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Ainara Muñoz Cabrejas

Relación de los patrones de consumo de hidratos de carbono y bebidas, con el síndrome metabólico y la enfermedad cardiovascular subclínica

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Autor

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Que la Tesis Doctoral titulada "Relación de los patrones de consumo de hidratos de carbono y bebidas, con el síndrome metabólico y la enfermedad cardiovascular subclínica" que presenta Dña. AINARA MUÑOZ CABREJAS al superior juicio del Tribunal que designe la Universidad de Zaragoza, ha sido realizada bajo mi dirección durante los años 2019-2024, siendo expresión de la capacidad técnica e interpretativa de su autor en condiciones tan aventajadas que le hacen merecedor del Título de Doctor, siempre y cuando así lo considere el citado Tribunal.

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Contenido general

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Tesis Doctoral en modalidad por compendio de publicaciones

La Tesis Doctoral que se presenta titulada "Relación de los patrones de consumo de hidratos de carbono y bebidas, con el síndrome metabólico y la enfermedad cardiovascular subclínica" se ajusta a la normativa vigente en la actualidad en la Universidad de Zaragoza, según Extracto del Acuerdo de 25/06/2020 del Consejo de Gobierno de la Universidad de Zaragoza por el que se aprueba el Reglamento sobre Tesis Doctorales (Título IV, Capítulo III), en cuanto a la modalidad denominada como compendio de publicaciones. La Tesis Doctoral cumple con los requisitos solicitados para las publicaciones en cuanto al lugar del doctorando en los artículos, el factor de impacto de la revista, y el tipo de indexación en el Journal Citation Report (JCR) de la Web of Science. Los estudios se han publicado en revistas relacionadas con las ciencias de la salud y medicina, centrándose en el perfil temático de nutrición y hábitos dietéticos asociados con la aparición de enfermedades cardiometabólicas.

A continuación, se relacionan los cuatro artículos publicados que componen la presente Tesis Doctoral:

1. **Muñoz-Cabrejas A**, Guallar-Castillón P, Laclaustra M, Sandoval-Insausti H, Moreno-Franco B. Association between Sugar-Sweetened Beverage Consumption and the Risk of the Metabolic Syndrome: A Systematic Review and Meta-Analysis. Nutrients. 2023 Jan 13;15(2):430. doi: 10.3390/nu15020430. PMID: 36678301.

2. **Muñoz-Cabrejas A**, Laclaustra M, Guallar-Castillón P, Casasnovas JA, Jarauta E, Sandoval-Insausti H, Donat-Vargas C, Moreno-Franco B. High-quality intake of carbohydrates is associated with lower prevalence of subclinical atherosclerosis in femoral arteries: The AWHS study. Clin Nutr. 2021 Jun;40(6):3883-3889. doi: 10.1016/j.clnu.2021.04.049. Epub 2021 May 14. PMID: 34134004.

3. **Muñoz-Cabrejas A**, Laclaustra M, Guallar-Castillón P, Sánchez-Recio R, Jarauta E, Casasnovas JA, Moreno-Franco B. Association of beverage consumption with subclinical atherosclerosis in a Spanish working population. Sci Rep. 2023 Apr 20;13(1):6509. doi: 10.1038/s41598-023-33456-w. PMID: 37081095.

4. **Muñoz-Cabrejas A,** Laclaustra M, Guallar-Castillón P, Casasnovas JA, Marco-Benedí V, Calvo-Galiano N, Moreno-Franco B. Low-quality carbohydrate intake is associated with a higher prevalence of metabolic syndrome: The AWHS Study. J Clin Endocrinol Metab. 2023 Dec 23:dgad706. doi: 10.1210/clinem/dgad706. PMID: 38141071.

Proyectos y contratos de investigación

La Tesis Doctoral que se presenta a continuación, así como la mayoría de los artículos que la conforman, se enmarcan en el proyecto de investigación Aragon Workers' Health Study (AWHS). Su realización se debe al convenio de colaboración entre la Comunidad Autónoma de Aragón, a través del Instituto Aragonés de Ciencias de la Salud (IACS) del Gobierno de Aragón, y la Fundación Centro Nacional de Investigaciones Cardiovasculares (CNIC) del Instituto de Salud Carlos III (ISCIII) del Ministerio de Ciencia e Innovación, junto a la colaboración entre General Motors España S.L. (GME) y la Comunidad Autónoma de Aragón (BOA Nº 198, 26 de noviembre de 2008).

Estancia de investigación

A lo largo del periodo de realización de la presente Tesis Doctoral, la doctoranda Dña. Ainara Muñoz Cabrejas realizó una estancia de investigación en la Unidad de Lípidos del Hospital Universitario Miguel Servet (Zaragoza, España).

Supervisor: Prof. Fernando Civeira Murillo. Duración: 1 mes (10/11/2022 – 10/12/2022). Temática de la estancia: Trastornos del metabolismo de los lípidos.

Listado de abreviaturas

AWHS	Aragon Workers' Health Study
CEICA	Clinical Research Ethics Committee of Aragon
CFCA	Cuestionario de frecuencia de consumo de alimentos
cHDL	Lipoproteínas de alta densidad
cLDL	Lipoproteínas de baja densidad
CQI	Índice de calidad de carbohidratos
HR	Hazard Ratio
IC 95%	Intervalo de confianza del 95%
IMC	Índice de Masa Corporal
METs	Metabolic Equivalents
NCEP- ATP III	National Cholesterol Education Programme - Adult Treatment Panel III
OR	Odds Ratio
RR	Riesgo Relativo
SD	Desviación estándar
SM	Síndrome metabólico

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Resumen general

Ante la creciente prevalencia de aterosclerosis subclínica y síndrome metabólico, es fundamental profundizar en la comprensión de la relación entre la alimentación, centrándonos en los hidratos de carbono y las bebidas azucaradas, y su influencia en la aparición y progresión de estas patologías. Un enfoque integral permitirá desarrollar estrategias efectivas preventivas y de tratamiento, con objeto de reducir la carga global de enfermedades cardiovasculares y mejorar la calidad de vida de la población.

Por tanto, el objetivo general de la presente Tesis doctoral es analizar la importancia de los hábitos nutricionales de la población adulta, en concreto la calidad de los carbohidratos consumidos y la ingesta de diferentes bebidas, y su relación con la probabilidad de presentar enfermedades cardiovasculares y metabólicas, concretamente aterosclerosis subclínica y síndrome metabólico.

La presente Tesis doctoral está compuesta por 4 artículos científicos, siendo uno de ellos de tipo metaanálisis, y siendo los otros 3 restantes estudios originales derivados del proyecto AWHS.

El metaanálisis de estudios observacionales se elaboró siguiendo las directrices PRISMA. Se realizaron búsquedas en las bases de datos PubMed y SCOPUS de estudios publicados hasta junio de 2022 que evaluaran la asociación entre el consumo de SSB (incluidos refrescos, zumos de fruta embotellados, bebidas energéticas y batidos) y la aparición de la MetS.

Por otro lado, el estudio de cohortes prospectivo AWHS consta de una muestra de 5678 participantes a las que se les evalúan periódicamente diferentes determinantes del estilo de vida (actividad física, sedentarismo, alimentación, etc.), diferentes marcadores de aterosclerosis y salud cardiovascular, y diferentes parámetros bioquímicos. A partir de ellos podemos obtener la prevalencia de diferentes enfermedades cardiometabólicas, y el grado de exposición a diferentes factores de riesgo a nivel comportamental, como en concreto en el caso de la dieta.

Entre los varones de mediana edad, una mayor adherencia a una dieta rica en hidratos de carbono de alta calidad se asocia con una menor prevalencia de aterosclerosis subclínica de la arteria femoral en comparación con un consumo inferior, además de una menor prevalencia de SM (siendo la hipertrigliceridemia el componente del SM que más contribuye a la reducción del riesgo). Estos resultados indican una relación precoz entre la calidad de los hidratos de carbono y el desarrollo de ECV y SM.

Por otro lado, el consumo de café, así como la leche entera se asocia perjudicialmente con la presencia de aterosclerosis subclínica. Además, la leche baja en grasa y el zumo de fruta presenta una asociación protectora para aterosclerosis subclínica en territorio carotídeo y femoral, respectivamente. Así pues, nuestros resultados sugieren que evitar el consumo de café, y consumir en su lugar leche baja en grasa o agua son opciones que no están relacionadas con resultados negativos y que podrían reducir el riesgo de aterosclerosis subclínica.

Por último, mayor consumo de SSB se asocia positivamente con la aparición de MetS. Los resultados de los estudios transversales muestran que los adultos en la categoría más alta de consumo tenían un 35% más de riesgo de padecer el SM en comparación con los de la categoría más baja de consumo. El resultado correspondiente de los estudios longitudinales fue un 18% más de riesgo de incidencia de SM.

Todas las evidencias presentes justifican la importancia del cambio de paradigma en cuanto a la alimentación, más allá del beneficio de la dieta mediterránea. La calidad de los componentes de la dieta, especialmente en el grupo más consumido, ha demostrado impactar en el metabolismo y favorecer el desarrollo de múltiples patologías.

1

Introducción

1.1. La enfermedad cardiovascular

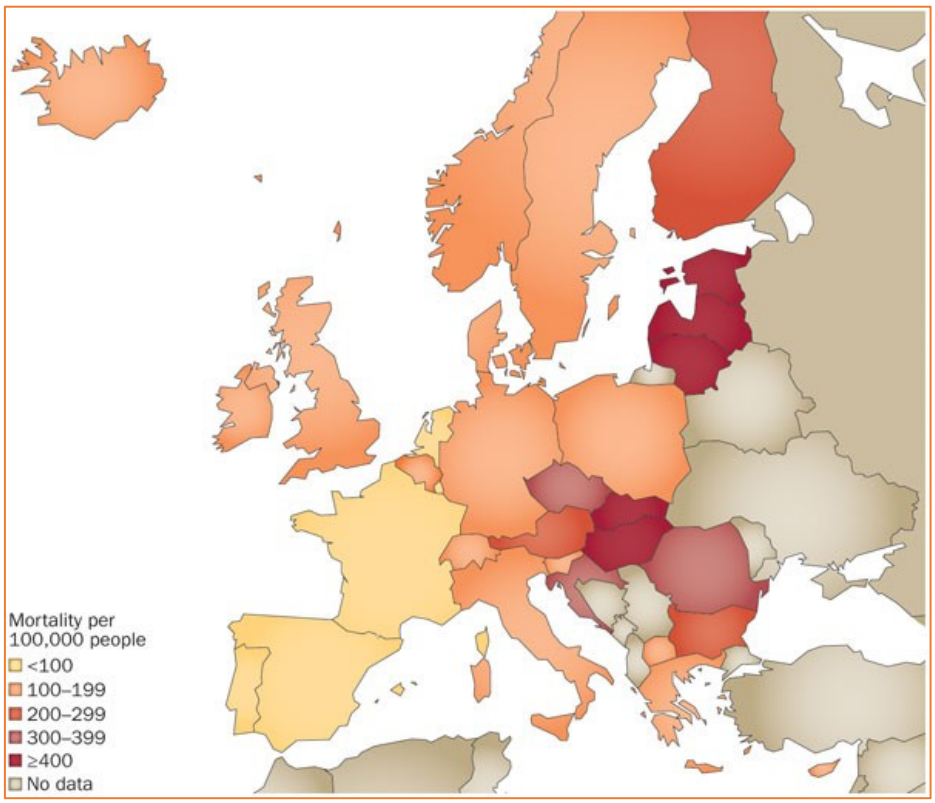
Las enfermedades no transmisibles, son enfermedades crónicas de larga duración, y a menudo de progresión lenta, que son responsables del 74% de los fallecimientos a nivel mundial. Las enfermedades cardiovasculares (ECV) suponen la mayoría de estas muertes (17,9 millones de personas cada año), seguidas del cáncer, las enfermedades respiratorias y la diabetes. La ECV provoca muchas muertes prematuras y produce una pérdida de años potenciales de vida de aproximadamente, como media, 11 años para los varones y 10 años para las mujeres (1).

La cardiopatía isquémica es la patología cardiovascular que causa mayor mortalidad mundial, siendo responsable de un 16% de los fallecimientos (2). En Europa más de 85 millones de personas conviven con alguna ECV. Además, en este continente se encuentra también a la cabeza de mortalidad, siendo la causante de casi 4 millones de muertes anuales (3). En España, según los últimos datos del Instituto Nacional de Estadística de 2021, las enfermedades del sistema circulatorio constituyen la primera causa de muerte, causando un 26,4% de los fallecimientos totales y una tasa de 251,8 fallecidos por cada 100.000 habitantes. Los varones padecen más enfermedad isquémica del corazón y las mujeres más enfermedad cerebrovascular. Por otra parte, la insuficiencia cardiaca es la tercera causa de mortalidad cardiovascular, y la principal causa de hospitalización en los mayores de 65 años (4).

En la comparación internacional, España tiene una de las tasas más bajas del mundo para enfermedad isquémica y está a un nivel intermedio para enfermedad cerebrovascular. Las bajas tasas de enfermedad, que también se observan en otros países mediterráneos, contrastan con la alta prevalencia de los factores de riesgo, como obesidad, hipertensión arterial, dislipemia o diabetes. Se ha hipotetizado acerca de los posibles factores protectores, habiéndose planteado la dieta mediterránea (rica en cereales integrales, fruta

y verdura, y legumbres), compuesta fundamentalmente por hidratos de carbono de alta calidad, como uno de los principales determinantes de este hecho (Figura 1) (5).

Figura 1: Mortalidad por enfermedad cardiovascular en Europa por cada 100.000 habitantes.



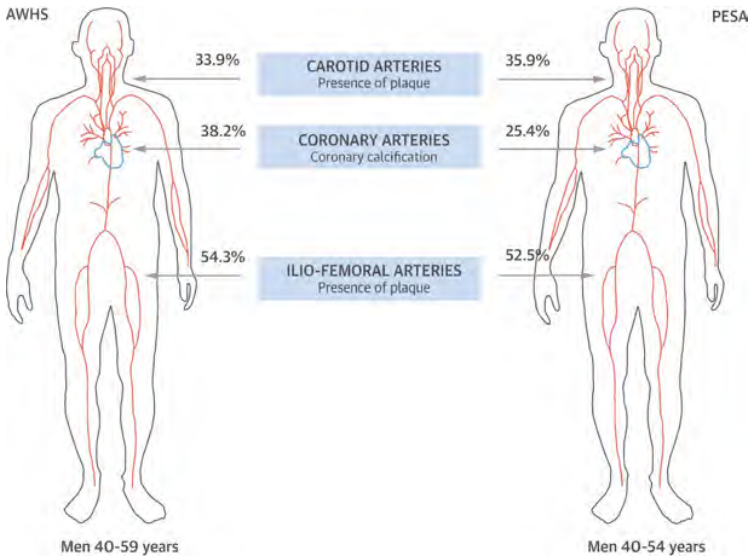
Fuente: La figura pertenece al artículo «Variation in ischaemic heart disease between EU countries»(5).

