définissant la DD seulement [33, 46, 49, 51].

L'identification des facteurs métaboliques prédictifs d'un stade précoce de la DD chez des sujets jeunes ou d'âge moyen en bonne santé nécessite un suivi de longue durée et un examen

échocardiographie détaillé. Une étude de cohorte chez des sujets initialement en bonne santé avec un suivi de longue durée peut apporter des connaissances supplémentaires.

La cohorte STANISLAS comprenant des sujets en bonne santé lors de la première visite (2014 adultes) [52] permet d'évaluer quels facteurs métaboliques peuvent prédire la DD observée 20 ans plus tard (définie par l'*European Association of Echocardiography* (EAE) et l'*American Society of Echocardiography* (ASE) [53]). Il serait en outre important de vérifier la validité des résultats en répliquant les analyses dans une cohorte longitudinale indépendante (par exemple une cohorte de 1463 sujets en Suède [54]). La connaissance des facteurs prédictifs de ce remodelage à un stade précoce chez les sujets sains est potentiellement importante pour la prévention.

La rigidité artérielle de l'aorte

La rigidité artérielle de l'aorte est une caractéristique du vieillissement artériel. Elle prédit les maladies cardiovasculaires telles que l'infarctus du myocarde, l'arrêt cardiaque et l'accident vasculaire cérébral et est aussi associée aux incapacités fonctionnelles physiques et cognitives chez les personnes âgées [55-60]. L'évaluation prospective des déterminants de la rigidité artérielle peut aider à identifier les facteurs modifiables potentiels du vieillissement vasculaire [31].

Comme exposé précédemment, l'obésité est considérée comme une épidémie dans beaucoup de pays et en particulier les pays à moyen et haut revenu [10, 41]. L'obésité générale et l'obésité abdominale, en particulier, sont associées avec les différentes maladies cardiovasculaires [10].

Cependant, la majorité des études n'ont pas trouvé de relation indépendante entre la rigidité artérielle et l'obésité générale mesurée par l'IMC et même, certaines études ont observé des associations contradictoires [30-32, 36, 39, 40]. En effet, plusieurs études ont rapporté un rôle protecteur de l'IMC [32, 36, 38]. Ces études différaient beaucoup selon les populations étudiées (selon l'âge, le sexe, l'IMC et la morbidité) et les approches méthodologiques (selon le type d'étude et la durée du suivi pour les études prospectives) [31]. Une étude longitudinale récente

avec une durée de suivi de 5 ans, portant sur les individus d'âge moyen, avait montré qu'une obésité générale et qu'une obésité centrale plus élevées étaient de forts prédicteurs de la rigidité artérielle [30]. Toutefois, peu d'études ont montré que l'obésité abdominale mesurée par le TT était plus associée avec la VOPcf que l'IMC [30, 35, 37].

L'association de l'obésité générale et l'obésité abdominale avec la rigidité artérielle demeure donc un problème insuffisamment documenté. La connaissance du risque à long terme associé de l'obésité générale et l'obésité abdominale sur la rigidité artérielle chez les individus en bonne santé permet d'identifier les personnes et leur profil à risque, et déterminer les interventions appropriées visant à améliorer l'hygiène de vie.

Le ratio entre le niveau d'obésité abdominale et celui d'obésité générale, défini par le ratio TT/IMC peut fournir une évaluation plus exacte de l'obésité abdominale (degré de renflement de l'abdomen, lequel peut être corrélé avec le dépôt de graisse abdominale). A notre connaissance, il n'y a pas d'études utilisant le ratio TT/IMC.

La cohorte STANISLAS donne l'opportunité d'étudier l'association entre le ratio TT/IMC et aussi l'IMC, le TT, le ratio TT/T et l'ABSI ("a body shape index" (ABSI = TT / ($IMC^{2/3}$ $Taille^{1/2}$)) [61] et la rigidité artérielle observée 20 ans plus tard dans une population de personnes initialement en bonne santé.

L'hypertension artérielle

Avec le vieillissement de la population et de l'augmentation de l'IMC, l'hypertension artérielle devient un problème plus crucial. En effet, sa prévalence s'accroît fortement avec l'âge (tableau 6).

L'hypertension artérielle a des conséquences importantes sur les incapacités fonctionnelles et sur les maladies et la mortalité cardiovasculaires [62, 63]. La promotion des comportements de santé (contrôle du poids, arrêt de la consommation du tabac, activité physique régulière, réduction

de la consommation du sel et du sucre et alimentation saine) [64, 65] et un traitement approprié peuvent réduire le niveau de la pression artérielle [66] et prévenir la morbidité et la mortalité dues aux complications de l'HTA [67, 68]. La mise en place précoce des soins et des actions de promotion des comportements de santé est importante et nécessite que les sujets ayant une HTA soit diagnostiqués tôt. Malheureusement, dans différents pays, 17 à 50 % des personnes hypertendues ne sont pas diagnostiquées et ne reçoivent pas les soins appropriés [69-73]. En France, la moitié des sujets hypertendus de 18 à 74 ans ne sont pas conscients de leur HTA [74, 75].

Tableau 6. Prévalence (%) d'hypertension artérielle selon l'âge en France (2006-2007)

	Hommes	Femmes
Age (ans)		
18-44	10	9
45-64	50	36
65-74	70	65

Source : Direction de la recherche, des études, de l'évaluation et des statistiques. La santé des femmes en France. Collection Etudes et statistiques. La Documentation Française [3].

Ce problème pose un défi important au système de soins primaires qui consiste à identifier les facteurs potentiels qui peuvent être associés à un risque accru d'avoir une HTA non-diagnostiquée parmi les sujets hypertendus. Une étude chez les femmes de 18 à 49 ans aux États-Unis montrait que le sous-poids, l'absence de cardiopathie ischémique ou de diabète, et un moindre recours aux soins primaires constituaient des barrières pour l'accès au diagnostic d'HTA [39]. Une autre étude réalisée chez les adultes de 40 à 74 ans au Royaume-Uni montrait une forte association entre l'HTA non-traitée et le sexe masculin, vivre seul, la consommation de tabac, une consommation plus élevée d'alcool et une bonne santé perçue [76]. La consommation de tabac et d'alcool est aussi associée à une moins bonne perception du risque, une attribution moindre des facteurs de

style de vie comme causes des maladies cardiovasculaires et une participation moindre au dépistage de l'HTA [77, 78].

Notre hypothèse est la suivante : parmi les individus hypertendus, ceux ayant une HTA non-diagnostiquée sont moins conscients de leur HTA et ne consultent pas un médecin généraliste pour évaluer leur pression artérielle. De plus, les caractéristiques à risque seraient complexes et demeurent peu documentées. Leur connaissance pourrait aider les médecins à suspecter et dépister précocement les sujets à risque d'avoir une HTA non-diagnostiquée et établir les soins et les actions de promotion des comportements de santé [79]. Ce problème peut être abordé par une étude transversale populationnelle utilisant les données de la cohorte STANISLAS. Vu l'état des connaissances sur le sujet, il est nécessaire d'explorer un grand nombre de facteurs suspectés. Ils comprennent les caractéristiques phénotypiques et biologiques, les caractéristiques à risques cardiovasculaires, la fréquence de recours aux soins primaires, et le style de vie (consommation de tabac et d'alcool et activités physiques et sportives régulières).

2. Objectifs

Ce travail de thèse avait pour but d'étudier des dysfonctions et des pathologies cardiovasculaires spécifiques qui sont la dysfonction diastolique, la rigidité artérielle et l'hypertension artérielle et les facteurs anthropométriques et métaboliques associés ainsi que la prise en charge en population générale. Cette recherche portait sur un échantillon de la population Lorraine (la cohorte STANISLAS comprenant 4295 parents et enfants initialement en bonne santé, issues de 1006 familles) suivi pendant 20 ans.

Le premier travail avait pour objectif d'identifier chez des adultes initialement en bonne santé, les facteurs anthropométriques et métaboliques associés à la dysfonction diastolique mesurée 20 ans plus tard. L'analyse a été répliquée dans une cohorte longitudinale indépendante de 1463 sujets en Suède.

Le deuxième travail avait pour but d'étudier, chez des adultes initialement en bonne santé, l'association entre le ratio TT/IMC, l'IMC, le TT, le ratio TT/T, "a body shape index" (ABSI = TT / (IMC$^{2/3}$ taille$^{1/2}$)) et la rigidité artérielle mesurée 20 ans plus tard.

Enfin, le troisième travail visait à identifier les facteurs associés à une HTA non-diagnostiquée parmi les sujets hypertendus. Cette recherche ciblait les caractéristiques socioéconomiques, biologiques et cardiovasculaires, des comportements de santé (statut tabagique, consommation d'alcool et activités physiques et sportives) et l'utilisation des soins primaires.

3. Association entre l'obésité et des caractéristiques métaboliques et le risque de développement à long terme d'une dysfonction diastolique dans une cohorte d'adultes initialement en bonne santé

La prévalence de la dysfonction diastolique varie entre 11 % et 35 %. Elle favorise le développement d'une fibrillation atriale et d'une insuffisance cardiaque et est associée à la mortalité toutes causes confondues. Le rôle pronostique des paramètres métaboliques sur la DD à long terme reste méconnu dans la population générale. Le but de ce travail était d'identifier les facteurs métaboliques associés à la DD vingt ans plus tard dans la population lorraine. Nous avons répliqué l'analyse dans une cohorte longitudinale indépendante de 1463 sujets en Suède.

Matériel et Méthodes

L'échantillon étudié comprenait 2014 adultes de la cohorte STANISLAS. Au début du suivi, en 1994-1995, les sujets ont été inclus après un examen de santé au centre de médecine préventive. Vingt ans plus tard (2011-2016), 896 adultes (44,5 %) ont participé à la dernière visite. Au début du suivi ont été mesurés les caractéristiques démographiques, le statut tabagique, le poids, la taille, l'IMC, le TT, le ratio TT/TH, la PAS, la PAD, la PP, la glycémie, le cholestérol total, le HDL, le LDL, le taux de TG et la PCR. A la fin du suivi, une échocardiographie a été réalisée avec un échocardiographe de dernière génération. La DD a été définie selon les recommandations de l'EAE/ASE.

Pour s'assurer que seulement les individus en bonne santé au début du suivi étaient considérés dans l'analyse statistique, les données étaient vérifiées et ont été exclus 168 sujets ayant une PAS ≥ 140 mm Hg ou PAD ≥ 90 mm Hg, une PCR >10 mg/L, une HTA traitée, un diabète, une maladie coronarienne traitée, une arythmie cardiaque traitée, une FEVG altérée ou manquante ou une DD manquante. Au total 728 sujets ont été retenus pour l'analyse.

L'analyse a été répliquée sur la cohorte des habitants de Malmö (Suède) du Malmö Preventive Project comprenant 33 346 sujets au début du suivi en 1974−1992. Ont été retenus pour l'analyse 1463 sujets pour lesquels les facteurs à risque étudiés ont été mesurés au début du suivi, la DD vingt-quatre ans plus tard, en 2002–2006. La comparaison des sujets ayant une DD avec ceux ayant une fonction diastolique normale a été faite en utilisant le modèle de régression logistique multivariée pour calculer les odds ratios ajustés sur le sexe et l'âge (ORsa). Dans ces modèles, les variables continues étaient standardisées (divisées par leur écart-type respectif). L'odds ratio correspondait donc à un risque pour une valeur accrue d'un écart-type de la variable considérée. Pour évaluer l'effet conjugué entre les variables anthropométriques (IMC, TT, ratio TT/TH) et les variables biologiques d'intérêt (TG et PCR) sur la DD, ces variables ont été dichotomisées puis l'échantillon a été divisé en quatre groupes en croisant chaque variable anthropométrique avec chaque variable biologique. Le seuil utilisé pour l'IMC était de 25 kg/m^2, celui pour le TT était de 94 cm pour les hommes et 80 cm pour les femmes, celui pour le ratio TT/TH était 0,90 pour les hommes et 0,85 pour les femmes. Le seuil pour le taux de TG et la PCR était leur valeur médiane respective.

Résultats

Parmi les 728 sujets, 191 sujets (26,2 %) avaient une DD. Dans les modèles de régression logistique prenant en compte le sexe et l'âge, les facteurs suivants étaient associés significativement avec DD : IMC (ORsa 1,28, IC 95 % : 1,08−1,52), TT (ORsa 1,48, IC 95 % : 1,18−1,84), ratio TT/TH (ORsa 1,53, IC 95 % : 1,16−2,02), PAS (ORsa 1,19, IC 95 % : 1,00-1,43) et TG (ORsa 1,18, IC 95 % : 1,00-1,40). Dans les modèles de régression logistique multivariée réalisés pour chaque variable anthropométrique (en prenant en compte l'âge, le sexe, la PAS, le taux de TG et la PCR), seulement le TT était associé avec la DD.

Comparés aux sujets ayant un IMC <25 kg/m^2 et un TT normal, seulement les sujets ayant un IMC ≥ 25 kg/m^2 avec un TT élevé ou un ratio TT/TH élevé avaient un risque plus élevé de DD

(ORsa 1,81, IC 95 % : 1,17-2,78 et ORsa 1,96, IC 95 % : 1,17-3,26, respectivement). Comparés aux sujets ayant un TT ou un ratio TT/TH normal et un taux de TG normal, seulement les sujets ayant un TT élevé ou un ratio TT/TH élevé et un taux élevé de TG avaient un risque accru de DD (ORsa 2,00, IC 95 % : 1,20-3,31 et ORsa 1,89, IC 95 % : 1,09-3,26, respectivement). Par contre, cette constatation n'était pas retrouvée pour l'IMC et le taux de TG, ni pour la PCR qu'elle soit combinée avec l'IMC, le TT ou le ratio TT/TH.

L'analyse a été répliquée dans une cohorte de Malmö comprenant 1463 sujets. Parmi les facteurs considérés au début du suivi (IMC, PAS, PAD, PP, cholestérol total, le taux de TG et glycémie), seulement l'IMC et le taux de TG étaient associés avec la DD (ORsa 1,20, IC 95 % : 1,06−1,36 et ORsa 1,17 IC 95 % : 1,03−1,32, respectivement) dans l'échantillon complet. Dans le sous-échantillon de sujets sans HTA et sans diabète au début du suivi, seulement le taux de TG était associé avec la DD (ORsa 1,20, IC 95 % : 1,04−1,40). Quand on examinait l'effet combiné de l'IMC et d'un taux élevé de TG sur la DD, seulement les sujets ayant un IMC$\geq$ 25 kg/m^2 et un taux élevé de TG avaient un risque accru de DD (ORsa 1,61, IC 95 % : 1,18−2,20) dans l'échantillon complet. Par contre, la conjonction de l'IMC$\geq$ 25 kg/m^2 et un taux élevé de TG n'était pas associée à un risque accru de DD dans le sous-échantillon de sujets sans HTA et sans diabète au début du suivi.

Conclusion

Cette étude montre que l'obésité abdominale combinée avec un taux élevé de TG est associée à un risque élevé de développer vingt ans après une dysfonction diastolique à un stade précoce. Le TT, le ratio TT/TH, le taux de TG et la PAS sont facilement mesurables. Ils peuvent aider à identifier les sujets à risque de dysfonction diastolique. Ces résultats peuvent avoir des implications dans la prévention et le management thérapeutique des sujets à risque.

Obesity and metabolic features associated with long-term developing diastolic dysfunction in an initially healthy population-based cohort

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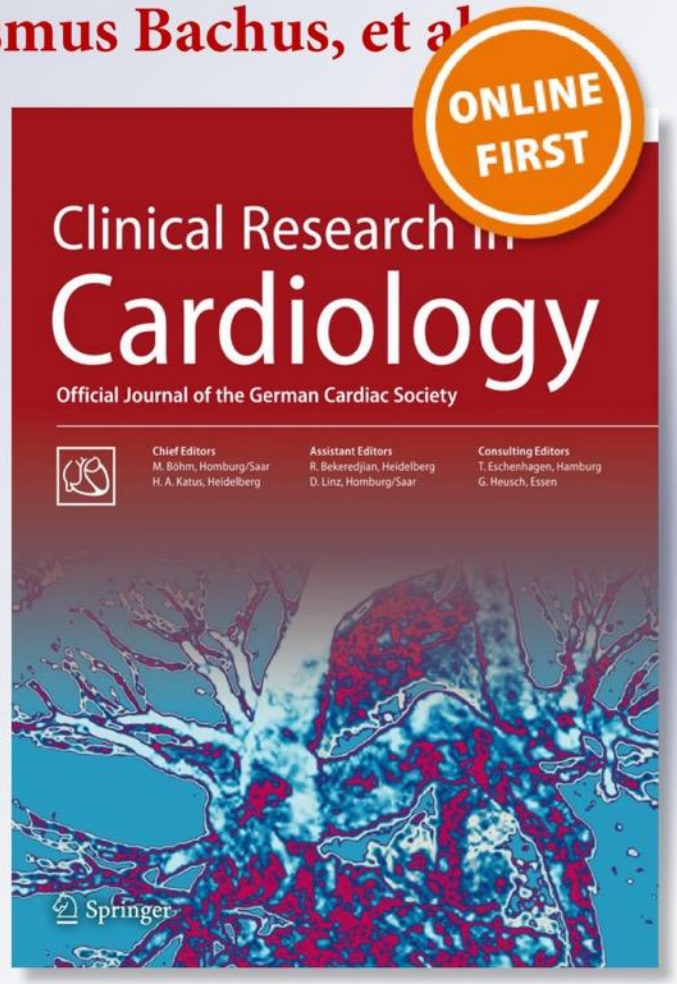

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ORIGINAL PAPER

Obesity and metabolic features associated with long-term developing diastolic dysfunction in an initially healthy population-based cohort

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Abstract

Background Diastolic dysfunction (DD) is increasingly common. However, its metabolic determinants are poorly known. This study aims to determine which metabolic and inflammatory features predict DD in initially healthy adults.

Methods We prospectively analyzed the association between metabolic features and DD in 728 initially healthy adults aged 30–60 from Eastern France enrolled in the STANISLAS population-based cohort. Clinical and biological cardiovascular features were collected at baseline (1994–1995). DD was assessed twenty years later (2011–2016) by echocardiography using current international guidelines. For replication purposes, 1463 subjects from the Malmö Preventive Project cohort were analyzed.

Results In the STANISLAS cohort, 191 subjects (26.2%) developed DD. In age-sex-adjusted logistic models, significant predictors of DD were body mass index (BMI, odds ratio for 1-standard-deviation increase (OR) 1.28, 95% CI 1.08–1.52), waist circumference (WC, OR 1.48, 95% CI 1.18–1.84), waist-hip ratio (OR 1.53, 95% CI 1.16–2.02), systolic blood pressure (OR 1.19, 95% CI 1.00–1.43) and triglycerides (TG, OR 1.18, 95% CI 1.00–1.40). Subjects with elevated WC (> 80th percentile) and TG (> 50th percentile) had a twofold higher DD risk (age-sex-adjusted odds ratio 2.00, 95% CI 1.20–3.31, $P = 0.008$), whereas no such interplay was observed for BMI. In the Malmö cohort, BMI was similarly associated with DD; participants with both elevated BMI and TG were at higher DD risk (age-sex-adjusted odds ratio 1.61, 95% CI 1.18–2.20, $P = 0.002$).

Conclusions Subjects with elevated WC and TG may have a higher long-term DD risk. Prevention targeting visceral obesity may help reduce the incidence of DD.

Keywords Diastolic dysfunction · Visceral fat · Triglycerides · Blood pressure · Healthy adults · Cohort study

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Introduction

Left ventricular diastolic dysfunction (DD) detected by echocardiography is frequent in population-based cohorts, ranging from 11 to 35% [1, 2]. DD predicts the development of atrial fibrillation, heart failure, excess all-cause mortality, and even a fivefold higher risk of 3–5-year mortality in asymptomatic patients [2–5]. Previous studies have shown that DD is associated with obesity (assessed by body mass index (BMI), waist circumference (WC) or waist-hip ratio (WHR)), systolic and diastolic blood pressures (SBP and DBP), and metabolic syndrome (defined as cumulated increased WC, increased fasting triglycerides (TG), high SBP/DBP or hypertensive therapy, decreased high-density lipoprotein cholesterol, and impaired fasting glucose) [1, 6–9]. Certain metabolic phenotypes, in particular abdominal obesity-related metabolic perturbations associated with elevated circulating cytokines, chronic inflammatory state and increased oxidative stress [10], may increase the risk of DD. Since systemic inflammation is hypothesized as a key determinant of the onset of diastolic abnormalities [11], low-grade inflammation related to visceral obesity may also be a strong predictor of DD. Currently, the paradigm of DD remains an open issue [11] and the respective prognostic roles of various metabolic parameters in DD still remain unclear in general populations. Previous studies examining the impact of obesity and metabolic syndrome on DD have been predominantly cross-sectional [7–9], investigating either specific age groups or older and diseased subjects. Furthermore, the follow-up of previous longitudinal studies has been short [1, 12, 13], and most of these studies have focused on certain DD components only [7, 8, 12, 13].

The identification of metabolic predictors of early stage DD in young and middle-aged healthy subjects requires both a long follow-up and systematic detailed echocardiographic examinations. A cohort study on an initially healthy population with a long follow-up may provide additional knowledge. Taking advantage of the 20-year follow-up achieved with the STANISLAS cohort including initially healthy adults at baseline (2014 subjects) [14], we aimed to examine which metabolic features predict subsequent 20-year DD as defined by the EAE/ASE [15]. Further analyses were replicated in an independent longitudinal cohort in Sweden in 1463 subjects.

Methods

Study design and population

The STANISLAS study is a population-based longitudinal cohort study including 4295 healthy subjects of French origin from 1006 families in Eastern France. They were initially recruited in 1994–1995 during a medical examination and reexamined every 5 years in 2011–2016. The study design has been described [14] (Supplemental Text 1). This report used longitudinal data comparing visit one in 1995 to the latest visit 4, 20 years after. This study focused on the parents (30–60 years at baseline) who participated in the last visit ($n = 896$, 44.5%). The Ethics Committee of the Lorraine region approved the study. Written informed consent was obtained from each participant.

The following were measured at baseline: age, sex, tobacco smoking status, height, weight, BMI (weight (kg)/height (m)^2), WC, hip circumference, waist-hip ratio (WHR), SBP, DBP, pulse pressure, serum concentrations of fasting glucose, total cholesterol, TG, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and C-reactive protein (CRP). Overweight (BMI $\geq$ 25 kg/m^2) was investigated because of the small number of obese subjects. WC and WHR were dichotomized using the World Health Organization's cut-off values (for WC, 94 cm for men and 80 cm for women; for WHR, 0.90 for men and 0.85 for women).

At the end of follow-up, echocardiography was performed with the standard ultrasound scanner Vivid 9 (General Electric Medical Systems, Horten, Norway) using a 2.5 MHz phased-array transducer. Left ventricular diastolic dysfunction was assessed according to the EAE/ASE recommendations: mild or grade 1 (DD1, impaired relaxation pattern), moderate or grade 2 (pseudo-normal left ventricular filling), and severe (restrictive filling) or grade 3 [15]. Grades 2 and 3 (DD2–3) were grouped together due to the small number of subjects. DD all grades was noted DD. The echocardiographic assessment of diastolic function was reproducible [16].

The study design included only healthy subjects. We excluded 33 subjects for the following reasons at baseline: CRP > 10 mg/L, arterial hypertension with medical treatment, diabetes mellitus, arrhythmia or coronary heart disease with medical treatment. We further excluded 111 subjects with SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg, 23 subjects with missing or abnormal systolic left ventricular function or volumes (left ventricular ejection fraction < 50% or indexed end-diastolic ventricular volume > 97 mL/m^2) [15], and 1 subject with missing septal e' velocity, lateral e' velocity or left atrial volume index at

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last visit. In total, 728 subjects were retained for analysis (Supplemental Fig. 1).

DD was not assessed at baseline. However, a subset of 624 subjects was analyzed and revealed that there were no subjects with left ventricular hypertrophy on baseline echocardiography [17] and only 11 subjects (1.5%) would have had a DD at baseline (Supplemental Text 1).

Malmö cohort

The above analyses were replicated for the population-based longitudinal cohort of inhabitants in Malmö (Sweden) of the Malmö Preventive Project (MPP) [18]. At baseline (1974–1992), 33,346 subjects had participated and after a 24-year follow-up (2002–2006), 18,240 subjects were re-examined. The study protocol has been described [18] (Supplemental Text 2). Echocardiography was carried out in a sample of 1,792 participants. At baseline, WC, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and CRP were not measured. A total of 1463 subjects were retained for analysis after excluding those with left ventricular ejection fraction < 50% or left ventricular end-diastolic volume index > 97 mm/m^2. The same analysis was then performed by further excluding those subjects with diagnosed hypertension, diabetes, baseline SBP > 140 mm Hg or baseline DBP > 90 mm Hg. The Lund University's ethical committee (Lund, Sweden) approved the study. Written informed consent was obtained from each participant.

Statistical analysis

Variance analysis or Chi-square tests were used to compare baseline characteristics between diastolic function groups. A multinomial logistic regression model was subsequently used to estimate age-sex-adjusted odds ratios (asOR) for each variable, comparing individuals who had DD1, DD2–3 or DD with those who had normal diastolic function. For continuous variables, odds ratios (OR) were estimated for each 1-standard-deviation increase. To determine whether variables were independently associated with DD, those significantly ($P < 0.05$) associated with DD or DD2–3 in the age-sex-adjusted analysis were included in multivariable logistic regression models (i.e. BMI, WC, WHR, SBP and TG). CRP was also included as a potential risk factor. To assess the interplay between anthropometric variables (BMI, WC and WHR) and biological variables of interest (TG and CRP) for DD, the population sample was divided into 4 groups according to dichotomized anthropometric and biological variables, after which asOR was computed. Absence of multicollinearity and goodness-of-fit (Hosmer–Lemeshow) were verified. A P value < 0.05 (2-sided) was considered statistically significant. Statistical analyses were performed using Stata SE 12.0 (StataCorp, College Station, TX, USA).

Results

The participants and non-participants at the end of follow-up had similar baseline characteristics (Supplemental Table 1). Table 1 shows that among the 728 participants, 191 subjects (26.2%) had DD, 123 had DD1 (16.9%) and 68 had DD2–3 (9.3%). The sample echocardiographic features are shown in the Supplementary material online (Table S2). The subjects with DD were older and had higher BMI, WC, SBP, and DBP than those without DD, with a gradient between DD1 and DD2–3.

Age-sex-adjusted logistic regression models

DD was strongly associated with baseline WC (asOR per 1-SD increase 1.48, 95% CI 1.18–1.84), WHR (asOR per 1-SD increase 1.53, 95% CI 1.16–2.02) and BMI (asOR per 1-SD increase 1.28, 95% CI 1.08–1.52) (Table 2).

DD2–3 was significantly associated with WC, WHR and BMI. DD2–3 was also associated with SBP (asOR per 1-SD increase 1.42, 95% CI 1.07–1.89) and TG (asOR per 1-SD increase 1.29, 95% CI 1.01–1.66).

BMI, SBP and TG remained significant for DD when their change during follow-up was also included in the models (Supplemental Table 3).

Multivariable logistic regression models

When a multivariable model was fitted for each anthropometric variable to adjust for age, sex, SBP, TG and CRP (Table 3), only WC was associated with DD and only BMI, WC and SBP were associated with DD2–3.

Further adjustment for comorbidities [rhythm disorder ($n = 79$), myocardial infarction ($n = 7$), diabetes without insulin ($n = 39$, no subject with diabetes requiring insulin), and heart failure ($n = 8$)] as well as HOMA index at last examination did not substantially change the results. None of the above parameters was found to be associated with DD while waist circumference still remained associated with DD (all grades, data not shown). The comorbidities and HOMA index were available at last examination only.

Interplay between BMI and WC or WHR

To determine the interplay between WC, WHR and BMI in increasing DD risk, the sample was divided into four groups according to WC (< or ≥ 94 cm for men and 80 cm for women), WHR (< or ≥ 0.90 for men and 0.85 for women), and BMI (non-overweight or overweight). Compared with

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Table 1 Characteristics of the sample at baseline (1994–1995) according to diastolic function at year 20 ($n=728$): mean (standard deviation) or %

Baseline covariates	Number of available values (%)	Normal function ($n=537$)	Diastolic dysfunction			*P* value	
			Grade 1 (DD1) ($n=123$)	Grade 2–3 (DD2–3) ($n=68$)	All grades (DD) ($n=191$)	(1)	(2)
Prevalence		*73.8*	*16.9*	*9.3*	*26.2*		
Age, years	728 (100)	40.9 (4.1)	42.5 (4.9)	43.4 (5.3)	42.8 (5.0)	<0.001	<0.001
Female sex	728 (100)	53.6	54.5	55.9	55.0	0.93	0.75
Smoking status	728 (100)					0.36	0.49
Never	*408 (56.0)*	54.7	64.2	51.5	59.7		
Former	*177 (24.3)*	25.0	19.5	27.9	22.5		
Current	*143 (19.6)*	20.3	16.3	20.6	17.8		
Body mass index[a]	728 (100)	23.8 (3.1)	24.1 (3.1)	25.2 (3.7)	24.5 (3.3)	0.002	0.008
Waist circumference, cm	727 (99.9)	79.2 (10.1)	80.5 (10.2)	83.2 (11.9)	81.5 (10.9)	0.008	0.010
Waist-hip ratio	727 (99.9)	0.82 (0.086)	0.83 (0.086)	0.83 (0.096)	0.83 (0.089)	0.16	0.07
Systolic blood pressure, mm Hg	725 (99.6)	119.0 (9.6)	119.9 (8.6)	122.1 (9.1)	120.8 (8.8)	0.03	0.03
Diastolic blood pressure, mm Hg	725 (99.6)	72.1 (8.9)	73.3 (8.4)	74.9 (10.4)	73.9 (9.1)	0.04	0.02
Pulse pressure, mm Hg	725 (99.6)	46.9 (8.6)	46.7 (7.3)	47.2 (7.7)	46.9 (7.4)	0.91	1.00
Total cholesterol, mmol/L	701 (96.3)	5.65 (0.96)	5.83 (1.00)	5.76 (1.06)	5.82 (1.02)	0.13	0.05
High-density lipoprotein cholesterol, mmol/L	700 (96.2)	1.45 (0.40)	1.46 (0.39)	1.41 (0.40)	1.44 (0.40)	0.73	0.83
Low-density lipoprotein cholesterol, mmol/L	697 (95.7)	3.76 (0.89)	3.90 (1.01)	3.84 (0.98)	3.88 (1.00)	0.26	0.11
Triglycerides, mmol/L	701 (96.3)	0.97 (0.60)	1.03 (0.65)	1.11 (0.59)	1.05 (0.63)	0.20	0.11
Blood glucose, mmol/L	701 (96.3)	5.01 (0.45)	5.03 (0.41)	5.06 (0.59)	5.05 (0.48)	0.62	0.37
C-reactive protein, mg/L	667 (91.6)	1.29 (1.48)	1.42 (1.71)	1.44 (1.85)	1.43 (1.75)	0.60[b]	0.31[b]

Comparison between: (1) normal function, DD1 and DD2–3; (2) normal function and DD (with ANOVA or Chi square independence test)

[a]Weight (kg)/height (m)^2

[b]The differences remained non-significant ($P=0.90$ and 0.68, respectively) when using the Kruskal–Wallis equality-of-populations rank test. The median value of C-reactive protein was 0.74 mg/L for subjects with DD and 0.72 mg/L for subjects without DD

non-overweight subjects with non-elevated WC, only overweight subjects with elevated WC or WHR were at increased DD risk (asOR 1.81, 95% CI 1.17–2.78 and 1.96, 95% CI 1.17–3.26, respectively) (Supplemental Fig. 2).

Interplay between anthropometric and biological variables

The population was divided into four groups according to WC (< or ≥ 94 cm for men and 80 cm for women) and either TG (< or ≥ median value = 1.00 mmol/L for men and 0.70 mmol/L for women) or CRP (< or ≥ median value [19] = 0.73 mg/L for men as for women). A similar interplay was also examined for WHR (< or ≥ 0.90 for men and 0.85 for women). Only the subjects having elevated WC or WHR and elevated TG were at increased DD risk [asOR 2.00 (95% CI 1.20–3.31) and 1.89 (95% CI 1.09–3.26), respectively] (Fig. 1). In contrast, no such interplay was observed when considering BMI in lieu of WC: a higher DD risk was also found for subjects with normal weight and elevated TG (1.64, 95% CI 1.06–2.51) as for overweight subjects with elevated TG (1.73, 95% CI 1.08–2.77) (Fig. 1).

No higher risk was observed for subjects with elevated CRP and elevated BMI, WC or WHR (Fig. 1).