La aterosclerosis es un proceso inflamatorio que afecta a las paredes de las arterias de mediano y gran tamaño de todo el sistema cardiovascular (6,7). En el lumen de estas arterias se producen depósitos de material graso, restos celulares y colesterol procedente de las lipoproteínas de baja densidad (cLDL) en forma de placas. Estas placas ocasionan cambios en la superficie interna de los vasos sanguíneos, volviéndolos irregulares y estrechando su luz, estenosando los vasos y dificultando el flujo sanguíneo. Cuando el proceso continúa, se puede producir una fisura en el recubrimiento de las placas, que normalmente están bajo el endotelio del vaso, ocasionando la rotura de la placa y la liberación de los fragmentos acumulados a la luz del vaso. Estos fragmentos activan agentes trombogénicos circulantes, formando un trombo o coágulo. Si el trombo es lo

suficientemente grande puede obstruir de forma parcial o completa la luz del vaso. En concreto, si obstruye una arteria coronaria, puede provocar un infarto de miocardio, mientras que, si obstruye una arteria cerebral, puede causar un accidente cerebrovascular (7,8).

La aterosclerosis se desarrolla a lo largo de toda vida, apareciendo los primeros cambios fisiopatológicos en la infancia, generándose los primeros depósitos de materiales grasos y colesterol, y progresando lentamente hasta que se manifiestan como aterosclerosis clínica en la edad adulta (9). La progresión de la aterosclerosis ocurre de manera asintomática e inadvertida, salvo que se detecte a través de exámenes específicos, hasta que ocurre un evento clínico agudo (10,11). Durante el periodo en el que únicamente puede ser detectada mediante exámenes clínicos, sin generar eventos cardiovasculares, se denomina aterosclerosis subclínica. Entre los territorios que habitualmente se ven afectados de manera más temprana por la aterosclerosis subclínica, y donde se llevan a cabo las mediciones clínicas para la detección de la aterosclerosis subclínica, se encuentran las arterias carótidas, las arterias coronarias y las arterias femorales (12,13) (Figura 2).

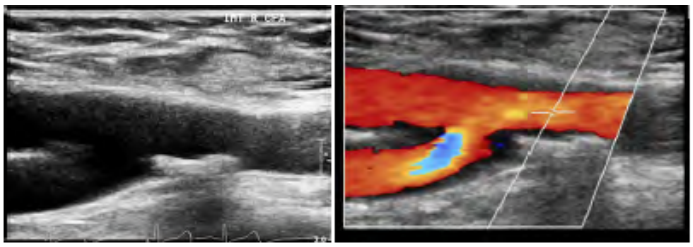
Figura 2: Prevalencia de aterosclerosis subclínica en diferentes territorios vasculares en participantes en los estudios AWHS y PESA



Fuente: La figura pertenece al artículo «Femoral and carotid subclinical atherosclerosis association with risk factors and coronary calcium. The AWHS study» (14). Licencia: 5264690941665 (Copyright Clearance licence number authorization).

Las exploraciones médicas en estos territorios permiten encontrar la enfermedad vascular antes de que cause síntomas, pudiendo tomar medidas preventivas (14). En concreto, las placas femorales son los indicadores ateroscleróticos periféricos más precoces y prevalentes, que pueden detectarse mediante técnicas no invasivas en la población de mediana edad (12,14). Además, han demostrado ser un potente marcador de lesiones coronarias, siendo la aterosclerosis subclínica femoral la que más se asocia con los factores de riesgo de ECV tradicionales (14) (Figura 3).

Figura 3: Imagen ecográfica de una placa aterosclerótica.



Fuente: Imagen obtenida a través del estudio AWHS.

1.2. Síndrome metabólico

El síndrome metabólico (SM) es un trastorno complejo y multifactorial que se caracteriza por la presencia de un conjunto de factores de riesgo cardiovascular y metabólico (15,16). Estos factores incluyen hipertensión arterial, dislipidemia aterogénica, obesidad abdominal, resistencia a la insulina y una elevación de la glucosa plasmática (17). El SM se ha convertido en un importante problema de salud pública a nivel mundial debido a su alta prevalencia y su asociación con un mayor riesgo de desarrollar ECV y diabetes tipo 2 (15–17). En concreto, los adultos que padecen SM, tienen el doble de riesgo de desarrollar ECV en los siguientes cinco a diez años, que los adultos que no lo padecen (18).

Por su carácter complejo, resulta complicado medir la prevalencia poblacional del SM. Por ello, diversos estudios epidemiológicos han tratado de estimar la prevalencia de SM en España. Por un lado, el estudio ENRICA, que englobó a 11.149 adultos, obtuvo una prevalencia del SM de del 22,7% (IC 95% 21,7-23,7) (19). Por otro lado, el estudio DARIOS, el cual incluyó datos individuales de 11 estudios, incluyendo a 24.670 individuos de 10 comunidades autónomas con edades entre los 35 y los 74 años, obtuvo

una prevalencia de SM del 31%, siendo del 29% (IC 95% 25-33%) en mujeres y del 32% (IC 95% 29-35%) en varones (20).

Dada la dificultad en la identificación y diagnóstico del SM, varias organizaciones han propuesto definiciones basadas en criterios sencillos para facilitar su diagnóstico. La primera definición fue formulada por un grupo de consulta de la Organización Mundial de la Salud (OMS) en 1998. Posteriormente, otros grupos como la International Diabetes Federation (IDF), National Cholesterol Education Program Adult Treatment Panel III (ATP III) y la American Association of Clinical Endocrinologists (AACE) han propuesto nuevos criterios diagnósticos o han modificado los componentes de la definición (21). El año 2009, un consenso de varias organizaciones líderes acordó mantener los criterios elaborados por la ATP III-2005, considerando la presencia de SM con al menos 3 de los 5 criterios siguientes: perímetro de cintura elevado (los puntos de corte varían en función de la región), glucemia en ayunas elevada (≥100 mg/dL o tratamiento antidiabético), tensión arterial elevada (tensión arterial sistólica ≥130 mmHg y/o tensión arterial diastólica ≥85 mmHg, o tratamiento antihipertensivo), triglicéridos séricos elevados (≥150 mg/dL o tratamiento para la hipertrigliceridemia), y colesterol de lipoproteínas de alta densidad (cHDL) sérico reducido (<40 mg/dL en varones y <50 mg/dL en mujeres) (18).

La hipertensión arterial y la dislipemia, características presentes en el síndrome metabólico, son además factores de riesgo importantes para las ECV. La tensión arterial elevada puede dañar los vasos sanguíneos y afectar el gasto cardíaco, aumentando el riesgo de eventos cardiovasculares (15). Por otro lado, la dislipemia implica desequilibrios en los niveles de lípidos en sangre, en concreto niveles elevados de triglicéridos, y una disminución del cHDL. Estos desequilibrios lipídicos contribuyen a su vez al desarrollo de aterosclerosis y aumentan el riesgo de la consecuente ECV (15,17).

El perímetro de cintura elevado, mayor de 102 cm en hombres y de 88 cm en mujeres, constituye la conocida obesidad central o abdominal (17). Este tipo de obesidad se caracteriza por una distribución de grasa en exceso alrededor de la cintura, asociándose con un mayor riesgo de enfermedades metabólicas. La acumulación de grasa en este área se asocia con la liberación de sustancias inflamatorias y hormonas que contribuyen a la resistencia a la insulina y la disfunción metabólica (22).

La resistencia a la insulina se produce cuando las células grasas, musculares y hepáticas no responden adecuadamente a la acción de la insulina, no pudiendo captar la glucosa en sangre (23). Como resultado, el páncreas aumenta su secreción de insulina para superar la débil respuesta de las células a la misma (24). Este mecanismo contrarregulador se produce para mantener la glucemia en un rango normal, pudiendo ser revertido mediante la pérdida de peso, actividad física y una buena alimentación. Sin embargo, cuando se mantiene una mala alimentación, esta hiperinsulinemia no es suficiente para hacer frente al exceso de glucosa plasmática, disparando las cifras de glucemia. Cuando las cifras de glucemia plasmática en ayunas están bastante elevadas y el páncreas no puede regular el mecanismo, se termina desarrollando diabetes mellitus tipo II (23,25).

El aumento de la incidencia del SM se ha atribuido al incremento de la obesidad, que a su vez se asocia a un estilo de vida sedentario (20) y a malos hábitos alimentarios (24,25). Su asociación con enfermedades cardiovasculares y diabetes mellitus tipo II lo han convertido en un tema de actuación prioritaria para las administraciones de salud. La comprensión de los mecanismos subyacentes y los enfoques terapéuticos dirigidos a abordar los diferentes componentes del síndrome metabólico son fundamentales para prevenir y tratar estas enfermedades de manera efectiva. Por lo tanto, los esfuerzos para prevenir el SM en el ámbito de la salud pública se han centrado en promover estilos de vida saludables, incluida una dieta sana (22,26).

1.3. Hábitos dietéticos

La obesidad, patología considerada la epidemia del siglo XXI por la OMS, puede conllevar patologías asociadas como la enfermedad coronaria, resistencia a la insulina y diabetes, hipertensión o dislipemia, suponiendo en la actualidad un problema de primera magnitud. El balance energético positivo, reflejado en el grado de adiposidad de un individuo es, seguramente, el factor dietético-conductual más importante en el desarrollo del riesgo de obesidad, y consecuentemente del desarrollo de patologías como el SM y la ECV (26–28). El efecto del sobrepeso y la obesidad sobre la ECV está mediado por ciertos marcadores como la hipertensión, la hiperglucemia, la reducción en los niveles de cHDL y el aumento del cLDL y colesterol total entre otros (26,27,29).

La evidencia científica ha puesto de manifiesto que la alimentación desempeña un papel fundamental en el desarrollo y progresión de estas enfermedades. Este impacto de la dieta puede ser estudiado, bien a través de nutrientes específicos, o a través del efecto de determinados alimentos o grupos de alimentos, o incluso mediante la evaluación de la adherencia a patrones dietéticos tradicionales.

Hidratos de carbono

En las últimas décadas, la occidentalización del estilo de vida ha llevado al abandono en la ingesta de determinados alimentos beneficiosos como frutas, verduras legumbres y cereales integrales, que ha derivado en un aumento en la prevalencia de patologías cardiometabólicas (30). En particular, el efecto del grupo de alimentos que abarca a los hidratos de carbono y las bebidas azucaradas han sido objeto de interés debido a su impacto en la salud cardiovascular, la aterosclerosis subclínica y el síndrome metabólico.

Los hidratos de carbono, especialmente los refinados y con alto índice glucémico, han sido asociados con un mayor riesgo de desarrollar patologías cardiovasculares, y en concreto, aterosclerosis subclínica (31). Estos carbohidratos pueden desencadenar respuestas inflamatorias, promover la acumulación de lípidos en las arterias y alterar el perfil lipídico, contribuyendo a la formación de placas ateroscleróticas.

Por otro lado, la aparición del síndrome metabólico está también estrechamente relacionado con la alimentación. La ingesta excesiva de hidratos de carbono, especialmente aquellos de rápida absorción y alto contenido glucémico, así como el consumo frecuente de bebidas azucaradas, se ha asociado con un mayor riesgo de desarrollar síndrome metabólico (32,33). El consumo excesivo de estos alimentos y bebidas pueden promover la obesidad abdominal, elevar la presión arterial, inducir dislipidemia y contribuir a la resistencia a la insulina.

Sin embargo, actualmente se considera que una dieta rica en hidratos de carbono es saludable y favorable. Este hecho se debe a la influencia que tiene la calidad de los carbohidratos consumidos, la cual parece ser más relevante que la cantidad consumida (34). La calidad de los hidratos de carbono es una entidad multidimensional que integra varios parámetros y, como tal, estos parámetros podrían actuar de forma sinérgica (34,35). Por ello, estudios recientes han evaluado la relación entre la calidad de los hidratos de

carbono y, tanto la ECV como el SM, mediante el estudio de indicadores aislados, principalmente la ingesta de fibra, el consumo de cereales integrales y el índice glucémico (IG) o la carga glucémica. Varios estudios han demostrado que el consumo de fibra dietética (36–38) y de cereales integrales (32,39,40) disminuyen el riesgo de ECV y SM, mientras que el consumo de cereales refinados y un IG elevado (41,42) se asociaban positivamente con los mismos.

En los últimos años, varios autores han evaluado la calidad global de los hidratos de carbono consumidos dentro de un patrón dietético mediante la elaboración de índice, denominado Índice de Calidad de los Hidratos de Carbono ("CQI", por sus siglas en inglés). La primera definición del CQI fue realizada por Zazpe et al. (43) y permitió a los científicos comparar participantes que contaban con diferentes cantidades de ingesta de hidratos de carbono de diversa calidad, así como describir el papel de los hidratos de carbono como grupo en el desarrollo de enfermedades. Las puntuaciones altas obtenidas en este índice se asocian a niveles más bajos de factores de riesgo cardiometabólico, asociándose a menor aparición de aterosclerosis subclínica (44) y ECV (45), y pudiendo retrasar la aparición de SM (46). En cambio, puntuaciones bajas se asocian a la aparición de diversos factores de riesgo como obesidad (47,48), perímetro de cintura elevado (49), una hemoglobina glicosilada elevada (50) e hipertensión (47), que a la larga podrían dar lugar a la aparición de patologías cardiovasculares o metabólicas.

Bebidas

Como parte de la dieta, las bebidas desempeñan un papel sustancial a la hora de cubrir las necesidades de agua, y son una fuente importante de calorías y nutrientes (51,52). Sin embargo, se sospecha que muchas, por algunos de sus componentes, son uno de los principales responsables de la actual epidemia de obesidad (53). En este grupo encontramos a prácticamente todos los tipos de bebidas, como la leche (entera y desnatada), el café, los zumos, las bebidas azucaradas y edulcoradas, y el alcohol. Si bien en algunos casos se ha demostrado su efecto perjudicial, como en el caso del alcohol (54) y de las bebidas azucaradas (55,56), en otros – como en el caso el café, los zumos de frutas o los distintos tipos de leche – las recomendaciones son controvertidas y tomar una postura clara es difícil para las distintas organizaciones sanitarias.