Replication of the analyses in the Malmö population cohort

The 1463 subjects studied had a similar mean baseline age than in the STANISLAS cohort (43.1 years, SD 7.8) and 69.9% were male (Supplemental Table 4). Among the baseline factors considered (BMI, SBP, DBP, pulse pressure, total cholesterol, TG and blood glucose), only BMI and TG were associated with DD [asOR 1.20 (95% CI 1.06–1.36) and 1.17 (95% CI 1.03–1.32), respectively] in the whole sample (Supplemental Table 5) whereas only TG was associated with DD (asOR = 1.20, 95% CI 1.04–1.40) in the subset of subjects without hypertension and diabetes at baseline ($N=927$; Supplemental Table 6). In multivariable analysis, BMI was associated with DD in the whole sample with similar OR as that in the STANISLAS cohort (1.15, 95% CI

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Table 2 Age-sex-adjusted odds ratios with logistic regression models of baseline factors associated with subsequent diastolic dysfunction after 20 years ($n=728$)

Baseline covariates[b]	1 SD	Diastolic dysfunction, grade 1 (DD1)[a] ($n=96$)			Diastolic dysfunction, grade 2–3 (DD2–3)[a] ($n=55$)			Diastolic dysfunction, all grades (DD)[a] ($n=151$)		
		OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Smoking status										
Never		1.00			1.00			1.00		
Former		0.68	0.40–1.14	0.144	1.38	0.74–2.58	0.418	0.88	0.57–1.34	0.539
Current		0.76	0.43–1.34	0.345	1.47	0.73–2.97	0.287	0.96	0.60–1.53	0.850
Body mass index	3.21	1.13	0.92–1.39	0.252	1.59	1.24–2.03	<0.001	1.28	1.08–1.52	0.005
Waist circumference, cm	10.4	1.26	0.97–1.65	0.084	1.94	1.41–2.67	<0.001	1.48	1.18–1.84	0.001
Waist-hip ratio	0.087	1.38	0.99–1.91	0.055	1.85	1.23–2.78	0.003	1.53	1.16–2.02	0.003
Systolic blood pressure, mm Hg	9.4	1.09	0.88–1.35	0.420	1.42	1.07–1.89	0.016	1.19	0.99–1.43	0.058
Diastolic blood pressure, mm Hg	9.0	1.10	0.89–1.36	0.377	1.33	1.00–1.77	0.049	1.17	0.98–1.40	0.085
Pulse pressure, mm Hg	8.3	0.99	0.81–1.21	0.937	1.07	0.82–1.40	0.595	1.02	0.86–1.21	0.825
Total cholesterol, mmol/L	0.98	1.20	0.98–1.47	0.085	1.08	0.82–1.41	0.585	1.15	0.97–1.37	0.110
High-density lipoprotein cholesterol, mmol/L	0.40	0.99	0.80–1.23	0.937	0.83	0.62–1.10	0.201	0.93	0.78–1.12	0.460
Low-density lipoprotein cholesterol, mmol/L	0.92	1.18	0.95–1.45	0.128	1.08	0.82–1.42	0.586	1.14	0.95–1.36	0.148
Triglycerides, mmol/L	0.61	1.12	0.90–1.38	0.306	1.29	1.01–1.66	0.041	1.18	0.99–1.40	0.066
Blood glucose, mmol/L	0.46	1.05	0.85–1.30	0.635	1.13	0.87–1.48	0.356	1.08	0.90–1.29	0.400
C-reactive protein, mg/L	1.56	1.10	0.91–1.34	0.330	1.13	0.87–1.46	0.370	1.11	0.94–1.32	0.227

SD standard deviation, *OR* odds ratio, *CI* confidence interval

[a]Vs. normal diastolic function

[b]There was a separate model for each covariate. All quantitative variables (except age) were divided by their SD. The OR corresponded to each 1-SD increase

1.00–1.31) whereas only TG remained associated with DD (1.17, 95% CI 1.00–1.37) in subjects without hypertension and diabetes at baseline.

With regard to the interplay between BMI and TG, only the subjects with elevated BMI and elevated TG had an increased DD risk (asOR 1.61, 95% CI 1.18–2.20) in the whole sample (Supplemental Fig. 3). In contrast, the conjunction of overweight and elevated TG was not associated with DD in subjects without diabetes or hypertension at baseline (1.34, 95% CI 0.91– 1.98, Supplemental Fig. 4).

The Hosmer–Lemeshow goodness-of-fit test showed that the various logistic models were correct ($P>0.30$).

Discussion

This prospective study in initially healthy adults shows that abdominal obesity measured as increased WC or WHR, and their combination with metabolic perturbations as assessed by elevated TG may confer a high risk of developing DD. However, since the percent of variance explained by the multivariable models was modest (approximately 5%), other untested parameters may be involved.

This is the first long-term follow-up (20 years) population-based cohort study using DD as defined by the guidelines from EAE/ASE [15]. In line with these results, we found that the conjunction of high BMI (WC not being measured) and TG in the whole cohort of Malmö inhabitants was associated with an increased risk of developing DD. These findings highlight that abdominal obesity may represent a strong predictor of DD at an early stage of the disease process.

Obesity and DD: does fat distribution matter?

In our study, WC and WHR had a stronger association with DD compared to BMI. Abdominal obesity may be a stronger predictor than BMI for long-term DD risk. Abdominal/visceral fat is the key feature of metabolic syndrome, a marker of "dysfunctional adipose tissue" [10] associated with a higher degree of adipokines secretion [20]. WC and WHR are more closely associated with atherosclerosis and myocardial infarction than BMI [21, 22]. However, while BMI does not distinguish body fat content from lean body mass [23], an association between BMI and DD was nonetheless observed in the whole sample of the Malmö study, although

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Table 3 Multivariable analysis of potential baseline risk factors for diastolic dysfunction after 20 years ($n = 728$)

Baseline covariates	1 SD	Diastolic dysfunction, grade 1 (DD1)[a] ($n = 96$)			Diastolic dysfunction, grade 2–3 (DD2–3)[a] ($n = 55$)				Diastolic dysfunction, all grades (DD)[a] ($n = 151$)			
		OR	95% CI	*P* value	OR	95% CI	*P* value	Adjusted R^2	OR	95% CI	*P* value	Adjusted R^2
Model 1[b,c]												
Body mass index	3.21	1.06	0.84–1.34	0.611	1.46	1.09–1.95	0.012	0.0448	1.19	0.98–1.45	0.087	0.0446
Systolic blood pressure, mmHg	9.4	1.08	0.86–1.35	0.507	1.38	1.01–1.88	0.045		1.17	0.96–1.42	0.121	
Triglycerides, mmol/L	0.61	1.05	0.84–1.31	0.668	1.04	0.77–1.40	0.809		1.05	0.86–1.27	0.653	
C-reactive protein, mg/L	1.56	1.07	0.87–1.31	0.515	0.99	0.74–1.33	0.971		1.05	0.87–1.25	0.626	
Model 2[b,c]												
Waist circumference, cm	10.4	1.15	0.84–1.56	0.382	1.72	1.17–2.53	0.006	0.0458	1.32	1.02–1.72	0.036	0.0461
Systolic blood pressure, mmHg	9.4	1.07	0.85–1.34	0.557	1.37	1.00–1.87	0.050		1.16	0.95–1.41	0.144	
Triglycerides, mmol/L	0.61	1.03	0.82–1.30	0.792	1.01	0.74–1.37	0.964		1.02	0.84–1.24	0.832	
C-reactive protein, mg/L	1.56	1.06	0.86–1.30	0.572	0.98	0.73–1.32	0.907		1.04	0.86–1.24	0.703	
Model 3[b,c]												
Waist–hip ratio	0.087	1.20	0.83–1.74	0.321	1.37	0.85–2.19	0.197	0.0405	1.26	0.92–1.72	0.157	0.0430
Systolic blood pressure, mmHg	9.4	1.07	0.86–1.35	0.534	1.43	1.04–1.95	0.026		1.18	0.97–1.43	0.100	
Triglycerides, mmol/L	0.61	1.03	0.82–1.29	0.823	1.08	0.81–1.45	0.594		1.05	0.86–1.27	0.660	
C-reactive protein, mg/L	1.56	1.07	0.87–1.31	0.503	1.06	0.81–1.40	0.657		1.07	0.89–1.27	0.466	

The multivariable models included only the covariates significantly associated ($P < 0.05$) with DD or DD2–3 (Table 2). C-reactive protein was also included as a potential risk factor. All quantitative variables were divided by their SD. The OR corresponded to each 1-SD increase

SD standard deviation, *OR* odds ratio, *CI* confidence interval

[a]Vs. normal diastolic function

[b]Age and sex were also included. [c] Similar results were found for all models when systolic blood pressure was replaced by diastolic blood pressure

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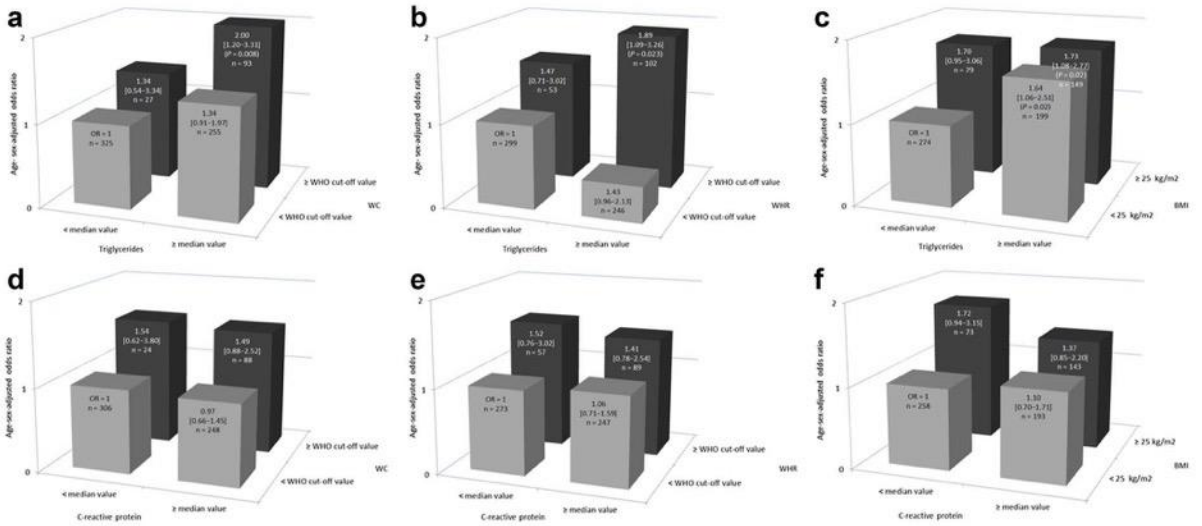

Fig. 1 Age-sex-adjusted odds ratio for diastolic dysfunction all grades when considering the interplay between: **a** waist circumference (WC) and triglycerides (TG), **b** waist-hip ratio (WHR) and TG, **c** body mass index (BMI) and TG, **d** WC and C-reactive protein (CRP), **e** WHR and CRP, and **f** BMI and CRP ($n = 728$)

not in the subgroup without hypertension and diabetes at baseline.

Interplay between abdominal obesity and inflammatory state or metabolic perturbations in DD

In our study, the subjects with increased WC/WHR and metabolic perturbations as assessed by elevated TG had a higher DD risk as opposed to those with elevated WC/WHR and lower TG, suggesting a role of visceral adiposity as a greater contributor to elevated TG than subcutaneous adipose tissue [24]. Visceral adiposity is associated with a high level of ectopic fat deposition as a consequence of both elevated free fat acid and TG blood levels [24, 25]. Elevated TG further triggers a low-grade inflammation state [25]. Additionally, visceral adipose tissue, infiltrated by macrophages, produces a systematic inflammatory state through the secretion of pro-inflammatory cytokines [26–28]. The usefulness of TG assessment in subjects with abdominal obesity resides in evaluating "triglyceridemic waist" reflected by the combination of elevated WC and elevated TG.

Since WC was not available in the Malmö study, we evaluated the interplay between BMI and TG only. We found that, in the whole sample, the conjunction of elevated BMI and TG was associated with an increased DD risk similar to that observed in the STANISLAS cohort for elevated WC/WHR and TG. However, when excluding patients with hypertension and diabetes at baseline, this association became non-significant. This replication analysis could suggest that the conjunction of elevated BMI and TG is a less sensitive marker of intra-abdominal fat in a healthy population, but conversely gains predictive power in a sicker population (i.e. with hypertension and diabetes). It should be noted that the mean BMI and TG values were higher in the Malmö cohort (Supplemental Table 4) than in the STANISLAS cohort (Table 1). Taken together, these results suggest that intra-abdominal fat may be an important metabolic predictor of developing long-term DD.

Of importance, a different pattern was observed with BMI: both overweight and non-overweight subjects with elevated TG had a similar DD risk (OR about 1.70). Elevated CRP did not increase DD risk associated with overweight. Thus, BMI may not be appropriate for detecting visceral fat even when combined with TG or CRP. In brief, the concomitant presence of elevated WC and biological abnormalities reflects a greater visceral fat, which in turn produces a higher DD risk.

Association between blood pressure and DD

Higher SBP was associated herein with a greater DD risk in an initially healthy population. This finding corroborates and extends our latest results from a cross-sectional study of participants with abdominal obesity [29]. Even though individuals had blood pressures within normal ranges and none displayed hypertension, high normal BP could nevertheless represent early stages of subsequent hypertension, which is one of the main conditions associated with diastolic dysfunction. SBP could thus represent a potential

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DD determinant, even within normotensive blood pressure ranges [5]. Whether WC is associated with DD through a hypertensive mechanism or other metabolic pathways is difficult to ascertain. However, after adjusting for baseline SBP, the association between WC and DD2–3 remained, suggesting a link between abdominal obesity and progression toward DD, irrespective of blood pressure level.

Nonetheless, in multivariable models, SBP was associated with DD2–3 but not significantly with DD, while DD2–3 was more associated with WC than SBP (OR 1.72 vs. 1.37). The association of SBP with DD was not confirmed in the Malmö cohort. This result suggests that, at an early stage of the disease process, abdominal obesity would have a stronger association with developing DD than elevated blood pressure. Furthermore, TG had a prominent role, but not CRP, in DD risk associated with abdominal obesity. Finally, as already highlighted, the modest percentage of variance explained by our multivariable model suggests that other important, albeit untested parameters may intervene.

Clinical perspectives

Despite ongoing research testing various medical treatments in patients with heart failure with preserved ejection fraction (HFpEF), there is currently no evidence-based treatment [30, 31]. The lifetime risk of subjects with asymptomatic DD [1, 2] of developing subsequent HFpEF remains elevated. Targeting high-risk individuals requires an efficient screening strategy, which is currently not available. Our results show that easily measurable WC/WHR, TG and blood pressure can help identify subjects at DD risk. The quantification of abdominal obesity in conjunction with the assessment of biological metabolic disturbances could prove useful in DD risk stratification. Lifestyle-intervention programs including sports/physical activity, relevant food intake, and reducing alcohol and sugar consumption, could reduce visceral adipose tissue in individuals with features of metabolic syndrome [32]. Such interventions in subjects with high DD risk could decrease this risk. Given the absence of evidence-based treatment for more advanced stages of the disease (i.e. HFpEF), testing early preventive pharmacological treatments in this high-risk group may also be appropriate.

Limitations

First, this study included healthy French adults from Southern Europe as defined by the ESC SCORE classification [33]. The studied Lorraine region presents a major adverse cardiac event rate which is intermediate-to-higher than the 'actual' event rate in Southern Europe [34]. While baseline DD was unknown, only 1.5% of subjects would have had baseline DD whereas 94% of DD would occur during follow-up. The change in DD between baseline and end of follow-up is difficult to assess since echocardiography has evolved considerably. Second, the CRP measured may be less accurate than high-sensitivity CRP and likely did not adequately measure the inflammatory state. Blood pressure was measured by three office measurements in a standardized manner. Third, we did not investigate glucose metabolism (which may be associated with DD) since there were no subjects with diabetes in the STANISLAS cohort at baseline. However, the HOMA index at last examination was not found associated with DD. Fourth, the percent of explained variance in our multivariable model (Table 3) of 5% was rather modest (but essentially unaltered even when comorbidities and HOMA index at last examination were additionally considered), suggesting that untested parameters may be strongly involved. Fifth, gender differences could not be accounted for owing to the relatively small number of participants of each sex resulting in a lack of power for statistical testing. Sixth, WC, WHR and CRP parameters were lacking in the Malmö dataset, therefore, a head-to-head multivariable modeling was not feasible. However, the overall findings were consistent in healthy subjects. Given the moderate clinical significance of the first stage of DD, an analysis focused on DD2–3 could be made in larger populations. Finally, results obtained stem from two studies in Eastern France and Malmö (Sweden).

Conclusion

The present study in young and middle-aged healthy individuals shows that abdominal obesity combined with increased triglycerides may confer a high risk of developing long-term DD. Easily measurable waist circumference, waist-hip ratio, triglycerides and blood pressure could help in identifying subjects at DD risk. These findings may have important implications in the preventive and therapeutic management of subjects at risk.

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Compliance with ethical standards

Ethical standards The Ethics Committee of the Lorraine region (*Comité Consultatif de Protection des Personnes qui se prêtent à une Recherche Biomédicale de Lorraine, and Comité Consultatif de Protection des Personnes Est-III*) approved the study, in agreement with French legislation on human biomedical research. Each subject gave his/her written informed consent to participate in this study.

Conflict of interest The authors declare that they have no competing interests.

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4. Association entre l'obésité abdominale et le risque de rigidité artérielle aortique accrue 20 ans plus tard dans une cohorte d'adultes initialement en bonne santé

La rigidité artérielle aortique prédit la survenue de maladies cardiovasculaires. Les études réalisées rapportent des résultats divergents sur l'association entre la rigidité artérielle et l'obésité générale ou l'obésité abdominale. Mais ces études concernaient des populations très diverses et étaient des enquêtes transversales ou prospectives avec une courte durée de suivi. Le ratio entre le niveau d'obésité abdominale et le niveau d'obésité générale, défini par le ratio TT/IMC, pourrait fournir une évaluation plus précise de la mesure de l'obésité abdominale. L'objectif de ce travail était d'étudier, chez des adultes initialement en bonne santé de la cohorte STANISLAS, l'association du ratio TT/IMC, de l'IMC, du TT, du ratio TT/T, et de l'"a body shape index" (ABSI = TT / (IMC$^{2/3}$ taille$^{1/2}$)) avec la rigidité artérielle mesurée 20 ans plus tard par la VOPcf.

Matériel et Méthodes

L'échantillon comprenait 2014 adultes de la cohorte STANISLAS. Au début du suivi, en 1994-1995, les sujets ont été inclus après un examen de santé au Centre de Médecine Préventive. Vingt ans plus tard (2011-2016), 995 adultes (52 %) ont participé à la dernière visite. Au début du suivi, ont été mesurés les caractéristiques démographiques, le statut tabagique, le poids, la taille, le TT, la PAS, la PAD, la fréquence cardiaque, la glycémie, le cholestérol total, le HDL, le LDL, le taux de TG et la PCR. Ont été calculés l'IMC, le ratio TT/IMC, le ratio TT/T et l'ABSI (proposé par Krakauer et al. [61] pour isoler la valeur additionnelle de TT vis-à-vis de l'IMC). A la fin du suivi, la VOPcf a été mesurée de façon non invasive selon les recommandations en vigueur.

L'association entre la VOPcf et les variables anthropométriques, la fréquence cardiaque et les variables biologiques a été évaluée par le coefficient de corrélation de Pearson et par les modèles de régression linéaire multiple pour calculer le coefficient de régression (β) en ajustant sur le sexe,

l'âge et la pression artérielle moyenne mesurées le jour où la VOPcf a été mesurée. Une analyse de sensibilité de l'association entre chaque variable anthropométrique et la VOPcf a été réalisée en prenant en compte le sexe, l'âge, la pression artérielle moyenne, la fréquence cardiaque, les variables métaboliques et la PCR.

Résultats

Au début du suivi, les sujets étaient âgés en moyenne de 41,6 ans. La VOPcf moyenne à la fin du suivi était de 9 m/s. La VOPcf était plus fortement corrélée avec le ratio TT/IMC et l'ABSI qu'avec TT, le ratio TT/T et les autres variables. Le modèle de régression ajusté sur le sexe, l'âge et la pression artérielle moyenne montrait qu'une augmentation d'un écart-type du ratio TT/IMC était associée à un accroissement de VOPcf de 0,32 m/s (β=0,32, IC 95 % 0,19-0,45, p<0,001). La VOPcf était moins fortement associée à ABSI (β=0,17, IC 95 % 0,022-0,32, p<0,05) et négativement associée à l'IMC, au TT, et au ratio TT/T ($-0{,}20 \leq \beta \leq -0{,}14$) (rôle protecteur). La VOPcf était associée positivement à la fréquence cardiaque, le LDL et la PCR.

L'association entre la VOPcf et les mesures anthropométriques étudiées était robuste quand nous considérions plusieurs modèles prenant en compte la fréquence cardiaque, les variables métaboliques, et la PCR. Dans tous ces modèles, le β pour le ratio TT/IMC restait plus élevé que celui d'ABSI alors que l'IMC, le TT, et le ratio TT/T avaient un β négatif, c'est-à-dire jouaient un rôle protecteur contre une VOPcf plus élevée. Le ratio TT/IMC était moins corrélé que l'IMC, le TT, le ratio TT/T, et l'ABSI à la PAS, la PAD, le HDL, le LDL, le taux de TG, la glycémie, et la PCR.

Conclusion

Chez les adultes initialement en bonne santé sans hypertension ni maladie cardiovasculaire, l'adiposité centrale, évaluée par le ratio TT/IMC, est un prédicteur robuste de la rigidité artérielle 20 ans plus tard. Il prédit mieux la rigidité artérielle que l'IMC, le TT, le ratio TT/T et l'ABSI.

Les programmes de prévention pourraient réduire l’adiposité centrale et donc le risque cardiovasculaire associé à la rigidité artérielle.

Original Article

Association between abdominal adiposity and 20-year subsequent aortic stiffness in an initially healthy population-based cohort

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Background: Aortic stiffness is a feature of arterial aging and is associated with dismal cardiovascular prognosis. We examined whether central and general adiposity is an independent predictor of accelerated aortic stiffening 20 years later in initially healthy midlife individuals.

Methods: Participants from the STANISLAS cohort study (826 initially healthy participants aged 30–60 from the Lorraine region in France) underwent clinical and biological measurements at baseline (1994–1995) and after ≈20 years (2011–2016). Adiposity measurements included waist circumference/BMI ratio, BMI, waist circumference, and 'body shape index' [waist circumference/(BMI$^{2/3}$ height$^{1/2}$)]. Real carotid–femoral pulse wave velocity (cfPWV) was measured at end of follow-up. Our primary analysis was to test the association between waist circumference/BMI ratio and cfPWV.

Results: In a multiple linear regression model adjusted for sex, age and mean arterial pressure, waist circumference-to-BMI ratio was positively associated (for 1SD increase) with higher cfPWV [regression coefficient $\beta = 0.32$, 95% confidence interval (CI) 0.19–0.45, $P < 0.001$]. The cfPWV was less strongly associated with body shape index ($\beta = 0.17$, 95% CI 0.022–0.32, $P < 0.05$) and negatively associated with BMI (−0.20, 95% CI −0.31 to −0.093, $P < 0.001$) and waist circumference (−0.14, 95% CI −0.28 to 0.00, $P < 0.05$). Sensitivity analyses demonstrated that the risk of cfPWV associated with waist circumference-to-BMI ratio remained significant after adjustment for heart rate, metabolic risk factors and inflammatory markers.

Conclusion: Central adiposity (and more specifically waist circumference-to-BMI ratio) is an independent predictor of 20-year subsequent aortic stiffness in initially healthy midlife subjects.

Keywords: aortic stiffness, initially healthy adults, longitudinal cohort study, obesity, pulse wave velocity

Abbreviations: β, regression coefficient; ABSI, a body shape index; cfPWV, real carotid-femoral pulse wave velocity; cfPWV-to-reference-value ratio, ratio between cfPWV and its reference value (%); STANISLAS, Suivi Temporaire Annuel Non Invasif de la Santé des Lorrains Assurés Sociaux; WHtR, waist-to-height ratio

INTRODUCTION

Aortic stiffness is a feature of arterial aging and a predictor of cardiovascular diseases, such as myocardial infarction, heart failure and stroke. Aortic stiffness is also associated with physical and cognitive functional disabilities in older people [1–6]. The prospective assessment of aortic stiffness determinants may help to identify potential vascular aging modifiers [7]. Obesity is considered an epidemic in middle-to-high income countries, and abdominal obesity in particular has been associated with several cardiovascular diseases [8]. The majority of studies have found no independent association between aortic stiffness and general obesity measured by BMI, although some studies have shown discrepancies in their association [7,9–13]. Several studies have conversely reported a protective role of BMI [11–13]. The studies greatly differed in terms of populations (different age, sex, BMI level and presence or not of diseased subjects), methodological approaches (cross-sectional study, short or long prospective study) [7]. A recent 5-year longitudinal study showed that higher general and central adiposity levels in later midlife are strong independent predictors of aortic stiffening [9]. However, only few studies have shown that abdominal obesity measured by waist circumference was more associated with pulse wave velocity than BMI [9,14,15]. The ratio between the level of abdominal obesity and the level of general obesity, as defined by waist

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circumference-to-BMI ratio may provide better accuracy for abdominal obesity assessment (degree of central bulge, that may correlate with abdominal fat deposits). To our knowledge, no study has investigated waist circumference-to-BMI ratio. Using the 20-year follow-up of initially healthy adults from the STANISLAS population-based cohort, we assessed the associations between waist circumference-to-BMI ratio, BMI, waist circumference, waist-to-height ratio (WHtR), 'a body shape index' (ABSI = waist circumference/($BMI^{2/3} \times height^{1/2}$)) [16] and subsequent aortic stiffness (as assessed by cfPWV).

METHODS

Study population and design

The STANISLAS study is a longitudinal population-based study of 1006 families from the Lorraine region (eastern France, 2.3 million inhabitants, 653 000 families in 2008), which comprised two parents (2014 individuals initially aged 30–60 years) and at least two children (2281 individuals initially aged 6–24 years) recruited in 1994–1995 during a medical examination at the Center for Preventive Medicine in eastern France. The subjects were of French origin and free of acute or chronic diseases (such as hypertension, diabetes, stroke, myocardial infarction, cancer, etc.). In the latest assessment performed in 2011–2016, 1902 volunteers from the initial population had participated. The present investigation focused on the parents ($n = 995$, participation rate 52.3%). Details of the cohort investigations and loss to follow-up are provided in the Supplemental Digital Content, http://links.lww.com/HJH/A947 and have been published [17].

Baseline risk factors

The following factors were gathered at baseline: age, sex, tobacco smoking status, height, weight, waist circumference, blood pressure, heart rate and biological measurements. Waist circumference was measured at the narrowest level. BMI was defined as weight in kilograms divided by the square of the height in meters. Waist-to-height ratio (WHtR) was defined by waist circumference/height.

To isolate the added value of waist circumference to BMI, ABSI = waist circumference/($BMI^{2/3} \times height^{1/2}$) was used as proposed by Krakauer and Krakauer [16]. We also investigated the ratio between abdominal and general adiposity defined by the waist circumference-to-BMI ratio [waist circumference (cm) divided by BMI (kg/m^2)].

SBP, DBP and heart rate were measured three times in all participants, at 1-min intervals, using an electronic sphygmomanometer after the participant had rested for at least 10 min. SBP, DBP and heart rate were calculated as the mean of the three measurements. Pulse pressure was calculated as SBP − DBP.

Serum concentrations of fasting glucose, total cholesterol and triglycerides were measured using commercially available kits on an AU5021 apparatus (all from Merck, Darmstadt, Germany) on fresh aliquots, and within 2 h. High-density lipoprotein was measured on a Cobas-Mira analyzer (Roche Diagnostics, Basel, Switzerland). Low-density lipoprotein cholesterol (LDL) was calculated according to the equation of Friedewald *et al.* [18]. C-reactive protein was measured by immunonephelometry on a Behring Nephelometer Analyzer (BN II; Dade-Behring, Marburg, Germany) with Behring reagents (Rueil-Malmaison, France) within 2 h after sampling.

Measurement of carotid–femoral pulse wave velocity at end of follow-up

Real carotid–femoral pulse wave velocity (cfPWV) [19] was measured noninvasively with the Complior (Alam Medical, France) in a quiet room after at least 10 min of rest in supine position. cfPWV was assessed following the recommendations of the European Network for Noninvasive Investigation of Large Arteries [20]. Two sensors were placed simultaneously on the carotid artery and on the femoral artery. Two measurements of cfPWV were performed with Complior and cfPWV was calculated as the mean of the two acquisitions. If the two first acquisitions differed by more than 0.5 m/s, a third measurement was performed and the cfPWV was calculated as the median of the three measurements. The onboard foot-to-foot algorithm based on the second derivative waveforms was used for the determination of the transit time (Δt). The carotid to femoral, carotid to sternal notch and sternal notch to carotid distances were measured with a measuring tape. The distance (ΔL) used for cfPWV calculation was 0.8 time the direct carotid–femoral distance. cfPWV (m/s) was calculated as: $cfPWV = \Delta L/\Delta t$.

The estimated reference value was calculated for each participant using the following equations provided by The Reference Values for Arterial Stiffness' Collaboration [21] (Supplemental Digital Content, http://links.lww.com/HJH/A947). The ratio between cfPWV and the estimated reference value (%, noted cfPWV-to-reference-value ratio) was subsequently defined by:

$$\text{cfPWV-to-reference-value ratio} = 100 \times \text{cfPWV}/\text{Estimated reference value.}$$

In order to retain only the healthy participants with no hypertension at cohort baseline, 36 participants with C-reactive protein greater than 10 mg/l, medical treatment for arterial hypertension, diabetes mellitus, medical treatment for arrhythmia or medical treatment for coronary heart disease were excluded, as well as 82 participants with office SBP at least 140 mmHg or office DBP at least 90 mmHg at baseline. Also excluded were 51 participants with missing cfPWV. In total, 826 participants were retained for analysis (Figure S1, Supplemental Digital Content, http://links.lww.com/HJH/A947).

Statistical analysis

Univariate analysis was first performed to provide frequency or mean (SD) for each dependent and explanatory variable. The associations of cfPWV (or cfPWV-to-reference-value ratio) with BMI, waist circumference, WHtR, ABSI or waist circumference-to-BMI ratio were then assessed using Pearson correlation coefficients, and multiple linear regression models to compute the regression coefficients (β) controlling

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TABLE 1. Characteristics of the study participants ($N = 826$)

	Number of participants (%)	Percentage or mean (SD)	Pearson correlation coefficient or mean (SD)	
			cfPWV, m/s	cfPWV-to-reference-value ratio [a], %
dPWV (m/s)	826 (100)	9.08 (1.75)		
cfPWV-to-reference-value ratio[a] (%)	826 (100)	96.1 (0.16)	0.827	
Characteristics at baseline				
Age (years)	826 (100)	41.6 (4.7)	0.305[‡]	−0.061
Sex	826 (100)		<0.001[c]	<0.001[c]
Male		47.9	9.57 (1.95)	98.2 (17.3)
Female		52.1	8.62 (1.39) [‡]	94.3 (14.0)
Smoking status	825 (99.9)		0.399[c]	0.211[c]
Never		54.1	9.01 (1.78)	95.6 (16.1)
Former		25.0	9.12 (1.71)	95.8 (16.0)
Current		21.0	9.21 (1.70)	98.0 (14.7)
Anthropometric measurements				
WC-to-BMI ratio [cm/(kg/m^2)]	824 (99.8)	3.35 (0.26)	0.288[‡]	0.211[‡]
BMI (kg/m^2)	826 (100)	24.1 (3.4)	0.014	−0.089[†]
Waist circumference (cm)	824 (99.8)	80.2 (10.7)	0.182[‡]	0.029
Waist-to-height ratio	824 (99.8)	0.48 (0.055)	0.113[‡]	−0.039[‡]
Waist-hip ratio	824 (99.8)	0.82 (0.090)	0.251[‡]	0.091[‡]
ABSI[b] (m/[(kg/m^2)$^{2/3}$m$^{1/2}$])	824 (99.8)	0.074 (0.0045)	0.289[‡]	0.013[‡]
Blood pressures and heart rate				
SBP (mmHg)	822 (99.5)	120.0 (9.8)	0.169[‡]	−0.039
DBP (mmHg)	822 (99.5)	73.1 (9.2)	0.134[‡]	−0.036
Pulse pressure (mmHg)	822 (99.5)	46.9 (8.5)	0.053	−0.007
Heart rate (bpm)	824 (99.8)	65.8 (10.0)	0.093[*]	0.091[*]
Metabolic measurements				
Total cholesterol (mmol/l)	796 (96.4)	5.72 (0.99)	0.164[‡]	0.078[§]
High-density lipoprotein cholesterol (mmol/l)	794 (96.1)	1.44 (0.40)	−0.152[‡]	−0.081[*]
Low-density lipoprotein cholesterol (mmol/l)	791 (95.8)	3.81 (0.93)	0.194[‡]	0.100[*]
Triglycerides (mmol/l)	796 (96.4)	1.02 (0.65)	0.154[‡]	0.058[§]
Blood glucose (mmol/l)	796 (96.4)	5.02 (0.47)	0.172[‡]	0.076[*]
Inflammatory marker				
C-reactive protein (mg/l)	753 (91.2)	1.39 (1.61)	0.077[*]	0.080[*]

ABSI, 'a body shape index'; cfPWV, real carotid–femoral pulse wave velocity at end of 20-year follow-up; *N*, number of available values; SD, standard deviation; WC, waist circumference.
[a]Ratio (%) = 100 x (cfPWV/Reference value).
[b]Ratio waist circumference/(BMI$^{2/3}$ × height$^{1/2}$); waist circumference in cm, BMI in kg/m^2 and height in meters.
[c]Variance analysis.
[*]$P < 0.05$,
[†]$P < 0.01$,
[‡]$P < 0.001$;
[§]$P < 0.10$ (close to significance).

for sex, age and mean blood pressure (DBP + 0.40 pulse pressure) at the time of the cfPWV measurement. These same analyses were performed for metabolic risk factors and C-reactive protein. Lastly, a sensitivity analysis of the association between each anthropometric measurement and cfPWV (or cfPWV-to-reference-value ratio) was first performed controlling for sex, age and mean blood pressure at the time of the cfPWV measurement (model 1), after which heart rate was added to model 1 (model 2), followed by metabolic risk factors added to model 1 (model 3), inflammatory marker added to model 1 (model 4) and finally all foregoing factors added to model 1 (model 5). The contribution of each set of covariates to the explanation of the association between waist circumference-to-BMI ratio and cfPWV (or cfPWV-to-reference-value ratio) was estimated by the change in β after its inclusion into the model, that is, explained fraction calculated by the formula: $(\beta_{\text{model 1}} - \beta_{\text{extended model}})/\beta_{\text{model 1}}$ [22]. 'Bootstrap' confidence intervals at 95% were computed for each regression coefficient on the basis of 1000 bootstrap samples using the percentiles method (2.5 and 97.5th percentiles). All tests were two-sided with a probability of less than 0.05 considered as significant. All statistical analyses were performed with the Stata software package (Stata Corporation, College Station, Texas, USA, 2011).

RESULTS

The characteristics of the participants are summarized in Table 1. Mean age at baseline was 41.6 years. Mean cfPWV at the end of follow-up was 9 m/s whereas the mean cfPWV-to-reference-value ratio was 96%. The waist circumference-to-BMI ratio followed a normal distribution (Figure S2, Supplemental Digital Content, http://links.lww.com/HJH/A947).

The cfPWV was more strongly correlated with waist circumference-to-BMI ratio and ABSI (Pearson correlation coefficient $r = 0.29$) than with waist circumference ($r = 0.18$) and WHtR ($r = 0.11$) (Table 1, Figure S3, Supplemental Digital Content, http://links.lww.com/HJH/A947) as well as other risk factors ($-0.15 < r < 0.20$). The cfPWV-to-reference-value ratio was also more strongly correlated with waist circumference-to-BMI ratio ($r = 0.21$) than with other risk factors including ABSI ($r \leq 0.13$).

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TABLE 2. Associations between baseline risk factors and real carotid–femoral pulse wave velocity at the end of the 20-year follow-up ($N = 826$): regression coefficient and 95% confidence interval

	1SD	cfPWV, m/s		cfPWV-to-reference-value ratio [a], %	
Characteristics at baseline					
Age (years)		0.096	0.073 to 0.12	**−0.30**[†]	−0.53 to −0.070
Women		**−0.49**[‡]	−0.71 to −0.26	**−5.36**[‡]	−7.60 to −3.12
Smoking status					
Never		0.00		0.00	
Former		−0.11	−0.38 to 0.16	−0.90	−3.61 to 1.81
Current		0.12	−0.16 to 0.40	0.45	−2.42 to 3.31
Anthropometric measurements					
Waist circumference-to-BMI ratio [cm /(kg/m^2)]	0.26	**0.32**[‡]	0.19 to 0.45	**3.34**[‡]	2.04 to 4.64
BMI (kg/m^2)	3.43	**−0.20**[‡]	−0.31 to −0.093	**−1.91**[‡]	−3.02 to −0.80
Waist circumference (cm)	10.7	**−0.14**[*]	−0.28 to 0.0	−1.19	−2.62 to 0.25
Waist-to-height ratio	0.055	**−0.16**[†]	−0.28 to −0.046	**−1.55**[†]	−2.75 to −0.35
Waist-hip ratio	0.090	0.0054	−0.17 to 0.18	0.24	−1.52 to 1.99
ABSI[b] m/[(kg/m^2)$^{2/3}$m$^{1/2}$]	0.0045	**0.17**[*]	0.022 to 0.32	**1.86**[*]	0.37 to 3.35
Heart rate (BPM)	10.0	**0.20**[‡]	0.095 to 0.31	**2.32**[‡]	1.22 to 3.42
Metabolic measurements					
Total cholesterol (mmol/l)	0.99	0.10	−0.010 to 0.21	1.03	−0.094 to 2.15
High-density lipoprotein cholesterol (mmol/l)	0.40	−0.086	−0.20 to 0.029	−0.57	−1.72 to 0.59
Low-density lipoprotein cholesterol (mmol/l)	0.93	**0.13**[*]	0.020 to 0.24	**1.25**[*]	0.12 to 2.39
Triglycerides (mmol/l)	0.65	0.056	−0.059 to 0.17	0.53	−0.63 to 1.70
Blood glucose (mmol/l)	0.47	0.099	−0.013 to 0.21	0.84	−0.29 to 1.98
Inflammatory marker					
C-reactive protein (mg/l)	1.61	**0.14**[†]	0.031 to 0.25	**1.38**[*]	0.25 to 2.51

All continuous variables (except age) were standardized (divided by 1SD). All β were adjusted for sex, age and mean blood pressure at the time of the cfPWV measurement (mean 95.7 mmHg (SD 10.3)).
ABSI, 'a body shape index'; cfPWV, real carotid–femoral pulse wave velocity; SD, standard deviation; β, regression coefficient.
[a]Ratio (%) = 100 × (cfPWV/reference value).
[b]Ratio waist circumference/(BMI$^{2/3}$ × height$^{1/2}$); waist circumference in centimeters, BMI in kg/m^2 and height in meters.
[*]$P < 0.05$.
[†]$P < 0.01$.
[‡]$P < 0.001$.

The waist circumference-to-BMI ratio was negatively correlated with BMI ($r = -0.33$; Figure S4, Supplemental Digital Content, http://links.lww.com/HJH/A947) and positively correlated with ABSI ($r = 0.79$; Figure S5, Supplemental Digital Content, http://links.lww.com/HJH/A947), the latter being less correlated with BMI ($r = 0.23$).

Table 2 shows that, based on the regression coefficient adjusted for sex, age and mean blood pressure at the time of the cfPWV measurement, a 1SD increase in waist circumference-to-BMI ratio was associated with a 0.32 m/s increase in cfPWV ($\beta = 0.32$, 95% CI 0.19–0.45, $P < 0.001$) and a 3.34% increase in cfPWV-to-reference-value ratio ($\beta = 3.3$, 95% CI 2.0–4.6, $P < 0.001$). Both cfPWV and cfPWV-to-reference-value ratio were less strongly positively associated with ABSI ($\beta = 0.17$, 95% CI 0.022–0.32, $P < 0.05$ and $\beta = 1.9$, 95% CI 0.37–3.3, $P < 0.05$, respectively). In contrast, both cfPWV and cfPWV-to-reference-value ratio were negatively associated with all BMI, waist circumference and WHtR ($-0.20 \leq \beta \leq -0.14$), thus showing a 'protective' association. Positive associations were found for heart rate, LDL and C-reactive protein. Women had both lower cfPWV and cfPWV-to-reference-value ratio.

When waist circumference and BMI were both included in the same regression model [16,23], the regression coefficient of waist circumference was $\beta = 0.41$ whereas that of BMI was $\beta = -0.51$ (Table S1, Supplemental Digital Content, http://links.lww.com/HJH/A947). Similar results but with lower β were observed when ABSI and BMI were both included in the same regression model (Table S1, Supplemental Digital Content, http://links.lww.com/HJH/A947). When both waist circumference-to-BMI ratio and BMI were included in the same model, the β of waist circumference-to-BMI ratio slightly decreased to 0.28 whereas that of BMI was nonsignificant ($\beta = -0.051$, $P = 0.509$), indicating that the role of waist circumference-to-BMI ratio in cfPWV was not dependent on BMI level (contrary to waist circumference and ABSI).

Table 3 shows that the associations between all anthropometric measurements and cfPWV (or cfPWV-to-reference-value ratio) were robust whenever considering several models controlling for heart rate (model 2), metabolic risk factors (model 3), inflammatory marker (model 4) and all foregoing factors (model 5). In all these models, the β for waist circumference-to-BMI ratio remained much higher than that for ABSI, whereas BMI, waist circumference and WHtR had negative β and thus a 'protective' association toward increased cfPWV (or cfPWV-to-reference-value ratio). The contributions of these sets of covariates were modest in explaining the association between cfPWV (or cfPWV-to-reference-value ratio) and waist circumference-to-BMI ratio (−28 to 0%) or ABSI (−6 to 18%). Their contributions had much higher magnitudes (−150 to −15%) in explaining the association between cfPWV (or cfPWV-to-reference-value ratio) and BMI, waist circumference or WHtR. The above results moreover remained unchanged when further adjusting for the HOMA index at the end of follow-up (data not shown).

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TABLE 3. Associations between waist circumference to BMI and other anthropometric measures and real carotid–femoral pulse wave velocity at the end of the 20-year follow-up ($N = 826$): regression coefficient and 95% confidence interval

Baseline predictors		cfPWV, m/s					cfPWV-to-reference-value ratio [a], %				
		β	95% CI	*P* value	Percentage[b]	Adjusted R^2	β	95% CI	*P* value	Percentage[b]	Adjusted R^2
Model including sex, age and mean blood pressure at the time of the cfPWV measurement						0.223					0.030
waist circumference-to-BMI ratio [cm/(kg/m^2)]	Model 1[c]	**0.32**	0.19 to 0.45	<0.001	100	0.244	**3.34**	2.01 to 4.64	0.009	100	0.058
	Model 1 with heart rate	**0.32**	0.20 to 0.45	<0.001	0	0.257	**3.36**	2.07 to 4.65	0.016	−1	0.078
	Model 1 with HDL, LDL, triglycerides blood glucose	**0.38**	0.24 to 0.51	<0.001	−19	0.250	**3.86**	2.50 to 5.21	0.003	−16	0.070
	Model 1 with C-reactive protein	**0.36**	0.23 to 0.50	<0.001	−12	0.241	**3.81**	2.41 to 5.21	<0.001	−14	0.069
	Model 1 with all factors	**0.41**	0.27 to 0.55	<0.001	−28	0.262	**4.14**	2.73 to 5.55	0.003	−24	0.096
BMI (kg/m^2)	Model 1[c]	**−0.20**	−0.31 to −0.09	<0.001	100	0.234	**−1.91**	−3.02 to −0.80	<0.001	100	0.042
	Model 1 with heart rate	**−0.23**	−0.34 to −0.12	<0.001	−15	0.250	**−2.21**	−3.31 to −1.11	<0.001	−16	0.066
	Model 1 with HDL, LDL, triglycerides blood glucose	**−0.29**	−0.41 to −0.17	<0.001	−45	0.243	**−2.70**	−3.93 to −1.47	<0.001	−41	0.055
	Model 1 with C-reactive protein	**−0.28**	−0.40 to −0.16	<0.001	−40	0.234	**−2.64**	−3.88 to −1.39	<0.001	−38	0.055
	Model 1 with all factors	**−0.40**	−0.53 to −0.27	<0.001	−100	0.264	**−3.67**	−5.01 to −2.34	<0.001	−92	0.090
Waist circumference (cm)	Model 1[c]	**−0.14**	−0.28 to 0.001	0.052	100	0.226	**−1.19**	−2.62 to 0.25	0.105	100	0.032
	Model 1 with heart rate	**−0.18**	−0.32 to −0.04	0.014	−29	0.240	**−1.58**	−3.01 to −0.15	0.030	−33	0.054
	Model 1 with HDL, LDL, triglycerides blood glucose	**−0.25**	−0.41 to −0.09	0.003	−79	0.230	**−2.03**	−3.67 to −0.40	0.015	−71	0.039
	Model 1 with C-reactive protein	**−0.21**	−0.37 to −0.05	0.010	−50	0.221	**−1.74**	−3.34 to −0.14	0.033	−46	0.039
	Model 1 with all factors	**−0.35**	−0.53 to −0.18	<0.001	−150	0.245	**−2.97**	−4.73 to −1.20	<0.001	−150	0.068
Waist-to-height ratio	Model 1[c]	**−0.16**	−0.28 to −0.05	0.007	100	0.229	**−1.55**	−2.75 to −0.35	0.011	100	0.036
	Model 1 with heart rate	**−0.21**	−0.33 to −0.09	<0.001	−31	0.245	**−2.02**	−3.22 to −0.81	<0.001	−30	0.061
	Model 1 with HDL, LDL, triglycerides blood glucose	**−0.26**	−0.40 to −0.13	<0.001	−62	0.236	**−2.33**	−3.69 to −0.96	<0.001	−50	0.046
	Model 1 with C to reactive protein	**−0.23**	−0.36 to −0.10	<0.001	−44	0.226	**−2.04**	−3.38 to −0.70	0.003	−32	0.045
	Model 1 with all factors	**−0.37**	−0.52 to −0.23	<0.001	−131	0.255	**−3.33**	−4.80 to −1.86	0.003	−115	0.079
ABSI[d] m/[(kg/m^2)$^{2/3}$m$^{1/2}$]	Model 1[c]	**0.17**	0.022 to 0.32	0.024	100	0.227	**1.86**	0.37 to 3.35	0.014	100	0.036
	Model 1 with heart rate	**0.14**	−0.012 to 0.28	0.072	18	0.238	**1.47**	−0.020 to 2.97	0.053	21	0.053
	Model 1 with HDL, LDL, triglycerides blood glucose	**0.18**	0.022 to 0.33	0.025	−6	0.226	**2.10**	0.52 to 3.67	0.009	−13	0.041
	Model 1 with C-reactive protein	**0.17**	0.011 to 0.33	0.036	0	0.218	**2.07**	0.46 to 3.68	0.012	−11	0.042
	Model 1 with all factors	**0.14**	−0.021 to 0.31	0.087	18	0.232	**1.78**	0.14 to 3.43	0.034	4	0.060

cfPWV, real carotid–femoral pulse wave velocity; CI, confidence interval; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SD, standard deviation; β, regression coefficient. All continuous variables (except age) were standardized (divided by 1SD). The SD was 3.43 kg/m^2 for BMI, 10.7 cm for waist circumference, 0.055 for waist-to-height ratio, 0.0045 m/[(kg/m^2)$^{2/3}$m$^{1/2}$] for ABSI, and 0.26 cm/(kg/m^2) for waist circumference-to-BMI ratio.
[a]Ratio (%) = 100 × (cfPWV/reference value).
[b]Contribution of covariates considered, that is, change in β computed with the following formula: $(\beta_{\text{model 1}} - \beta_{\text{extended model}})/\beta_{\text{model 1}}$.
[c]Model 1 provided β adjusted for sex, age and mean blood pressure at the time of the cfPWV measurement.
[d]Ratio waist circumference/(BMI$^{2/3}$ × height$^{1/2}$); waist circumference in centimeters, BMI in kg/m^2 and height in meters.

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Nonparametric confidence intervals computed using the bootstrap approach were very close to those obtained by the standard method (Table S2, Supplemental Digital Content, http://links.lww.com/HJH/A947).

Of note, waist circumference-to-BMI ratio was less correlated than BMI, waist circumference, WHtR and ABSI with SBP, DBP, HDL, LDL, triglycerides, blood glucose and C-reactive protein (Table S3, Supplemental Digital Content, http://links.lww.com/HJH/A947).

Replication of the analyses in Table 3 with estimated cfPWV determined by the Weber formula [19] yielded similar results (Table S4, Supplemental Digital Content, http://links.lww.com/HJH/A947).

Finally, replication of the analyses in Table 3 with predictors at the end of follow-up (cross-sectional analyses, Table S5, Supplemental Digital Content, http://links.lww.com/HJH/A947) found that the β of waist circumference-to-BMI ratio was slightly lower than that in Table 3 (0.25 vs. 0.32), which was not explained by any set of covariates (contribution −8 to 0%). The β of BMI, waist circumference and WHtR in model 1 were the same to those in Table 3, although the contributions of the sets of covariates were lower, whereas the β for ABSI became nonsignificant.

DISCUSSION

Main findings

The present prospective population-based study in initially healthy midlife subjects shows that abdominal adiposity, measured by the waist circumference-to-BMI ratio, was associated with 20-year subsequent aortic stiffness. This waist circumference-to-BMI ratio (rather than BMI, waist circumference, WHtR and ABSI), thus appears as a simple and key indicator to study the association between abdominal adiposity and cfPWV. Sensitivity analyses taking into account heart rate, metabolic risk factors and inflammatory marker show that this association was strong, with confidence intervals computed using the bootstrap approach confirming the validity of these results. Our novel findings may have clinical and public health implications for early abdominal adiposity prevention and management.

First, it should be noted that waist circumference has been shown in a large international cohort [24] to be a good surrogate of abdominal/visceral fat. Indeed, visceral adipose fat measured with computed tomography (gold-standard method) is more strongly correlated with waist circumference (correlation coefficient = 0.86) than with dual-energy X-ray absorptiometry (between 0.70 and 0.79), BMI (between 0.67 and 0.71) and WHtR (0.81) [25,26].

Our results furthermore suggest that BMI may play a protective role in aortic stiffness. This is in keeping with studies by Corden *et al.* [12] in healthy adults from the United Kingdom (mean age = 40.3 years, mean BMI = 25.5 kg/m^2), Nagayama *et al.* [27] in healthy Japanese subjects (mean age 47.1 years, mean BMI = 22.9 kg/m^2), Schillaci *et al.* [11] in treated hypertensive subjects and Nordstrand *et al.* [13] in morbidly obese male patients. Conversely, Fu *et al.* [14] found no association between BMI or waist circumference and aortic stiffness.

Unlike the above studies, surveys by Brunner *et al.* [9] (in civil servants in London, mean age = 65.5 years, mean BMI = 26.5 kg/m^2, 15% with chronic diseases and 34% with antihypertensive medication), Recio-Rodriguez *et al.* [15] (primary care setting, age 20–75 years, mean BMI = 27.9 kg/m^2), Wildman *et al.* [28] (healthy American adults, age 20–77 years with obese subjects >21%) and by Scuteri *et al.* [29] (Italian subjects, age 14–102 years, mean BMI = 28.4 kg/m^2 in subjects aged 65+ years) reported that both BMI and waist circumference were associated with increased cfPWV. Sutton-Tyrrel *et al.* [10] found a similar association with abdominal visceral fat measured with computed tomography (healthy American adults, age 70–79 years).

The discrepancies between the aforementioned findings may be partly explained by differences in age, sex, BMI level and presence or not of diseased subjects. Indeed, the studies, which found that BMI and waist circumference were associated with increased aortic stiffness generally included a greater number of older, obese or diseased subjects [9,15]. The Corden *et al.* [12] study found that body fat was associated with reduced aortic stiffness under 50 years whereas conversely associated with increased aortic stiffness after 50 years. The Nordstrand *et al.* [13] study found contradictory results in men and women as well as between age groups (BMI associated with reduced aortic stiffness in younger subjects, and with increased aortic stiffness in older subjects).

Importantly, although our cohort included healthy midlife individuals at baseline (mean age = 41.7 years) with relatively low BMI (mean = 24.1 kg/m^2), using waist circumference-to-BMI ratio allowed us to show that abdominal/visceral fat strongly predicted long-term subsequent cfPWV. This harmful role of abdominal adiposity in aortic stiffness is consistent with other studies conducted in various populations [9,10,15,28,29].

Another important result of our study was that the association between waist circumference-to-BMI ratio and cfPWV was less dependent on SBP, DBP, LDL, triglycerides, blood glucose and C-reactive protein than the other anthropometric parameters. The waist circumference-to-BMI ratio may hence, more specifically reflect central adiposity. Of further importance, based on the regression coefficient, the role of waist circumference-to-BMI ratio in cfPWV was clearly higher than that of all other studied risk factors.

What does the association between waist circumference-to-BMI ratio and cfPWV represent in terms of physiology? In our study, higher waist circumference-to-BMI ratio and higher cfPWV concerned participants with higher waist circumference in the three obese, overweight and normal-weight groups (Figures S2 and S3). Hence, the aortic stiffness associated with elevated abdominal adiposity would concern higher BMI as well as normal BMI. Importantly, the association between aortic stiffness and abdominal adiposity (reflected by waist circumference-to-BMI ratio) would be independent of BMI. This finding is in concordance with those of Kim *et al.* [30] and Wohlfahrt *et al.* [31] who found that higher central adiposity in non-obese individuals was associated with higher PWV. However, such studies are rare. Therefore, the 20-year subsequent altered cfPWV may be associated with cardiometabolic dysregulation, but also lifestyle during the

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follow-up. Indeed, excess body fat in normal-weight subjects is associated with metabolic dysregulation and a higher level of subclinical vascular inflammation [32]. It may also be responses to dietary intake, reduced lean muscle mass or lack of exercise [33]. Weight loss achieved through increased physical activity without caloric restriction results in reduced abdominal obesity and less insulin resistance [34].

Advantages of waist circumference-to-BMI ratio

The risk associated with BMI for cardiovascular outcomes may follow a U-curve [16]. Our cohort included few obese participants (4.8%) such that a higher risk may not be observed for increased BMI. Both BMI and waist circumference are collinear, although waist circumference substantially varies for a fixed BMI [24], hence an elevated waist circumference-to-BMI ratio would mean a greater fraction of abdominal/visceral fat. Herein, the waist circumference-to-BMI ratio followed a normal distribution. An elevated waist circumference-to-BMI ratio was observed for all BMI values, albeit mainly for normal BMI (Figure S4, Supplemental Digital Content, http://links.lww.com/HJH/A947). The role of waist circumference-to-BMI ratio in cfPWV was independent of BMI. Thus, the relative proportion of abdominal adiposity in general adiposity strongly predicted cfPWV independently of general adiposity level.

Waist circumference-to-BMI ratio and ABSI showed an agreement in their association with cfPWV. However, why was the association stronger for waist circumference-to-BMI ratio than for ABSI? ABSI represents the ratio of waist circumference to an estimated waist circumference for fixed weight and height. This estimated waist circumference did not reflect the general adiposity of each subject. Indeed, the ABSI was constructed to be independent of body weight, height and BMI [16]. This condition may lead to neglect a proportion of abdominal fat that is a part of body weight. Thus, the formulae defining ABSI may not be valid and would need to be determined for each population. In our study, ABSI was not independent of BMI. The waist circumference-to-BMI ratio may thus overcome these limitations.

Clinical implications

We showed that, in midlife healthy adults, waist circumference-to-BMI ratio would be a simple measure of abdominal/visceral adiposity to study long-term arterial early aging and to precociously identify and monitor individuals at risk. Normal-weight subjects with an excess of body fat were the most affected. These individuals may be unaware of their heightened cardiometabolic risk, given that they had a normal BMI. As risk self-awareness is the first step in behavioral and therapeutic lifestyle changes, it may be relevant to incorporate waist circumference-to-BMI ratio in clinical practice. The cardio-metabolic dysregulation in normal-weight subjects with an excess of body fat (such as insulin resistance, altered lipid profile and metabolic syndrome) are potentially remediable. Lifestyle-intervention programs including sports/physical activity, relevant food intake and reducing alcohol and sugar consumption, could reduce visceral adiposity in individuals with metabolic syndrome [35]. Aerobic exercise (fast walking, jogging and swimming) in midlife may reduce cfPWV [36].

Strengths and weaknesses of the study

The current large population-based cohort study focused on the long-term effect of general and central adiposity on arterial stiffness in healthy midlife subjects. The cfPWV was not measured at baseline. Our findings are original and highlight the key interest of early prevention to reduce central adiposity and its consequence on arterial stiffness. We acknowledge that, although visceral adiposity was not directly measured using imaging methodology, waist circumference as currently measured is a better surrogate of abdominal/visceral fat than both dual-energy X-ray absorptiometry and BMI [25,26]. As this study included initially healthy French adults from southern Europe (as defined by the ESC SCORE classification [37]), the findings might not be generalizable to higher risk populations. However, the Lorraine region presents a major adverse cardiac events rate, which is classified as intermediate and thus higher than the 'true' southern Europe event rate [38].

In conclusion, central adiposity, as assessed by waist circumference-to-BMI ratio, is a robust predictor of 20-year subsequent aortic stiffness in midlife initially healthy subjects with no hypertensive status or overt cardiovascular disease. It predicts aortic stiffness better than BMI, waist circumference, WHtR and ABSI. Prevention programs could reduce central adiposity, and consequently the increased cardiovascular risk associated with increased aortic stiffness.

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Conflicts of interest

There are no conflicts of interest.

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5. Facteurs associés à une hypertension artérielle non-diagnostiquée

Dans différents pays, entre 17 et 50 % des sujets ayant une hypertension artérielle (HTA) ne sont pas diagnostiqués et ne reçoivent pas de soins. En France, 48 % des adultes de 18 à 74 ans hypertendus ne sont pas conscients de leur HTA. Il est important d'identifier les facteurs associés à un risque accru d'HTA non-diagnostiquée parmi les sujets hypertendus. L'objectif de ce travail était d'explorer les caractéristiques socioéconomiques, biologiques et cardiovasculaires, des comportements de santé (statut tabagique, consommation d'alcool et activités physiques et sportives) et l'utilisation des soins primaires qui pouvaient être associés au risque d'HTA non-diagnostiquée parmi les sujets hypertendus.

Matériel et Méthodes

L'échantillon étudié comprenait 2014 adultes de la cohorte STANISLAS. Les sujets ont été inclus après un examen de santé au Centre de Médecine Préventive en 1994-1995. Parmi les 1902 survivants, 995 (52,3 %) avaient participé à la dernière visite en 2011-2016.

A cette dernière visite, les caractéristiques suivantes ont été recueillies par questionnaire : âge, sexe, statut tabagique, consommation d'alcool, activités physiques et sportives régulières, état de santé perçu, trouble de la mémoire, maladies cardiovasculaires, diabète, traitement hypolipémiant, antécédent d'HTA, antécédents familiaux d'HTA (parents et fratrie), la perception de l'HTA comme une maladie grave et le nombre de consultations par an de médecine générale (MG). La taille, le poids, le TT, l'IMC, la glycémie, le cholestérol total, les triglycérides, la pression artérielle systolique casuelle (PASc), la pression artérielle diastolique casuelle (PADc), la pression pulsée, la fréquence cardiaque et la mesure ambulatoire de la pression artérielle pendant 24h (MAPA 24h) ont aussi été mesurés.

L'HTA non-diagnostiquée était définie par les pressions artérielles casuelles ≥140/90 mm Hg et MAPA 24h ≥130/80 mm Hg mais sans antécédent d'HTA. Au total, 281 sujets hypertendus de

50 à 76 ans avaient été retenus pour l'analyse. L'analyse statistique consistait à comparer 59 sujets ayant une HTA non-diagnostiquée et 222 sujets ayant une HTA traitée à la dernière visite à l'aide de modèles de régression logistique multivariés.

Résultats

Parmi les sujets ayant une HTA non-diagnostiquée, 20 % avaient une HTA grade 2+ définie par la PASc ≥160 ou PADc≥100 mm Hg. Parmi les sujets ayant une HTA traitée, 68 % étaient contrôlés pour les pressions artérielles casuelles, 60 % pour la MAPA 24h et 47 % à la fois pour les pressions artérielles casuelles et la MAPA 24h.

Le modèle de régression logistique multivarié retenait cinq facteurs significativement associés à l'HTA non-diagnostiquée : sexe masculin (odds ratio ajusté ($OR_{ajusté}$) 4,61, IC 95 % : 1,97−10,8), TT moins élevé ($OR_{ajusté}$ 1,05 pour une baisse de 1 cm, IC 95 % : 1,02−1,09), absence de maladies cardiovasculaires/diabète ($OR_{ajusté}$ 8,51, IC95% : 2,42−29,8), absence d'antécédents familiaux d'HTA ($OR_{ajusté}$ 3,15, IC 95 % : 1,51−6,60) et un nombre moins élevé de consultations de MG ($OR_{ajusté}$ 3,18 par augmentation d'1-categorie, IC 95 % : 1,96−5,15). Ce modèle donnait un pseudo R^2 de 0,32. Ces cinq facteurs étaient unidimensionnels. L'analyse factorielle en composantes principales montrait une première valeur propre (0,51) deux fois plus élevée que la seconde valeur propre (0,25). Le coefficient alpha de Cronbach était de 0,35. Un score de risque pouvait être défini comme le nombre de critères positifs. Le pourcentage d'HTA non-diagnostiquée augmentait fortement avec le nombre de critères positifs : 0, 24, 57 et 72 % pour 0, 3, 4 et 5 critères, respectivement.

Conclusion

Notre étude, chez des adultes âgés de 50 à 76 ans, donne des résultats permettant de mieux comprendre pourquoi certains sujets hypertendus ont leur hypertension non-diagnostiquée. Ces sujets ayant une hypertension non-diagnostiquée sont plus souvent des hommes, ont un IMC

moins élevé et un TT moins élevé, ont moins souvent des maladies cardiovasculaires/diabète ou des antécédents familiaux d'HTA et consultent moins souvent un MG. D'autre part, la présence concomitante d'un nombre élevé de ces critères renforce fortement le non-diagnostic. Les MG devraient être vigilants sur le fait que des sujets ayant ces critères peuvent avoir une HTA. Nos résultats nécessitent d'autres études qualitatives ou quantitatives pour identifier précocement les sujets ayant une HTA non-diagnostiquée.

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Primary Care Epidemiology

Health-related determinants of undiagnosed arterial hypertension: a population-based study

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Abstract

Background. Undiagnosed arterial hypertension is frequent. Whether it is associated with gender and the absence of cardiovascular-disease warning signs is unknown. Knowledge of the features of undiagnosed-hypertension subjects may help their identification in primary care.

Objective. To examine whether gender, alcohol consumption, smoking status, health status, cardiovascular diseases/diabetes, familial hypertension history, anti-cholesterol treatment, GP-consultation frequency, body mass index (BMI), waist circumference and metabolic measurements were associated with having undiagnosed hypertension among hypertensive subjects.

Methods. This population-based study included 281 hypertensive adults (aged 50–76 years): 222 subjects with diagnosed and treated-hypertension and 59 undiagnosed-hypertension subjects (no hypertension history, office and 24-h ambulatory blood pressures ≥140/90 and ≥130/80 mmHg, respectively). Subjects' characteristics, clinical and biological measurements, health problems and blood pressures were collected. Data were analyzed using adjusted odds ratios (OR) computed with multivariable logistic regression models.

Results. Undiagnosed-hypertension represented 21% of hypertensive subjects. Multivariable logistic regression modeling showed that five risk factors were associated with undiagnosed-hypertension among hypertensive subjects: male gender (OR = 4.61, $P < 0.001$), no cardiovascular diseases/diabetes (OR=8.51, $P < 0.001$), no familial hypertension history (OR = 3.15, $P = 0.002$), number of GP consultations per year (3+, 1–2, and 0; OR = 3.18 per 1-category increase, $P < 0.001$), and lower waist circumference (OR = 1.05 per 1-cm decrease, $P = 0.002$). Living alone, alcohol consumption, health status, anti-cholesterol treatment, BMI, and blood glucose were also significant factors ($P < 0.05$) in bivariate analysis.

Conclusion. Undiagnosed-hypertension subjects exhibit specific features associated with their hypertension awareness. These findings help understand undiagnosed-hypertension risk patterns and enable better identification of affected subjects for lifestyle management and care.

Key words. Adults, behaviours, determinants, primary care, undiagnosed-hypertension.

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Introduction

Hypertension represents 7% of global disability-adjusted life years and is the strongest contributor to the global burden of disease and death from cardiovascular-disease worldwide (1,2). Appropriate management of health behaviour changes (weight control, smoking cessation, higher physical activity levels, reduced salt and alcohol intake, and healthy diets) (3,4) and treatment can reduce BP levels (5) and prevent morbidity and mortality from preventable complications of hypertension (6,7). Timely care and health behaviour management are important and necessitate that all subjects meeting criteria for hypertension be diagnosed early. Unfortunately, 17–50% of individuals meeting hypertension criteria are undiagnosed and do not receive care (8–12). In France, half of 18–74 year-old hypertensive adults are unaware of their hypertension (13,14).

A primary-care challenge is to identify potential factors that are associated with a higher risk of having undiagnosed hypertension among individuals meeting hypertension criteria. A study in 18–49 year-old American women has shown that barriers to hypertension diagnosis include being underweight, absence of ischemic heart disease or diabetes and lower primary-care use (15). Another study in 40–74 year-old adults in the UK found strong positive associations between untreated hypertension and male gender, smoking, self-reported good health, higher alcohol consumption and living alone (16). Alcohol consumption and smoking are moreover related to lower perceived risk, less attribution of cardiovascular diseases to lifestyle factors and lower participation in hypertension screening (17,18).

We hypothesize that reasons for undiagnosed hypertension may be that the subjects concerned are unaware of their hypertension and do not consult a general practitioner (GP) to evaluate their BP. In addition, undiagnosed-hypertension risk patterns are rather complex and remain poorly documented. In light of the above, using a population-based cross-sectional study, the present study aimed at exploring a wide range of factors including phenotypic and biological factors, cardiovascular risk features, primary-care use, lifestyle (smoking status, alcohol consumption and sports/physical activity), and marital status which may be associated with having undiagnosed hypertension among hypertensive subjects. The knowledge of the risk patterns associated with these factors may be useful for primary care and especially for GPs, enabling to precociously suspect and detect undiagnosed hypertensive subjects, as well as establish timely care and health behaviour management (19).