Las bebidas azucaradas, ricas en carbohidratos simples y azúcares añadidos, son consideradas una parte importante del consumo excesivo de azúcares añadidos en las sociedades actuales. A pesar de las múltiples recomendaciones llevadas a cabo por distintos organismos internacionales, hoy en día todavía el consumo diario excede el 10% de las calorías totales recomendadas para una ingesta diaria normal (28,57). Las bebidas azucaradas engloban todas aquellas bebidas que incluyen azúcares añadidos en su composición, como sacarosa, jarabe de maíz con alto contenido en sacarosa o concentrados de zumos de frutas. Por tanto, comprende tanto a los refrescos azucarados, como a los zumos embotellados, bebidas energéticas y batidos. Debido a su composición, presentan la capacidad de inducir en el organismo resistencia a la insulina, inflamación sistémica y dislipidemia; conocidos precursores de determinadas ECV y del SM (55,58,59).

Ante la creciente prevalencia de aterosclerosis subclínica y el SM, es fundamental profundizar en la comprensión de la relación entre la alimentación, centrándonos en los hidratos de carbono y las bebidas azucaradas, y su influencia en la aparición y progresión de estas patologías. Un enfoque integral permitirá desarrollar estrategias preventivas y de tratamiento efectivas, con objeto de reducir la carga global de ECV y mejorar la calidad de vida de la población.

2

Hipótesis

Los hábitos dietéticos, como componentes de los denominados estilos de vida, son capaces de influir en la probabilidad de desarrollar enfermedades no transmisibles, entre ellas las cardiometabólicas como, la aterosclerosis subclínica y el síndrome metabólico.

Tradicionalmente, se han llevado a cabo recomendaciones basadas en la adherencia a un tipo de patrón dietético determinado, como es la dieta mediterránea. Sin embargo, pocas recomendaciones han hecho hincapié en mejorar la calidad de los componentes de aquellos patrones dietéticos.

La presente Tesis Doctoral, a través de los artículos que la componen, pretende aumentar el conocimiento de la epidemiología entre la asociación de determinados componentes del estilo de vida como la calidad de los hidratos de carbono y de las bebidas consumidas, y la presencia de síndrome metabólico y aterosclerosis subclínica, en una cohorte de adultos trabajadores de mediana edad.

3

Objetivos

El *objetivo general* de la presente Tesis Doctoral es analizar la importancia de los hábitos nutricionales de la población adulta, en concreto la calidad de los carbohidratos consumidos y la ingesta de diferentes bebidas, y su relación con la probabilidad de presentar enfermedades cardiovasculares y metabólicas, concretamente aterosclerosis subclínica y síndrome metabólico.

Los *objetivos específicos* enmarcados en cada uno de los cuatro artículos que componen esta Tesis Doctoral son:

Artículo I (1). Actualizar y resumir la información actual sobre la asociación entre el consumo de bebidas azucaradas (refrescos, zumos de fruta embotellados, bebidas energéticas y batidos), y el síndrome metabólico en adultos.

Artículo I (2). Realizar un metaanálisis sobre la asociación del consumo de bebidas azucaradas y el síndrome metabólico en adultos, que incluye las nuevas pruebas disponibles, evita los estudios que fueron mal clasificados, y muestra los resultados de acuerdo con su diseño del estudio.

Artículo II. Estimar el impacto del consumo de hidratos de carbono de calidad en la presencia de aterosclerosis subclínica en las arterias femorales y carótidas, en trabajadores varones de una fábrica de automóviles, mediante el empleo de un índice de calidad de carbohidratos (CQI).

Artículo III. Estudiar la asociación del consumo de bebidas no alcohólicas con la presencia de aterosclerosis subclínica en las arterias carótida y femoral, en una muestra de adultos varones trabajadores de una factoría de automoción.

Artículo IV. Estudiar la asociación entre la adherencia al índice de calidad de carbohidratos (CQI) y la aparición de síndrome metabólico en una muestra española bien caracterizada de trabajadores adultos.

4

Material y métodos

En el presente apartado se van a desarrollar las metodologías empleadas para elaborar la presente Tesis Doctoral en modalidad por compendio de artículos. Debido a las características de la misma, se detallarán los procedimientos generales de las dos metodologías distintas empleadas para la obtención de resultados. Estas corresponden a revisión sistemática y metaanálisis para el objetivo específico I, y análisis transversal en estudios de investigación originales para los tres objetivos restantes. La metodología concreta de cada estudio individual puede consultarse en la correspondiente sección de *Resultados* del presente manuscrito.

4.1. Revisión sistemática y metaanálisis

El metaanálisis que se elaboró en la presente Tesis Doctoral fue desarrollado siguiendo el *Cochrane Handbook for Systematic Reviews of Intervention* (60). Los resultados fueron detallados siguiendo las guías *Meta-analysis of Observational Studies in Epidemiology* (MOOSE) (61) and *Preferred Reporting Items for Systematic Reviews and Meta-analyses* (PRISMA) (62).

Se realizó una revisión de estudios observacionales para evaluar la asociación entre el consumo de bebidas azucaradas y el desarrollo de síndrome metabólico. Las bases de datos consultadas incluyeron Pubmed y SCOPUS. Se extrajeron artículos incluidos en las mismas desde el inicio de la base de datos hasta junio de 2022 (incluido). Además, se realizó una búsqueda manual secundaria, obteniendo artículos basados en referencias bibliográficas. Los términos de búsqueda reflejaron las principales fuentes de bebidas azucaradas, el resultado de interés, así como una limitación para los idiomas.

Los criterios de inclusión se definieron basándose en los siguientes aspectos: (a) estudios que evaluasen las relaciones bebidas azucaradas-SM, o refrescos-SM, o bebidas energéticas-SM, o batidos-SM en estudios epidemiológicos poblacionales (transversales o longitudinales) llevados a cabo en humanos; (b) estudios que reporten medidas de

Hazard Ratio (HR), Riesgos Relativos (RR) u Odds Ratio (OR) con un intervalo de confianza del 95%; (c) y estudios con información suficiente y que reportasen estimadores de riesgo para el SM de acuerdo con las categorías de consumo de SSB o cuando el consumo de SSB fuera considerado como una variable continua.

Los criterios de exclusión fueron definidos, a su vez, como: (a) estudios llevados a cabo en niños, adolescentes o embarazadas, debido a la no normatividad de algunos criterios de definición del SM en esas poblaciones, impidiendo la comparación de la población; (b) estudios que asociaran el SM con patrones dietéticos o que realizasen sustitución de bebidas azucaradas por bebidas edulcoradas; (c) estudios que reportasen resultados de bebidas azucaradas totales, sin distinguir entre sus categorías (bebidas azucaradas y edulcoradas); (d) estudios llevados a cabo en poblaciones específicas (p.ej. grupos de prevención cardiovascular secundaria o en pacientes con enfermedad renal); (e) estudios con baja calidad metodológica, debido a que la validez de los resultados del estudio resultaban amenazados. Adicionalmente, excluimos revisiones, metaanálisis, artículos de conferencia y artículos en los que el texto completo no se encontraba disponible, así como aquellos que no proporcionasen la información necesaria para llevar a cabo el metaanálisis.

Valoración del sesgo y métodos estadísticos

Se extrajo la información relevante de los estudios seleccionados mediante dos revisores independientes. En ella se incluyó: tamaño muestral, características de los participantes, medición de la exposición (bebidas azucaradas), evaluación dietética, diagnóstico de SM, así como las estimaciones centrales de la asociación (HR, RR u OR) junto con sus IC del 95% para el riesgo de SM al comparar los niveles de consumo de SSB más altos frente a los más bajos. Cuando se presentaron modelos con diferentes grados de ajuste, se seleccionaron los resultados de los modelos totalmente ajustados.

Las evaluaciones de la calidad de los estudios incluidos se realizaron utilizando la escala de comprobación de valoración crítica del Joanna Briggs Institute para estudios transversales y longitudinales, según procediera (63).

El Joanna Briggs Institute elaboró esta escala a fin de evaluar la calidad metodológica de un estudio y determinar en qué medida ha tenido en cuenta la posibilidad de sesgo en su

diseño, realización y análisis. El rango de puntuaciones mínimas y máximas en estas escalas oscilan entre 1 y 8 para diseños transversales, y entre 1 y 11 para estudios de cohortes.

En base a las puntuaciones obtenidas en nuestro estudio, se excluyeron los estudios con una puntuación inferior a 7 sobre 8 para los diseños transversales e inferior a 9 sobre 11 para los estudios de cohortes.

Como métodos estadísticos, se calcularon las OR agrupadas tanto para los estudios transversales como de cohortes. La heterogeneidad se evaluó mediante la Q de Cochran y la estadística I^2. Se utilizaron modelos de efectos aleatorios para estimar las OR agrupadas con su IC del 95% debido a que la heterogeneidad entre los estudios era superior al 50%. Cuando un artículo informaba de los datos por separado para hombres y mujeres, se introdujeron los datos como estudios independientes. El sesgo de publicación se examinó mediante inspección visual de los gráficos en embudo y calculando el test de Egger (64). Los resultados del test de Egger se interpretan analizando los valores obtenidos de p, es decir, resultados de este test con valores de $p < 0,05$, indican la presencia de sesgo de publicación. Para llevar a cabo el metaanálisis, los análisis se realizaron con Review Manager (versión 5.4.1) y el software estadístico R (versión 4.0.4).

4.2. Proyecto AWHS

Muestra y diseño de proyecto

El proyecto AWHS es un estudio longitudinal prospectivo de cohorte, comenzado en 2009 y compuesto por 5678 trabajadores de una fábrica automovilística ubicada en Figueruelas (Zaragoza), iniciado con el propósito de evaluar las diferentes trayectorias de los factores de riesgo cardiovascular tradicionales y emergentes, y su asociación con las anomalías metabólicas y la aterosclerosis subclínica en la población española de mediana edad libre de cualquier ECV clínica.

Para el desarrollo de la presente Tesis Doctoral, se han empleado datos de una submuestra de 2617 participantes varones con edades comprendidas entre los 39 y 59 años, que fueron seleccionados entre los años 2011 y 2014 para llevar a cabo exámenes complementarios

de aterosclerosis subclínica por imagen básica, la cumplimentación de cuestionarios de dieta, actividad física y estilos de vida, así como una anamnesis clínica adicional.

Pruebas y exploraciones del proyecto

Medida de aterosclerosis subclínica

Para valorar la presencia de aterosclerosis subclínica en las arterias carótidas y femorales, se empleó la ultrasonografía. Las imágenes de ultrasonografía fueron obtenidas empleando el sistema de ultrasonidos Philips IU22 (Philips Healthcare, Bothell, WA, USA). Las imágenes por ultrasonidos fueron adquiridas mediante sondas lineales bidimensionales de alta frecuencia (Philips Transducer L9-3, Philips Healthcare), empleando el protocolo del Bioimage Study para las arterias carótidas (65), y un protocolo diseñado específicamente para las arterias femorales (66). Se obtuvieron barridos de inspección en el lado derecho e izquierdo de los territorios carotídeo (común, interno, externo y bulbo) y femoral. La presencia de placa se definió como una estructura focal que sobresale en la luz de la arteria al menos 0,5 mm o ≥ 50% del grosor de la capa intima media circundante. Todas las mediciones se analizaron utilizando fotogramas seleccionados con el electrocardiograma correspondientes a las diástoles terminales (onda R) (67).

Valoración de síndrome metabólico

Para valorar y diagnosticar la presencia de síndrome metabólico en los participantes, se siguieron las recomendaciones diagnósticas según la definición modificada del *National Cholesterol Education Program - Adult Treatment Panel III* (NCEP- ATP III) (15), la cual diagnostica SM cuando los participantes cumplen al menos 3 de los 5 criterios siguientes: perímetro de cintura elevado (≥102 cm), glucemia en ayunas elevada (≥100 mg/dL o tratamiento antidiabético), tensión arterial elevada (tensión arterial sistólica ≥130 mmHg y/o tensión arterial diastólica ≥85 mmHg, o tratamiento antihipertensivo), triglicéridos séricos elevados (≥150 mg/dL o tratamiento farmacológico para la hipertrigliceridemia), y colesterol alta densidad (cHDL) reducido (<40 mg/dL).

Valoración de la ingesta alimentaria

Para la evaluación de la ingesta dietética, se administró un cuestionario semicuantitativo de frecuencia de consumo de alimentos (CFCA), previamente validado para población española, en el cual, cada participante proporcionó información acerca de la ingesta media de 136 alimentos durante el año anterior al día de la entrevista, incluyendo preguntas sobre toma de suplementos o la adhesión a dietas especiales. Para cada alimento se especificó el tamaño de la ración y se dio a elegir entre nueve frecuencias de consumo, desde "nunca o casi nunca" hasta "más de seis veces al día". Se tuvieron en cuenta las variaciones estacionales y las diferencias entre los patrones de consumo de días de trabajo y de fin de semana (Anexo 1). Los datos derivados del cuestionario fueron posteriormente transformados en nutrientes de acuerdo con dos tablas españolas de composición de alimentos (68,69).

Para valorar la calidad de los carbohidratos consumidos, se calculó un índice global (CQI) (21), teniendo en cuenta los siguientes componentes:

1) La ingesta de fibra dietética (g/d).
2) El índice glucémico (IG).
3) La ratio cereales integrales/cereales totales.
4) La ratio hidratos de carbono sólidos/hidratos de carbono totales.

La ingesta de fibra dietética se calculó según las tablas españolas de composición de alimentos elaboradas por los autores Mataix (70) y Moreiras (71). El IG se calculó como un IG ponderado que se basó en el IG de cada alimento individual que se obtuvo de las anteriores tablas españolas de composición de alimentos, y utilizando una fórmula definida previamente (47). El consumo de cereales integrales se estimó como la suma del "consumo de pan integral", el "consumo de cereales integrales" y el "consumo de galletas integrales". La ingesta de cereales totales se calculó sumando todos los tipos de cereales, definidos como la ingesta de cereales integrales, cereales refinados y sus productos (incluidos el pan refinado, los cereales refinados para el desayuno, el arroz blanco, la pasta refinada, la pizza y diferentes galletas, así como los productos de pastelería). Los hidratos de carbono líquidos se calcularon sumando los hidratos de

carbono ingeridos a partir de bebidas azucaradas y zumos de fruta. Los hidratos de carbono sólidos representaban el contenido en hidratos de carbono del resto de alimentos.