Methods

Study population and design

This study was based on data from the STANISLAS familial cohort study in Eastern France. Details of the cohort investigations have been published (20) and are provided in the Supplementary data. The initial parent sample consisted of 2014 adults initially aged 30–60 years, of French origin, and free of all acute or chronic diseases. They were recruited in 1994–1995 during a medical examination at the Center for Preventive Medicine in Eastern France. Among the 1902 surviving subjects, 995 (52.3%) participated in the last examination in 2011–2016. The Ethics Committee of the Lorraine region approved the study. Written informed consent was obtained from each participant.

Measurements

The following were gathered through questionnaires: age, gender, tobacco smoking status, alcohol consumption (number of glasses per week), regular sports/physical activity, perceived health status, memory disorder, cardiovascular diseases, diabetes, anti-cholesterol treatment, history of hypertension, familial hypertension history (parents and siblings), and number of GP consultations per year. Height, weight, and waist circumference (WC, at the narrowest level) were also measured. Body mass index (BMI) was defined as weight/height^2 (kg/m^2). WC was dichotomized using the World Health Organization's cut-off values (<94 cm vs. higher for men; <80 cm versus higher for women).

Office BP and heart rate were measured 3 times, at 1-minute intervals, under standardized conditions (in supine position, after 10 minutes of rest) using an automatic oscillometric device (Physiogard SM 785 Niox; Odam, Wissenbourg, France); the arm with the higher BP was retained. Office systolic BP (OSBP), diastolic BP (ODBP), and heart rate were calculated as the mean of the three measurements. Pulse pressure was calculated as OSBP-ODBP. Office hypertension based on office BP was defined by OSBP ≥ 140 mmHg and/or ODBP ≥ 90 mmHg.

Measurement of 24-hour ambulatory blood pressure

All participants underwent a 24-hour recording of ambulatory BP using the Spacelabs 90207 ambulatory monitor (Spacelabs Medical). The BP system was programmed to measure every 15 minutes from 6 AM to 10 PM and every 30 minutes from 10 PM to 6 AM (Supplementary data) (20). Based on 24-hour ambulatory BPs, ambulatory hypertension was defined as systolic BP≥130 mmHg and/or diastolic BP≥80 mmHg.

Undiagnosed hypertension was defined as office BPs≥140/90 mmHg and 24-hour ambulatory BPs≥130/80 mmHg but without hypertension history (21).

Serum concentrations of fasting glucose, total cholesterol and triglycerides were measured within 2 hours on fresh aliquots using commercially available kits on an AU5021 apparatus (all from Merck, Darmstadt, Germany).

Perceived good health status was assessed with the question defined by the World Health Organization's quality of life "How satisfied are you with your health?" (response: good, very good or neither poor nor good versus poor or very poor) (22). Memory disorder was evaluated using the question "Do you have any memory trouble or difficulty?" (response: no versus yes).

Regular sports/physical activity was measured with the question "Do you regularly practice any sports or physical activity?" (response: no versus yes) which was confirmed by questions regarding the beginning, the frequency, the level and the time spent for various sports and physical activities practiced.

The frequency of GP consultation was defined by the question: "During the last-year, have you consulted your general practitioner?" (response: number of times per year). The number of consultations was categorized into three levels: 3+ = 1, 1 or 2 = 2 and 0 = 3). A low number of GP-consultations was defined as <3 consultations (versus ≥3).

Perception of hypertension as a severe disease was evaluated using the question: "To what extent do you feel that hypertension is?" (response: 1 = a non-severe or rather non-severe disease, 2 = a severe disease or 3 = a very severe disease).

In order to ensure that only healthy subjects at cohort baseline were considered in the analysis and to focus on hypertension occurring between baseline and the last examination, the data were verified and 24 subjects were excluded with medical treatment for hypertension, diabetes mellitus, arrhythmia or coronary heart disease, as well as 85 subjects with SBP ≥ 140 mmHg or DBP ≥ 90 mmHg at baseline.

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Also excluded were 141 subjects with missing ambulatory BP, 40 subjects with white-coat hypertension (no hypertension history with office BPs ≥ 140/90 mmHg and ambulatory BPs < 130/80 mmHg) (21), and 82 subjects with masked hypertension (office BPs < 140/90 mmHg and ambulatory BPs ≥ 130/80 mmHg) (21).

In total, 281 hypertensive subjects were retained for analysis: 222 subjects with treated hypertension and 59 subjects with undiagnosed hypertension (21) during the last examination (Supplementary Figure S1).

Statistical analysis

The association between undiagnosed hypertension and various determinants were assessed using the chi-square test (for qualitative variables) or variance analysis (for continuous variables), and logistic regression models to compute age-gender-adjusted odds ratios (OR_{ag}) and 95% confidence intervals (CI). Thereafter, a multivariable logistic regression model (including only the factors significantly associated with undiagnosed hypertension ($P < 0.05$)) with stepwise forward procedure retaining only significant determinants ($P < 0.05$) was used to compute adjusted odds ratios ($OR_{adjusted}$). To facilitate understanding, factors with significant $OR_{ag} < 1$ (protective factors), that is, higher BMI, higher WC and higher blood glucose, were inverted in the text (as risk factors with $OR_{ag} > 1$, with the 95% CI limits also inverted) but not in the Tables. For the factors retained (Table 3), their one-dimensionality was verified by factor analysis and their internal consistency by Cronbach's alpha. For WC and number of GP-consultations, the corresponding dichotomized variables were used. A risk score was defined as the number of positive criteria (range = 0–5). A P-value <0.05 (2-sided) was considered statistically significant. All statistical analyses were performed with the Stata software package (Stata Corporation, College Station, Texas, USA, 2011).

Results

Among the 281 hypertensive subjects (aged 49.7–76 years), 222 were treated and 59 (21.0%) were undiagnosed. Table 1 shows that 20% of undiagnosed-hypertension subjects had grade 2+ hypertension according to office BP (OSBP ≥ 160 or ODBP ≥ 100 mmHg). Among treated-hypertension subjects, 68%, 60% and 47% were controlled according to office BP, 24-hour ambulatory BP, and both office and 24-hour ambulatory BP, respectively.

Table 2 reveals that the undiagnosed-hypertension subjects were more often male, living alone, had higher alcohol consumption, more often had perceived good health, no cardiovascular diseases/diabetes, no anti-cholesterol treatment, no familial hypertension history and fewer GP-consultations (OR_{ag} reaching 14). They also had lower BMI (OR_{ag} = 1/0.87 = 1.15 per 1-kg/m² decrease), lower WC (OR_{ag} = 1/0.95 = 1.05 per 1-cm decrease) and lower blood glucose (OR_{ag} = 1/0.55 = 1.82 per 1-mmol/L decrease).

Table 3 shows that, among these determinants, multivariable logistic regression model with forward stepwise procedure retained only five significant factors ($P < 0.05$): male gender ($OR_{adjusted}$ = 4.61, 95% CI = 1.97–10.8), lower WC ($OR_{adjusted}$ = 1.05 for 1-cm decrease, 95% CI = 1.02–1.09), no cardiovascular diseases/diabetes ($OR_{adjusted}$ = 8.51, 95% CI = 2.42–29.8), no familial hypertension history ($OR_{adjusted}$ = 3.15, 95% CI = 1.51–6.60) and fewer GP-consultations ($OR_{adjusted}$ = 3.18 per 1-category increase, $P < 0.001$, 95% CI = 1.96–5.15) (pseudo R^2 = 0.32). These criteria (WC and number of yearly GP-consultations being dichotomized) were unidimensional (factor analysis showed that the 1st eigenvalue (0.51) was much higher than the 2nd eigenvalue (0.25)). The Cronbach alpha was 0.35. Figure 1 shows that the percentage of undiagnosed hypertension strongly increased with overall risk score (number of positive criteria) from 0% for 0 criterion to 72% for 5 criteria.

Table 1. Blood pressures and heart rate of undiagnosed-hypertension and treated-hypertension subjects: %, mean (SD), age-gender-adjusted odds ratio and 95% CI (2011–2016)

	Treated-hypertension (n = 222)	Undiagnosed-hypertension (n = 59)	Bivariate analysis
	% or mean (SD)	% or mean (SD)	P-value
Systolic blood pressure, mmHg			
Office blood pressure	132.8 (15.3)	149.8 (9.4)	<0.001
24-hour ambulatory blood pressure	123.0 (10.6)	133.1 (5.7)	<0.001
Diastolic blood pressure, mmHg			
Office blood pressure	75.2 (8.4)	84.3 (6.6)	<0.001
24-hour ambulatory blood pressure	75.5 (7.8)	82.0 (5.5)	<0.001
Office pulse pressure, mmHg	57.5 (11.1)	65.5 (10.5)	<0.001
Office heart rate, bpm	61.6 (9.3)	64.2 (9.3)	0.055
Office hypertensive grade			<0.001
Normal: OSBP < 140 and ODBP < 90	68.0	0.0	
Grade 1: OSBP 140–159 or ODBP 90–99	26.6	79.7	
Grade 2: OSBP 160–179 or ODBP 100–109	5.0	18.6	
Grade 3: OSBP ≥ 180 or ODBP ≥ 110	0.4	1.7	
Hypertensive grade according to 24-hour ambulatory blood pressure			<0.001
Normal: ASBP < 135 and ADBP < 85	59.9	0.0	
Hypertension: ASBP ≥ 135 or ADBP ≥ 85	40.1	100.0	
Normal office blood pressure and normal 24-hour ambulatory blood pressure:			
(OSBP < 140 and ODBP < 90) and (ASBP < 135 and ADBP < 85)	47.3	0.0	<0.001

Abbreviations: n, number of subjects; SD, standard deviation; OR_{ag}, age-sex-adjusted odds ratio; CI, confidence interval; SBP, systolic blood pressure (mmHg); DBP, diastolic blood pressure (mmHg); OSBP, office SBP; ODBP, office DBP, ASBP, 24-hour ambulatory SBP; ADBP, 24-hour ambulatory DBP.

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Table 2. Characteristics of undiagnosed-hypertension and treated-hypertension subjects: %, mean (SD), age-gender-adjusted odds ratio and 95% CI (2011–2016)

	Treated-hypertension (n = 222)	Undiagnosed-hypertension (n = 59)	Chi^2 test or variance analysis	OR_{ag}	95% CI
	% or mean (SD)	% or mean (SD)	(P value)		
Age, year	60.9 (4.7)	60.8 (4.7)	0.871	0.96	0.90–1.03
Men versus women	51.3	71.2	0.006	2.63‡	1.36–5.09
Family status (living alone versus others)	9.5	22.0	0.008	2.80†	1.28–6.14
Educational level			0.802		
University (reference)	19.8	20.3		1.00	
Middle and high schools	61.7	57.6		1.01	0.48–2.15
Primary school	18.5	22.0		1.27	0.51–3.16
Alcohol consumption per week (unit or glass)	9.5 (14.8)	15.1 (17.8)	0.013	1.01	1.00–1.03
Current or ex-smokers (versus never-smokers)	57.2	59.3	0.770	0.80	0.43–1.49
No regular sports/physical activity[a]	57.7	67.8	0.158	1.52	0.82–2.82
Health-related factors					
Perceived good health status[b]	59.9	76.3	0.020	2.13*	1.10–4.15
No memory disorder[c]	82.4	89.8	0.168	2.03	0.81–5.12
No cardiovascular diseases and diabetes[d]	62.6 [h]	94.9 [i]	< 0.001	14.05‡	4.19–47.1
No anti-cholesterol treatment[d]	58.6	88.1	< 0.001	6.29‡	2.67–14.8
No familial hypertension history[d]	35.1	64.4	< 0.001	3.11‡	1.68–5.76
Number of GP consultations per year[e]	1.20 (0.50)	1.93 (0.83)	< 0.001	4.32‡	2.76–6.77
Perception of hypertension as a severe disease[f]	2.14 (0.55)	2.10 (0.66)	0.616	0.87	0.53–1.44
Anthropometric and metabolic measurements					
Body mass index[g], kg/m²	28.1 (4.8)	26.0 (3.4)	0.002	0.87‡	0.80–0.95
Waist circumference, cm	96.2 (13.3)	92.6 (11.0)	0.058	0.95†	0.93–0.98
Total cholesterol, mmol/L	5.57 (1.15)	5.74 (0.98)	0.291	1.31	0.99–1.73
High density lipoprotein cholesterol, mmol/L	1.44 (0.35)	1.50 (0.40)	0.317	2.32*	1.00–5.38
Triglycerides, mmol/L	1.25 (1.20)	1.17 (0.58)	0.613	0.88	0.58–1.32
Blood glucose, mmol/L	5.46 (1.09)	5.14 (0.66)	0.031	0.55†	0.35–0.86

Abbreviations: SD, standard deviation; OR_{ag}, age-sex-adjusted odds ratio (for 1-unit increase for quantitative variable); CI, confidence interval; GP, general practitioner.

*$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$.

[a]Regular sports/physical activity was measured with the question "Do you regularly practice any sports or physical activity?" (no versus yes) which was confirmed by questions regarding the beginning, the frequency, the level and the time spent for various sports and physical activities practiced.

[b]Perceived health status was assessed with the question "How satisfied are you with your health?" (good, very good or neither poor nor good versus poor or very poor).

[c]Memory disorder was evaluated using the question "Do you have any memory trouble or difficulty?" (no versus yes).

[d]versus presence of at least one.

[e]In three categories: 3+ = 1, 1–2 = 2 and 0 = 3. The frequency of subjects in these categories was respectively 84.7%, 10.8% and 4.5% in treated hypertension subjects; and 37.3%, 32.2% and 30.5% in undiagnosed-hypertension subjects.

[f]Quantitative variable with value between 1 = non or rather non-severe, 2 = severe and 3 = very severe.

[g]Weight/height² (kg/m²).

[h]37.4% of subjects had at least one disease (rhythm disorder 17.1%, valvulopathy 7.2%, obliterative arterial disease of the lower limbs 0.9%, heart failure 4.5%, infarction 4.1%, stroke 3.6% and diabetes without insulin 10.4%).

[i]5.1% of subjects had at least one disease (rhythm disorder 1.7% and diabetes without insulin 5.1%).

Discussion

Main findings

This study reveals five determinants of undiagnosed hypertension, namely male gender, lower WC, no cardiovascular diseases/diabetes, no familial hypertension history and fewer GP-consultations, all of which are easily gathered during GP consultation. Living alone, higher alcohol consumption, perceived good health status, no anti-cholesterol treatment, lower BMI and lower blood glucose were also significant determinants although in bivariate analysis only. These novel findings help understand undiagnosed-hypertension risk patterns and thus better identify affected subjects for appropriate lifestyle management and care.

In the literature, the frequency of undiagnosed-hypertension among individuals meeting hypertension criteria has been found to range between 17–50% (8–12); in the present study, this frequency was 21%. Three previous studies in France in adults aged ≥35 and 18–74 years observed that 33% and 48% of hypertensive subjects were not diagnosed (11,13,14). This discrepancy may be explained by the fact that the STANISLAS cohort herein included healthy mid-life subjects at baseline and that our analysis focused on hypertension at the end of a 20-year follow-up. Contrary to certain studies

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Table 3. Factors associated with undiagnosed-hypertension (versus treated-hypertension) (n = 281): adjusted odds ratio and 95% confidence interval (2011–2016)

	$OR_{adjusted}$	P value	95% CI
Logistic regression model[a] with stepwise forward procedure retaining significant factors (P < 0.05) only			
Men (versus women)	4.61	< 0.001	1.97–10.8
No cardiovascular diseases or diabetes[b]	8.51	< 0.001	2.42–29.8
No familial hypertension history[b]	3.15	0.002	1.51–6.60
Number of GP consultations per year[c]	3.18[d]	< 0.001	1.96–5.15
Waist circumference, cm	0.95[d]	0.002	0.92–0.98
Pseudo R^2		0.319	

Abbreviations: n, number of subjects; GP, general practitioner; $OR_{adjusted}$, adjusted odds ratio; CI, confidence interval.

[a]The model included only the factors associated with having undiagnosed hypertension with $P < 0.05$ (see Table 2). The model with no stepwise procedure did not retain more significant factors than the model with stepwise procedure.

[b]versus presence of at least one.

[c]In three categories: 3+ = 1, 1–2 = 2 and 0 = 3.

[d]For 1-unit increase for each quantitative variable.

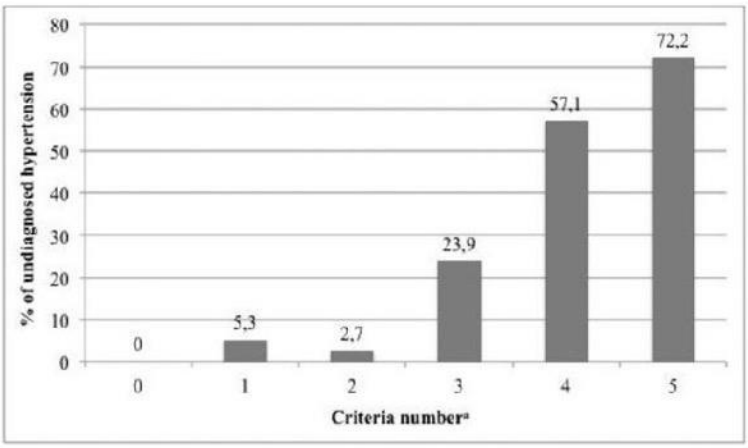

Figure 1. Percentage of undiagnosed-hypertension subjects according to risk score (number of positive criteria) (2011–2016). [a]The criteria were: male gender, lower waist circumference according to the World Health Organization's cut-off values (<94 cm for men and <80 cm for women), no cardiovascular diseases/diabetes, no familial hypertension history and <3 GP-consultations per year.

(13,23), we did not find a role of age given the relatively narrow age range (50–76 years, including 88% of subjects between 53–66 years). Furthermore, the study populations and methodologies also differed, especially the definition of hypertension. In our study, hypertension was defined by office BP (mean of three concomitant measurements), 24-hour ambulatory BP and hypertension history.

A few easily gathered factors during GP consultation were found strongly associated with having undiagnosed hypertension among hypertensive subjects

Our study established that undiagnosed-hypertension subjects were more likely male, with lower WC, no cardiovascular diseases/diabetes, no familial hypertension history and fewer GP-consultations. These findings are consistent with two available studies in American women (18–49 years) and British adults (40–74 years) which showed that male gender, being underweight, no ischemic heart disease/diabetes and fewer primary-care uses were potential barriers to hypertension diagnosis (15,16). Of note, WC and GP-consultations frequency observed herein for undiagnosed-hypertension subjects were similar to those for normotensive subjects in the same cohort (n = 342; data not shown).

Furthermore, we found that <6% of undiagnosed-hypertension subjects had 1 or 2 criteria, in contrast to 24% and 72% having 3 and 5 criteria, respectively. Hence, the concomitant presence of >2 criteria strongly increased the risk of undiagnosed-hypertension.

In accordance with our initial hypotheses, the higher risk for men may be explained by the latter being less aware of hypertension and less knowledgeable of cardiovascular risk factors than women (24–26). Undiagnosed-hypertension subjects moreover appear to less frequently consult GPs and hence have a lower chance of having their hypertension diagnosed more precociously (15). Wall et al. affirmed that, in the United States, potentially millions of individuals with uncontrolled high blood pressure are being seen by healthcare professionals each year but remain undiagnosed and "hiding in plain sight" within clinical settings (27). In our study, among undiagnosed-hypertension subjects, 69.5% had at least one and 37.3% had ≥3 GP-consultations per year. The undiagnosed-hypertension subjects thus display specific features that may not alert them of the risks of hypertension, are unaware of these risks and neglect their hypertension, and fail to consult GPs to assess their hypertensive status. Our findings help understand why despite decades of public health education, many adults are unaware of their hypertension (8–13,24,28).

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Other factors to be considered to better understand undiagnosed-hypertension risk patterns

We found that undiagnosed-hypertension subjects had other specific features that also explain why their hypertension had not been diagnosed: living alone, higher alcohol consumption, perceived good health, lower BMI, no anti-cholesterol treatment and lower blood glucose. Because of their interdependence with the previous factors, these determinants were significant ($P < 0.05$) in bivariate analysis but not in multivariable analysis. These results are consistent with a study in 40–74 year-old adults in the UK which found that living alone, self-reported good health and higher alcohol consumption were associated with untreated hypertension (16).

Certain hypotheses may be proposed to explain the above results. First, living alone is associated with poor social support and higher socioeconomic difficulties which, in turn, are associated with hypertension as well as physical/mental health problems and poor perception of care needs (29,30). Second, alcohol consumption appeared to be much higher among undiagnosed-hypertension subjects than among treated-hypertension subjects. Even low alcohol consumption can impair brain function, judgment and alertness (31). Third, the subjects who perceive having good health may consult a GP less often and have thus had fewer opportunities to exchange with the GP and have their office BP measured. For lower BMI/WC, the subjects concerned may believe that they do not have an excess hypertension risk. The fact that lower WC was retained but not lower BMI in our multivariable model suggests that lower WC may be seen by the subjects as associated with a lower hypertension risk than lower BMI. In the same manner, subjects with no anti-cholesterol treatment may less suspect their hypertension. It should be noted that the undiagnosed-hypertension subjects had similar BMI and blood glucose than the normotensive subjects (data not shown). Even if BMI, WC and blood glucose had not been measured and known, their better values could result from healthy behaviours (including weight control, regular physical/sports activity, reduced salt and alcohol intake and healthy diets) which may lead these subjects not to suspect their hypertension. This assumption may also concern perceived good health and lower primary-care use.

Finally, the features of the undiagnosed-hypertension subjects revealed in our study may raise the question as to whether or not they have the same type of hypertension than the treated-hypertension subjects. Further research is needed to address this issue.

Implications for practice

Our findings shed additional light on the risk patterns regarding the worrisome problem of non-diagnosed hypertension in adults reported worldwide (23,32,33). While the early detection of hypertension is universally recommended, recommendations vary across countries in terms of BP-measurement frequency, high-hypertension-risk criteria and measurements used (office BP, patient's self-assessment and 24-hour ambulatory BP) (23,32,33). In France, the National Heath Authority recommends regular BP measurements but without indications regarding BP-measurement frequency and individual risk features (23). These unclear recommendations and discrepancies may leave BP monitoring reliant on the knowledge and habits of the physician and on the awareness of patients of hypertension risk without warning signs.

Our findings in 50–76 year-old adults show that hypertension is more likely undiagnosed among subjects with the following criteria: male gender, no familial hypertension history and no cardiovascular diseases/diabetes, lower WC and fewer GP-consultations. We believe that physicians should be vigilant in that individuals with these criteria may have underlying hypertension, especially among those exhibiting several criteria. Therefore, BP should be regularly measured by any method for persons with low risk in addition to those at increased risk for high BP as indicated by the recommendations in various countries (23,32,33). When a high BP (≥140/90 mmHg) or even a high-normal BP (130–139/85–89 mmHg) is observed, confirmation of hypertension diagnosis may be achieved by BP monitoring over time, even by BP self-measurements and/or 24-hour ambulatory BP measurements.

Moreover, we found that alcohol consumption was much higher among the undiagnosed-hypertension subjects than among the normotensive individuals (data not shown). Implementation of interventions to reduce alcohol consumption in individuals who consume more than two drinks per day may reduce BP level (34).

Our results may help primary-care physicians shape their information exchange with patients and to detect those with undiagnosed-hypertension during consultations, and finally to establish timely healthy behaviour management, care and follow-up. In order to not lose sight of patients with possible hypertension, the GPs should inform the latter as to their risk after the first observed elevated BP (in or outside the clinical setting).

Our findings may also be useful for education and postgraduate training of GPs regarding the contexts leading some hypertensive subjects to never having their hypertension diagnosed. This issue mainly regards critical nontechnical skills that meet a growing worldwide interest for their understanding and teaching to healthcare providers (35). Indeed, a more effective communication could be established by increasing the physicians' awareness of communicative differences and by empowering patients to express their concerns and preferences (36). Patient-centred care and continuity of care are essential for primary care (37,38) and are associated with better quality of care and better health (39).

Strengths and limitations

Our study features certain strengths. First, as current research has mainly focused on non-controlled hypertension, the present provides an additional component to the poor literature regarding undiagnosed hypertension. Second, both office BP (three measurements performed concomitantly) and 24-hour ambulatory BP were used to define undiagnosed hypertension. Third, they allowed us to identify and exclude both white-coat and masked hypertensions with no hypertension history from the analysis.

Some limitations should also be acknowledged. First, the studied Lorraine region presents a major cardiac event rate which is intermediate-to-higher than the 'actual' event rate in Southern Europe (40). Second, the participation rate at last examination (52%), 20 years after the cohort baseline, was high especially for surveys in France. As the participants had better values than the nonparticipants for most anthropometric and metabolic measurements (Supplementary Table S1), the odds ratios found may be underestimated. Third, the exclusion of subjects with missing ambulatory BP may also underestimate the odds ratios. Indeed, these subjects more often displayed low education, living alone, no regular sports/physical activity, no familial hypertension history, higher adiposity, higher hypertension grade, no memory disorder and less often good health status (Supplementary Table S2). Finally, for statistical tests, the most significant factors, particularly in multivariable analysis with stepwise procedure, had high odds ratios with $P < 0.001$.

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Conclusion

Our study in 50–76 year-old adults provides further understanding as to why certain hypertensive subjects had their hypertension undiagnosed, the latter being more likely male, with lower WC, no cardiovascular diseases/diabetes or familial hypertension history and fewer GP-consultations. Furthermore, the concomitant presence of a higher number of these criteria appears to strongly reinforce the absence of diagnosis. Physicians should therefore be vigilant in that individuals featuring these criteria may have underlying hypertension. Our results call for further qualitative and/or quantitative research for their early detection and appropriate lifestyle management and care.

Supplementary material

Supplementary material is available at *Family Practice* online.

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Informed consent: All study participants gave a written informed consent to participate.

Conflicts of interest: None.

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6. Discussion générale

Nos travaux comportent deux parties principales. La première partie étudiait prospectivement le risque à long terme de la dysfonction diastolique et de la rigidité artérielle et leurs associations avec les facteurs anthropométriques et métaboliques. Nos résultats montrent que les facteurs anthropométriques et métaboliques ne leur étaient pas associés de façon semblable. Ces résultats appellent une discussion générale sur les associations des mesures de l'obésité générale et de l'adiposité abdominale avec la dysfonction diastolique et la rigidité artérielle (section 6.1).

En ce qui concerne l'hypertension artérielle, notre travail était consacré à l'identification des facteurs associés à une hypertension artérielle non-diagnostiquée parmi les sujets hypertendus. La discussion des résultats obtenus sera présentée dans la section 6.2.

6.1. Association des mesures de l'obésité générale et de l'adiposité abdominale avec la dysfonction diastolique et la rigidité artérielle

Rappelons d'abord le contexte de nos travaux. Dans la littérature, les travaux réalisés portaient sur des populations très variées (population générale, population en bonne santé, population de malades, groupes d'âge spécifiques, patients ayant des maladies spécifiques comme le diabète, etc.) et utilisaient des approches variées (enquête transversale, étude prospective longitudinale avec une durée de suivi souvent courte) [31, 35-38, 40 56, 61]. La définition des problèmes étudiés et celle de leurs facteurs de risque étaient également souvent différentes. Comme les populations étudiées avaient des caractéristiques souvent différentes, le niveau d'obésité générale et celui d'adiposité abdominale différaient également. A cause de ces différences, les résultats obtenus, par exemple dans le cas de la VOPcf, étaient parfois concordants mais souvent divergents et ne permettaient pas d'aboutir à une conclusion unanime. Plus précisément, des études avaient rapporté des associations

négatives, nulles ou positives entre l'obésité générale et l'adiposité abdominale et la VOPcf (section 4) [31, 35-38, 40, 56, 61].

La compréhension du problème pourrait être facilitée si nous étudions une population de personnes initialement en bonne santé et la suivions pendant une longue durée pour étudier la genèse des maladies cardiovasculaires dont certaines ont un temps de latence assez long. C'est le cas de la cohorte STANISLAS sur laquelle portait nos recherches. Cependant, cette cohorte est une cohorte familiale qui contenait initialement deux parents et deux enfants dans la région lorraine. Ce choix a induit, au début du suivi, un âge entre 30 et 60 ans pour les parents et inférieur à 25 ans pour les enfants. Toutefois, être en bonne santé à un certain âge, par exemple après 50 ans, ne serait pas le fruit du hasard mais plutôt dû à des conditions et une hygiène de vie plus saines. Les personnes de faible éducation et de milieux sociaux défavorisés se retrouvaient être moins représentées probablement à cause de l'exclusion des sujets malades. Comme la prévalence de l'obésité et celle des maladies augmentent généralement avec l'âge, le niveau de sélection au recrutement serait plus faible chez les parents jeunes que chez les parents plus âgés [5]. En France, la prévalence de l'obésité augmente avec l'âge [5]. La genèse des maladies cardiovasculaires durant le suivi en serait donc influencée. D'autre part, la présence des deux parents au recrutement initial excluait les parents séparés, divorcés et décédés, et par conséquent leurs enfants.

Notre recherche prospective avec un long suivi de vingt ans montre que la DD était fréquente et plus fortement associée à l'adiposité abdominale mesurée par le TT et le ratio TT/TH qu'à l'obésité générale mesurée par l'IMC au début du suivi. L'association entre la DD et le TT était robuste et demeurait significative contrairement aux associations entre la DD et l'IMC et le ratio TT/TH après la prise en compte de la PAS, du taux de TG et de la PCR. De plus, la combinaison d'une l'adiposité abdominale élevée (TT ou TT/TH) avec des perturbations métaboliques mesurées par un taux élevé de TG, conféraient un risque élevé de développer une DD. Ce résultat suggère un rôle de l'adiposité viscérale car elle contribue à un taux plus élevé de TG que l'adiposité sous cutanée. Notons que la

présence à la fois d'un IMC élevé et d'un taux élevé de TG n'était pas associée à un risque plus élevé de DD. La présence à la fois d'un TT ou d'un ratio TT/TH élevé et d'un IMC élevé renforçait le risque associé à chacun de ces paramètres anthropométriques séparément suggérant que l'adiposité abdominale et l'obésité générale pourraient avoir chacune un certain rôle.

Dans notre travail sur la rigidité artérielle, le TT et le ratio TT/T ainsi que l'IMC au début du suivi jouaient un rôle protecteur sur la VOPcf vingt ans plus tard. Le ratio TT/TH était non-significatif. Mais les coefficients de régression de TT et de l'IMC différaient nettement, ce qui nous a conduit à explorer le problème de façon plus approfondie. Nous avons pensé que le ratio entre le niveau d'obésité abdominale et celui d'obésité générale, défini par le ratio TT/IMC pouvait fournir une évaluation plus exacte de l'obésité abdominale (degré de renflement de l'abdomen, lequel pouvait être corrélé avec le dépôt de graisse abdominale). Nous avons observé que la VOPcf était associée positivement à l'adiposité abdominale évaluée par le ratio TT/IMC. L'ABSI était aussi associé positivement à la VOPcf mais à un degré moindre probablement car l'ABSI a été construit pour mesurer l'adiposité abdominale indépendamment de l'IMC. L'association entre la VOPcf et le ratio TT/IMC était robuste et restait significative après la prise en compte de la fréquence cardiaque, des facteurs métaboliques et de la PCR. L'obésité abdominale semblait être un meilleur prédicteur du risque à long terme de DD et de la VOPcf que l'obésité générale.

Dans la littérature, les recherches effectuées ont montré des résultats discordants en ce qui concerne les associations entre l'obésité générale (mesurée par l'IMC) et l'adiposité abdominale (mesurée par le TT, le ratio TT/T et le ratio TT/TH) et les différentes dysfonctions et maladies cardiovasculaires [31, 35-38, 40 56, 61]. Cependant, de nombreuses études ont montré que les dysfonctions et maladies cardiovasculaires (dont la DD et la VOPcf) sont plus fortement (positivement) associées aux mesures anthropométriques de l'adiposité abdominale qu'à l'IMC [17, 18, 30, 35, 37, 80, 81]. Il faut noter que le TT est un bon marqueur de la graisse abdominale/viscérale [82]. En effet, la graisse viscérale mesurée par la tomodensitométrie (gold-standard) est plus

fortement corrélée au TT (coefficient de corrélation de Pearson r = 0,86) qu'au DEXA (0,70 < r < 0,79) et à l'IMC (0,67 < r < 0,71) [83, 84]. Cependant, la distribution de l'adiposité abdominale et celle de l'obésité générale peuvent être très différentes. Dans la cohorte Stanislas, parmi les sujets ayant un IMC ≥ 25 kg/m^2 environ la moitié (124 / 242 sujets) avaient un TT au-dessus de la limite de l'Organisation mondiale de la Santé tandis que parmi les sujets ayant un TT au-dessus de cette limite, 124/128 sujets soit 97 % avaient un IMC ≥ 25 kg/m^2 (article sur la DD, figure S2, Annexe A2).

Le ratio TT/IMC apparaît, dans notre étude, comme un paramètre approprié pour étudier l'association entre l'adiposité abdominale/viscérale avec la VOPcf. Notre résultat (βsa = 0,32 pour un accroissement de TT d'un écart-type) est confirmé par une autre méthode d'analyse utilisée dans la littérature. Une étude prospective de mortalité sur les femmes aux États-Unis avec un suivi de 16 ans proposait de catégoriser le TT en quintiles et d'utiliser l'IMC en variable d'ajustement. Elle rapportait qu'après ajustement sur l'IMC et des cofacteurs potentiels, le risque relatif suivait une tendance croissante selon le quintile de TT (partant du plus bas au plus élevé) pour la mortalité cardiovasculaire [1,00, 1,04, 1,04, 1,28 et 1,99 (IC 95 % = 1,44-2,73)] [17]. Malgré la grande taille de l'échantillon (44 636 personnes), le risque était significatif seulement pour le dernier quintile. Dans notre échantillon, après ajustement sur l'IMC, le sexe et l'âge, une tendance croissante de risque pour la VOPcf était observée entre le 2e, 3e et 4e quartiles du TT (βsa 0,16 (p=0,371), 0,77 (p=0,001), et 1,01 (p=0,002), respectivement, versus le 1er quartile, résultats non présentés). Le risque pour la VOPcf augmentait donc avec la valeur du TT indépendamment de celle de l'IMC. Toutefois, des études récentes ont émis des réserves sur cette approche car les valeurs de TT, du ratio TT/T et du ratio TT/TH différaient entre les catégories de l'IMC [15] et réciproquement. Dans notre échantillon, le TT différait fortement entre les catégories d'IMC (moyenne 75,0±7,4 cm pour un poids normal, 88,9±7,1 cm pour un surpoids et 100,5±10,5 cm pour une obésité, p<0,001, résultats non présentés). Cette tendance suggère que l'accumulation de graisse abdominale/viscérale augmente avec l'IMC.

Dans nos travaux, l'adiposité abdominale apparait comme le facteur le plus associé à la DD et à la VOPcf. La DD (en particulier la DD2-3) était plus fortement associée avec TT qu'avec PAS, PAD et le taux de TG, tandis que les autres paramètres biologiques n'étaient pas associés à la DD. De façon

analogue, la VOPcf était plus fortement associée avec le ratio TT/IMC qu'avec la fréquence cardiaque, LDL et PCR, tandis que les autres paramètres biologiques n'étaient pas associés à la VOPcf. L'adiposité abdominale semble donc le facteur le plus important parmi les facteurs composant le syndrome métabolique (TT, taux de TG, PAS, PAD, traitement antihypertenseur, HDL et glycémie veineuse) et le facteur de première importance central dans le diagnostic clinique comme l'ont précisé d'autres auteurs [20]. La signification physiopathologique de l'adiposité abdominale semble plus claire que celle du syndrome métabolique.

Nos résultats suggèrent que des mesures de prévention soient mises en œuvre pour réduire l'adiposité abdominale et aussi l'obésité générale. Les interventions visant à améliorer l'hygiène de vie (incluant l'activité physique et sportive, l'alimentation, la réduction de la consommation d'alcool et de sucre) pourraient réduire l'adiposité viscérale chez des sujets avec un syndrome métabolique [85]. La prise de conscience du risque est la première étape dans la modification des comportements de santé et de l'hygiène de vie à visée thérapeutique. Certains sujets ayant un poids normal et un excès de graisse corporelle [12, 13, 15, 17, 86] pourraient être affectés sans être conscients de leur risque cardiométabolique. L'exercice aérobie (marche rapide, course à pied et natation) pourrait réduire la VOPcf [87]. Ces interventions chez des sujets à haut risque d'avoir une DD ou une VOPcf plus élevée, pourraient réduire leur risque. En pratique, la mesure de l'adiposité abdominale et celle de l'obésité générale (basées sur l'IMC et le TT) sont simples à réaliser en particulier durant la consultation, notamment en soins primaires. La surveillance de ces paramètres et de leur évolution permettrait de repérer et suivre précocement les individus à risque, même parmi les sujets jeunes en bonne santé.

6.2. Facteurs associés à une hypertension artérielle non-diagnostiquée

Dans la première partie de ce travail, nous avons identifié des facteurs de risque à long terme, et surtout des facteurs anthropométriques, pour la dysfonction diastolique et la rigidité artérielle. Dans la deuxième partie, nous nous sommes intéressés aux individus ayant déjà une hypertension

artérielle et avons déterminé les facteurs associés à HTA non-diagnostiquée (absence de primo-diagnostic).

Notre recherche montre que parmi les adultes ayant une vraie hypertension, l'absence de primo-diagnostic était fréquente et était associée à un TT moins élevé. Elle était aussi plus fréquente chez les hommes et chez les sujets ayant moins souvent des maladies cardiovasculaires ou diabète, des antécédents familiaux d'hypertension, et des recours aux soins primaires. De plus, notre recherche montre que la proportion de l'HTA non-diagnostiquée augmentait fortement avec le nombre de critères (<6 % pour 0-2 critères à 72 % pour 5 critères). La présence de plusieurs critères permettait donc d'identifier une HTA non-diagnostiquée. D'autres facteurs tels que vivre seul, une consommation d'alcool plus élevée, un bon état de santé perçu, l'absence de traitement hypolipémiant, un IMC plus bas, et une glycémie plus basse favorisaient aussi l'absence du primo-diagnostic.

Compte tenu de la rareté des études réalisées, nos résultats sont particulièrement originaux et pourraient être utiles pour les soins de premier recours. Nos résultats corroborent les rares études disponibles. Ces études ont aussi trouvé que le sexe masculin, vivre seul, une consommation d'alcool plus élevée, le sous-poids, l'absence de maladies cardiaques ischémiques ou diabète, une bonne santé déclarée et une utilisation moindre des services de soins primaires étaient des barrières pour le diagnostic ou le traitement de l'HTA [39, 76]. Nos résultats peuvent être expliqués par les hypothèses suivantes : les facteurs identifiés sont associés aux difficultés relationnelles, à une moins bonne perception des besoins de soins [50, 88], une altération de la fonction cérébrale, du jugement et de la vigilance [89], et donc à une opportunité moindre de mesurer leurs pressions artérielles. La présence de certains facteurs considérés comme protecteurs pour les maladies cardiovasculaires (IMC, TT et/ou glycémie plus bas, absence de traitement hypolipémiant et d'antécédents familiaux) pourraient suggérer aux sujets concernés, et à leur médecin, un moindre risque d'HTA et donc à ne pas suspecter leur HTA.

Bien que les individus ayant une HTA non-diagnostiquée avaient des caractéristiques anthropométriques, biologiques et cliniques meilleures que les individus ayant une HTA traitée, leurs caractéristiques étaient nettement moins bonnes que les sujets normotendus. Une récente

revue de littérature souligne que, chez les médecins, plusieurs barrières limitent la prise de conscience et le contrôle des pressions artérielles des patients : un manque perçu de compétence (19 %), un manque de connaissance perçue (17 %), un manque d'intention lié à la capacité perçue pour prendre en charge et contrôler l'HTA (49 %), une influence sociale des pairs (38 %), et un désaccord avec les recommandations pour le repérage et le traitement de l'HTA (36 %) [90]. On peut émettre l'hypothèse que ces barrières contribueraient à limiter le primo-diagnostic d'HTA chez les sujets qui ont essentiellement dans notre étude une HTA de grade 1 et des facteurs de risque moins prononcés que les sujets traités. Certains patients méconnaitraient et/ou sous-estimeraient leur niveau de risque d'HTA, en particulier en présence de plusieurs critères considérés protecteurs de maladies cardiovasculaires. Certains médecins pourraient de pas faire régulièrement des mesures de pression artérielle quand les caractéristiques individuelles ne suggèrent pas la nécessité de détecter une hypertension. Les patients ayant des pressions artérielles élevées devraient retenir l'attention indépendamment du contexte et de leurs caractéristiques.

Nos résultats pourraient aider à mieux comprendre pourquoi une grande proportion de sujets hypertendus ne sont pas diagnostiqués dans différents pays [8, 28, 30, 49, 55, 56, 91-98] et à mieux repérer les sujets à risque pour la surveillance et une prise en charge appropriée. Cependant, nos résultats nécessitent d'être confirmés par d'autres recherches dans différents pays. Comme la fréquence de consultation de médecine générale était fortement associée avec l'HTA non-diagnostiquée, les populations dans les zones manquant de médecins généralistes pourraient être plus exposées que les autres populations et nécessiteraient donc une étude ciblée. Enfin, nos résultats pourraient être validés sur un échantillon de patients choisis au hasard parmi les patients en consultation de médecine générale afin d'étudier la possibilité de les utiliser, en routine, sur le terrain.

7. Perspectives

Extension des recherches sur la dysfonction diastolique et l'hypertension artérielle

Dans notre recherche sur la rigidité artérielle aortique, l'utilisation du ratio TT/IMC permet de montrer l'association entre l'obésité abdominale et le risque de rigidité artérielle aortique 20 ans plus tard. Le ratio TT/IMC pourrait fournir une évaluation plus précise de la mesure de l'obésité abdominale. Nous ne l'avons pas utilisé pour la DD et l'hypertension artérielle. Un prolongement de nos travaux serait donc d'explorer si le ratio TT/IMC permettrait aussi de montrer l'association entre l'obésité abdominale et la DD et l'hypertension artérielle ?

Comme le ratio TT/IMC n'était pas colinéaire avec l'IMC (coefficient de corrélation modéré, section 4), le couple (IMC, ratio TT/IMC) pourrait être utilisé pour analyser simultanément le rôle de l'obésité générale et de l'adiposité abdominale sur la DD et sur l'hypertension artérielle 20 ans plus tard. L'utilisation du ratio TT/IMC seul peut négliger le rôle de l'IMC comme il représenterait le niveau d'adiposité abdominale pour une valeur fixée de l'IMC. Même si l'ABSI était construit pour être indépendant de l'IMC, comme sa formule a été établie sur un échantillon déterminé, nous avions trouvé qu'il était modérément corrélé avec l'IMC (section 4). Ce travail amènerait à étudier aussi l'ABSI qui était aussi non colinéaire avec l'IMC et les autres paramètres anthropométriques (TT, TT/TH et TT/T) selon le degré de leur colinéarité avec l'IMC.

Recherches à poursuivre avec la prochaine 5ème visite de la cohorte STANISLAS

Quand la cohorte sera prolongée par une 5ème visite, dans quelques années, avec un protocole comprenant les mêmes mesures de la fonction diastolique, de la rigidité artérielle ainsi que les mesures casuelles et ambulatoires de pressions artérielles, nous aurons plusieurs opportunités importantes pour approfondir les problèmes abordés dans le présent travail.

Bien que, selon notre estimation, la prévalence de la dysfonction diastolique au début du suivi était faible (1,5 %), disposer de la mesure de la dysfonction diastolique à la prochaine 5ème visite en plus de la 4ème visite est un atout majeur. Le suivi déjà réalisé de 20 ans semble un peu court

comme les participants étaient en bonne santé au début du suivi. Être en bonne santé à un âge moyen n'était pas le fruit du hasard mais le résultat d'une hygiène de vie relativement bonne et peut-être aussi des caractéristiques cardiovasculaires moins à risque. Le temps de latence de différentes maladies serait alors plus long que celui dans la population générale sans sélection. La proportion de sujets obèses était faible, ce qui limite la possibilité d'étudier l'obésité. Le pourcentage des sujets ayant DD2-3 était relativement faible pour étudier la gravité de la DD. Un allongement du suivi de quelques années peut alors surpasser ces problèmes. L'évolution temporelle de la dysfonction diastolique peut alors être étudiée vis-à-vis des facteurs de risque à la 1ère visite et à la 4ème visite et de leur évolution entre la 4ème et la 5ème visite. Il faut noter qu'à la 2ème visite et à la 3ème visite, une partie de la cohorte seulement a été examinée.

La recherche sur la rigidité artérielle et l'hypertension profitera aussi des avantages ci-dessus pour la recherche sur la DD. En effet, on aura la mesure de la rigidité artérielle en deux temps différents (4ème et 5ème visites).

Concernant l'hypertension, outre l'avantage de disposer des mesures de pression artérielle casuelle et ambulatoire (MAPA 24h), nous serons renseignés sur le mouvement ou la transition des personnes entre les catégories suivantes : normo-tension, hypertension blouse blanche, hypertension masquée, et hypertension vraie. Toutes ces catégories sont à considérer, à chaque visite, selon qu'elles ne sont pas diagnostiquées ou au contraire diagnostiquées et traitées. Les données ainsi recueillies donneront une énorme perspective d'étudier le rôle dans ces transitions des facteurs de risque cardiovasculaires comprenant l'hygiène de vie et la santé mentale. Les troubles mentaux ont une forte prévalence dans la population et sont connus pour jouer un rôle sur des maladies cardiovasculaires comme par exemple l'hypertension. Étudier le rôle des troubles dépressifs comme facteur de risque et médiateur ou confondant dans les catégories d'hypertension, c'est répondre à la nécessité de la société de s'attaquer à deux problèmes majeurs de santé. Par

exemple, la dépression comme l'hypertension ont une forte prévalence et sont associées aux incapacités fonctionnelles.

Hypertension artérielle non-diagnostiquée

Notre travail sur l'hypertension artérielle non-diagnostiquée mérite d'être approfondi par l'exploration des facteurs et situations personnels, familiaux et sociaux ainsi que les contextes et circonstances pouvant amener les personnes concernées à ne pas suspecter, à négliger leur hypertension, et à ne pas faire évaluer leur pression artérielle. Les personnes concernées peuvent-elles définir leur niveau de risque d'hypertension parmi les degrés de risque nécessitant une surveillance définis par les experts dans différents pays (leur appréciation peut être comparée à une évaluation avec les données de la cohorte STANISLAS) ? L'intervalle de temps depuis la dernière mesure de la pression artérielle par un médecin peut être aussi considéré par rapport aux recommandations des experts. L'accès aux soins est-il difficile (problème financier, manque de temps ou de moyen de transport, empêchement familial comme surveiller les enfants au domicile, absence de médecin à proximité) ?

Hypertension artérielle blouse blanche

Les données actuellement disponibles de la cohorte STANISLAS permettent d'étudier et de mieux caractériser l'hypertension blouse blanche (PA casuelles ≥ 140/90 mm Hg et MAPA 24h < 130/80 mm Hg). Les résultats attendus pourraient être utiles pour le diagnostic de l'hypertension et pour le suivi des sujets concernés au cours du temps.

L'hypertension blouse blanche reste un important champ de recherche. Selon certains auteurs, elle serait associée à l'anxiété générée par la mesure de la pression artérielle en raison d'expérience traumatisante durant des consultations qui peut empêcher la mesure exacte [94, 99]. Comme la pression artérielle ambulatoire pourrait mieux prédire les maladies cardiovasculaires que les

pressions casuelles, l'hypertension blouse blanche peut être associée à un faible risque cardiovasculaire [100, 101]. D'autres études ont trouvé que l'hypertension blouse blanche était associée à un risque plus faible de morbidité et de mortalité que l'hypertension vraie [100, 102]. Cependant, certaines investigations ont observé que l'hypertension blouse blanche était essentiellement systolique et n'était pas une situation clinique innocente mais associée à des valeurs plus élevées de glycémie, de cholestérol et triglycérides, de rigidité artérielle ainsi qu'à une prévalence plus élevée de diabète, syndrome métabolique, et d'hypercholestérolémie et un excès de mortalité par rapport aux sujets normotendus [100, 103-106]. Une récente méta-analyse avait conclu que les personnes ayant une hypertension blouse blanche avaient un taux plus élevé de maladies cardiovasculaires et de mortalité que les personnes normotendues [107]. Ces résultats hétérogènes peuvent être attendus à cause de l'hétérogénéité des populations étudiées (population générale, personnes malades, groupes d'âge, etc.), les facteurs de risques considérés et les approches méthodologiques employées. D'autres recherches sont donc nécessaires pour mieux caractériser et comprendre l'hypertension blouse blanche.

Il serait intéressant d'étudier une population initialement en bonne santé (sans pressions artérielles élevées) et de comparer, après un long suivi, les caractéristiques anthropométriques, cliniques et biologiques des sujets ayant une hypertension blouse blanche à celles des sujets ayant une hypertension vraie mais aussi à celles des sujets normotendus. Cette analyse pourra être réalisée de façon transversale sur les données à la fin du suivi et aussi prospectivement sur les données au début du suivi. Cette étude peut être menée sur la cohorte STANISLAS. Elle permettrait d'éviter de limiter les résultats qui seront obtenus à une population avec un profil particulier. Les résultats obtenus pourraient apporter une réponse à la question suivante : parmi les patients ayant une pression artérielle casuelle élevée (≥ 140/90 mm Hg) durant la consultation, existe-il des caractéristiques spécifiques pouvant aider les médecins à identifier les sujets ayant une hypertension blouse blanche ? C'est un problème important, car la mesure de la pression artérielle ambulatoire n'est pas toujours disponible/possible. La MAPA reste un examen coûteux.

Ce problème reste insuffisamment étudié ; la plupart des études réalisées sont focalisées sur la comparaison entre l'hypertension blouse blanche et la normotension et se limitaient à un petit nombre de facteurs seulement, réduisant ainsi la portée des résultats.

D'autre part, quels prolongements pourrions-nous donner à cette recherche ? La prochaine 5ème visite donnera l'opportunité d'étudier le devenir de l'hypertension blouse blanche et de l'évolution de différents facteurs de risque, notamment les facteurs étudiés ici. Pour obtenir plus encore d'informations décisives, et vu la faisabilité en raison du nombre relativement faible de sujets, il serait intéressant de mener une étude de suivi spécifique ciblée sur les sujets ayant une hypertension blouse blanche en évaluant la pression artérielle casuelle et ambulatoire chaque année, et explorer l'anxiété et la dépression à chaque mesure.

8. Conclusion générale

Nos recherches, chez des adultes d'âge moyen initialement en bonne santé, montrent que l'obésité générale et l'adiposité abdominale prédisent la dysfonction diastolique et que l'adiposité abdominale prédit la rigidité artérielle aortique et l'hypertension artérielle vraie observées 20 ans plus tard. Les associations entre ces dysfonctions ou maladies cardiovasculaires et l'obésité générale ou l'obésité abdominale diffèrent selon les variables anthropométriques utilisées (IMC pour l'obésité générale et TT, ratio TT/T, ratio TT/TH, ABSI et ratio TT/IMC pour l'adiposité abdominale/viscérale).

La dysfonction diastolique est associée positivement et fortement avec l'adiposité abdominale/viscérale mesurée par le TT, et à un moindre degré, avec l'obésité générale mesurée par l'IMC. Concernant la dysfonction diastolique, l'adiposité abdominale combinée avec un taux plus élevé de triglycérides est associée à un risque élevé de développer vingt ans après une dysfonction diastolique à un stade précoce.

Mais, nous observons que la rigidité artérielle est associée négativement au TT et à l'IMC, probablement en raison d'une adiposité relativement modérée. Par contre, le ratio TT/IMC est associé positivement avec la rigidité artérielle. Il isolerait mieux l'adiposité abdominale/viscérale de l'obésité générale que les autres variables anthropométriques. Il semble intéressant comme il permet de montrer un rôle néfaste à long terme de l'adiposité abdominale/viscérale même quand l'IMC est normal, et d'étudier l'influence de celle-ci sur la rigidité artérielle.

Par contre, parmi les adultes ayant une vraie hypertension, l'absence de primo-diagnostic est plus fréquente chez les sujets ayant un TT moins élevé. Elle est aussi plus fréquente chez les hommes et chez les sujets ayant moins souvent des maladies cardiovasculaires ou diabète, des antécédents familiaux d'hypertension, et des recours aux soins primaires. Enfin, nos résultats

peuvent avoir des implications dans l'identification précoce des sujets à risque, la prévention et le management thérapeutique.

9. Production scientifique

Publications dans des revues à comité de lecture

1. **Kénora Chau**, Nicolas Girerd, Martin Magnusson, Zohra Lamiral, Erwan Bozec, Ludovic Merckle, Margret Leosdottir, Erasmus Bachus, Zied Frikha, Joao-Pedro Ferreira, Jean-Pierre Després, Patrick Rossignol, Jean-Marc Boivin and Faiez Zannad. Obesity and metabolic features associated with long-term developing diastolic dysfunction in an initially healthy population-based cohort. Clinical Research in Cardiology 2018;107(10):887-896. Facteur d'impact = 4,76.

2. **Kénora Chau**, Nicolas Girerd, Erwan Bozec, Joao-Pedro Ferreira, Kévin Duarte, Julie-Anne Nazarre, Martine Laville, Athanase Benetos, Faiez Zannad, Jean-Marc Boivin and Patrick Rossignol. Association between abdominal obesity and 20-year subsequent aortic stiffness in the initially healthy population-based Stanislas cohort. Journal of Hypertension 2018; 36(10):2077-2084. Facteur d'impact = 4,08.

3. Kénora Chau, Nicolas Girerd, Faiez Zannad, Patrick Rossignol and Jean-Marc Boivin. Health-related determinants of undiagnosed arterial hypertension: a population-based study. Family Practice 2018; sous presse. Facteur d'impact = 1,80.

Publications de résumé seul dans des revues à comité de lecture

4. **Kénora Chau.** Facteurs métaboliques et inflammatoires associés au risque de développement à long terme (20 ans) d'une dysfonction diastolique parmi les adultes en bonne santé de la cohorte Stanislas. Rev Epidemiol Sante Publique 2015;63(1):56. (Abstract)

Présentations dans des congrès nationaux et internationaux

5. **Kénora Chau**, Nicolas Girerd, Patrick Rossignol, Zohra Lamiral, Erwan Bozec, Ludovic Merckle, Jean-Pierre Després, Faiez Zannad, Jean-Marc Boivin. Metabolic and inflammatory features associated with long-term risk for developing diastolic dysfunction in initially healthy population. 20e Congrès de la Société Française de Pharmacologie et Thérapeutique (SFTP), Nancy, 19-21 avril 2016. Présentation affichée.

6. **Kénora Chau**, Nicolas Girerd, Faiez Zannad, Patrick Rossignol, Jean-Marc Boivin. Risque d'hypertension artérielle non-diagnostiquée et place du médecin généraliste : étude prospective chez des adultes initialement en bonne santé. Congrès annuel CNGE (Collège

National des Généralistes Enseignants), Grenoble, 23-25 novembre 2016. Présentation affichée.

7. **Kénora Chau**, Nicolas Girerd, Faiez Zannad, Jean-Marc Boivin, Patrick Rossignol. Quels sont les facteurs de risques cardiovasculaire permettant de distinguer les hypertendus blouse blanche des vrais hypertendus en primo-diagnostic d'hypertension : étude en population générale. Congrès CMGF (Congrès Médecine Générale France), Paris, 30 mars-1er avril 2017. Présentation orale.

8. **Kénora Chau**, Nicolas Girerd, Faiez Zannad, Jean-Marc Boivin, Patrick Rossignol. Fort gradient d'âge pour l'accès au primo-diagnostic d'hypertension et facteurs associés en population générale. Congrès CMGF (Congrès Médecine Générale France), Paris, 30 mars-1er avril 2017. Présentation affichée.

9. **Kénora Chau**, Nicolas Girerd, Faiez Zannad, Jean-Marc Boivin, Patrick Rossignol. Better monitoring of long-term hypertension risk and potential predictors in initially healthy midlife adults: a population-based cohort study. 27th European Meeting on Hypertension and Cardiovascular Protection, Milan, 16-19 June 2017. Présentation orale.

10. **Kénora Chau**, Nicolas Girerd, Faiez Zannad, Jean-Marc Boivin, Patrick Rossignol. Strong association between low education and uncontrolled hypertension: a population-based study. 27th European Meeting on Hypertension and Cardiovascular Protection, Milan, 16-19 June 2017. Présentation affichée.

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12. **Kénora Chau**, Nicolas Girerd, Faiez Zannad, Jean-Marc Boivin and Patrick Rossignol. Prédicteurs potentiels d'hypertension à long terme chez des adultes d'âge moyen en bonne santé : étude de cohorte. Société Française d'Hypertension Artérielle, Paris, 14-15 décembre 2017. Présentation orale.

13. **Kénora Chau**, Nicolas Girerd, Damien Gonthier, Faiez Zannad, Patrick Rossignol and Jean-Marc Boivin. Forte association entre faible niveau d'étude et hypertension artérielle non contrôlée : étude en population générale. Société Française d'Hypertension Artérielle, Paris, 14-15 décembre 2017. Présentation orale.

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Annexe A : Données supplémentaires pour les publications

A1. Association entre l'obésité et des caractéristiques métaboliques et le risque de développement à long terme d'une dysfonction diastolique dans une cohorte d'adultes initialement en bonne santé

SUPPLEMENTAL MATERIALS

Obesity and metabolic features associated with long-term developing diastolic dysfunction in an initially healthy population-based cohort

Table of contents

Supplemental Text 1. Additional information on the methods……...……...…… 2
Supplemental Text 2. Were our findings replicated for the population cohort of inhabitants in Malmö? ….. 5
Abbreviations…….. 7
Supplemental Table 1. Comparison of baseline features of participants and non-participants at last check-up. 8
Supplemental Table 2. Echocardiographic features of the sample according to diastolic function grade (end of follow-up) ……..... 9
Supplemental Table 3. Factors associated with subsequent diastolic dysfunction (all grades) after 20 years…. 10
Supplemental Table 4. Baseline characteristics of the subjects in the Malmö Preventive Project cohort…… 11
Supplemental Table 5. Age-sex-adjusted odds ratios computed with logistic regression models of baseline factors for subsequent diastolic dysfunction (all grades) after a 24-year follow-up, including subjects with diabetes and hypertension (Malmö Preventive Project cohort) …….. 12
Supplemental Table 6. Age-sex-adjusted odds ratios computed with logistic regression models of baseline factors for subsequent diastolic dysfunction (all grades) after a 24-year follow-up, excluding subjects with diabetes and hypertension (Malmö Preventive Project cohort) ….……...…… 13
Supplemental Figure 1. Flow chart of study participants…… 14
Supplemental Figure 2. Age-sex-adjusted odds ratio (OR) for diastolic dysfunction (DD, all grades) when considering the interplay between waist circumference (WC) or waist-hip ratio (WHR) and body mass index (BMI)……. 15
Supplemental Figure 3. Age-sex-adjusted odds ratio (OR) for diastolic dysfunction (DD, all grades) when considering the interplay between body mass index (BMI) and triglycerides in the sample, including subjects with diabetes and hypertension (Malmö Preventive Project cohort)……. 16
Supplemental Figure 4. Age-sex-adjusted odds ratio (OR) for diastolic dysfunction (DD, all grades) when considering the interplay between body mass index (BMI) and triglycerides in the sample, excluding subjects with diabetes and hypertension (Malmö Preventive Project cohort)…… 17
References…….…… 18

Supplemental Text 1. Additional information on the methods

Study design and population

The Stanislas study was a longitudinal population-based study of 1,006 families which comprised two parents (2,014 individuals initially aged 30−60 years) and at least two children (2281 individuals initially aged 6−24 years) recruited in 1994−1995 (baseline) during a medical examination at the Center for Preventive Medicine in Eastern France. The subjects were of French origin and free of acute or chronic diseases (such as hypertension, diabetes, stroke, myocardial infarction, cancer, etc.).

At the end of follow-up (2011−2016), a request to participate explaining the aims of the study was sent by mail and subsequently by up to eight telephone calls at various times of the day (lunch time, evening). The address and telephone number were completed or gathered via data from hospital records, the Center for Preventive Medicine and the internet. The present study focused on the parents only. Among the 2,014 parents who had participated at baseline, 112 subjects were deceased. Among the 1902 parents eligible, 523 subjects were lost (unknown address) and 483 subjects refused, leaving 896 participants (44.5%).

The Ethics Committee of the Lorraine region (*Comité Consultatif de Protection des Personnes qui se prêtent à une Recherche Biomédicale de Lorraine, and Comité Consultatif de Protection des Personnes Est-III*) approved the study, in agreement with French legislation on human biomedical research. Each subject gave his/her written informed consent to participate in this study.

Measures

WC was measured at the narrowest level. Hip circumference was measured at the maximum level over light clothing.

DBP and SBP were determined as an average of three successive measurements under standardized conditions (in a supine position, after 10 min of rest) using an automatic oscillometric device (Physiogard SM 785 Niox; Odam, Wissenbourg, France). Pulse pressure was calculated as SBP−DBP.

Serum concentrations of fasting glucose, total cholesterol and TG were measured using commercially available kits on an AU5021 apparatus (all from Merck, Darmstadt, Germany) on fresh aliquots, and within 2 h. High-density lipoprotein cholesterol was measured on a Cobas-Mira analyzer (Roche Diagnostics). Low-density lipoprotein cholesterol was calculated according to the equation of Friedewald, Levy and Fredrickson [1]. C-reactive protein (CRP) was measured by immunonephelometry on a Behring Nephelometer Analyzer (BN II; Dade-Behring, Marburg, Germany) with Behring reagents (Reuil-Malmaison, France) within 2 h after sampling.

Echocardiography at the end of follow-up

Echocardiographic image acquisition

Examinations were performed by an experienced echocardiographer in the left lateral decubitus position with a commercially available standard ultrasound scanner (Vivid 9, General Electric Medical Systems, Horten, Norway) using a 2.5 MHz phased-array transducer. The echo/Doppler examination included parasternal long and short axis views and three standard apical views. For each view, at least three consecutive cardiac cycles were recorded during quiet respiration [2].

From the three apical views, cine-loop acquisitions were recorded. Pulsed-wave Doppler was performed in the apical 4-chamber view to obtain mitral inflow velocities to assess LV filling. Recording for isovolumic relaxation time measurement was obtained by simultaneous recording of the aortic and mitral flows. Pulsed-wave Doppler Tissue Imaging was performed in the apical view to acquire mitral annular velocities. The sample volume was positioned at 1 cm of the septal and lateral insertion sites of the mitral leaflets and adjusted as necessary (usually 5–10 mm) to cover the longitudinal excursion of the mitral annulus in both systole and diastole. Pulmonary venous flow velocities were recorded into the right upper pulmonary vein from the apical 4-chamber view. Color flow imaging was used for the proper location of the sample volume and the 2-mm sample volume was placed 5 mm into the pulmonary vein for optimal recording of the spectral waveforms.

All acquired images and media were stored on a secured network server as digital clips, using a unique identification number and analyzed on a dedicated workstation (EchoPAC PC, version 110.1.0, GE Healthcare).

Examination of diastolic function

LV mass: LV mass was measured from 2-dimensional (2D) echocardiography, using the recently published guidelines of the American Society of Echocardiography. Septal wall thickness, posterior wall thickness and LV internal diastolic diameter were measured from the parasternal 2D long axis view. These measurements were subsequently used in the cube-function formula for American Society of Echocardiography guidelines to calculate LV mass [3].

Left atrial (LA) volume: Its measurement was obtained from the biplane method of disks (modified Simpson's rule) using apical 4-chamber and apical 2-chamber views at ventricular end systole [3].

Mitral Inflow: The following parameters were studied: peak early filling (E-wave) and late diastolic filling (A-wave) velocities, E/A ratio, deceleration time (DT) of early filling velocity and mitral A-wave duration obtained at the tip of the mitral valve leaflets.

Pulmonary Venous Flow: Measurements included peak systolic velocity, peak anterograde diastolic velocity, the peak reversal A-wave (Ar) velocity in late diastole and the duration of Ar velocity.

Tissue Doppler Annular Early and Late Diastolic Velocities: Measurements included systolic, early diastolic and late diastolic velocity of the septal and lateral mitral annulus [4].

Assessment of LVEF: LVEF was calculated using the biplane Simpson's method.

The echocardiographic assessment of diastolic function was reproducible [5]. Indeed, inter-observer intra-class correlation coefficients were >0.90 for all analyzed parameters except for LVEF (0.87) and both mitral and pulmonary A wave duration (0.83 and 0.73 respectively). The mean relative inter-observer differences were <5% for all parameters except for pulmonary A wave duration (6.5%). Limits of agreement of relative differences were narrow (<15%), except for mitral A wave duration and velocity (both <20%) as well as left ventricular mass and pulmonary A wave duration (both <30%). Intra-observer agreements with regard to the presence and severity of diastolic dysfunction were excellent (Kappa 0.93 and 0.88, respectively).

The echocardiographic features of the study sample according to diastolic function grade are shown in Supplemental Table 2.

DD was not assessed at baseline. However, a subset of 624 subjects was analyzed and revealed that there were no subjects with left ventricular hypertrophy on baseline echocardiography [6]. Further analysis in 170 subjects of this subset included in the present study, all individuals had normal left ventricular mass index (mean=75.8g/m^2, SD=12.0 g/m^2, range 49.3 to 103.7 g/m^2 for men; mean=66.6g/m^2, SD=12.9 g/m^2, range 36.0 to 105.8 g/m^2 for women). Furthermore, the DD was not associated with left ventricular mass index at baseline (variance analysis gave P=0.47 in men and 0.30 in women), but strongly associated with left ventricular mass index at the end of follow-up (Supplemental Table 2).

By applying the DD rate at end of follow-up to sex-age structure (5-year age groups) on the sample at baseline (using the method of standardized mortality ratio), only 11 subjects (1.5%) would have had a DD at baseline. This prevalence of 1.5% would be overestimated because the subject had better health et cardiovascular features at baseline than at end of follow-up.