Cada componente contribuyó a la puntuación de la siguiente manera (29):

- Para la ingesta de fibra alimentaria, los participantes se clasificaron en cuartiles y se les asignaron una puntuación del 1 al 4. Una mayor ingesta de fibra aumentaba la puntuación final.

- Para el IG, los participantes se clasificaron en cuartiles, pero los puntos se asignaron a la inversa, de 4 a 1. Los valores de IG más bajos aumentaban la puntuación final.

- Para la proporción de cereales integrales/cereales totales, los participantes se clasificaron en tres grupos. Los que no consumían cereales integrales recibieron 1 punto, y el resto se dividieron en dos grupos de igual tamaño y recibieron 2 y 3 puntos. Así, este componente se categorizó en tres grupos en función de la baja variabilidad del consumo de cereales integrales en la muestra. Las proporciones más altas aumentaron la puntuación final.

- Para la proporción de carbohidratos sólidos/carbohidratos totales, se clasificó a los participantes en cuartiles y se les asignaron una puntuación de 1 a 4. Las proporciones más altas aumentaron la puntuación final.

Por último, el CQI se construyó sumando todas las puntuaciones de los componentes (de 4 a 15). Clasificamos a los participantes en cuatro intervalos de 3 puntos de esta puntuación final. Los valores más altos de CQI significaron una mejor calidad de los carbohidratos consumidos.

Tabla 1: Componentes y algoritmo empleado para calcular el índice de calidad de los carbohidratos (CQI)

Componentes del CQI	Rango del índice (puntos) (4-15)	Puntuaciones según los grupos del componente (puntos de corte)			
Ingesta fibra alimentaria (g/d)	1-4	G1 = 1	G2 = 2	G3 = 3	G4 = 4
Índice glucémico	1-4	G1 = 4	G2 = 3	G3 = 2	G4 = 1
Ratio cereales enteros/cereales totales	1-3	G1 = 1	G2=2	G3 = 3	
Ratio carbohidrato sólido/carbohidrato total	1-4	G1 = 1	G2 = 2	G3 = 3	G4 = 4

Datos clínicos

Los siguientes datos clínicos se obtuvieron de los exámenes médicos anuales llevados a cabo por la empresa mediante procedimientos estandarizados. Estos exámenes aportaron información acerca de la historia clínica de los participantes, incluyendo antecedentes personales y familiares de ECV precoz, toma actual de medicamentos, o diagnósticos previos de hipertensión arterial, hipercolesterolemia o diabetes mellitus.

El examen médico incluyó mediciones de presión arterial, frecuencia cardíaca, talla, peso, y circunferencia de cintura. La obtención de la presión arterial y de la frecuencia cardíaca en reposo se llevó a cabo a través de un tensiómetro digital OMRON M10-IT (OMRON Healthcare Co. Ltd., Japón), registrando la media de 3 lecturas automáticas consecutivas. Por otro lado, los datos acerca del peso se obtuvieron con la báscula SECA (modelo 778), y del perímetro de cintura mediante la cinta métrica flexible no extensible (GulicK modelo 67019) que se verificaba y revisaba mensualmente frente a otra cinta calibrada cada 3 años. Las mediciones se realizaban en el punto medio entre la cresta ilíaca y el punto más bajo del margen costal en la línea axilar media en un plano horizontal (paralelo al suelo), al final de una espiración no forzada, con los brazos relajados a lo largo del cuerpo y las piernas ligeramente separadas.

Las concentraciones de glucosa, triglicéridos, cHDL y colesterol total se determinaron en condiciones de ayuno >8 h mediante espectrofotometría con el equipo ILab 650 de

Instrumentation Laboratory. Las concentraciones de cLDL se calcularon usando la fórmula de Friedewald cuando los valores de triglicéridos eran < 400 mg/dL (72).

La hipertensión se definió como tener una presión arterial sistólica ≥140 mmHg, o una presión arterial diastólica ≥90 mmHg, o el uso autodeclarado de medicación antihipertensiva (73). La diabetes se definió como plasma en ayunas ≥126 mg/dl o tratamiento autodeclarado con medicación hipoglucemiante (73). La dislipidemia se definió como tener colesterol total ≥240 mg/dl, o cLDL ≥160 mg/dl, o cHDL <40mg/dl, o uso autodeclarado de fármacos hipolipemiantes (16).

Datos sociodemográficos y de estilos de vida

Los participantes completaron un cuestionario adicional sobre características sociodemográficas que incluyó: edad, estado civil, numero de convivientes en la unidad familiar, nivel de estudios (primarios, bachillerato, formación profesional y universitarios), situación laboral actual, tipo de puesto de trabajo (manual o de oficina), y turno de trabajo (rotatorio mañana-tarde, rotatorio mañana-tarde-noche, central, o noche). La principal ocupación de la fábrica está diseñada para permitir la fabricación continua de automóviles, por lo que los trabajadores se distribuyen en turnos fijos o rotatorios. En los turnos nocturnos y rotatorios (90% de los participantes de la muestra) la mayoría de los trabajadores tenían estudios primarios y pertenecían casi en su totalidad a la mano de obra manual.

Los datos acerca de estilos de vida, tales como el hábito tabáquico, la actividad física o el sedentarismo, se obtuvieron mediante entrevista. En cuanto al hábito tabáquico, se clasificó a los participantes como “fumadores” si eran fumadores actuales (si declararon haber fumado en el último año), “ex fumadores" (si habían fumado al menos 50 cigarrillos a lo largo de su vida, pero no en el último año), o “no fumadores” (si declararon no haber fumado nunca).

Para evaluar la actividad física de los participantes del proyecto AWHS, en las entrevistas se empleó la versión española validada (74) del cuestionario de frecuencia de realización de actividad física utilizado en el Nurses’ Health Study (75) y el Health Professionals’ Follow-up Study (76) (Anexo 2). Para calcular el nivel de actividad física total realizado por cada participante, se asignó un coste metabólico a cada actividad utilizando los METs

establecidos en el compendio de actividades físicas propuesto por Ainsworth (77). Se computó el volumen de actividad llevado a cabo por cada participante y se multiplicó por el tiempo medio que el participante indicó haber practicado esa actividad durante el último año. De la suma total de todas las actividades realizadas, se obtuvo el valor total semanal de la actividad física de cada participante medido en MET-h/semana.

4.3. Ética

El proyecto AWHS se llevó a cabo siguiendo los Principios Éticos reconocidos por la Declaración de Helsinki de 1975 (enmendada en la 64ª Asamblea General, llevada a cabo en Fortaleza (Brasil), en octubre de 2013), las Normas de Buena Práctica Clínica (BPC) (78) y cumpliendo la legislación y la normativa legal española que regula la investigación clínica en humanos (Real Decreto 223/2004 sobre regulación de ensayos clínicos). El proyecto fue aprobado por el Comité de Ética de Investigación Clínica de Aragón (CEICA), recibiendo un dictamen favorable de dicho comité (Anexo 3).

Como requisito indispensable para su inclusión en el estudio, todos los participantes tuvieron que firmar de manera previa a su participación un consentimiento informado (Anexo 4). En el mismo se incluían tanto los objetivos del estudio, como de las pruebas a las que se verían sometidos si accedían a su participación en el mismo, como del manejo y tratamiento de los datos y resultados obtenidos a través de dichas pruebas. Además, se explicó detalladamente a los posibles participantes las posibles incidencias y complicaciones o efectos secundarios que pudieran surgir durante y/o posteriormente a la realización de las pruebas médicas, y se resolvieron las dudas que los mismos presentasen.

4.4. Análisis estadísticos

A continuación, se describen los diferentes análisis estadísticos comunes empleados en los diferentes artículos que componen la presente Tesis Doctoral. No obstante, dado que algunos de los métodos descritos a continuación únicamente son utilizados en uno de los artículos, se insta a consultar la siguiente sección de **Resultados y Discusión,** para conocer en mayor detalle los análisis estadísticos llevados a cabo en la sección *material y métodos* de cada estudio en particular.

El software utilizado para llevar a cabo los diferentes análisis estadísticos fue el software de programación estadística R (v. 3.4.4 y v. 4.0.4, R Foundation for Statistical Computing, Vienna, Austria). El nivel de significación estadística para todos los test se fijó en $p<0,05$.

Metaanálisis (forest plot, análisis de heterogeneidad y sesgo de publicación)

Para llevar a cabo el metaanálisis, se calcularon las OR combinadas para los tipos de estudios analizados. En los análisis se combinaron los tamaños del efecto de los estudios incluidos ponderando los datos según el tamaño o varianza de cada estudio. Para poder evaluar si existía diversidad sustancial entre los estudios incluidos, y, por tanto, poder emplear un modelo de análisis respecto a otro, se analizó la heterogeneidad mediante el estadístico I^2 de Cochran. En este caso, la heterogeneidad entre los estudios era mayor del 50%, por lo que para calcular las OR combinadas se utilizaron modelos de efectos aleatorios, el cual aportaba un IC del 95% más amplio que su modelo contrario de efectos fijos, el cual se emplea para estudios cuya heterogeneidad entre ellos sea menor del 50%. Si un artículo informaba datos por separado para hombres y mujeres, los datos se trataban como estudios independientes cuando los artículos originales informaban datos por sexo en análisis de subgrupos.

Por otro lado, se evaluó la presencia de sesgo de publicación en el desarrollo del metaanálisis. Para llevarlo a acabo, se examinaron visualmente los funnel plots (o gráficos de embudo) de los estudios transversales y de cohortes, y se corroboró mediante la prueba de Egger (los valores de $p < 0,05$ indican sesgo de publicación), como una forma de completar un método inexacto para evaluar el sesgo de publicación como son los gráficos de embudo.

Análisis descriptivos

En los tres artículos originales que componen la presente Tesis Doctoral se han llevado a cabo análisis descriptivos de las principales variables de interés analizadas. Estos análisis han sido realizados para toda la muestra y para diferentes subgrupos, creados, en cada caso, en función de diferentes variables de interés. Las variables continuas se han presentado a través de su media y desviación estándar (SD), mientras que las variables categóricas han sido presentadas a través del número de participantes (n) y su porcentaje

(%). La normalidad en la distribución de las variables continuas se analizó mediante el test de Kolmogorov-Smirnov.

Se estudiaron las diferencias existentes entre los diferentes grupos, a través de prueba del test t de student para muestras independientes cuando se trataba de dos grupos, o a través de pruebas de análisis de las varianzas (ANOVA) con ajuste de Bonferroni para las pruebas posthoc cuando se trataba de más de dos grupos. En el caso de las variables categóricas, se estudió la diferencia en la distribución entre grupos a través de tablas de contingencia aplicando el test Chi-cuadrado.

Análisis de regresión

En los tres estudios originales se utilizaron modelos de regresión logística binaria con el objeto de emplear los coeficientes resultantes para calcular el OR de presencia de la enfermedad o condición estudiada en cada situación determinada, en función de la variable de exposición seleccionada. En cada caso se introdujo un ajuste en el análisis en base a las potenciales variables de confusión identificadas, que incluía las ya reconocidas por la comunidad científica para esa patología.

En concreto, en los artículos que relacionan el CQI con la presencia de aterosclerosis o de SM, se plantean diversos métodos estadísticos. Al analizar la asociación entre el índice y la presencia de placas ateroscleróticas en arterias femorales (derecha y/o izquierda, contabilizadas conjuntamente como un territorio circulatorio afectado), arterias carótidas y en cualquiera de estos territorios (suma de los dos anteriores) se examinó mediante regresión logística (para suma > 0 en los últimos). Además, se utilizaron cuatro enfoques para describir y probar estadísticamente la extensión de la aterosclerosis en estudio:

1) Se calculó el número medio de territorios afectados (0, 1 ó 2) para describir la extensión.

2) Se cuantificó el porcentaje de presencia de al menos un territorio afectado (uno o más), calculando OR para la presencia de uno o más territorios afectados frente a ningún territorio afectado con regresión logística, que es la misma que la descrita anteriormente para aterosclerosis en cualquier territorio.

3) Se midió el porcentaje de participantes con dos territorios afectados (calculando la OR para la presencia de 2 territorios afectados frente a 0 o 1 territorio afectado con regresión logística).

4) Se estimó la OR ordinal con regresión logística ordinal de la extensión de aterosclerosis.

Además, por ser la primera aproximación de la creación de un CQI, se realizó un análisis alternativo con el CQI categorizado en quintiles para demostrar la solidez y facilitar la comparación con trabajos anteriores.

Por otro lado, al analizar la asociación entre el índice y la presencia de SM, ésta se realizó mediante regresión logística tanto para SM como para cada uno de sus componentes.

En cuanto al ajuste de los modelos estadísticos empleados en estos artículos, en ambos estudios los modelos se ajustaron por los factores de riesgo conocidos tanto para ECV como para SM. En concreto, los modelos se ajustaron por edad, tipo de trabajo, índice de masa corporal, tabaquismo, hipertensión, dislipemia, diabetes, energía total (Kcal/día), ingesta de proteínas (g/día), ingesta total de grasas (g/día), ingesta de alcohol (g/día) y MET totales-h/semana.

Por último, la asociación entre las bebidas y la presencia de placas ateroscleróticas en las arterias carótidas (medidas igual que en el caso anterior) y las arterias femorales se examinó mediante regresión logística. Se realizaron análisis separados para cada grupo de bebidas, así como análisis mutuamente ajustados teniendo en cuenta todos los grupos. La asociación de los grupos de bebidas con la presencia de aterosclerosis se estimó mediante OR y se calculó de dos formas: como 100 g al día de la bebida, que es una cantidad normativa utilizada habitualmente en epidemiología nutricional que permite la comparación con otros estudios; y por desviación estándar de consumo, informada como log OR, para comprender qué bebida tenía una asociación más fuerte con la presencia de aterosclerosis al considerar su variación real en la muestra. Para evaluar mejor la importancia relativa de cada grupo de bebidas en la salud, se tradujeron las OR a años de envejecimiento arterial dividiendo el coeficiente de cada grupo de bebidas por el coeficiente de edad, obtenido en el mismo modelo de regresión. Los modelos se ajustaron en función de la edad, IMC, tabaquismo, hipertensión, dislipidemia, diabetes, consumo

de alcohol (gr/día), y total de MET-h/semana. Las variables de confusión se seleccionaron previamente entre aquellas que en investigaciones anteriores sobre dieta y aterosclerosis subclínica habían influido en los resultados, y aquellas variables de interés dietético que históricamente podían ser potenciales factores de confusión.