Text 2. Were our findings replicated for the population cohort of inhabitants in Malmö?

The aim of this section was to replicate our analyses for the birth cohort of inhabitants in Malmö of the Malmö Preventive Project (MPP) [7]. Between 1974 and 1992, birth cohorts of inhabitants in Malmö, Sweden, were invited to participate in the cohort study with a total of 33,346 individuals attending. In contrast to the Stanislas cohort, concomitant disease was not an exclusion criterion however, aside from very uncommon hypertension. Re–

examination of 18,240 surviving participants was conducted during 2002–2006. In a sample of 1,792 participants, echocardiography recordings were carried out. These subjects were randomly selected from groups defined by glucometabolic status: normal fasting plasma glucose; impaired fasting plasma glucose; new–onset type 2 diabetes mellitus; and prevalent diabetes mellitus; with oversampling in groups of subjects with glucometabolic disturbances to ensure sufficient numbers of subjects studied from each group resulting in a prevalence of diabetes of 36.2% [7]. A full description of the MPP baseline clinical characteristics is provided in Supplemental Table 4.

The full description of the echocardiography protocol has been published [7]. In short, conventional echocardiography Doppler and echocardiographic tissue Doppler imaging (TDI) were conducted with a 3V2c transducer (Acuson Sequoia, Mountain View, CA, USA) or a 3 transducer (Sonos 5500 Philips, Andover, MA, USA). LV diastolic function was assessed using transmitral pulsed Doppler flow as well as TDI in the four-chamber view. LV mass calculations were based on two-dimensional end-diastolic measurements in the parasternal long axis view at the level of the mitral tips consistent with M-mode criteria and subsequently indexed for body surface area. Intra- and inter-observer variability has been examined.

Among the 1,792 participants, were excluded subjects with LVEF<50% or LVEDI>97 mm/m^2 (n=127, 7.2%). In total 1463 subjects were retained for analyses. The mean age was 43.1 (SD 7.8) and 69.9% were male. Among these subjects, 857 (58.6%) had a diastolic dysfunction (all grades combined) at end of follow-up. It should be noted that waist circumference, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and C-reactive protein were not measured at baseline. Thus, they could not be considered herein. The results are shown in Supplemental Table 5 and Supplemental Figure 3.

Thereafter, were excluded subjects with hypertension (n=479, 27.1%), diabetes (n=67, 3.8%), SBP>140 mm Hg (n=171, 9.7%) or DBP>90 mm Hg (n=330, 18.7%). Finally, 927 subjects were retained for analysis. Among these subjects, 508 (54.8%) had a diastolic dysfunction (all grades combined). The results obtained are shown in Supplemental Table 6 and Supplemental Figure 4.

Abbreviations

A	Duration of atrial wave on mitral inflow
Ar	Duration of pulmonary vein flow A wave reversal
BMI	Body mass index
CI	Confidence interval
CRP	C-reactive protein
DBP	Diastolic blood pressure
DD	Diastolic dysfunction
DD1	Diastolic dysfunction grade 1
DD2−3	Diastolic dysfunction grade 2−3
DT	Deceleration time of early filling velocity
LA	Left atrial
LV	Left ventricular
LVEF	Left ventricular ejection fraction
OR	Odds ratio
SBP	Systolic blood pressure
SD	Standard deviation
TG	Triglycerides
WC	Waist circumference
WHR	Waist-hip ratio

Supplemental Table 1. Comparison of baseline features of participants and non-participants at last check-up (n=2014): Mean (SD) or %

	Non-participants (n = 1,118)	**Participants (n = 896)**
Age, years	41.0 (5.2)	41.9 (4.8)
Female sex	49.8	50.3
Smoking status		
Never	43.5	53.5
Former	22.8	25.9
Current	33.7	19.6
Body mass index[a]	24.9 (3.9)	24.5 (3.7)
Waist circumference, cm	82.5 (11.4)	81.4 (11.3)
Waist-hip ratio	0.84 (0.093)	0.83 (0.091)
Systolic blood pressure, mm Hg	124.0 (13.6)	122.8 (12.3)
Diastolic blood pressure, mm Hg	75.6 (10.2)	74.8 (10.1)
Pulse pressure, mm Hg	48.5 (10.0)	48.0 (9.3)
Total cholesterol, mmol/L	5.81 (1.10)	5.74 (0.98)
High-density lipoprotein cholesterol, mmol/L	1.39 (0.40)	1.42 (0.40)
Low-density lipoprotein cholesterol, mmol/L	3.87 (0.99)	3.83 (0.93)
Triglycerides, mmol/L	1.20 (1.13)	1.10 (0.98)
Blood glucose, mmol/L	5.11 (0.51)	5.06 (0.50)
C-reactive protein, mg/L	2.37 (4.89)	1.59 (2.24)

[a] Weight (kg)/height (m)^2.

Supplemental Table 2. Echocardiographic features of the sample according to diastolic function grade (end of follow-up) (N=728): Mean (standard deviation) or %

Parameters	**Normal (n = 537)**	**Diastolic dysfunction grade 1 (DD1) (n = 123)**	**Diastolic dysfunction grade 2−3 (DD2−3) (n = 68)**	***P*-value**
Left ventricular ejection fraction, %	66.4 (5.8)	65.8 (6.1)	67.2 (6.2)	0.14
Left ventricular end-diastolic volume index, mL/m^2	49.1 (12.5)	46.2 (12.6)	48.8 (15.1)	0.10
Left ventricular mass index, g/m^2	79.0 (18.1)	83.8 (18.0)	86.8 (22.1)	0.001
Septal e' velocity, cm/s	9.19 (1.93)	6.78 (1.00)	6.69 (1.01)	< 0.001
< 8, cm/s	23.6	95.9	97.1	< 0.001
Lateral e' velocity, cm/s	11.87 (2.34)	8.34 (1.60)	8.10 (1.78)	< 0.001
< 10, cm/s	16.0	93.5	90.9	< 0.001
Left atrial volume index, mL/m^2	22.2 (7.0)	23.9 (7.6)	24.5 (9.2)	0.007
≥ 34, mL/m^2	4.9	16.2	20.3	< 0.001
E wave velocity, m/s	0.67 (0.13)	0.55 (0.11)	0.71 (0.14)	< 0.001
A wave velocity, m/s	0.67 (0.16)	0.71 (0.14)	0.69 (0.13)	0.010
Mitral E/A ratio	1.05 (0.31)	0.80 (0.17)	1.04 (0.23)	< 0.001
Deceleration time of early filling velocity, ms	220 (53)	231 (61)	199 (47)	< 0.001
Average E/e'	6.47 (1.41)	7.41 (1.46)	9.77 (2.01)	< 0.001
Time difference between it and mitral A-wave duration (Ar – A)	-28.2 (33.3)	-33.7 (24.9)	-31.1 (33.4)	0.33

Supplemental Table 3. Factors associated with subsequent diastolic dysfunction (all grades) after 20 years (n=728): Age-sex-adjusted odds ratios with logistic regression models for baseline value and 20-year change for each covariate

	1 SD at baseline	Value at baseline			Change during follow-up [a]		
Covariates[b]		**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Body mass index	3.21	1.24	1.04−1.48	0.015	1.26	1.05−1.52	0.013
Waist circumference, cm	10.4	1.45	1.16−1.81	< 0.001	1.17	0.95−1.44	0.133
Waist-hip ratio	0.087	1.57	1.17−2.10	0.002	1.10	0.88−1.37	0.419
Systolic blood pressure, mm Hg	9.4	1.29	1.06−1.57	0.013	1.12	1.01−1.24	0.035
Diastolic blood pressure, mm Hg	9.0	1.35	1.07−1.71	0.011	1.19	1.00−1.41	0.052
Pulse pressure, mm Hg	8.3	1.15	0.93−1.43	0.199	1.08	0.96−1.21	0.220
Total cholesterol, mmol/L	0.98	1.17	0.94−1.45	0.154	1.02	0.86−1.22	0.797
High-density lipoprotein cholesterol, mmol/L	0.40	0.79	0.63−0.98	0.034	0.72	0.56−0.92	0.010
Low-density lipoprotein cholesterol, mmol/L	0.92	1.17	0.93−1.46	0.185	1.02	0.85−1.23	0.812
Triglycerides, mmol/L	0.61	1.45	1.16−1.81	0.001	1.35	1.11−1.64	0.003
Blood glucose, mmol/L	0.46	1.10	0.92−1.31	0.304	1.07	0.98−1.16	0.149
C-reactive protein, mg/L	1.56	1.14	0.96−1.36	0.133	1.04	1.00−1.08	0.068

Abbreviations: SD, standard deviation; OR, odds ratio; CI, confidence interval.
[a] Defined for 20 years = [((Value at last examination – Value at first examination) x20)/ Follow-up duration] / 1SD.
[b] There was a separate model for each covariate including its baseline value (divided by 1 SD) and change during follow-up.

Supplemental Table 4. Baseline characteristics of the subjects in the Malmö Preventive Project cohort

	Including subjects with diabetes and hypertension (n=1463)	**Excluding subjects with diabetes and hypertension (n=927)**
Age, years	43.1 (7.8)	41.6 (7.6)
Female sex	30.1	26.4
Smoking status		
Never	n.a	n.a
Former	n.a	n.a
Current	41.3	n.a
Body mass index[a]	24.9 (3.6)	24.2 (3.1)
Waist circumference, cm	n.a	81.4 (11.3)
Waist-hip ratio	n.a	0.83 (0.091)
Systolic blood pressure, mm Hg	125.8 (14.6)	120.3 (10.5)
Diastolic blood pressure, mm Hg	86.5 (9.2)	83.3 (7.1)
Pulse pressure, mm Hg	n.a	n.a
Total cholesterol, mmol/L	5.65 (1.13)	5.55 (1.07)
High-density lipoprotein cholesterol, mmol/L	n.a	1.42 (0.40)
Low-density lipoprotein cholesterol, mmol/L	n.a	3.83 (0.93)
Triglycerides, mmol/L	1.43 (0.90)	1.34 (0.98)
Blood glucose, mmol/L	5.15 (0.81)	5.02 (0.50)
C-reactive protein, mg/L	n.a	n.a
Prevalent diabetes, percent	4.3	0
Prevalent hypertension, percent	28.7	0
Prevalent cardiovascular disease, percent	0.2	0.1
Prevalent heart failure disease, percent	0	0
Prevalent atrial fibrillation disease, percent	0.1	0.1

n.a.: not available

Supplemental Table 5. Age-sex-adjusted odds ratios computed with logistic regression models of baseline factors for subsequent diastolic dysfunction (all grades) after a 24-year follow-up, including subjects with diabetes and hypertension (Malmö Preventive Project cohort) (n=1463)

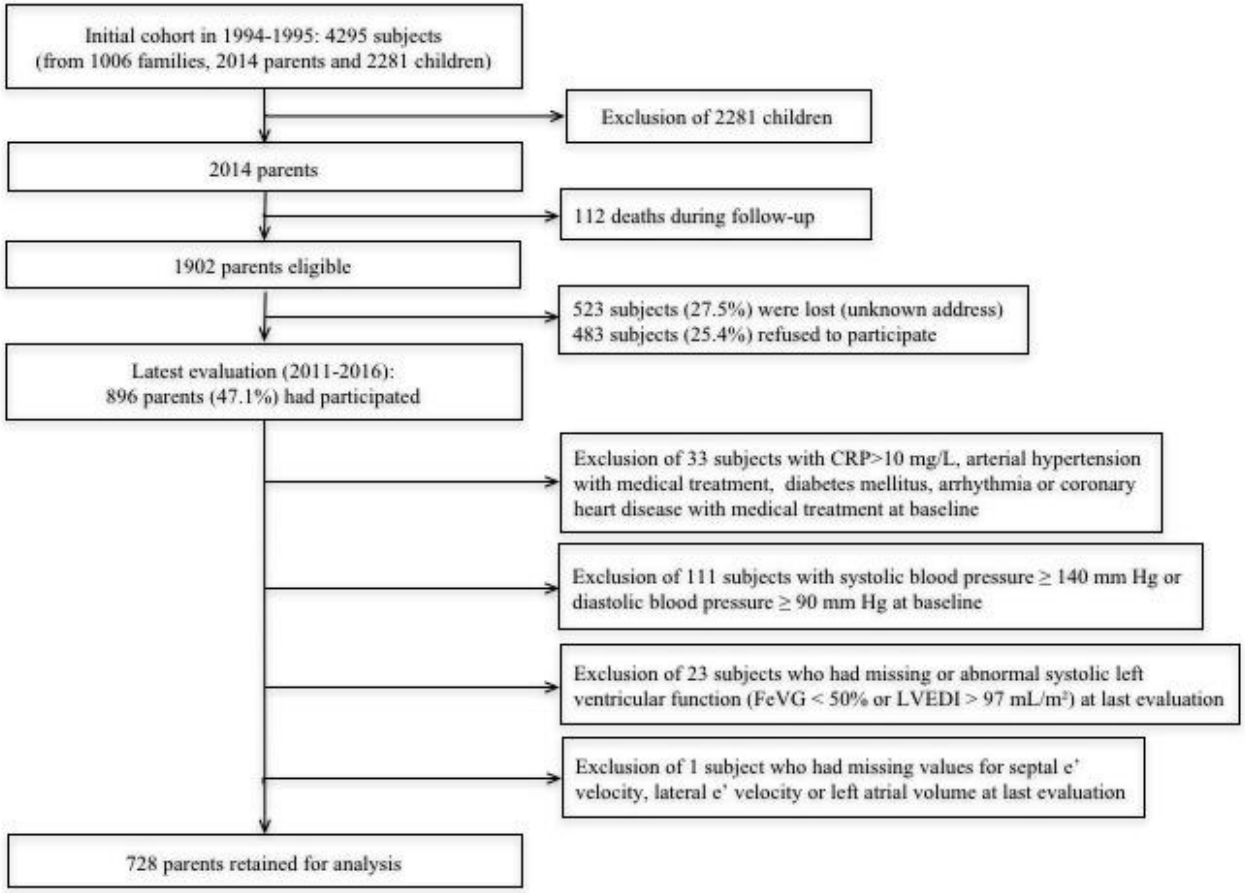
Baseline covariates	**Number of available values (%)**	**1 SD**	**OR**	**95% CI**	***P*-value**
Age-sex-adjusted odds ratios					
Current smoking	1453 (99.3)		0.95	0.75−1.20	0.668
Body mass index, kg/m^2	1463 (100)	3.6	**1.20**	1.06−1.36	0.005
Systolic blood pressure, mm Hg	1444 (98.7)	14.6	1.03	0.91−1.16	0.608
Diastolic blood pressure, mm Hg	1444 (98.7)	9.2	1.11	0.99−1.25	0.086
Pulse pressure, mm Hg	1444 (98.7)	11.0	0.96	0.85−1.08	0.456
Total cholesterol, mmol/L	1461 (99.9)	1.13	1.12	0.99−1.26	0.070
Triglycerides, mmol/L	1460 (99.8)	0.90	**1.17**	1.03−1.32	0.016
Blood glucose, mmol/L	1455 (99.5)	0.81	1.03	0.91−1.15	0.663
Multivariable analysis with sex, age, body mass index, diastolic blood pressure, total cholesterol and triglycerides					
Body mass index, kg/m^2	1463 (100)	3.6	**1.15**	1.00−1.31	0.050
Diastolic blood pressure, mm Hg	1444 (98.7)	9.2	1.04	0.92−1.18	0.512
Total cholesterol, mmol/L	1461 (99.9)	1.13	1.07	0.94−1.22	0.312
Triglycerides, mmol/L	1460 (99.8)	0.90	1.09	0.95−1.25	0.204

Abbreviations: SD, standard deviation; OR, odds ratio; CI, confidence interval.
Values in bold: significant OR ($P<0.05$).

Supplement Table 6. Age-sex-adjusted odds ratios computed with logistic regression models of baseline factors for subsequent diastolic dysfunction (all grades) after a 24-year follow-up, excluding subjects with diabetes and hypertension (Malmö Preventive Project cohort) (n=927)

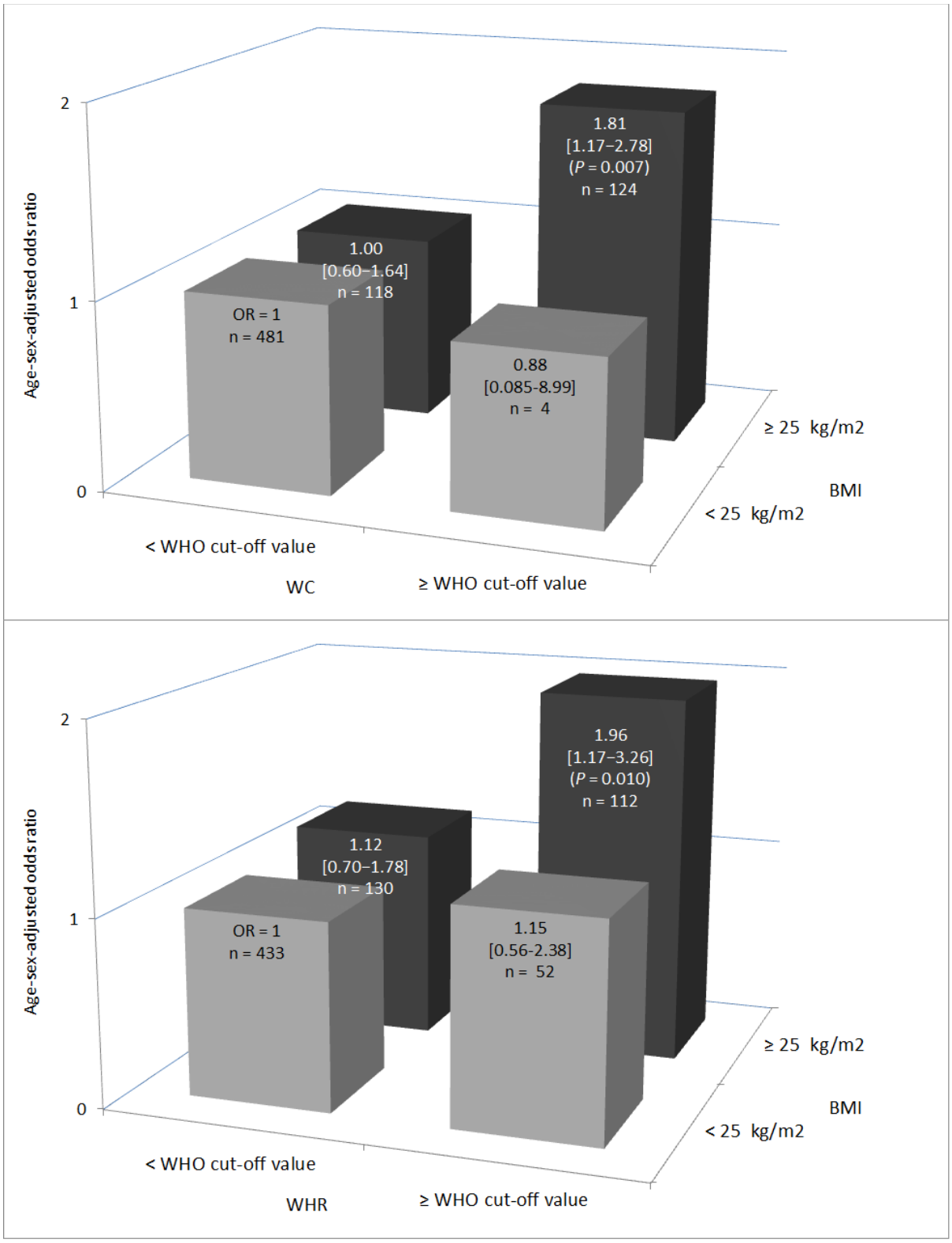
Baseline covariates	**Number of available values (%)**	**1 SD**	**OR**	**95% CI**	***P*-value**
Age-sex-adjusted odds ratios					
Current smoking	926 (99.9)		1.00	0.75−1.34	0.984
Body mass index, kg/m^2	927 (100)	3.1	1.11	0.96−1.29	0.154
Systolic blood pressure, mm Hg	927 (100)	10.1	1.02	0.88−1.19	0.765
Diastolic blood pressure, mm Hg	927 (100)	6.4	1.15	0.99−1.33	0.076
Pulse pressure, mm Hg	927 (100)	9.1	0.94	0.81−1.08	0.372
Total cholesterol, mmol/L	925 (99.8)	1.07	1.09	0.94−1.26	0.276
Triglycerides, mmol/L	924 (99.7)	0.74	**1.20**	1.04−1.40	0.016
Blood glucose, mmol/L	920 (99.2)	0.50	1.04	0.90−1.20	0.635
Multivariable analysis with sex, age, body mass index, diastolic blood pressure and triglycerides					
Body mass index, kg/m^2	927 (100)	3.1	1.05	0.90−1.23	0.528
Diastolic blood pressure, mm Hg	927 (100)	6.4	1.10	0.94−1.28	0.226
Triglycerides, mmol/L	924 (99.7)	0.74	**1.17**	1.00−1.37	0.044

Abbreviations: SD, standard deviation; OR, odds ratio; CI, confidence interval.
Values in bold: significant OR (P<0.05).

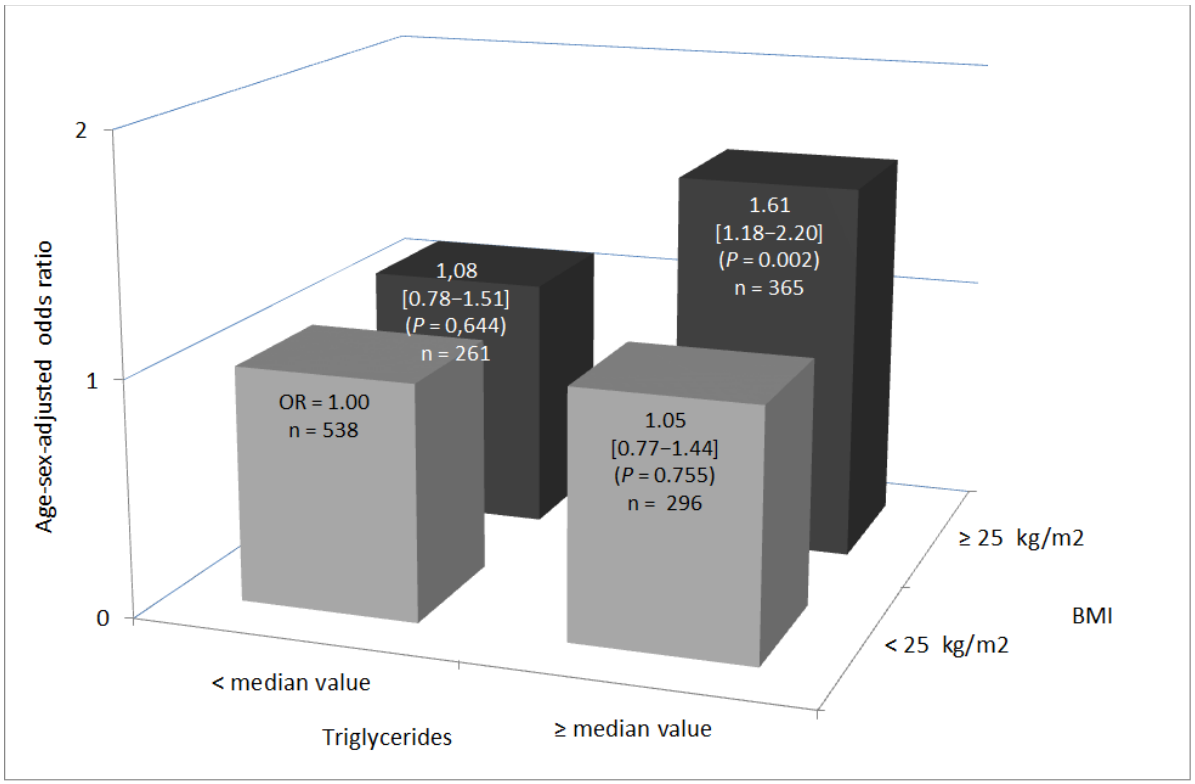


Abbreviations: FeVG, left ventricular ejection fraction; LVEDI, indexed end-diastolic ventricular volume.

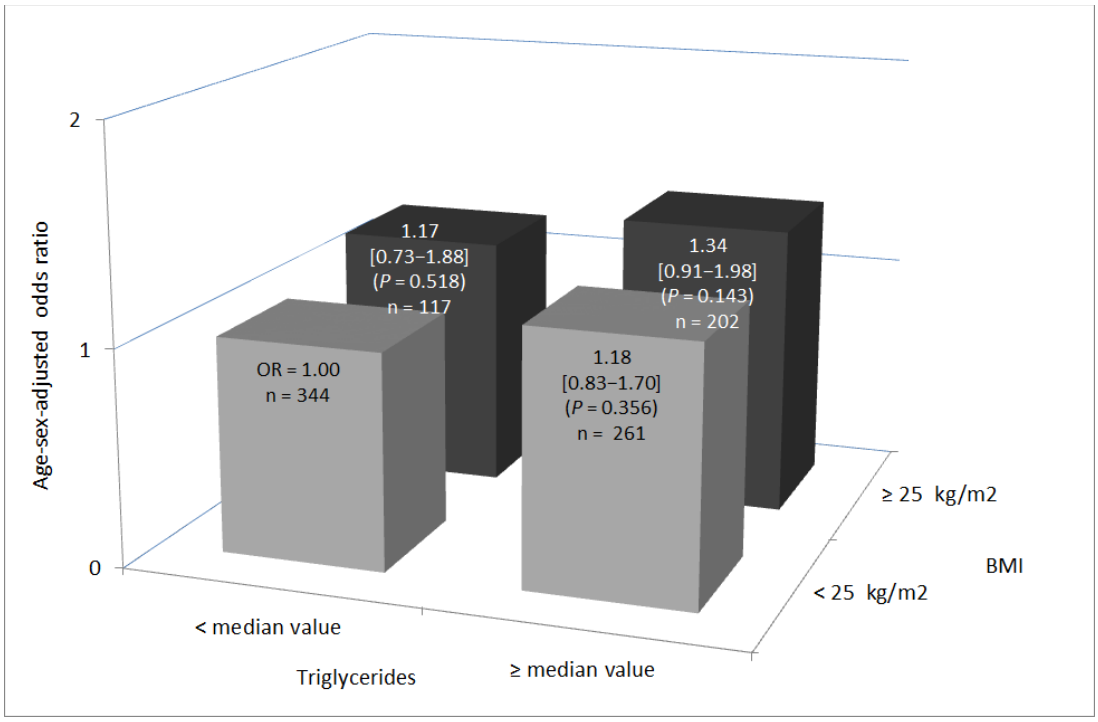
Supplemental Figure 1. Flow chart of study participants



Supplemental Figure 2. Age-sex-adjusted odds ratio (OR) for diastolic dysfunction (DD, all grades) when considering the interplay between waist circumference (WC) or waist-hip ratio (WHR) and body mass index (BMI) (n=728)



Supplemental Figure 3. Age-sex-adjusted odds ratio (OR) for diastolic dysfunction (DD, all grades) when considering the interplay between body mass index (BMI) and triglycerides in the sample, including subjects with diabetes and hypertension (Malmö Preventive Project cohort) (n=1463)



Supplemental Figure 4. Age-sex-adjusted odds ratio (OR) for diastolic dysfunction (DD, all grades) when considering the interplay between body mass index (BMI) and triglycerides in the sample, excluding subjects with diabetes and hypertension (Malmö Preventive Project cohort) (n=927)

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A2. Association entre l'obésité abdominale et le risque de rigidité artérielle aortique 20 ans plus tard dans une cohorte d'adultes initialement en bonne santé

SUPPLEMENTAL DIGITAL CONTENT

Association between abdominal adiposity and 20-year subsequent aortic stiffness in the initially healthy population-based STANISLAS cohort

Kénora CHAU, Nicolas GIRERD, Erwan BOZEC, João Pedro FERREIRa, Kévin DUARTE, Julie-Anne NAZARE, Martine LAVILLE, Athanase BENETOS, Faiez ZANNAD, Jean-Marc BOIVIN, Patrick ROSSIGNOL

Each subject gave his/her written informed consent to participate in this study, which was approved by the Ethics Committee of the Lorraine region (*Comité Consultatif de Protection des Personnes qui se prêtent à une Recherche Biomédicale de Lorraine, and Comité Consultatif de Protection des Personnes Est-III*), in agreement with French legislation on human biomedical research.

At the end of follow-up (2011−2016), a request to participate explaining the aims of the study was sent by mail and thereafter by up to eight telephone calls at different times of the day (lunch time, evening). The address and telephone number were completed or gathered via data from hospital records, the Center for Preventive Medicine and the internet. Among the 2,014 parents who had participated at baseline, 112 subjects were deceased. Among the 1902 parents eligible, 523 subjects were lost (unknown address) and 384 subjects refused, leaving 995 participants (52.3%).

WC is typically used as a risk indicator supplementary to BMI; however, their strong correlation makes it difficult to isolate the added value of WC [1]. To overcome this difficulty, Krakauer and Krakauer have recently proposed "a body shape index" (ABSI= WC / ($BMI^{2/3}$ x $Height^{1/2}$)) to express the excess risk of mortality from high WC in a convenient form that is complementary to BMI and to

other known risk factors [1]. This index, built on a sample of USA adults 18+ years, appeared to be better than BMI and WC. However, it was designed to be an index independent of weight and height. Because abdominal obesity is correlated with weight, the ABSI would neglect a certain amount of abdominal obesity. We believe that the levels of abdominal obesity and general obesity vary substantially between individuals, and that the risk for certain cardiovascular diseases is more elevated when the excess of abdominal obesity is higher for a fixed level of BMI. In order to focus more specifically on abdominal obesity, we propose a new indicator to measure the ratio between the level of abdominal obesity and the level of general obesity, herein defined by WC-to-BMI ratio.

The predicted reference normal value ($cfPWV_{ref}$) was calculated for each subject using the following equations provided by *The Reference Values for Arterial Stiffness' Collaboration* [2]:

$cfPWV_{ref} = 0.83 \times 10\text{-}3 \times age^2 + 5.55$	if SBP <120 mm Hg and DBP <80 mm Hg
$cfPWV_{ref} = 0.99 \times 10^{-3} \times age^2 + 5.69$	if SBP 120-129 mm Hg or DBP 80-84 mm Hg
$cfPWV_{ref} = 1.05 \times 10^{-3} \times age^2 + 5.91$	if SBP 130-139 mm Hg or DBP 85-89 mm Hg
$cfPWV_{ref} = 1.18 \times 10^{-3} \times age^2 + 6.17$	if SBP 140-159 mm Hg or DBP 90-99 mm Hg
$cfPWV_{ref} = 0.85 \times 10^{-3} \times age^2 + 0.044 \times age + 5.73$	if SBP ≥160 mm Hg or DBP ≥100 mm Hg

where age, SBD and DBP are values at cfPWV measurement e.g. at end of follow-up.

The cfPWV expressed as the percentage of $cfPW_{ref}$ (noted "% Predicted cfPWV") was then computed:

$$\%Predicted\text{-}cfPWV = 100 \times cfPWV / cfPWV_{ref.}$$

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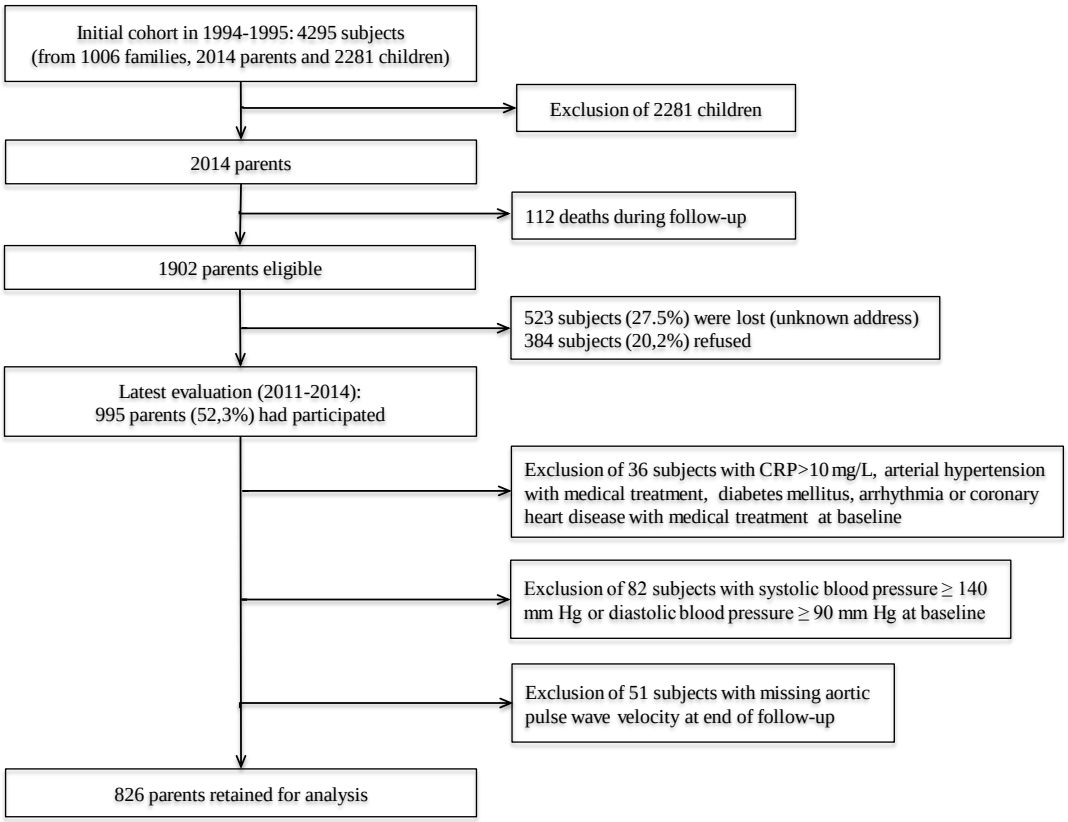
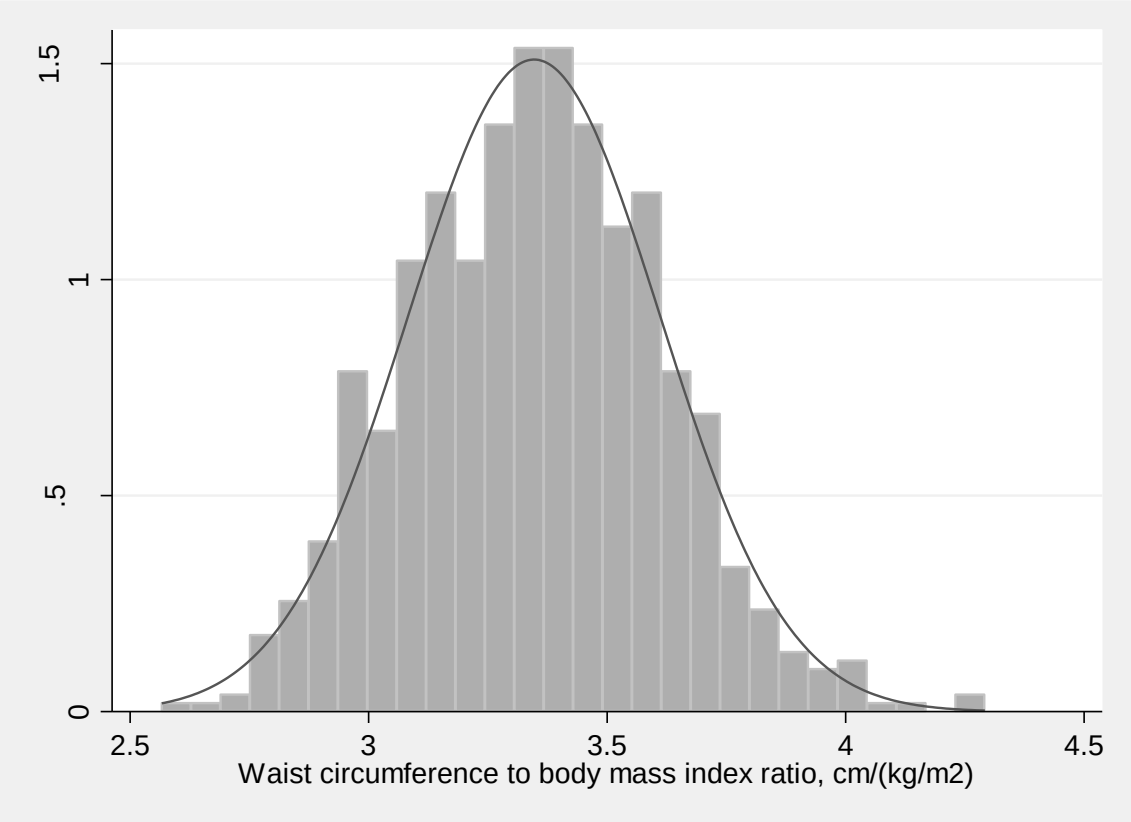


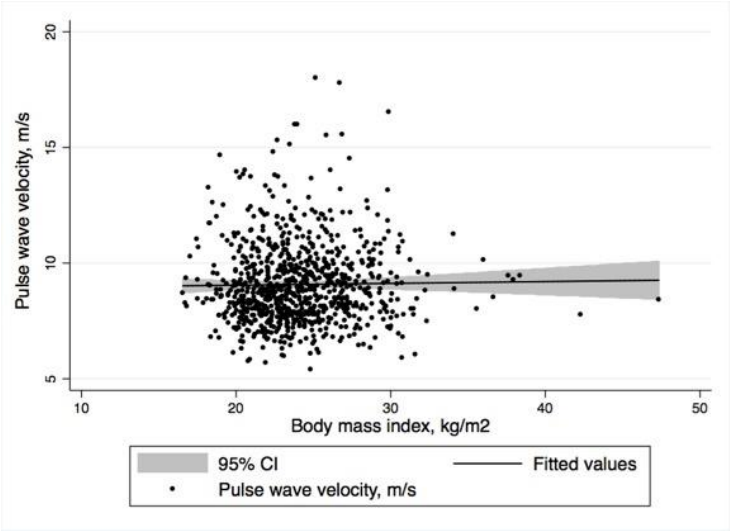
FIGURE S1. Flow chart of study participants



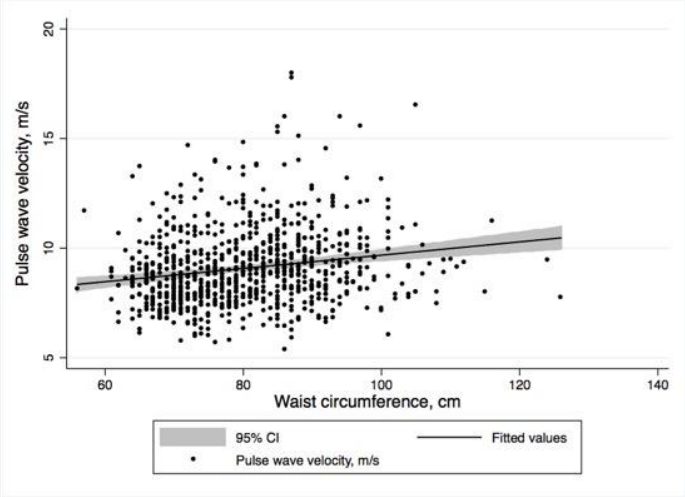
Mean 3.35 cm/(kg/m^2) (SD 0.26)
The variable followed a normal distribution
[Pr(Skewness) = 0.182, Pr(Kurtosis) = 0.778, adjusted chi^2 = 1.86, *P*=0.394]

	waist circumference to body mass index ratio		
	< mean value (3.35) (N=417)	≥ mean value (3.35) (N=407)	*P*-value
Body mass index, kg/m^2			
Mean (SD)	24.6 (3.5)	23.5 (3.0)	< 0.001
Obesity			< 0.001
Normal weight (<25)	62.6	70.0	
Overweight (25-29.9)	30.0	28.0	
Obese (≥30)	7.4	2.0	
Waist circumference, cm			
≥94 in men and ≥80 in women	20.1	15.5	0.080

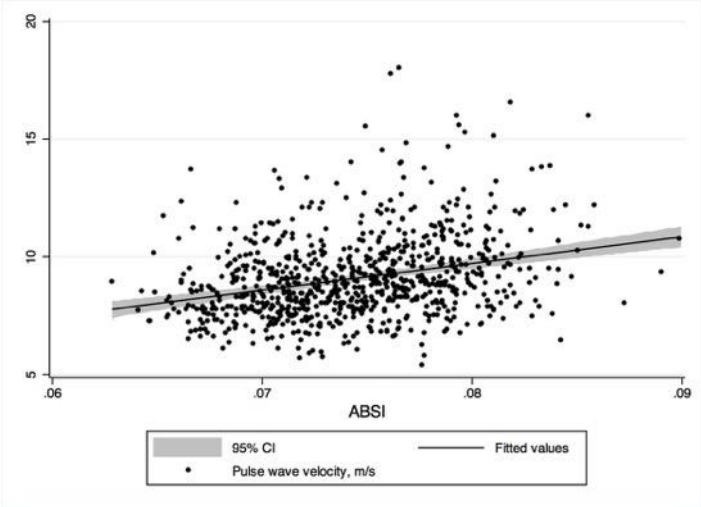
FIGURE S2. Distribution of waist circumference to body mass index ratio (with an overlaid normal density having the same mean and SD)



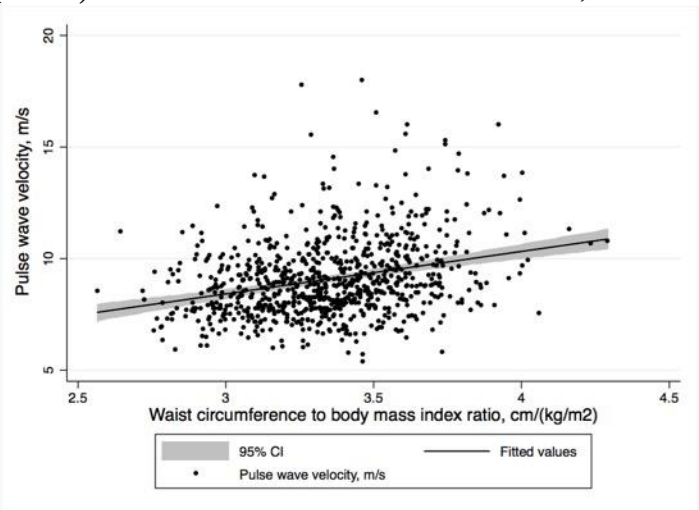
Pearson correlation coefficient = 0.014, non-significant (P>0.05)



Pearson correlation coefficient = 0.182, *P*<0.001



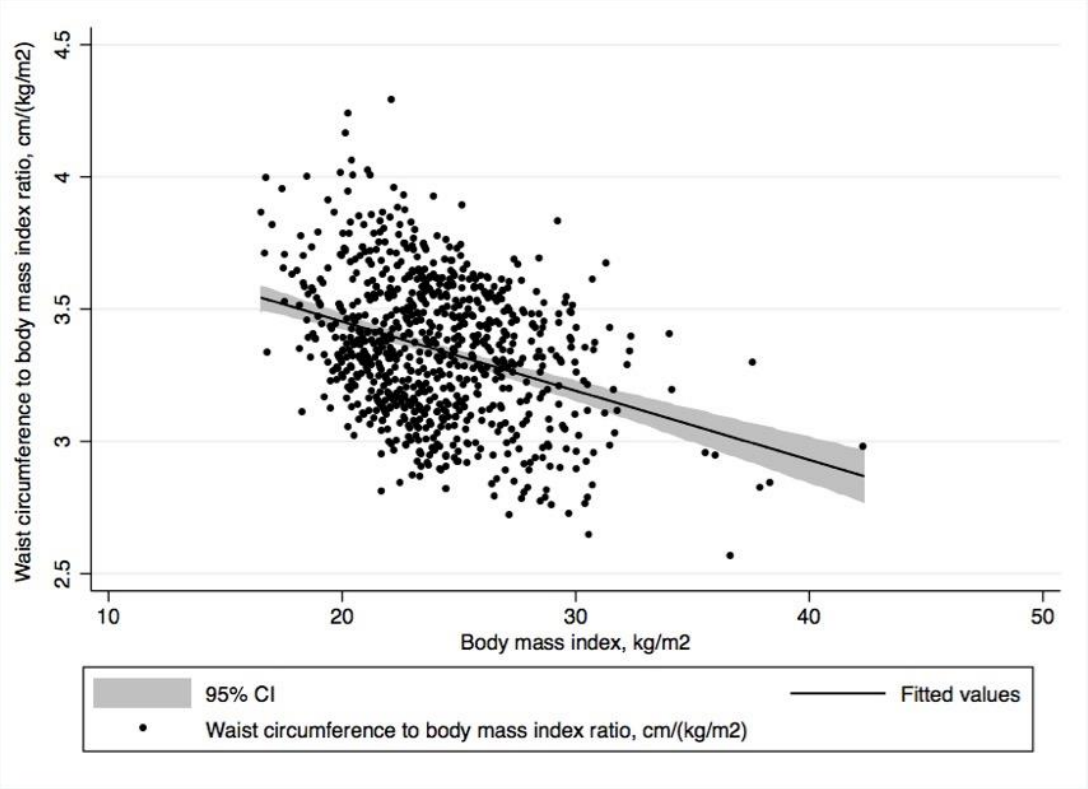
Pearson correlation coefficient = 0.289, *P*<0.001



Pearson correlation coefficient = 0.288, *P*<0.001

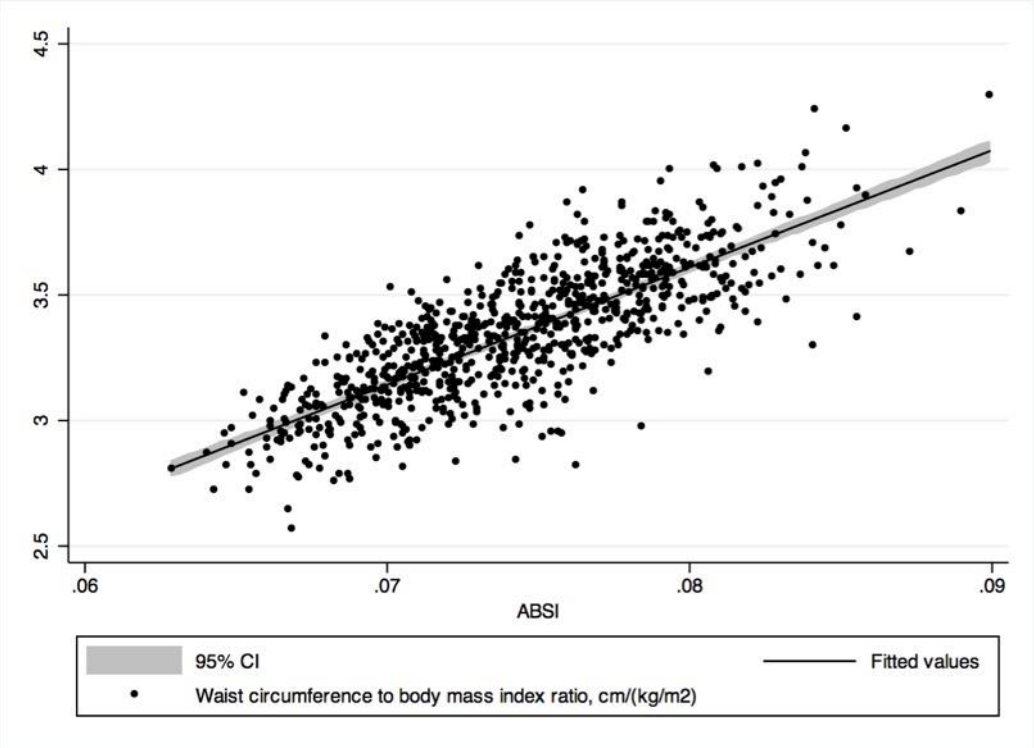
ABSI= WC(m) / (BMI(kg/m^2)$^{2/3}$ x Height(m)$^{1/2}$) where WC: waist circumference and BMI: body mass index.

FIGURE S3. Scatter plot of pulse wave velocity and each anthropometric measure (N=826)



Pearson correlation coefficient = -0.330, *P*<0.001

FIGURE S4. Scatter plot of body mass index and waist circumference to body mass index ratio (N=826)



Pearson correlation coefficient = 0.79, *P*<0.001

ABSI= WC(m) / (BMI(kg/m^2)$^{2/3}$ x Height(m)$^{1/2}$) where WC: waist circumference and BMI: body mass index.

FIGURE S5. Scatter plot of ABSI and waist circumference to body mass index ratio (N=826)

TABLE S1. Association between baseline anthropometric factors and pulse wave velocity at end of 20-year follow-up (N=826): regression coefficient and 95% confidence interval

	1SD	β	95% CI	P-value
Model 1 [a]				
WC-to-BMI-ratio, cm/(kg/m^2)	0.26	**+0.28**	0.11 – 0.45	< 0.001
Body mass index, kg/m^2	3.43	-0.051	-0.20 – 0.10	0.509
Model 2 [a]				
Waist circumference, cm	10.7	**+0.41**	0.12– 0.71	< 0.001
Body mass index, kg/m^2	3.43	**-0.51**	-0.7 – -0.27	0.006
Model 3 [a]				
ABSI [c], m/[(kg/m^2)$^{2/3}$m$^{1/2}$]	0.0045	**+0.18**	0.030– 0.32	0.018
Body mass index, kg/m^2	3.43	**-0.22**	-0.33– -0.10	< 0.001

Bold types: significant β.

[a] Each model included the two anthropometric parameters, and sex, age and mean BP at the time of cfPWV measurement.

TABLE S2: Associations between baseline waist circumference to body mass index ratio and pulse wave velocity at end of 20-year follow-up (n=826): regression coefficient (estimated from global sample) and bootstrap confidence interval (based on 1000 resamples and using percentiles method)

		cfPWV, m/s		CfPWV-to-reference-value-ratio, %	
Baseline predictors		**β**	**Bootstrap 95% CI**	**β**	**Bootstrap 95% CI**
WC-to-BMI-ratio, cm /(kg/m^2)	Model 1 [a]	**0.32**	0.18 – 0.45	**3.34**	1.96 – 4.70
	Model 1 + heart rate	**0.32**	0.20 – 0.45	**3.36**	2.02 – 4.67
	Model 1 + HDL, LDL, triglyceride, blood glucose	**0.38**	0.24 – 0.52	**3.86**	2.51 – 5.33
	Model 1 + C-reactive protein	**0.36**	0.23 – 0.50	**3.81**	2.43 – 5.27
	Model 1 + all factors	**0.41**	0.26 – 0.55	**4.14**	2.58 – 5.62
Body mass index, kg/m^2	Model 1 [a]	**-0.20**	-0.31 – -0.095	**-1.91**	-3.07 – -0.80
	Model 1 + heart rate	**-0.23**	-0.34 – -0.12	**-2.21**	-3.32 – -1.10
	Model 1 + HDL, LDL, triglyceride, blood glucose	**-0.29**	-0.42 – -0.18	**-2.70**	-3.98 – -1.56
	Model 1 + C-reactive protein	**-0.28**	-0.41 – -0.16	**-2.64**	-3.99 – -1.41
	Model 1 + all factors	**-0.40**	-0.55 – -0.26	**-3.67**	-5.24 – -2.38
Waist circumference, cm	Model 1 [a]	**-0.14**	-0.27 – -0.007	-1.19	-2.58 – 0.17
	Model 1 + heart rate	**-0.18**	-0.32 – -0.034	**-1.58**	-2.99 – -0.10
	Model 1 + HDL, LDL, triglyceride, blood glucose	**-0.25**	-0.42 – -0.075	**-2.03**	-3.71 – -0.39
	Model 1 + C-reactive protein	**-0.21**	-0.36 – -0.054	**-1.74**	-3.21 – -0.20
	Model 1 + all factors	**-0.35**	-0.55 – -0.18	**-2.97**	-4.87 – -1.25
Waist-to-height-ratio	Model 1 [a]	**-0.16**	-0.27 – -0.055	**-1.55**	-2.72 – -0.42
	Model 1 + heart rate	**-0.21**	-0.33 – -0.091	**-2.02**	-3.20 – -0.81
	Model 1 + HDL, LDL, triglyceride, blood glucose	**-0.26**	-0.40 – -0.12	**-2.33**	-3.76 – -0.95
	Model 1 + C-reactive protein	**-0.23**	-0.35 – -0.11	**-2.04**	-3.31 – -0.85
	Model 1 + all factors	**-0.37**	-0.53 – -0.23	**-3.33**	-4.91 – -1.89
ABSI, [b]	Model 1 [a]	**0.17**	0.024 – 0.32	**1.86**	0.32 – 3.33

m/[(kg/m^2)$^{2/3}$m$^{1/2}$]	Model 1 + heart rate	0.14	-0.012 – 0.28	1.47	-0.089 – 2.89
	Model 1 + HDL, LDL, triglyceride, blood glucose	**0.18**	0.016 – 0.34	**2.10**	0.52 – 3.79
	Model 1 + C-reactive protein	**0.17**	0.013 – 0.33	**2.07**	0.43 – 3.74
	Model 1 + all factors	0.14	-0.041 – 0.32	**1.78**	0.020 – 3.54

Abbreviations: cfPWV, pulse wave velocity; β, regression coefficient; CI, confidence interval; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; BMI, body mass index; WC, waist circumference; SD, standard deviation.
All continuous variables (except age) were standardized (divided by 1SD). The value of SD was 3.43 kg/m^2 for BMI, 10.7 cm for WC, 0.055 for waist-to-height-ratio, 0.0045 m /[(kg/m^2)$^{2/3}$m$^{1/2}$] for ABSI, 0.26 cm /(kg/m^2) for WC-to-BMI-ratio, 10.0 bpm for heart rate, 0.41 mmol/L for HDL, 0.93 mmol/L for LDL, 0.65 mmol/L for triglyceride, 0.47 mmol/L for blood glucose, and 1.61 mg/L for C-reactive protein.
[a] Model 1 provided β adjusted for sex, age and mean blood pressure at the time of the cfPWV measurement.
[b] Ratio WC / (BMI$^{2/3}$ x height$^{1/2}$); WC in m, BMI in kg/m^2 and height in m.

TABLE S3. Pearson correlation coefficients between each anthropometric parameter and blood pressure, heart rate, metabolic measures and C-reactive protein at baseline (N=826)

	WC-to-BMI-ratio	BMI	WC	WHtR	ABSI [a]
Blood pressures and heart rate					
Systolic blood pressure	0.18‡	0.25‡	0.37‡	0.30‡	0.30‡
Diastolic blood pressure	0.14‡	0.21‡	0.30‡	0.23‡	0.23‡
Heart rate	-0.14‡	0.002	-0.082*	0.037	-0.061*
Metabolic measures					
Total cholesterol	0.11†	0.19‡	0.26‡	0.24‡	0.23‡
High density lipoprotein cholesterol	-0.11†	-0.40‡	-0.48‡	-0.45‡	-0.34‡
Low density lipoprotein cholesterol	0.12†	0.25‡	0.34‡	0.31‡	0.28‡
Triglycerides	0.15‡	0.39‡	0.50‡	0.46‡	0.38‡
Blood glucose	0.068	0.25‡	0.30‡	0.24‡	0.17‡
Inflammatory marker					
C-reactive protein	-0.088*	0.25‡	0.20‡	0.23‡	0.061

Abbreviations: N, number of subjects; BMI, body mass index; WC, waist circumference; ABSI, "A Body Shape Index"; WHtR, waist-to-height-ratio.
*$P<0.05$, † $P<0.01$, ‡$P<0.001$.
[a] Ratio WC/($BMI^{2/3}$ x $height^{1/2}$)

TABLE S4. Associations between baseline waist circumference to body mass index ratio and other anthropometric measures and estimated pulse wave velocity[a] at end of 20-year follow-up (N=826): regression coefficient and 95% confidence interval

Baseline predictors		Estimated cfPWV, m/s			
		β	95% CI	*P*-value	% [b]
WC-to-BMI-ratio, cm/(kg/m^2)	Model 1 [c]	**0.40**	0.27−0.53	< 0.001	100
	Model 1 + heart rate	**0.40**	0.28−0.53	< 0.001	0
	Model 1 + HDL, LDL, triglyceride, blood glucose	**0.44**	0.31−0.57	< 0.001	-10
	Model 1 + C-reactive protein	**0.44**	0.30−0.57	< 0.001	-10
	Model 1 + all factors	**0.46**	0.32−0.60	< 0.001	-15
Body mass index, kg/m^2	Model 1 [c]	**-0.36**	-0.46− -0.25	< 0.001	100
	Model 1 + heart rate	**-0.38**	-0.49− -0.28	< 0.001	-6
	Model 1 + HDL, LDL, triglyceride, blood glucose	**-0.43**	-0.55− -0.32	< 0.001	-19
	Model 1 + C-reactive protein	**-0.43**	-0.55− -0.31	< 0.001	-19
	Model 1 + all factors	**-0.53**	-0.66− -0.40	< 0.001	-47
Waist circumference, cm	Model 1 [c]	**-0.34**	-0.48− -0.20	< 0.001	100
	Model 1 + heart rate	**-0.37**	-0.51− -0.24	< 0.001	-9
	Model 1 + HDL, LDL, triglyceride, blood glucose	**-0.43**	-0.59− -0.27	< 0.001	-26
	Model 1 + C-reactive protein	**-0.39**	-0.55− -0.24	< 0.001	-15
	Model 1 + all factors	**-0.52**	-0.69− -0.35	< 0.001	-53
Waist-to-height-ratio	Model 1 [c]	**-0.34**	-0.45− -0.22	0.007	100
	Model 1 + heart rate	**-0.38**	-0.49− -0.26	< 0.001	-12
	Model 1 + HDL, LDL, triglyceride, blood glucose	**-0.42**	-0.56− -0.29	< 0.001	-24
	Model 1 + C-reactive protein	**-0.39**	-0.52− -0.26	< 0.001	-15
	Model 1 + all factors	**-0.52**	-0.66− -0.38	< 0.001	-53
ABSI,[d] m/[(kg/m^2)$^{2/3}$m$^{1/2}$]	Model 1 [c]	0.095	-0.051−0.24	0.203	100
	Model 1 + heart rate	0.062	-0.084−0.21	0.404	–
	Model 1 + HDL, LDL, triglyceride, blood glucose	0.12	-0.037−0.27	0.138	–
	Model 1 + C-reactive protein	0.10	-0.053−0.26	0.193	–
	Model 1 + all factors	0.090	-0.072−0.25	0.275	–

Abbreviations: cfPWV, pulse wave velocity; β, regression coefficient; CI, confidence interval; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; BMI, body mass index; WC, waist circumference; SD, standard deviation.

All continuous variables (except age) were standardized (divided by 1SD). The value of SD was 3.43 kg/m^2 for BMI, 10.7 cm for WC, 0.055 for waist-to-height-ratio, 0.0045 m /[(kg/m^2)$^{2/3}$m$^{1/2}$] for ABSI, 0.26 cm /(kg/m^2) for WC-to-BMI-ratio, 10.0 bpm for heart rate, 0.41 mmol/L for HDL, 0.93 mmol/L for LDL, 0.65 mmol/L for triglyceride, 0.47 mmol/L for blood glucose, and 1.61 mg/L for C-reactive protein.

[a] Determined by the Weber formula [3].

[b] Contribution of covariates considered i.e. change in β computed with the following formula: ($\beta_{\text{model 1}} - \beta_{\text{extended model}}$) / β_{model1}.

[c] Model 1 provided β adjusted for sex, age and mean blood pressure at the time of the cfPWV measurement.

[d] Ratio WC / (BMI$^{2/3}$ x height$^{1/2}$); WC in m, BMI in kg/m^2 and height in m.

TABLE S5. Associations between waist circumference to body mass index ratio and other anthropometric measures and pulse wave velocity at end of 20-year follow-up (cross-sectional analysis) (N=826): regression coefficient and 95% confidence interval

Predictors at end of follow-up		cfPWV, m/s				CfPWV-to-reference-value-ratio, %			
		β	95% CI	*P*-value	% [a]	β	95% CI	*P*-value	% [a]
WC-to-BMI-ratio cm/(kg/m²)	Model 1 [b]	**0.25**	0.13−0.36	< 0.001	100	**2.60**	1.44−3.76	< 0.001	100
	Model 1 + heart rate	**0.27**	0.16−0.38	< 0.001	-8	**2.85**	1.71−3.99	< 0.001	-10
	Model 1 + HDL, LDL, triglyceride, blood glucose	**0.27**	0.15−0.39	< 0.001	-8	**2.81**	1.61−4.00	< 0.001	-8
	Model 1 + C-reactive protein	**0.25**	0.14−0.37	< 0.001	0	**2.64**	1.47−3.81	< 0.001	-2
	Model 1 + all factors	**0.27**	0.16−0.39	< 0.001	-8	**2.84**	1.66−4.02	< 0.001	-9
Body mass index, kg/m²	Model 1 [b]	**-0.20**	-0.31− -0.096	< 0.001	100	**-1.98**	-3.06− -0.90	< 0.001	100
	Model 1 + heart rate	**-0.27**	-0.38− -0.16	< 0.001	-35	**-2.73**	-3.83− -1.64	< 0.001	-38
	Model 1 + HDL, LDL, triglyceride, blood glucose	**-0.27**	-0.39− -0.15	< 0.001	-35	**-2.60**	-3.82− -1.39	< 0.001	-31
	Model 1 + C-reactive protein	**-0.21**	-0.32− -0.10	< 0.001	-5	**-2.06**	-3.17− -0.94	< 0.001	-4
	Model 1 + all factors	**-0.31**	-0.43− -0.19	< 0.001	-55	**-3.07**	-4.29− -1.84	< 0.001	-55
Waist circumference, cm	Model 1 [b]	**-0.14**	-0.26− -0.029	0.014	100	**-1.29**	-2.47− -0.12	0.031	100
	Model 1 + heart rate	**-0.21**	-0.33− -0.096	< 0.001	-50	**-2.03**	-3.22− -0.84	< 0.001	-57
	Model 1 + HDL, LDL, triglyceride, blood glucose	**-0.19**	-0.32− -0.065	0.003	-36	**-1.73**	-3.04− -0.42	0.010	-34
	Model 1 + C-reactive protein	**-0.15**	-0.27− -0.032	0.013	-7	**-1.31**	-2.52− -0.11	0.033	-2
	Model 1 + all factors	**-0.24**	-0.37− -0.11	< 0.001	-71	**-2.15**	-3.48− -0.83	< 0.001	-67
Waist-to-height-ratio	Model 1 [b]	**-0.16**	-0.27− -0.055	0.003	100	**-1.53**	-2.61− -0.44	0.006	100
	Model 1 + heart rate	**-0.23**	-0.34− -0.12	< 0.001	-44	**-2.31**	-3.41− -1.21	< 0.001	-51
	Model 1 + HDL, LDL, triglyceride, blood glucose	**-0.21**	-0.33− -0.093	< 0.001	-31	**-1.99**	-3.20− -0.79	< 0.001	-30
	Model 1 + C-reactive protein	**-0.17**	-0.28− -0.058	0.003	-6	**-1.57**	-2.69− -0.45	0.006	-3
	Model 1 + all factors	**-0.26**	-0.38− -0.14	< 0.001	-62	**-2.49**	-3.72− -1.27	0.003	-63

ABSI[c], m/[(kg/m^2)$^{2/3}$m$^{1/2}$]	Model 1 [b]	0.072	-0.041−0.19	0.213	100	0.87	-0.29−2.02	0.142	100
	Model 1 + heart rate	0.048	-0.064−0.16	0.400	33	0.60	-0.55−1.74	0.307	31
	Model 1 + HDL, LDL, triglyceride, blood glucose	0.071	-0.044−0.19	0.228	-1	0.86	0.32−2.03	0.152	1
	Model 1 + C-reactive protein	0.075	-0.039−0.19	0.198	-4	0.90	-0.27−2.06	0.130	-3
	Model 1 + all factors	0.055	-0.059−0.17	0.348	24	0.67	-0.48−1.83	0.255	23

Abbreviations: cfPWV, pulse wave velocity; β, regression coefficient; CI, confidence interval; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; BMI, body mass index; WC, waist circumference; SD, standard deviation.
All continuous variables (except age) were standardized (divided by 1SD). The value of SD was 4.6 kg/m^2 for BMI, 13.2 cm for WC, 0.075 for waist-to-height-ratio, 0.0051 m /[(kg/m^2)$^{2/3}$m$^{1/2}$] for ABSI, 0.30 cm /(kg/m^2) for WC-to-BMI-ratio, 8.9 bpm for heart rate, 0.38 mmol/L for HDL, 0.84 mmol/L for LDL, 0.78 mmol/L for triglyceride, 0.89 mmol/L for blood glucose, and 5.57 mg/L for C-reactive protein.
[a] Contribution of covariates considered i.e. change in β computed with the following formula: ($\beta_{\text{model 1}} - \beta_{\text{extended model}}$) / $\beta_{\text{model 1}}$.
[b] Model 1 provided β adjusted for sex, age and mean blood pressure at the time of the cfPWV measurement.
[c] Ratio WC / (BMI$^{2/3}$ x height$^{1/2}$); WC in m, BMI in kg/m^2 and height in m.

A3. Facteurs associés à une hypertension artérielle non-diagnostiquée

Supplementary data

Methods

The STANISLAS study is a longitudinal population-based study of 1,006 families which comprised two parents (2,014 individuals initially aged 30-60 years) and at least two children (2281 individuals initially aged 6-24 years) recruited in 1994-1995 during a medical examination at the Center for Preventive Medicine in Eastern France. The subjects of French origin and free of all acute or chronic diseases were invited to participate. At the end of follow-up (2011−2016), a request to participate explaining the aims of the study was sent by mail and subsequently by up to eight telephone calls at different times of the day (lunch time, evening). The address and telephone number were acquired or gathered via data from hospital records, the Center for Preventive Medicine and the internet. Among the 2,014 parents who had participated at baseline, 112 subjects were deceased. Among the eligible 1902 parents, 523 subjects were lost (unknown address) and 384 subjects refused, leaving 995 participants (52.3%). Details of the cohort investigations and loss of follow-up are shown in Figure S1.