5

Resultados

Los resultados obtenidos del desarrollo de la presente Tesis doctoral se muestran en los derivados artículos publicados. A continuación, se nombran los mismos por orden de aparición.

Artículo 1: Association between Sugar-Sweetened Beverage Consumption and the Risk of the Metabolic Syndrome: A Systematic Review and Meta-Analysis.

Artículo 2: High-quality intake of carbohydrates is associated with lower prevalence of subclinical atherosclerosis in femoral arteries: The AWHS study.

Artículo 3: Association of beverage consumption with subclinical atherosclerosis in a Spanish working population.

Artículo 4: Low-quality carbohydrate intake is associated with a higher prevalence of metabolic syndrome: The AWHS Study.

nutrients

MDPI

Review and meta-analysis article

Association between sugar sweetened beverage consumption and the risk of the metabolic syndrome: a systematic review and meta-analysis

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Abstract: (1) Background: The increasing occurrence of the Metabolic Syndrome (MetS) is largely related to harmful food habits. Among them, the consumption of sugar-sweetened beverages (SSBs) is noteworthy. However, to our knowledge, there are not enough high-quality methodological studies summarizing the association between the intake of SSBs and the MetS. Therefore, the aim of this study is to examine the existing published results on this association among adults, by synthesizing the existing evidence. (2) Methods: Systematic review and meta-analysis of observational studies following the PRISMA guidelines. PubMed and SCOPUS databases were searched for studies published until June 2022 that assessed the association between SSB consumption (including soft drinks, bottled fruit juices, energy drinks, and milkshakes), and the occurrence of the MetS. Random effect models were used to estimate pooled Odds Ratios (ORs) with their 95% coefficient interval, and I2 was used to assess heterogeneity. (3) Results: A total of 14 publications from six different countries were included in this meta-analysis (9 cross-sectional and 5 cohort studies). For the cross-sectional studies, which included 62,693 adults, the pooled OR for the risk of the MetS was 1.35 (95% CI 1.15, 1.58; I2 57%) when the highest versus the lowest categories of SSB consumption were compared. For the cohort studies, which included 28,932 adults, the pooled OR was 1.18 (95% CI 1.06, 1.32; I2 70%). (4) Conclusions: The consumption of SSBs was positively associated with an increased risk of the MetS. The published literature supports public health strategies and the need to reduce the consumption of SSBs to prevent the MetS.

Keywords: Sugar sweetened beverages; metabolic syndrome; cardiovascular disease; systematic review; meta-analysis.

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1. Introduction

The metabolic syndrome (MetS) is a cluster of cardiovascular risk factors that includes atherogenic dyslipidemia, abdominal obesity, high blood pressure, as well as high blood glucose. The MetS has been positively associated with the development of type 2 diabetes mellitus and cardiovascular disease (CVD) [1,2]. Thus, it has been showed that

adults who have the MetS are at twice the risk of developing CVD over the next five-to-ten years when compared to adults without the MetS [3].

The prevalence of MetS is on the increase worldwide, and becoming a public health concern [4–6]. This increase is largely due to unhealthy eating habits among the population. Out of these unhealthy eating habits, the intake of added sugars is still exceeding over the limits of 10% of the recommended daily calories [7,8]. There is a growing worry that the intake of added sugars derives in a positive energy balance, contributing to an increase in weight gain [7,8], obesity [8,9], type 2 diabetes [10,11], and finally in an increased risk of developing the MetS and CVD [11,12].

Part of this intake of added sugars comes from sugar sweetened beverage (SSB) consumption, which includes soft drinks, bottled fruit juices, energy drinks, as well as milkshakes. Artificial sweetened beverages (ASBs) are not considered to be SSBs, since sugar is not used within their manufacturing process.

The available evidence from cross-sectional studies has shown that SSB consumption is associated with a higher risk of the MetS in adults [13,14], although cross-sectional studies cannot establish causality. Nevertheless, prospective studies showed inconclusive results. For example, a cohort study showed a positive association only in women [15], another only with a high SSB consumption [16], and some prospective studies showed no association [17,18].

Current available evidence on the association of SSB consumption and the MetS includes three previous meta-analysis. The first one was performed by Malik et al. in 2010 [19]. It has been twelve years since this publication, and an update is needed as new scientific evidence has been produced. On the other hand, the meta-analysis by Narain et al. [20] conducted in 2016, omitted relevant articles. Finally, the meta-analysis by Zhang et al. performed in 2020 [21] included some studies in which the independent association of SSBs could not be separated. For example, results coming from dietary patterns as well as from total sweetened beverages (comprising both, SSBs as well as ASBs) were included in this meta-analysis. Finally, the distinction between cross-sectional and prospective analysis was not made.

Therefore, the aim of the present study was to update and summarize the current information on the association between the consumption of SSBs (soft drinks, bottled fruit juices, energy drinks, and milkshakes), and the MetS in adults by performing a meta-analysis that includes the new available evidence, avoids studies that were misclassified, and shows results according to their study design.

2. Materials and Methods

2.1 Data sources and Searches

This meta-analysis followed the *Cochrane Handbook for Systematic Reviews of Intervention* [22]. Results were reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [23] and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines [24].

A review of observational studies was conducted to assess the association between the consumption of SSBs and the MetS. Data sources included Pubmed and SCOPUS from database inception to June 2022 (included). In addition, a secondary manual search was conducted including articles from bibliographic references. Search terms reflected the main sources of SSBs, the outcome of interest, as well as a limitation for languages (Table 1).

Table 1. Search strategy in selected databases.

PubMed	(("sugar sweetened beverages"[MeSH Terms] OR ("sugar sweetened"[All Fields] AND "beverages"[All Fields]) OR "sugar sweetened beverages"[All Fields] OR ("sugar"[All Fields] AND "sweetened"[All Fields] AND "soft"[All Fields] AND "drinks"[All Fields]) OR "sugar sweetened soft drinks"[All Fields] OR ("fruit and vegetable juices"[MeSH Terms] OR ("fruit"[All Fields] AND "vegetable"[All Fields] AND "juices"[All Fields]) OR "fruit and vegetable juices"[All Fields] OR ("fruit"[All Fields] AND "juices"[All Fields]) OR "fruit juices"[All Fields]) OR ("energy drinks"[MeSH Terms] OR ("energy"[All Fields] AND "drinks"[All Fields]) OR "energy drinks"[All Fields]) OR ("milkshake"[All Fields] OR "milkshakes"[All Fields])) AND ("metabolic syndrome"[MeSH Terms]) AND (("english"[Language] OR "spanish"[Language]) AND "adult"[MeSH Terms])) AND ((english[Filter] OR spanish[Filter]) AND (alladult[Filter])).
SCOPUS	TITLE-ABS-KEY ("sugar sweetened soft drinks" OR "fruit juices" OR "energy drinks" OR "milkshakes") OR INDEXTERMS ("sugar sweetened beverages" OR "fruit and vegetable juices" OR "energy drinks") AND INDEXTERMS ("metabolic syndrome") AND (LIMIT-TO (SRCTYPE , "j")) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (LANGUAGE , "English") OR LIMIT-TO (LANGUAGE , "Spanish")).

2.2 Study selection

Inclusion criteria were defined based on the following aspects: (a) studies assessing the SSBs-MetS, or soft drinks-MetS, or bottled fruit juices-MetS, or energy drinks-MetS, or milkshakes-MetS relationships in population-based epidemiological studies (cross-sectional or longitudinal studies) and conducted in human adults; (b) studies reported Hazard Ratios (HR), Relative Risk (RR) or Odds Ratio (OR) with 95% Confidence Intervals (CI); (c) and studies with sufficient information also reported on risk estimates for the MetS according to categories of SSB consumption or when SSB consumption was considered as a continuous variable.

Exclusion criteria were defined based on: (a) studies conducted in children, adolescents or pregnant women, due to the fact that in these populations some criteria for the definition of the MetS are not normative, and therefore, the MetS definition could not be comparable; (b) studies assessing the association of the MetS with dietary patterns, or substitution analyses when substituting SSBs or ASBs; (c) studies reporting results on total sweetened beverages, without distinguishing their categories (SSBs and ASBs); (d) studies conducted in selected populations (e.g. on secondary cardiovascular prevention or on patients with kidney disease). (e) studies with low epidemiological quality because the validity of study results is threatened. Additionally, we excluded reviews, meta-analyses, conference articles, and articles for which the full text was not available, or articles with important missing information for the meta-analysis (Figure 1).

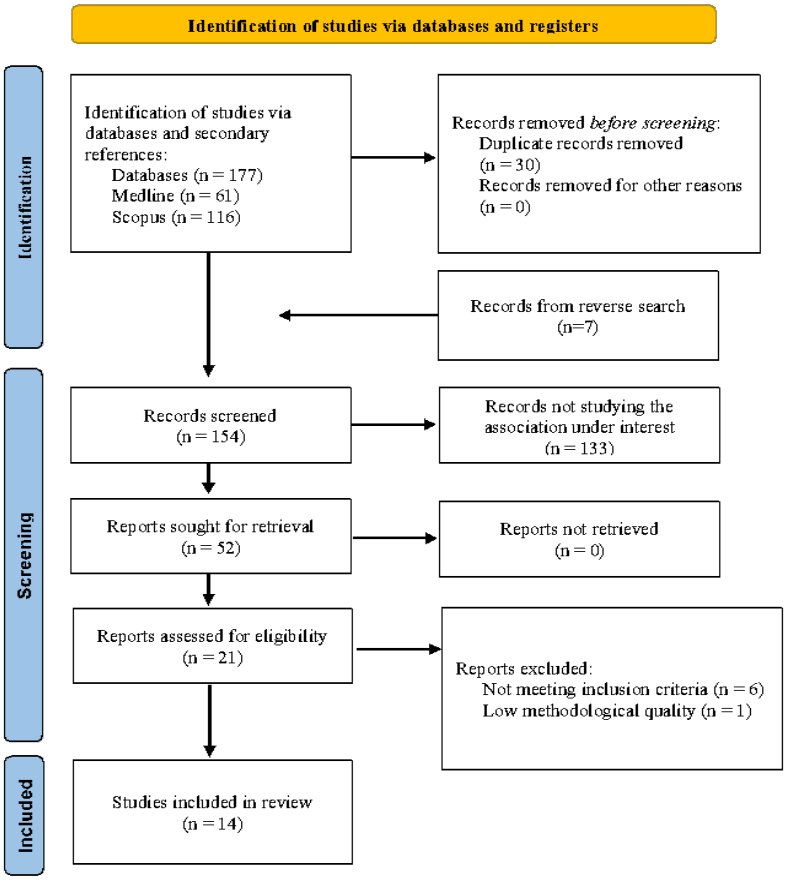


Figure 1. PRISMA 2020 flow diagram for systematic reviews.

2.3 Data extraction and quality assessment

Two independent reviewers (AMC and BMF) extracted relevant data from the selected studies, including sample size, participants' characteristics, exposure measurement (sources of SSBs), dietary assessment, diagnosis of the MetS, as well as the central estimates for the association (HR, RR, or OR) along with their 95% CIs for the MetS risk when comparing the highest vs. the lowest levels of SSB consumption. When models with different degrees of adjustment were reported, results from the fully adjusted models were selected.

Quality assessments for the included studies were performed using the Joanna Briggs Institute's (JBI) critical appraisal checklist for cross-sectional and longitudinal studies as appropriate [25]. We excluded studies rating lower than 7 out of 8 for cross-sectional designs, and lower than 9 out of 11 for cohort studies.

2.4 Statistical methods/Analysis

We calculated pooled ORs for cross-sectional studies as well as cohort studies. Heterogeneity was assessed by using the Cochran's Q and the I^2 statistic. Random effects

models were used to estimate the pooled ORs with their 95% CI due the fact that heterogeneity among studies was I^2ε50%. When an article reported data separately for men and women, we introduced the data as independent studies. Publication bias was examined through visual inspection of the funnel plots and by calculating the Egger's test [26] (p values < 0.05 indicate the presence of publication bias). Analyses were performed with Review Manager (version 5.4.1) and R statistical software (version 4.0.4).

3. Results

We identified fourteen high-quality articles [nine cross-sectional [14,27–34] and five cohort studies [15–18,35]] yielding findings on the following relationships: SSBs-MetS, or soft drinks-MetS, or bottled fruit juices-MetS, or energy drinks-MetS, or milkshakes-MetS. More in particular, we found eight articles studying the SSBs-MetS relationship [14,16,18,29–31,34,35], four articles studying soft drinks-MetS relationship [15,28,33,34], two articles assessing bottled fruit juices-MetS relationship [16,27], one article that studied energy drinks-MetS relationship [32], and zero articles assessing milkshakes-MetS relationship. We excluded the article by Dhingra et al. [36] due to not meeting the quality requirements (Tables 1 and 2).

Table 1. Characteristics of the cross-sectional studies sorted by inclusion status and chronological year of publication.