Measurements

High-density lipoprotein cholesterol (HDL) was measured on a Cobas-Mira analyzer (Roche Diagnostics). Low-density lipoprotein cholesterol (LDL) was calculated according to the equation of Friedewald et al. (1). C-reactive protein (CRP) was measured by immunonephelometry on a Behring Nephelometer Analyzer (BN II; Dade-Behring, Marburg, Germany) with Behring reagents (Rueil-Malmaison, France) within 2 h after sampling.

Measurement of 24-hour ambulatory blood pressure.

All participants underwent a 24-hour recording of ambulatory BP using the Spacelabs 90207 ambulatory monitor (Spacelabs Medical). The monitoring cuff was placed around the participant's non-dominant arm. The BP system was programmed to measure every 15 minutes from 6 AM to 10 PM and every 30 minutes from 10 PM to 6 AM. Self-reported sleep-wake times were used to divide ABP monitoring data into daytime and nocturnal periods. The BP indices were calculated from 24-hour, daytime, and nighttime measurements. Based

on 24-hour ambulatory BPs, ambulatory hypertension was defined by systolic BP≥130 mmHg and/or diastolic BP≥80 mmHg. Furthermore, participants completed a diary describing their main daily activities (e.g., eating, sleeping) and were asked to avoid excessive exercise during the 24-hour recording. Central reading of the recordings was performed by a trained technician blinded to the participants' clinical features. Data were considered for further analysis if they met the following criteria: the recording lasted ≥24 hours, ≥70% of the expected number of readings were available, no missing data for >2 consecutive hourly intervals, and ≥2 valid measurements were obtained per hour (2). Definition of hypertension history was based on assistant physician registries and/or ongoing treatment for hypertension. Participants without these criteria were considered to have no history of hypertension.

References

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2. Ferreira JP, Girerd N, Bozec E, Mercklé L, Pizard A, Bouali S, Eby E, Leroy C, Machu JL, Boivin JM, Lamiral Z, Rossignol P, Zannad F. Cohort Profile: Rationale and design of the fourth visit of the STANISLAS Cohort: a familial longitudinal population-based cohort from the Nancy region of France. Int J Epidemiol. 2017 Dec 6. doi: 10.1093/ije/dyx240. [Epub ahead of print]

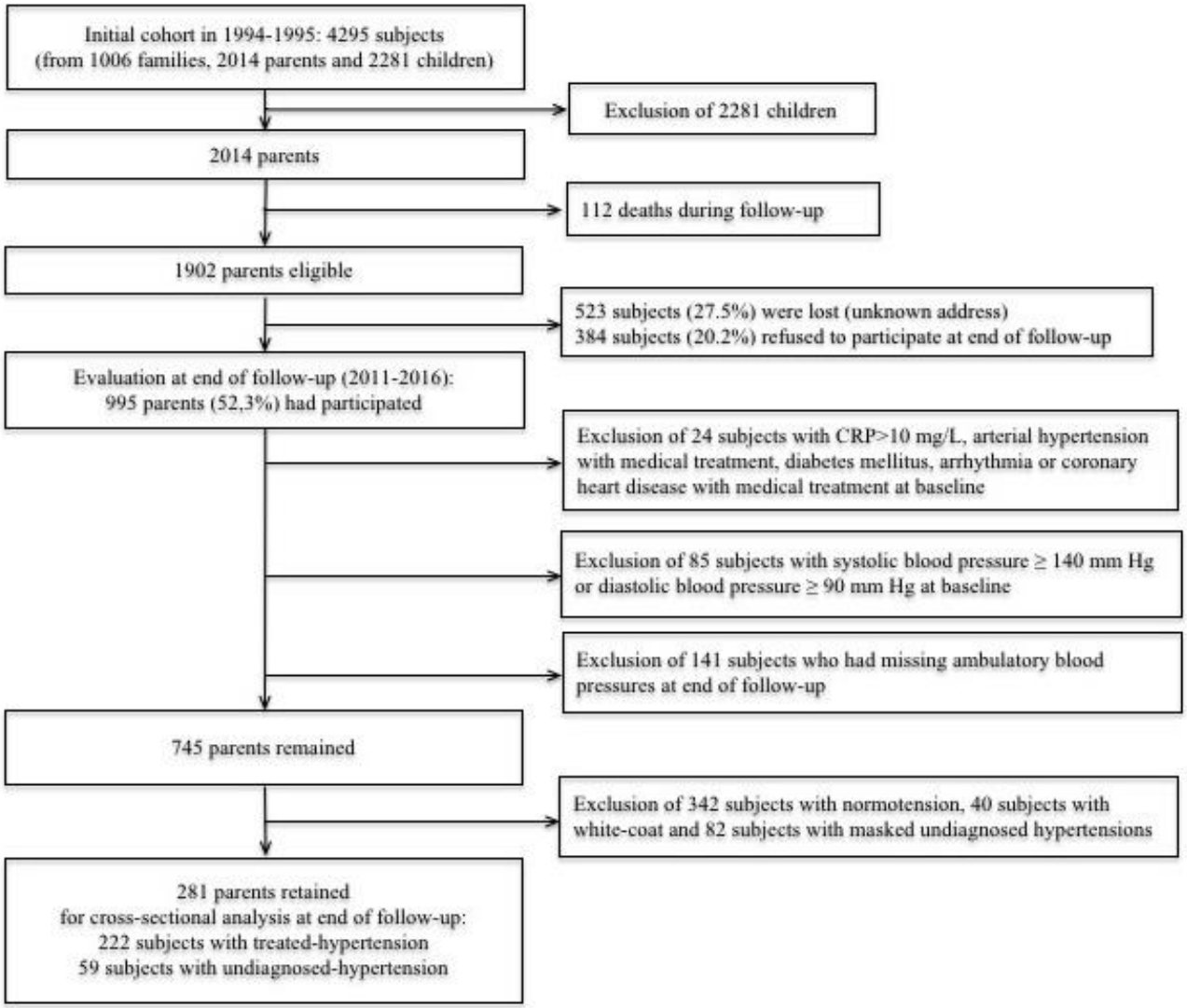

Figure S1. Flow chart of study participants (2011-2016)

Table S1. Comparison between participants and non-participants according to their features at cohort baseline (n=2014) (2011-2016)

	Non-participants (n=1,019) % or mean (SD)	Participants (n=995) % or mean (SD)
Age, year	41.0 (5.2)	41.9 (4.8)
Men (vs. women)	50.2	49.7
Educational level		
University	21.4	31.3
Middle and high school	45.9	48.2
Primary school	32.7	20.5
Smoking status		
Never	47.1	53.8
Former	22.6	25.9
Current	34.3	20.3
Anthropometric and metabolic measurements		
Body mass index[a], kg/m^2	25.0 (3.9)	24.4 (3.7)
Waist circumference, cm	82.8 (11.4)	81.3 (11.2)
Systolic blood pressure, mmHg	124.5 (13.8)	122.5 (12.2)
Diastolic blood pressure, mmHg	75.8 (10.3)	74.6 (9.9)
Pulse pressure, mmHg	48.6 (10.1)	47.9 (9.2)
Heart rate, bpm	67.3 (10.8)	65.9 (10.3)
Total cholesterol, mmol/L	5.81 (1.10)	5.74 (0.98)
Triglycerides, mmol/L	1.20 (1.14)	1.10 (0.98)
Blood glucose, mmol/L	5.12 (0.52)	5.06 (0.49)

Abbreviations: n, number of subjects; SD, standard deviation.
At cohort baseline, all subjects lived in couple and were healthy.
[a] Weight (kg)/height (m)^2.

Table S2. Comparison between subjects with measured and those with missing 24-h ambulatory blood pressures: % or mean (SD) (2011-2016)

	Subjects with measured ambulatory blood pressures (n=745)	Subjects with missing ambulatory blood pressures (n=141)	Chi^2 test or variance analysis (*P*-value)
Age, year	60.1 (4.5)	59.5 (4.4)	0.121
Men (vs. women)	47.9	48.2	0.947
Living alone	15.2	31.2	< 0.001
Educational level			< 0.001
University	23.5	18.4	
Middle and high school	61.1	50.4	
Primary school	15.4	31.2	
Health-related factors			
Alcohol consumption per week (unit or glass)	9.3 (13.3)	9.0 (13.3)	0.787
Current or ex-smoker (vs. non-smokers)	56.5	60.3	0.406
No regular sports/physical activity [a]	51.3	60.3	0.049
Perceived good health status [b]	75.2	60.3	< 0.001
No memory disorder [c]	83.5	75.9	0.030
No familial hypertension history	55.2	67.4	0.007
Number of GP consultations per year [d]	1.70 (0.80)	1.84 (0.88)	0.237
Perception of hypertension as a severe disease [e]	2.13 (0.55)	2.02 (0.69)	0.033
Anthropometric measurements			
Body mass index [f], kg/m^2	26.3 (4.3)	28.4 (5.7)	< 0.001
Waist circumference, cm	91.4 (12.7)	96.4 (15.4)	< 0.001
Office blood pressures and heart rate			
SBP, mmHg	128.1 (15.1)	129.1 (15.5)	0.517
DBP, mmHg	73.8 (8.4)	74.9 (9.8)	0.203
Pulse pressure, mmHg	54.2 (10.9)	54.1 (10.6)	0.915
Heart rate, bpm	61.8 (8.6)	63.4 (10.7)	0.061
Hypertension grade measured with office blood pressures			< 0.001
SBP<140 mmHg & DBP<90 mmHg	72.2	62.4	
SBP 140-159 mmHg or DBP 90-99 mmHg	19.1	18.4	
SBP 160-179 mmHg or DBP 100-109 mmHg	3.1	2.8	
SBP≥180 mmHg or DBP≥110 mmHg	0.7	16.3	

Abbreviations: SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure.

[a] Regular sports/physical activity was measured with the question “Do you regularly practice any sports or physical activity?” (response: no vs. yes) which was confirmed by questions regarding the beginning, the frequency, the level and the time spent for various sports and physical activities practiced.

[b] Perceived health status was assessed with the question “How satisfied are you with your health?” (good, very good or neither poor nor good vs. poor or very poor).

[c] Memory disorder was evaluated using the question “Do you have any memory trouble or difficulty?” (no vs. yes).

[d] In three categories: 3+ =1, 1-2=2, and 0=3.

[e] Quantitative variable with value between 1= non or rather non-severe, 2=severe, and 3= very severe.

[f] Weight (kg)/height^2 (m^2).

Annexe B : Abstracts des présentations orales et affichées

Communications orales et affichées dans les congrès, présentées dans l'ordre chronologique :

1. **Kénora Chau**, Nicolas Girerd, Patrick Rossignol, Zohra Lamiral, Erwan Bozec, Ludovic Merckle, Jean-Pierre Després, Faiez Zannad, Jean-Marc Boivin. Metabolic and inflammatory features associated with long-term risk for developing diastolic dysfunction in initially healthy population. 20e Congrès de la Société Française de Pharmacologie et Thérapeutique (SFTP), Nancy, 19-21 avril 2016. Présentation affichée.

2. **Kénora Chau**, Nicolas Girerd, Faiez Zannad, Patrick Rossignol, Jean-Marc Boivin. Risque d'hypertension artérielle non-diagnostiquée et place du médecin généraliste : étude prospective chez des adultes initialement en bonne santé. Congrès annuel CNGE (Collège National des Généralistes Enseignants), Grenoble, 23-25 novembre 2016. Présentation affichée.

3. **Kénora Chau**, Nicolas Girerd, Faiez Zannad, Jean-Marc Boivin, Patrick Rossignol. Quels sont les facteurs de risque cardiovasculaires permettant de distinguer les hypertendus blouse blanche des vrais hypertendus en primo-diagnostic d'hypertension : étude en population générale. Congrès CMGF (Congrès Médecine Générale France), Paris, 30 mars-1er avril 2017. Présentation orale.

4. **Kénora Chau**, Nicolas Girerd, Faiez Zannad, Jean-Marc Boivin, Patrick Rossignol. Fort gradient d'âge pour l'accès au primo-diagnostic d'hypertension et facteurs associés en population générale. Congrès CMGF (Congrès Médecine Générale France), Paris, 30 mars-1er avril 2017. Présentation affichée.

5. **Kénora Chau**, Nicolas Girerd, Faiez Zannad, Jean-Marc Boivin, Patrick Rossignol. Better monitoring of long-term hypertension risk and potential predictors in initially healthy midlife adults: a population-based cohort study. 27th European Meeting on Hypertension and Cardiovascular Protection, Milan, 16-19 June 2017. Présentation orale.

6. **Kénora Chau**, Nicolas Girerd, Faiez Zannad, Jean-Marc Boivin, Patrick Rossignol. Strong association between low education and uncontrolled hypertension: a population-based study. 27th European Meeting on Hypertension and Cardiovascular Protection, Milan, 16-19 June 2017. Présentation affichée.

7. **Kénora Chau**, Nicolas Girerd, Erwan Bozec, Zohra Lamiral, Ludovic Merckle, Faiez Zannad, Jean-Marc Boivin, Patrick Rossignol. Association between Abdominal Obesity and 20-year Subsequent Aortic Stiffness in Initially Healthy People: a Population-based Cohort study. 27th European Meeting on Hypertension and Cardiovascular Protection, Milan, 16-19 June 2017. Présentation affichée.

8. **Kénora Chau**, Nicolas Girerd, Faiez Zannad, Jean-Marc Boivin and Patrick Rossignol. Prédicteurs potentiels d'hypertension à long terme chez des adultes d'âge moyen en bonne santé : étude de cohorte. Société Française d'Hypertension Artérielle, Paris, 14-15 décembre 2017. Présentation orale.

9. **Kénora Chau**, Nicolas Girerd, Damien Gonthier, Faiez Zannad, Patrick Rossignol and Jean-Marc Boivin. Forte association entre faible niveau d'étude et hypertension artérielle non contrôlée : étude en population générale. Société Française d'Hypertension Artérielle, Paris, 14-15 décembre 2017. Présentation orale

20e Congrès de la Société Française de Pharmacologie et Thérapeutique (SFTP)
Nancy, 19-21 avril 2016
(Communication affichée, #00279)

Metabolic and inflammatory features associated with long-term risk for developing diastolic dysfunction in initially healthy population

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Abstract

Introduction: Diastolic dysfunction (DD) is common and predicts heart failure morbidity and mortality[1]. Given the scarcity of population-based cohorts with long-term follow-up and echocardiographic data, metabolic determinants of DD at an early stage of the disease are poorly known. The present study aimed to determine which features of metabolic syndrome and inflammation predict subsequent long-term DD in initially healthy adults.

Material and methods: We prospectively analyzed the association between metabolic features and DD in 564 initially healthy adults aged 30-59 from eastern France enrolled in the Stanislas population-based Cohort. Clinical and biological cardiovascular risk features were collected at baseline (1994-1995). DD was assessed twenty years later (2011-2014) by echocardiography using current international guidelines[2]. The data were analyzed using variance analysis, chi-square tests, multinomial or binomial logistic regression model. In these models, for continuous variables, odds ratios were estimated for each 1-standard-deviation (SD) increase.

Results: In total, 155 subjects (27.5%) developed DD. In age-sex-adjusted logistic models, significant predictors of DD were body mass index (odds ratio for 1-SD increase OR=1.31, 95%CI=1.08-1.60) and waist-to-height-ratio (WHtR, 1.41, 1.15-1.74). Were close to significance: systolic blood pressure (SBP, 1.20, 0.97-1.48), diastolic blood pressure (1.20, 0.98-1.47) and triglycerides (TG, 1.19, 0.97-1.45). Of particular significance, subjects with elevated WHtR (>80th percentile) and TG or with a lesser degree CRP (>median value) were at a higher risk of developing DD (OR=2.77, 95%CI=1.57-4.90, P<0.001 and OR=1.89, 95%CI=1.06-3.36, P=0.03).

Discussion / Conclusion: In conclusion, subjects with elevated WHtR combined with increased TG or elevated blood pressures without hypertension are at higher risk for developing long-term DD. Prevention targeting visceral obesity and its related inflammation may help reduce the incidence of DD and subsequent heart failure.

References:

1. Achong N, Wahi S, Marwick TH. Evolution and outcome of diastolic dysfunction. Heart. 2009;95:813−818.
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Grenoble, 23-25 novembre 2016

Présentation affichée

Risque d'hypertension artérielle non-diagnostiquée et place du médecin généraliste : étude prospective chez des adultes initialement en bonne santé

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Résumé

Contexte et objectifs : Beaucoup de sujets ont une hypertension artérielle (HTA) non-diagnostiquée. Cette étude examine si ces sujets ont un grade d'hypertension similaire aux sujets traités et s'ils ont déjà des valeurs augmentées de pressions artérielles systoliques (PAS), diastoliques (PAD) et de triglycéridémie (TG) et plus d'insatisfaction des conseils du médecin généraliste (MG).

Méthodes : Chez 627 adultes en bonne santé, âgés de 30 à 59 ans (cohorte Stanislas), ont été recueillies des facteurs sociodémographiques, cliniques et biologiques en 1994 puis 20 ans plus tard, la satisfaction des conseils du MG et l'HTA (antécédent d'HTA, traitement antihypertenseur, MAPA) en 4 catégories : sans HTA ni traitement (G0), HTA équilibrée sous traitement (G1), HTA persistante sous traitement (G2) et HTA non-diagnostiquée (G3). Les données ont été analysées avec le modèle de régression logistique.

Résultats : A la fin du suivi, G0, G1, G2 et G3 comprenaient respectivement 53,6, 16,0, 9,2 et 20,4 % des sujets. G2 et G3 avaient un profil similaire selon le grade d'HTA (respectivement 32,0 et 39,7 % un grade 1 ; 7,0 et 6,9 % un grade 2). Par rapport à G0, seul G3 était associé significativement à l'insatisfaction des conseils du MG (OR ajusté sur sexe, âge, niveau d'étude et catégorie socioprofessionnelle ORa=1,94, $p<0,05$). Par rapport à G0, les groupes G1, G2 et G3 étaient significativement associés avec PAS (ORa 2,23, 2,28 et 1,73 respectivement), PAD (1,43, 2,03 et 1,76 respectivement) et TG (1,58, 1,77, 1,31 respectivement).

Conclusion : Après 20 ans de suivi, environ la moitié des sujets hypertendus ne sont pas diagnostiqués. L'insatisfaction des conseils du MG et une corpulence plutôt normale initialement seraient associées au manque de dépistage de l'HTA malgré des PAS, PAD et TG précocement plus élevés (en restant normaux).

Congrès CMGF (Congrès Médecine Générale France)
Paris, 30 mars-1er avril 2017
Présentation orale

Quels sont les facteurs de risque cardiovasculaires permettant de distinguer les hypertendus blouse blanche des vrais hypertendus en primo-diagnostic d'hypertension : étude en population générale

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Résumé

Objectifs : L'hypertension blouse blanche (HTNbb) serait liée au sexe, à l'âge, à l'anxiété et à l'obésité du patient. Elle demeure incomplètement élucidée. Ce travail identifiait les facteurs expliquant le phénomène en population générale.

Méthode : La population étudiée comprenait 1178 sujets (45,7 % d'hommes, âge moyen 50±13 ans, étendue 25−88 ans) qui avaient des mesures casuelles de pressions artérielles (CPA) et ambulatoires (MAPA 24 heures), mesures anthropométriques et métaboliques, PCR, anxiété, consommation d'alcool, statut tabagique et état de santé perçu. L'analyse ciblait les sujets sans hypertension connue ou traitée (119 sujets). Elle comparait 46 sujets ayant une HTNbb (CPA+MAPA−) aux 73 sujets ayant CPA+MAPA+. Les données sont analysées par les modèles de régression logistique et l'analyse discriminante linéaire multiple.

Résultats obtenus : Comparé au groupe CPA+MAPA+, celui HTNbb comprenait significativement plus de femmes (50 contre 29 %), moins de fumeurs/ex-fumeurs (41 contre 63 %), plus d'anxiété (56 contre 38 %), avait une pression artérielle diastolique moins élevée (moyenne=79,5±6,3 contre 84,6±7,3 mmHg) et consommait moins d'alcool. La différence est proche de la signification pour la pression artérielle systolique (146,5±6,3 contre 148,7±9,0 mmHg, p=0,089) et LDL (3,88±0,92 contre 3,59±0.89, p=0.092). L'analyse discriminante montrait que l'anxiété seule expliquait peu l'effet blouse blanche (bien-classés 60 %), guère mieux en ajoutant le sexe (63 %), nettement mieux en ajoutant les autres facteurs précédents (74 %, sauf le tabagisme), et plus encore (atteignant un maximum de 78 %) en ajoutant l'IMC, périmètre abdominal, fréquence cardiaque, HDL, triglycéridémie, glycémie (alors que ces derniers facteurs ne différenciaient pas significativement les deux groupes, p>0.25). La réplication de l'analyse, sur les sujets hypertendus connus ou traités, donnait des résultats assez similaires avec un pourcentage de bien-classés de 72 %.

Conclusion : HTNbb serait souvent repérable par des facteurs anthropométriques, métaboliques et personnels, facilitant la décision sur la prise en charge d'hypertension.

Mots clés : Hypertension blouse blanche, déterminants, sexe, anthropométrie, facteurs métaboliques, anxiété, consommation d'alcool.

Congrès CMGF (Congrès Médecine Générale France)
Paris, 30 mars-1er avril 2017

Présentation affichée

Fort gradient d'âge pour l'accès au primo-diagnostic d'hypertension et facteurs associés en population générale

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Résumé

Objectifs. La précocité du primo-diagnostic d'hypertension (HTA) est importante pour sa prise en charge et prévenir ses conséquences. Cette étude examinait si l'hypertension non-diagnostiquée (ndHTA) différait entre les groupes d'âge 24-39, 40-59 et 60+ ans.

Méthode. Parmi les 1178 participants d'une cohorte populationnelle au dernier examen clinique et biologique (25-88 ans), 309 sujets avaient une hypertension traitée et/ou définie à la fois par les mesures casuelles et ambulatoires de pressions artérielles au-dessus des seuils (>140/90 et >130/80 mmHg, respectivement), et 73 sujets avaient une ndHTA. Les relations médecin généraliste/patient ont été aussi recueillies. Les données ont été analysées avec les modèles de régression logistique.

Résultats. La fréquence de ndHTA était respectivement de 17,7, 24,6 et 50,0 % chez les sujets de 60+, 40-59 et 24-39 ans (p=0.002). Comparés aux sujets de 60+ ans, ceux de 40-59 et 24-39 ans avaient un odds ratio ajusté sur le sexe (OR) de 2,21 (IC 95 %=1,19-4,10, p<0.01) et 6,16 (IC 95 %=2,42-15,7, p<0.001). Le risque variait peu en prenant en compte l'éducation, la consommation d'alcool, le statut tabagique, l'anxiété et l'état de santé (OR 2,42 et 6,41). L'insatisfaction des conseils du MG sur les facteurs de risque cardiovasculaires et la non-adhérence aux prescriptions expliquaient peu le risque chez les sujets de 40-59 ans (7 %) mais partiellement chez ceux de 24-39 ans (30 %). La perception de l'hypertension comme une maladie grave n'avait aucun rôle (<1 %). Le risque était majoré de 50 % en tenant compte des mesures casuelles de pressions artérielles (OR de 2,86 et 8,83). Il était peu expliqué par : indice de masse corporelle, périmètre abdominal, HDL, LDL, triglycéridémie, glycémie et PCR (<8 % pour les deux groupes d'âge).

Conclusion. Le primo-diagnostic d'HTA doit être amélioré surtout chez les plus jeunes. Son absence est expliquée partiellement par l'insatisfaction des conseils du médecin généraliste et la non-adhérence aux prescriptions chez les sujets de <40 ans.

Mots clés : Hypertension, primo-diagnostic, facteurs de risque, gradient d'âge, médecine générale.

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Topic: Cardiovascular Risk Factors
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Better monitoring of long-term hypertension risk and potential predictors in initially healthy midlife adults: a population-based cohort study

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Abstract

Objective. The risk of hypertension and their modifiable risk factors should be early monitored. We studied whether alcohol consumption, smoking status, general and central adiposity, office systolic and diastolic blood pressures, hear rate, metabolic features and inflammatory indicator in initially healthy midlife adults could predict 20-year subsequent hypertensive status.

Methods. The sample included 738 initially healthy adults, aged 30-60, in France enrolled in a population-based cohort. Clinical and biological cardiovascular risk features were collected at baseline (1994-1995). At end of follow-up (2011-2016) office blood pressures (OBP) and 24-hour ambulatory blood pressures (ABPM) were measured. Among the participants, 344 subjects were free of hypertension (no hypertension history, both OBP<140/90 and ABPM<130/80 mmHg) and 277 subjects had hypertension (treated hypertension and/or both OBP≥140/90 and ABPM≥130/80 mmHg). Data were analyzed using logistic regression models and predictive logistic discriminant analysis.

Results. Logistic regression models shows that significant baseline predictors of hypertension at end of follow-up included: age (sex-age-education-adjusted odds ratio 1.05, P<0.01), female sex (0.55, P<0.001), body mass index (1.49 for 1SD, P<0.001), waist circumference (1.95 for 1SD, P<0.001), office systolic blood pressure (2.23 for 1SD, P<0.001), diastolic blood pressure (1.77 for 1SD, P<0.001), hear rate (1.30 for 1SD, P=0.003), high density lipoprotein cholesterol (0.73 for 1SD, P<0.001), triglycerides (1.69 for 1SD, P<0.001) and C-reactive protein (1.20 for 1SD, P=0.04). Were close to significance (P<0.10) low education (primary school) and low-density lipoprotein cholesterol. Smoking status, alcohol consumption, total cholesterol and blood glucose were not significant. Discriminant analysis shows that the subjects with hypertension and those with no hypertension were slightly differentiated by sex, age, educational level, alcohol consumption and smoking status (correctly classified 59.4%), but highly by adding adiposity, systolic and diastolic blood pressures, heart rate, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, blood glucose and C-reactive protein (71.1%).

Conclusions. Clinical and biological cardiovascular risk features highly predict long-term hypertension. They are generally modifiable and may be used to better and early monitor the long-term hypertension risk.

Keywords: Hypertension, risk factors, population-based cohort, adiposity, metabolic factors.

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Présentation affichée

Strong association between low education and uncontrolled hypertension: a population-based study

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Abstract

Objective. Uncontrolled hypertension affects 40 to 50% of French hypertensive patients. Most studies have focused on treatments. Low education is associated with poor living conditions, nutrition, health perception and cardiovascular diseases. This study sought to examine whether low education was associated with uncontrolled hypertension.

Methods. Data were from a population-based cohort at last examination (2011-2016). Subjects' characteristics, low education (primary school vs higher education), clinical and biological measures, health problems, and office and 24-hour ambulatory blood pressures (BPs) were collected. Among the 738 adults involved (aged 49-81), 105 subjects had treated hypertension and controlled BPs (office BPs <140/90 and 24h ambulatory BPs <130/80 mmHg), and 43 subjects had a treated hypertension but uncontrolled BPs (both office BPs ≥140/90 and 24h ambulatory BPs ≥130/80 mmHg). We excluded the subjects with no history nor treated hypertension (whatever their office and ambulatory BPs) and those with treated hypertension and a white-coat or masked hypertension. Data were analyzed using logistic regression models.

Results. Low education was associated with uncontrolled hypertension: sex and age adjusted odds ratio 2.41 (95% CI 1.00−5.87, *P*=0.05). The association remained significant with further adjustment for body mass index and waist circumference (2.55, 95% CI 1.03−6.34, *P*=0.04); high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglyceride and blood glucose (2.85, 1.13−7.22, *P*=0.03); C-reactive protein (2.73, 1.10−6.78, *P*=0.03). The association remained significant with further adjustment for alcohol consumption, smoking status, poor health status, anxiousness, memory disorder and number of cardiovascular diseases/diabetes (2.72, 1.03−7.21, *P*=0.04); and also after adjustment for dissatisfaction with GP's counsels about cardiovascular risk factors, poor-adherence habit, perception of hypertension as a severe disease, and number of GP consultations per year (2.73, 1.05−7.11, *P*=0.04).

Conclusions. Low education is associated with an increased risk of uncontrolled hypertension. The risk is independent of anthropometric, metabolic, inflammatory, anxiousness, adherence to treatment, and health-related factors. Further research on the living conditions, nutrition, sports and physical activities, and treatments prescribed are needed.

Keywords: uncontrolled hypertension, low education, population-based study

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Association between Abdominal Obesity and 20-year Subsequent Aortic Stiffness in Initially Healthy People: a Population-based Cohort study

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Abstract

Objective. We examined whether central and general adiposity is an independent 20-year predictor of accelerated aortic stiffening in initially healthy midlife people.

Methods. Stanislas cohort study participants (826 initially healthy people aged 30-60 from eastern France) underwent clinical and biological measurements at baseline (1994-1995). General adiposity was measured by body mass index (BMI), central adiposity by waist circumference (WC), "a body shape index" (ABSI= WC/(BMI$^{2/3}$ Height$^{1/2}$)) and waist-circumference-to-body-mass-index-ratio (WC-to-BMI-ratio). At the end of the 20-year follow-up (2011-2016), the pulse wave velocity (Real cfPWV) was measured. Data were analyzed using multiple linear regression models

Results. In linear regression models adjusted for sex, age and mean arterial pressure, the WC-to-BMI-ratio was positively associated (for 1-standard-deviation increase) with a 0.32 m/s increase in cfPWV (regression coefficient 0.32, 95% confidence interval: 0.19−0.45, P<0.001). The cfPWV was less strongly associated with ABSI (0.17, 0.022−0.32, P<0.05). It was also less strongly and negatively associated with BMI and WC. The WC-to-BMI-ratio was the only significant anthropometric risk factor when all BMI, WC and ABSI were also included in the regression model. Sensitivity analysis shows that the risk of cfPWV associated with WC-to-BMI-ratio remained highly significant after further adjustment for heart rate, metabolic risk factors and inflammatory marker.

Conclusions. Central adiposity is a robust predictor of 20-year subsequent aortic stiffness in initially healthy midlife people. The WC-to-BMI-ratio may be proposed to study cfPWV as a simple additional indicator to distinguish general and central adiposity in midlife healthy people.

Keywords: aortic stiffness; initially healthy adults; obesity; cohort study.

Dysfonction diastolique, rigidité artérielle aortique et hypertension : facteurs anthropométriques et métaboliques associes et prise en charge en population générale

Résumé

L'augmentation de l'obésité durant les dernières décennies expose la population à un risque accru de problèmes métaboliques et des maladies cardiovasculaires. Ce travail étudiait, d'une part, l'association de l'obésité avec la dysfonction diastolique et la rigidité artérielle aortique vingt ans plus tard chez des adultes initialement en bonne santé. Cette étude montrait que l'obésité générale mesurée par l'indice de masse corporelle et l'adiposité abdominale mesurée par le tour de taille étaient associées positivement à la dysfonction diastolique. Mais elles semblaient jouer un rôle protecteur sur la rigidité artérielle. Le ratio "tour de taille/indice de masse corporelle" semblait mieux isoler l'adiposité abdominale/viscérale de l'obésité générale, et était associé positivement à la rigidité artérielle. Il permettrait de montrer un rôle néfaste à long terme de l'adiposité abdominale/viscérale sur la rigidité artérielle même quand le poids est normal. La présence combinée de l'obésité abdominale (mesurée par le tour de taille) et d'un taux plus élevé de triglycérides était associée à un risque élevé de dysfonction diastolique. Dans la deuxième partie, nous nous sommes intéressés aux individus ayant déjà une hypertension artérielle. Ce travail montrait que, parmi les sujets ayant une hypertension, ceux ayant une hypertension non-diagnostiquée avaient un profil spécifique (plus souvent de sexe masculin, un tour de taille moins élevé, et moins souvent de maladies cardiovasculaires/diabète, antécédents familiaux d'hypertension et consultations de soins primaires moins fréquents). La présence concomitante d'un nombre élevé de ces critères renforçait fortement l'absence de primo-diagnostic. Nos résultats peuvent aider dans l'identification précoce des sujets à risque, la prévention et le management thérapeutique.

Mots clés : Dysfonction diastolique, rigidité artérielle, hypertension artérielle, obésité, facteurs métaboliques

Abstract

Worldwide increasing obesity over the last decades expose the population to an increased risk of metabolic perturbations and cardiovascular diseases. This research investigated first the association of obesity with diastolic dysfunction and aortic stiffness observed 20 years later in initially healthy adults. General obesity measured with body mass index and abdominal adiposity measured with waist circumference were positively associated with diastolic dysfunction. But, these anthropometric parameters played a protective role in aortic stiffness. The ratio "waist circumference / body mass index" appeared to better isolate abdominal adiposity from general obesity and was then positively associated with aortic stiffness. It allowed to evidence a harmful role of abdominal adiposity in aortic stiffness, even in subjects with normal body weight. The presence of abdominal adiposity (measured with waist circumference) combined with an elevated level of triglycerides was associated with a higher risk of diastolic dysfunction. In the second part, our research focused on hypertensive indifviduals. It showed that among hypertensive subjects, those having undiagnosed-hypertension had specific features (being more often male, having less elevated waist circumference, and having fewer cardiovascular diseases/diabetes, familial hypertension history, and primary care uses). The concomitant presence of a higher number of these criteria appeared to strongly reinforce the absence of diagnosis. Our findings may help to early identify subjects at risk, and to establish prevention and therapeutic management.

Keywords: Diastolic dysfunction, aortic stiffness, hypertension, obesity, metabolic factors