Author (year)	Country	Age range (y)	Sex	Characteristics of subjects	Sample size	Exposure	Exposure categories	Dietary assessment	Diagnosis criteria for the Metabolic Syndrome (Number of events)	OR (95%CI) for highest vs. lowest intake	Adjustment for confounders	Quality score (JBI criteria not met)
Denova-Gutiérrez et al. (2010)	Mexico	20-70y	M-W	Participants from the Health Workers Cohort Study in the Mexican states of Morelos and Mexico.	5,240 participants (1,488 men and 3,752 women)	SSB: colas, flavored sodas, flavored water with sugar and diet colas.	0 servings/day,1 serving/day, 1–2 servings/day,2 servings/day.	FFQ.	NCEP ATP III (cut-off for plasma glucose level of ≥5.6 mmol/l). (n=1394)	2.0 (1.10, 3.64). p value (not shown)	Age, sex, BMI, weight change within past year, physical activity, energy intake, alcohol intake, SFA intake, PUFA intake, trans fatty acid intake, smoking, and place of residence.	8/8 Included
Khosravi-Boroujeni et al. (2012)	Iran	>19y	M-W (stratified)	Participants from the Isfahan Healthy Heart Program (IHHP).	1,752 participants (782 men and 970 women)	SSB: soft drinks plus artificially sweetened fruit juices.	<1 time/week, 1-3 times/week, ≥times/week.	FFQ.	ATP III. (n in men= data not shown) (n in women= data not shown)	SSB: Men: 1.17 (0.56-2.44) p=0.57 SSB: Women: 0.80 (0.46-1.39) p=0.59.	Age, BMI, smoking, physical activity, total energy intake, dietary intake of meat, grains, pulses, fruit, vegetable, dairy, HVOs, and non-HVOs.	8/8 Included
Chung et al. (2015)	South Korea	≥30y	M-F (stratified)	Participants from the 2007–2011 Korea National Health and Nutrition Examination Survey (KNHANES).	13,972 participants (5,432 men, and 8,540 women).	Soft drinks	Rarely, ≤1 time/month, 2-3 times/month, 1 time/week, 2-3 times/week, ≥ 4 times/week.	Dietary questionnaire and 24-hour dietary recall.	NCEP ATP III, [waist circumference (WHO ethnicity-specific cut-off values for the Asian population) ≥90 cm for men and 80 cm for women]. (n= data not shown)	Men: 1.19 (0.80-1.77), p=0.7890. Women: 1.74 (1.00-3.03), p<0.0001.	Age, sex, family income, education, current smoking status, physical activity total, energy intake, and alcohol intake.	8/8 Included
Chichton et al. (2015	USA and Luxemburg	23-98y (MSLS), 18-69y (ORISCAV-LUX)	M-W	Participants from MSLS study and ORISCAV-LUX study.	2,126 participants (803 from MSLS and 1323 from ORISCAV-LUX).	Soft drinks	Non-consumers, one per day, two or more per day.	FFQ.	NCEP ATP III. (n in MSLS= 353) (n in ORISCAV-LUX = 346)	MSLS: 1.7 (0.7-4.5), p>0.05 ORISCAV-LUX: 0.8 (0.3-1.8), p=0.05	Age, sex, education, smoking, physical activity, total energy intake, alcohol intake, intake of vegetables, fruit, grains, meat, and diet soft drinks.	8/8 Included

Author (year)	Country	Age range (y)	Sex	Characteristics of subjects	Sample size	Exposure	Exposure categories	Dietary assessment	Diagnosis criteria for the Metabolic Syndrome (Number of events)	OR (95%CI) for highest vs. lowest intake	Adjustment for confounders	Quality score (JBI criteria not met)
Ejtahed et al. (2015)	Iran	19-70y	M-W	Participants from the fourth phase of TLGS (2009 to 2011).	5,852 participants (2,516 men and 3,336 women)	SSB: soft drinks plus and bottle fruit juices.	Using quartile cutoffs (<6.7, 6.7 to 21.8, 21.9 to 57.1, >57.1 g/day). Participants with dietary SSB intakes <6.7 g/day were considered as the reference group.	FFQ.	NCEP ATP III. (n=data not shown)	1.3 (1.06–1.59) p=0.03	Age, sex, education, smoking, physical activity, and total energy intake.	8/8 Included
Velasquez-Melendez et al. (2016)	Brazil	35-74y	M-W	Participants from the ELSA-Brasil study.	8,826 participants (3,950 men, and 4,876 women).	Soft drinks	<0.1 serving/day, 0.1 to <0.4 serving/day, 0.4 to <1 serving/day, and ≥1 serving/day	Beverage frequency questionnaire.	NCEP ATP III. (n=1314)	1.95 (1.60-2.38) p<0.001	Age, sex, income, education, smoking, physical activity, energy intake, alcohol intake, and daily consumption of fruit and vegetables.	8/8 Included
Shin et al. (2018)	South Korea	35-65y	M-W (stratified)	Participants from the 2012-2016 KNHANES.	12,112 participants (5,308 men, and 6,804 women).	SSB: soda beverages, fruit juices and sweetened rice drinks	Non-SSB drinkers, ≤ 2 times/week, 3-6 times/week, and ≥ 1 times/day	FFQ.	NCEP ATP III, [waist circumference (WHO ethnicity-specific cut-off values for the Asian population) ≥90 cm for men and 80 cm for women]. (n in men=1717) (n in women=1518)	. Men: 1.07 (0.85-1.35) p=0.0989 Women: 1.61 (1.20-2.16) p=0.0003.	Age, family income, educational, energy intake, alcohol intake, , smoking status, and physical activity.	8/8 Included
Choi et al. (2019)	South Korea	19-74y	M-W	Participants from the KNHANES study.	10,460 participants (4,082 men and 6,378 women)	Fruit juices.	Rarely, 1 to 3 times/month, and ≥1 time/week.	FFQ.	NCEP ATP III, [waist circumference (World Health Organization ethnicity-specific cut-off values for the Asian population) ≥90 cm for men and 80 cm for women]. (n= data not shown)	1.18 (0.96-1.45) p=0.1161	Age, sex, family income, education, BMI, smoking, physical activity, total energy intake, alcohol intake, sugar intake from processed food, dietary pattern 1, and dietary pattern 2.	8/8 Included

Author (year)	Country	Age range (y)	Sex	Characteristics of subjects	Sample size	Exposure	Exposure categories	Dietary assessment	Diagnosis criteria for the Metabolic Syndrome (Number of events)	OR (95%CI) for highest vs. lowest intake	Adjustment for confounders	Quality score (JBI criteria not met)
Trapp et al. (2020)	Australia	20y and 22y	M-W	Participants from the Raine Study Generation 2.	2,353 participants (1,236 of 20y, and 1,117 of 22y)	Energy drinks	none/rare (never to ≤ once/month); occasional (>once/month to <once/week); and frequent (≥once/week)	Self-reported questionnaire.	International Diabetes Foundation. (n after 20y=73) (n after 22y=92)	20y: 1.11 0.57-2.19), p>0.05 22y: 1.28 (0.71-2.31), p>0.05.	Sex, family income, mother's education, education, smoking, physical activity, energy intake, alcohol intake, and dietary pattern.	7/8 (JBI: 2) Included
Dhingra et al. (2007)	USA	Adults	M-W	Participants from the Framingham Offspring Study.	8,997 participants (4,126 men and 4,871 women).	Soft drinks.	1 to 6 soft drink/week, ≥1 soft drink/day.	FFQ.	NCEP ATP III. (n=2777)	1.81 (1.28-2.56). p value (not shown)	Age, sex, physical activity, smoking, energy intake, dietary intake of SFA, trans fat, fiber, magnesium, and glycemic index.	5/8 (JBI: 3, 4, 8) Excluded

BMI: Body Mass Index; CI: Confidence Interval; FFQ: Food Frequency Questionnaire; HVOs: Hydrogenated Vegetal Oil; JBI: Joanna Briggs Institute; M-W: Men-Women; NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III; OR: Odds Ratio; PUFA: Polyunsaturated Fatty Acids; SFA: Saturated Fatty Acids; SSB: sugar sweetened beverage.
JBI criteria for analytical cross-sectional studies: (1) criteria for inclusion; (2) detailed description of the study subjects; (3) exposure measurement; (4) standard criteria used for exposure measurement; (5) confounding factors; (6) strategies to deal with confounders; (7) outcome measurement; and (8) statistical analysis.

Table 2. Characteristics of the cohort studies sorted by inclusion status and chronological year of publication.

Author (year)	Country	Age range (y)	Sex	Characteristics of subjects	Sample size	Follow-up	Exposure	Exposure categories	Dietary assessment	Diagnosis criteria for the Metabolic Syndrome (Number of events)	OR (95%CI) for highest vs. lowest intake	Adjustment for confounders	Quality score (JBI criteria not met)
Lutsey (2008)	USA	45-64y	M-W	Participants from ARIC study.	9,514 participants (4,197 men and 5,317 women)	9-year-follow-up	SSBs	Tertiles of beverage consumption (T1 considered as reference).	FFQ.	American Heart Association guidelines. (n= 3782)	1.09 (0.99-1.19), p=0.07	Age, sex, center, race, education, smoking, physical activity, energy intake, consumption of meat, dairy, fruit and vegetables, whole grains, and refined grains.	9/11 (JBI: 9, 10) Included
Duffey (2010)	USA	18-30y	M-W	Participants from de Coronary Artery Risk Development in Young Adults (CARDIA) study.	3,596 participants.	Data were used from exam years 0 (1985–1986, baseline), 7 (1992–1993), and 20 (2005–2006).	SSBs	Quartiles of beverage consumption (average of years 0 and 7).	FFQ.	ATP III. (n= 459)	1.03 (0.96,1.11), p=0.401	Age, sex, CARDIA center race, weight, smoking, physical activity, energy intake, alcohol intake, energy from low-fat milk, whole-fat milk, and fruit juices.	9/11 (JBI: 9, 10) Included
Barrio-Lopez (2013)	Spain	>18	M-W	Participants from The Seguimiento Universidad de Navarra (SUN) Proyect.	8,157 participants.	6-year-follow-up	SSBs: sugar-sweetened carbonated colas and fruit-flavored carbonated sugar soft drinks.	Quintiles of change in beverage consumption (quintile 1 for those participants who decreased most of their consumption and quintile 5 for those participants who increased most of their consumption), considering the first quintile as the reference category.	FFQ.	The International Diabetes Federation, the American Heart Association, and National Heart, Lung, and Blood Institute. (n= 361)	2.0 (1.30, 3.08), p= 0.038	Age, sex, BMI, smoking, physical activity, energy intake, alcohol intake, soft drink consumption, consumption of red meat, French fries, fast food, and adherence to the Mediterranean dietary pattern.	10/11 (JBI: 10) Included

Author (year)	Country	Age range (y)	Sex	Characteristics of subjects	Sample size	Follow-up	Exposure	Exposure categories	Dietary assessment	Diagnosis criteria for the Metabolic Syndrome (Number of events)	OR (95%CI) for highest vs. lowest intake	Adjustment for confounders	Quality score (JBI checklist)
Ferreira-Pêgo (2016)	Spain	Men aged 55–80y, and women aged 60–80y	M-W	Patients from the PREDIMED study.	1,868 participants.	October 2003 to June 2009	SSBs and bottled fruit juices.	<1 serving/week, 1-5 servings/week, >5 servings/week.	FFQ.	The International Diabetes Federation, the American Heart Association, and National Heart, Lung, and Blood Institute. (n for SSBs= 936) (n for bottled fruit juices= 944)	SSBs: 1.43 (1.00,2.05), p=0.27. Bottled fruit juices: 1.14 (1.04,1.25), p=0.31.	Age, sex, intervention group, BMI, smoking, physical activity, cumulative energy intake, alcohol intake, alcohol squared in grams per day, cumulative mean consumption of vegetables, legumes, fruit, cereals, meat, fish, bakery, dairy products, olive oil, and nuts, and MetS components at baseline.	9/11 (JBI: 9, 10) Included
Kang (2017)	South Korea	50-69y	M-W (stratified)	Participants from KoGES cohort study.	5,797 participants (3,027 men and 2,770 women)	10-year-follow-up.	Soft drinks	none or rarely, <1 serving/week, ≥1 serving/week to <4 servings/week and ≥4 servings/week.	FFQ.	NCEP ATP III. (n in men = 1046) (n in women =1083)	Men: 1.09 (0.79, 1.50), p=0.9531. Women: 1.82 (1.24, 2.67), p<0.001.	Age, income, education, BMI, smoking physical activity, energy intake, alcohol intake, percentage of fat, fiber intake, and the presence of diseases.	9/11 (JBI: 9, 10) Included
Dhingra (2007)	USA	Adults	M-W	Participants from Framingham Offspring Study from the fourth through the seventh (1998-2001) examination cycles.	6,039 participants (2,569 men and 3,470 women)	4-year-follow-up	Soft drinks.	1 to 6 soft drink/week, ≥1 soft drink/day.	FFQ.	NCEP ATP III. (n=1150)	1.29 (0.98-1.70) p value (not shown)	Age, sex, smoking, physical activity, energy intake, dietary intake of SFA, trans fat, fiber, magnesium, and glycemic index.	7/11 (JBI: 2, 3 9, 10) Excluded

BMI: Body Mass Index; CI: Confidence Interval; FFQ: Food Frequency Questionnaire; JBI: Joanna Briggs Institute; M-W: Men-Women; NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III; OR: Odds Ratio; SFA: Saturated Fatty Acids; SSB: sugar sweetened beverage.
JBI criteria for cohort studies: (1) similar groups and from the same population; (2) exposure measured similarly in exposed and unexposed groups; (3) exposure measurement; (4) confounding factors; (5) strategies to deal with confounders; (6) free of the outcome at the start of the study; (7) outcome measurement; (8) follow-up time reported and sufficient; (9) losses to follow-up; (10) strategies to address incomplete follow-up; and (11) statistical analysis.

Six studies were conducted with data from Asia [14,15,27,28,30,31], three studies from Europe [16,34,35], five studies from America [17,18,29,33,34], and one study was conducted from Oceania [32], and corresponding to eight different countries. All studies analyzed both sexes, but only four studies showed additional sex-specific analysis [14,15,28,31]. Among all the studies, more than half defined the MetS based on National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines [14,15,27–30,33,34]. After quality assessment, most of the studies rated 8 in the JBI score for cross-sectional studies, and 9 for longitudinal studies.

3.1 Cross-sectional studies results

In cross-sectional studies, which included 62,693 adults, the results show a 35% (pooled OR 1.35, 95%CI 1.15,1.58, p=0.0002) increase in the MetS risk for adults with a high SSB consumption, with moderate heterogeneity among the studies (I^2=57%; $P_{heterogeneity}$=0.005) (Figure 2). Publication bias was not observed by examination of the funnel plot (Supplementary figure 1) nor the Egger's test (P=0.685).

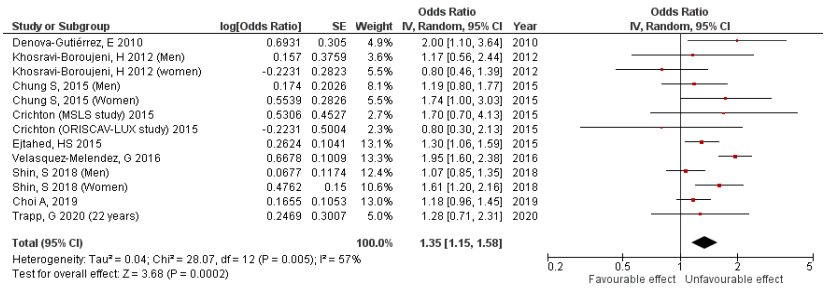
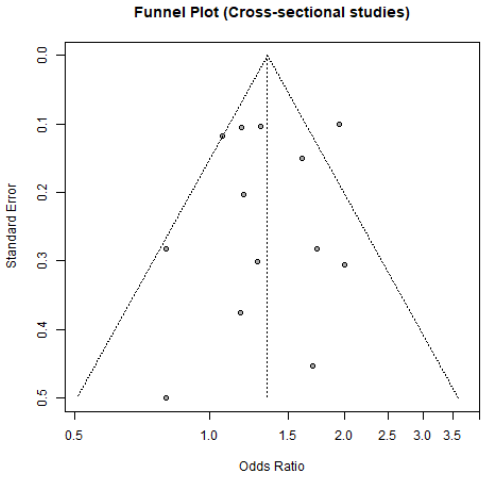


Figure 2. Cross-sectional studies forest plot.



Supplemental figure 1. Cross-sectional studies funnel plot.

3.2 Cohort studies results

The results for the analysis of cohort studies, which included 28,932 adults, show an 18% (pooled OR 1.18, 95%CI 1.06,1.32, p=0.003) increase in the MetS risk for adults with a high SSB consumption, with a high heterogeneity among the studies (I^2=70%; $P_{heterogeneity}$=0.003) (Figure 3). We observed publication bias by examination of the funnel plot (Supplementary figure 2) and the Egger's test (P=0.019). Also, among cohort studies, a meta-regression was performed by regressing the logarithms of the ORs against the year of the publication of the articles. We found that for every one year increase, the risk of the MetS increased by 2.3%, but without reaching statistical significance (p=0.458).

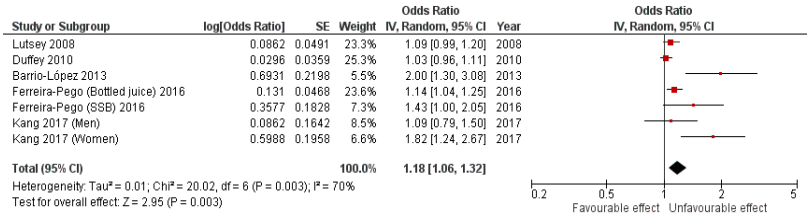
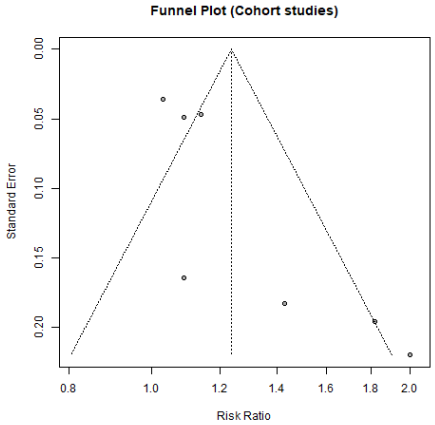


Figure 3. Cohort studies forest plot.



Supplemental figure 2. Cohort studies funnel plot.

3. Discussion

The findings from our meta-analyses, based on results from the 14 high-quality population-based epidemiological studies and including a total of 91,625 adults, show a positive link between SSB consumption and the risk of the MetS. Results from cross-sectional studies show that adults in the highest category of consumption had a 35% greater risk of the occurrence of the MetS when compared with those in the lowest category of consumption. The corresponding result for the longitudinal studies was an 18% greater risk of the incidence of the MetS. For the cohort studies, some evidence of publication bias was identified.

Our results are in accordance with the previous meta-analyses that assessed the relationship between SSB consumption and the MetS, despite the existence of methodological differences. The meta-analysis by Malik et al. [19] pooled the results of three prospective cohort studies, in which SSB consumption was associated with a 20% increased risk of developing the MetS (pooled OR 1.20, 95%CI 1.02, 1.42), although some degree of error cannot be ruled out due to the inclusion of ASB consumption. Pooled results from the meta-analysis by Narain et al. [20] in which both, children as well as adults were included, showed that the cross-sectional analysis suggested a 46% increased risk of the MetS (pooled OR 1.46, 95%CI 1.18, 1.81, p=0.0005). Also, three prospective cohort studies were meta-analyzed, but statistical significance was not achieved (pooled OR 1.47, 95%CI 0.89, 2.43, p=0.13). Again, in this meta-analysis, results from ASB consumption were included. In the meta-analysis by Zhang et al. [21], the results suggested that there was a 56% increased risk of the MetS when extreme groups of consumption were compared. As the previous one, it was conducted in both, children as well as in adults. They obtained a 19% increased risk for every 250 ml/day of SSBs consumed. In this last meta-analysis, they mixed cross-sectional and cohort studies, and for some included studies it was not possible to separate the effects for the consumption of SSBs from ASB consumption.

The positive association between SSB consumption and the risk of the MetS might be explained by multiple potential biological mechanisms. First of all, SSB consumption leads to weight gain, dyslipidemia, as well as insulin resistance due to the high added sugar content and their common elaboration with different varieties of fructose. The extra calories consumed from SSBs are not usually offset by a lower intake of energy from solid food nor with an increment in energy expenditure, in turn, leading to weight gain. SSBs, as forms of liquid carbohydrates, produce less satiety than the equivalent amount of carbohydrates from solid food [37].(37) Additionally, excessive SSB consumption increases lipogenesis secondary to hepatic fructose metabolism [38,39]. Also, fructose is metabolized by the liver, resulting in dyslipidemia [40] and in liver induced hyperuricemia, again leading to insulin resistance as well as an increased risk of the MetS [41,42]. Moreover, the high glycemic load after SSB consumption promotes pro-inflammatory cytokines released in response to hyperglycemia [43].

In our meta-analysis, it is of note, that the number of servings were not comparable across studies, and so we were only able to compare extreme categories of SSB consumption. Therefore, it is possible that some degree of non-differential misclassification somewhat weakened the pooled estimate. Also, there is a substantial variation in study designs and in the exposure assessment across studies, which can explain the large degree of heterogeneity. However, despite the existence of heterogeneity, central estimates were greater than 1 in all cohort studies.

Publication bias was explored in our meta-analysis to assess the presence of findings in favor of positive results [44]. In cross-sectional studies, a visual inspection of funnel plots and a standard test suggested no evidence of publication bias, but we observed publication bias when cohort studies were analyzed. However, there is of note that, among cohort studies, 4 studies have been published with results close to one. Also, the low number of articles included could contribute to publication bias, and the Egger's test is less reliable when lower than 10 studies are meta-analyzed [45,46].

All studies included in our meta-analysis considered adjustments for potential confounding factors such as sociodemographic, clinical, as well as lifestyle and dietary factors. SSB consumption is usually associated with a higher intake of saturated, trans-saturated fatty acids, daily caloric intake, lower dietary fiber [17], and lower levels of physical activity [29,31]. For most of the studies a positive association persisted after adjustments, suggesting an independent effect of SSBs on the occurrence of MetS. However, some residual confounding due to incomplete adjustment could still persist, resulting in an overestimation in the strength of the association. This overestimation could be more relevant among cross-sectional studies, as few studies adjusted their results for

BMI nor dietary factors other than energy intake [27,29,31], while all prospective studies took into account dietary confounding factors.

Our study has some strengths. First, the inclusion of original articles missed in previous meta-analyses. Second, we excluded studies with incomplete data, misclassifications, or errors in data analysis, as well as studies with low methodological quality. Third, the *Cochrane Handbook for Systematic Reviews of Intervention* and the PRISMA guidelines were followed when performing the meta-analysis as well as when reporting the results. Lastly, we show data on cross-sectional and on cohort studies, and we provide explanations for the weaker results in prospective studies.

Our study also has some limitations. Most of the included studies were cross-sectional, preventing us from establishing a temporal relationship between SSB consumption and the occurrence of the MetS, although separate analysis according to their design attenuated this limitation. Second, our results show a high degree of heterogeneity among studies. This heterogeneity might be related to differences in the exposure measurement, the MetS diagnosis criteria, the length of the follow-up periods, as well as the adjustment for confounders, although the association was positive for all the included cohort studies. Also, this meta-analysis is limited by the existing evidence. A scarcity of prospective cohort studies was shown, also resulting in publication bias. Finally, that the number of servings were not comparable across studies, probably deriving in an underestimation of the association.

5. Conclusions

A higher SSB consumption is positively associated with the MetS occurrence. In the future, publication of more studies assessing the prospective association is desirable. Meanwhile, public health authorities must pay attention in order to implement general public strategies to discourage SSB consumption and promote the prevention of the MetS.

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Original Article

High-quality intake of carbohydrates is associated with lower prevalence of subclinical atherosclerosis in femoral arteries: The AWHS study

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SUMMARY

Background and aims: High-quality of the carbohydrates consumed, apart from their total amount, appear to protect from cardiovascular disease (CVD). However, the relationship between the quality of carbohydrates and the early appearance of atherosclerosis has not yet been described. Our objective was to estimate the association between the quality of dietary carbohydrates and subclinical atherosclerosis in femoral and carotid arteries.

Methods: Cross-sectional study of femoral and carotid atherosclerosis assessed using ultrasounds of 2074 middle-aged males, 50.9 (SD 3.9) years old, with no previous CVD, and pertaining to the Aragon Workers' Health Study (AWHS) cohort. Food frequency questionnaires were used to calculate a carbohydrate quality index (CQI) defined as: consumption of dietary fiber, a lower glycemic index, the ratio of whole grains/total grains, and the ratio of solid carbohydrates/total carbohydrates. The presence of plaques across four CQI intervals was studied using adjusted logistic regression models.

Results: The CQI showed a direct inverse association with subclinical atherosclerosis in femoral territories. Participants with a higher consumption of high-quality carbohydrates (13–15 points) were less likely to have femoral plaques when compared with participants in the lowest index interval (4–6 points) (OR = 0.59; 95% CI = 0.39, 0.89; p = 0.005). No association was found between the CQI and the presence of subclinical atherosclerosis in carotid territories. A lower consumption of high-quality carbohydrates tended to be associated with a greater atherosclerosis extension, considered as the odds for having more affected territories (p = 0.011).

Conclusions: Among middle-aged males, a high-quality intake of carbohydrates is associated with a lower prevalence of femoral artery subclinical atherosclerosis when compared with a lower consumption. Thus, indicating an early relationship between the quality of carbohydrates and the development of CVD.

Abbreviations: AWHS, Aragon Workers' Health Study; BMI, Body Mass Index; CEICA, Clinical Research Ethics Committee of Aragon; CHD, Coronary Heart Disease; CQI, Carbohydrate Quality Index; CVD, Cardiovascular Disease; FFQ, Food Frequency Questionnaire; GI, Glycemic Index; HDL-c, High-Density Lipoprotein Cholesterol; LDL-c, Low-Density Lipoprotein Cholesterol; Non HDL-c, Non High-Density Lipoprotein Cholesterol; OR, Odds Ratio; RR, Relative Risk; SD, Standard Deviation.

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1. Introduction

Atherosclerosis is a multifactorial process responsible for a large proportion of cardiovascular disease (CVD) [1]. In addition to being the leading cause of death and disability in the world, CVD is also responsible for an important socioeconomic burden [1–3].

Behavioral and metabolic risk factors play a key role in the etiology and progression of atherosclerosis [1,4]. Accordingly, prevention efforts against CVD focus on preventable cardiovascular risk factors, such as modifying dietary patterns [1,5–7].

One dietary pattern of recent interest is the study of the type of carbohydrates and their quality. Carbohydrate quality is a multidimensional entity integrating several parameters and, as such, its elements can act in a synergic way. This is why, recent studies have assessed the relationship between carbohydrate quality and CVD through studying isolated indicators, mainly fiber intake, whole-grain consumption, and glycemic index (GI) or glycemic load. Several studies have shown that the consumption of dietary fiber [8,9] and whole-grains [10–13] decreases the risk of CVD, while a high GI [14–16] increases it. Likewise, some studies have shown how fiber [17] or whole-grain intake [18,19], as well as a low dietary GI [20,21] reduced atherosclerotic plaques.

In recent years, only a few studies have assessed overall carbohydrate quality integrating all previously defined indicators in a single index, known as the carbohydrate quality index (CQI) [22]. A high adherence to this index has shown a reduction in CVD as well as in some cardio-metabolic factors, which eventually can determine the development of CVD [23–25]. Nevertheless, no previous studies have assessed at what point in life this link is established, for example, in early adulthood indicated by the presence of subclinical atherosclerosis, or late in adulthood.

Subclinical atherosclerosis can be measured in several body locations, including carotid, femoral, and coronary arteries. However, without medical explorations it can remain clinically undetected throughout life, or until an acute clinical event occurs [26,27]. Among the subclinical locations, femoral plaques are the earliest and the most prevalent peripheral atherosclerotic indicators, that are available for detection using non-invasive techniques in the middle-aged population [28,29]. Hence, femoral subclinical atherosclerosis has the strongest association with traditional CVD risk factors, as well as being a strong marker of coronary lesions [28].

To our knowledge, the association of the quality of carbohydrates consumed with subclinical atherosclerosis in peripheral arteries has not previously been investigated. As a result, our objective was to estimate the impact that the quality carbohydrate consumption could have on the presence of subclinical atherosclerosis in femoral and carotid arteries. We studied this association with a sample of male factory workers from Spain.

2. Materials and methods

2.1. Study design and population

The association between carbohydrate quality and subclinical atherosclerosis was cross-sectionally studied with participants from the Aragon Workers' Health Study (AWHS), whose design and methodology have been previously described [30]. The AWHS is a prospective cohort study based on data from the annual physical examinations of workers in an automotive assembly plant with the aim to characterize risk factors for metabolic abnormalities and subclinical atherosclerosis. Between 2011 and 2014, study participants aged 39–59 and free of CVD at baseline underwent subclinical atherosclerosis imaging as well as an interview with questionnaires on cardiovascular and lifestyle factors, including diet. Of the 2616 participants who attended these extended examinations, we excluded the following participants: females due to their small number (n = 132), those with missing data on subclinical atherosclerosis imaging exams (n = 316), and those with missing data on diet, and on CVD risk factors (BMI, blood pressure, cholesterol, and smoking) (n = 94). The final sample comprised 2074 males (Supplemental Fig. 1). All participants gave their written informed consent. The study was approved by the Clinical Research Ethics Committee of Aragon (CEICA).

2.2. Data collection

2.2.1. Atherosclerosis imaging

The presence of plaques in carotid and femoral arteries was assessed using a Philips IU22 ultrasound system (Philips Healthcare, Bothell, WA). Ultrasound images were acquired with linear high-frequency 2-dimensional probes (Philips Transducer L9-3, Philips Healthcare), using the Bioimage Study protocol for the carotid arteries [31], as well as a specifically designed protocol for the femoral arteries [32]. Inspection sweeps were obtained on the right and left side of the carotid (common, internal, external, and bulb) and femoral territories. Plaque was defined as a focal structure protruding ≥0.5 mm into the lumen, or reaching a thickness ≥50% of the surrounding intima-media thickness. All measurements were analyzed using electrocardiogram gated frames corresponding to the end-diastole (R-wave) [33].

2.2.2. Diet assessment and carbohydrate quality index (CQI) calculation

Data used in the analysis were obtained with a previously validated food frequency questionnaire (FFQ) [34]. This questionnaire collects data on the frequency of consumption of 136 food items, including questions about the consumption of supplements and special diets. The FFQ gathers the average annual consumption for each food included, considering nine frequencies from "never or almost never" to "more than six times a day". Additionally, dietary energy, macronutrient, and micronutrient intake were derived using Spanish food composition tables [35,36].

To assess carbohydrate quality, we calculated the CQI [22], considering the following components: dietary fiber intake (g/d), GI, whole grain/total grain ratio, and solid carbohydrate/total carbohydrate ratio. Dietary fiber intake was directly derived from the FFQ. GI was calculated as a weighted GI based on the individual GI for each food item and using a previously proposed formula [25]. The GI for individual food items were obtained from various sources, including international food tables [36,37]. We estimated whole-grain consumption as the sum of 'whole bread consumption', 'integral cereal consumption', and 'whole wheat cookies consumption'. The intake of total grains was calculated by summing the intake of whole grains, refined grains, and their products (including refined bread, breakfast refined cereals, white rice, refined pasta, pizza and different biscuits, as well as pastry products). Liquid carbohydrates were calculated by summing up carbohydrates from sugar-sweetened beverages and fruit juice, and solid carbohydrates accounted for the carbohydrate content of the rest of the foods.

Before calculating the score, each component was pre-processed as follows [22]: for dietary fiber intake, and solid carbohydrate/total carbohydrate ratio, the participants were categorized into quartiles, and then, the belonging category ordinal was used as the component value (ranging from 1 to 4); for the GI, where lower values increase the final score, the quartile order was reversed (so that, those in the fourth quartile received 1 point, and those in the first quartile received 4 points); and for the whole grain/total grain ratio, participants were categorized into three groups, those that did not consume whole grains received 1 point, and the rest were divided

into two equally sized groups and received 2 and 3 points. Finally, the CQI was constructed by summing up all the component scores (ranging from 4 to 15). We classified participants into four 3-point intervals of this final score. Higher CQI values mean better quality of the carbohydrate consumed (Table 1).

The components of CQI were categorized into four groups due to their moderate variability in this sample of middle-aged participants that prevented using the five groups originally described [22] in some components (Supplemental Table 1).

2.2.3. Sociodemographic, clinical, and biological data

Age, sex, type of work (blue collar or white collar), clinical, and laboratory data were obtained in the annual medical examination performed in the factory, including BMI, waist circumference, blood pressure, medical history, and the current use of medication. Laboratory measurements were performed on blood samples collected in fasting (>8 h) conditions. Fasting serum glucose, triglycerides, total cholesterol, and high-density lipoprotein cholesterol (HDL-c) were measured by spectrophotometry (Chemical Analyzer ILAB 650, Instrumentation Laboratory). Low-density lipoprotein cholesterol (LDL-c) levels were calculated using the Friedewald equation when triglycerides were lower than 400 mg/dl. We defined arterial hypertension as having systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or self-reported use of antihypertensive medication [38]. Dyslipidemia was defined as having total cholesterol ≥240 mg/dl, LDL-c ≥160 mg/dl, HDL-c <40 mg/dl, or self-reported use of lipid-lowering drugs [39]. Diabetes was defined as fasting plasma ≥126 mg/dl or self-reported treatment with hypoglycemic medication [38]. Smoking habits were categorized as never smoker or ever smoker if the participant had smoked at least 50 cigarettes in their lifetime.

Physical activity was assessed using the validated Spanish version [40] of the questionnaire on the frequency of engaging in physical activity used in the Nurses' Health Study [41] and the Health Professionals' Follow-up Study [42]. To compute the volume of activity performed by each participant, a metabolic cost was assigned to each activity using Ainsworth's compendium for physical activities [43], and multiplied by the time the participant reported practicing that activity. From the sum of all activities, we obtained a value of overall weekly METs-h.

2.3. Statistical methods/analysis

Descriptive analysis of baseline characteristics of the study participants classified by CQI categories were reported as mean and standard deviation (SD) for continuous variables or as percentage for categorical variables. The association between CQI categorized into four groups (4–6, 7–9, 10–12, and 13–15 points) and the presence of atherosclerotic plaques in femoral arteries (right and/or left, accounted jointly as one circulatory affected territory), carotid arteries (right and/or left, accounted jointly as one circulatory affected territory), and at any of these territories (sum of previous two) was examined using logistic regression (for sum > 0 in the later). Additionally, four approaches were used to describe and statistically test study atherosclerosis extension: 1) Average number of affected territories 0, 1, or 2 was calculated to describe the extension; 2) the percentage of presence of at least one (one or more) affected territory was also calculated (calculating odds ratios —OR— for presence of one or more affected territories vs no affected territories with logistic regression, which is the same as the one described above for atherosclerosis at any territory); 3) the percentage of participants with two affected territories (calculating OR for presence of 2 affected territories vs 0 or 1 affected territory with logistic regression); and 4) calculating ordinal OR with ordinal logistic regression of atherosclerosis extension. Models were adjusted for age, type of work, BMI, smoking status, hypertension, dyslipidemia, diabetes, total energy (Kcal/day), protein intake (g/day), total fat intake (g/day), alcohol intake (g/day), and total METs-h/week. P values below 0.05 were considered statistically significant. R statistical software (ver. 3.4.4) was used for the analysis.

Additionally, an alternative analysis with CQI index categorized in quintiles (Supplemental Table 1) was performed for demonstrating robustness and to facilitate comparison with previous work.

3. Results

The sample included 2074 males with a mean age of 50.9 (SD 3.9) years. Compared with individuals in the lowest CQI interval, participants with the highest one had a slightly higher probability to be white collar workers and showed a higher concentration of HDL-c, and a lower concentration of triglycerides. Likewise, they were less likely to be smokers (Table 2).

Concerning to lifestyle behaviours, participants with the highest CQI consume less carbohydrates and more protein than the lowest CQI interval. Moreover, they practice more physical activity (higher METs-h/week) (Supplemental Table 2).

The prevalence of the presence of atheroma plaques among participants was 56.7% in femoral territory. There was a significant inverse association between CQI index and the presence of plaques in this territory. Compared with participants with the lowest CQI, those with the highest CQI had less prevalence of femoral plaques (60.4% vs. 51.4%). Fully adjusted odds for femoral plaques among participants with the highest CQI were reduced to 0.59 (95% CI: 0.39, 0.89) times the odds of those with the lowest CQI (Table 3, Fig. 1). Overall, there was a linear dose–response in the protective direction. Assessing the association of CQI as a continuous variable with the presence of femoral plaques, the odds for having femoral plaques were reduced by 5.6% (95% CI: 1.8%, 9.3%; p = 0.005) for each unit of CQI increase.

The prevalence of atheroma plaques among participants in the carotid territory was 36.6%. Data showed a downward trend as the quality of the carbohydrates consumed increased, but statistical significance was not reached (Fully adjusted OR of the highest vs. the lowest CQI was: 0.90; 95% CI: 0.60, 1.36) (Table 3).

In addition, we assessed the association of CQI with the number of affected territories, interpreted as atherosclerosis extension

Table 1
Components and algorithm used to calculate the carbohydrate quality index.

Components of carbohydrate quality index	Index range (points) (4–15)	Scores according to the groups of the component (cut-off points)			
Dietary fiber intake (g/d)	1–4	G1 = 1 (0, 20.1]	G2 = 2 (20.1, 24.4]	G3 = 3 (24.4,29.3]	G4 = 4 (29.3, max)
Glycemic index	1–4	G1 = 4 (0, 48.8]	G2 = 3 (48.8,51.9]	G3 = 2 (51.9,54.0]	G4 = 1 (54.0, max)
Ratio of whole grains/total grains	1–3	G1 = 1 0		G2 = 2 (0,0.246]	G3 = 3 (0.246, max)
Ratio of solid carbohydrates/total carbohydrates	1–4	G1 = 1 (0, 0.947]	G2 = 2 (0.947,0.977]	G3 = 3 (0.977,0.996]	G4 = 4 (0.996, max)

Max = Maximum.

Table 2
Baseline characteristics of the AWHS participants according to the carbohydrate quality index categories.

N = 2074	Overall	Carbohydrate Quality Index				*p* for trend
		4-6 points	7-9 points	10-12points	13-15 points	
		n = 293	n = 941	n = 665	n = 175	
Age, years	50.9 (3.9)	50.4 (4.2)	51.0 (3.9)	51.0 (3.8)	50.9 (3.7)	0.183
White collar, %	11.7 [242]	9.2 [27]	10.4 [98]	14.3 [95]	12.6 [22]	0.022
BMI, kg/m^2	27.6 (3.3)	27.4 (3.4)	27.6 (3.2)	27.7 (3.3)	27.6 (3.5)	0.289
Waist circumference, cm	97.3 (8.8)	96.8 (8.9)	97.6 (8.7)	97.2 (9.0)	96.7 (9.0)	0.655
Systolic blood pressure, mm Hg	125.4 (13.9)	125.0 (13.3)	125.7 (13.7)	124.9 (14.1)	126.4 (15.4)	0.824
Diastolic blood pressure, mm Hg	82.4 (9.4)	82.5 (9.2)	82.6 (9.2)	82.0 (9.5)	82.7 (10.2)	0.636
Total cholesterol, mg/dl	220.1 (36.3)	220.6 (38.7)	218.9 (34.9)	221.9 (36.7)	219.0 (38.1)	0.607
HDL-c, mg/dl	53.0 (11.4)	52.0 (10.7)	51.9 (10.9)	54.6 (11.9)	54.8 (12.1)	<0.001
Non-HDL-c, mg/dl	167.1 (35.1)	168.6 (37.9)	166.9 (33.6)	167.3 (35.4)	164.2 (37.0)	0.331
LDL-c, mg/dl	137.9 (31.3)	137.6 (33.8)	137.2 (30.4)	138.7 (30.9)	138.9 (33.7)	0.406
Triglycerides, mg/dl	150.2 (97.2)	157.8 (92.2)	153.7 (104.9)	144.7 (87.0)	139.5 (98.3)	0.008
Fasting glucose, mg/dl	97.7 (17.5)	96.5 (16.7)	97.6 (18.1)	97.8 (16.4)	99.9 (19.4)	0.075
Ever-smokers, %	77.1 [1600]	81.2 [238]	78.0 [734]	74.4 [495]	76.0 [133]	0.031
Hypertension, %	37.4 [776]	34.8 [102]	37.7 [355]	37.3 [248]	40.6 [71]	0.325
Dyslipidemia, %	49.2 [1020]	49.1 [144]	48.5 [456]	49.0 [326]	53.7 [94]	0.426
Diabetes, %	5.6 [116]	5.1 [15]	5.6 [53]	4.8 [31]	9.1 [16]	0.318

BMI: body mass index; HDL-c: High-density lipoprotein cholesterol; Non-HDL-c: non-High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol. Values are mean (standard deviation) or % [number]. P value for trend from unadjusted regression models.

Table 3
Association between the carbohydrate quality index categories and the presence of plaques in peripheral arteries in AWHS participants.

Participants (N = 2074)	Carbohydrate Quality Index				*p* for trend[b]
	4–6 points OR (95%CI)	7–9 points OR (95%CI)	10–12 points OR (95%CI)	13–15 points OR (95%CI)	
	293	941	665	175	
Femoral plaques, % (n)	60.4% (n = 177)	58.0% (n = 546)	54.6% (n = 363)	51.4% (n = 90)	
Age-adjusted	Ref.	0.84 (0.64, 1.11)	0.73 (0.55, 0.97)	0.64 (0.43, 0.94)	0.005
Multivariable-adjusted[a]	Ref.	0.84 (0.62, 1.11)	0.74 (0.54, 1.00)	0.59 (0.39, 0.89)	0.005
Carotid plaques, % (n)	36.5% (n = 107)	37.7% (n = 355)	35.2% (n = 234)	36.0% (n = 63)	
Age-adjusted	Ref.	0.99 (0.75, 1.31)	0.89 (0.67, 1.20)	0.93 (0.62, 1.38)	0.280
Multivariable-adjusted[a]	Ref.	1.00 (0.75, 1.33)	0.90 (0.67, 1.23)	0.90 (0.60, 1.36)	0.271

AWHS, Aragon Workers' Health Study; OR, odds ratio; CI, confidence interval.
N, total number of participants; n, number of subjects with plaques.
[a] Adjusted for age, type of work (blue collar or white collar), BMI, smoking status (ever smoker or never smoker), hypertension, dyslipidemia, diabetes, total energy (Kcal/day), protein intake (g/day), total fat intake (g/day), alcohol intake (g/day), and total METs-h/week.
[b] *P* for trend is calculated using CQI as continuous variable.

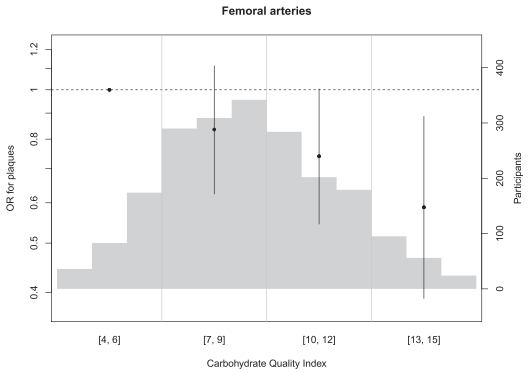

Fig. 1. Odds Ratios (95% Confidence Interval) for the presence of femoral plaques according to carbohydrate quality index categories.

(Supplemental Table 3). The mean count of affected territories decreases as CQI increased. In multivariable logistic regression models we found that the CQI was negatively associated with the presence of two affected territories (p for trend = 0.017). Although the presence of any atherosclerosis (one or more affected territories) showed a similar downward tendency in adjusted models, statistical significance was not reached in this case. This was further tested and proved with the most appropriate statistical modeling, which should be considered the conclusive test for this association, in an ordinal logistical regression model (p = 0.011).

Likewise, when we assess associations between CQI (with components scores in five groups, Supplemental Table 1) and presence of atheroma plaques, results obtained were similar on trend and significance (Supplemental Table 4, Supplemental Table 5, Supplemental Fig. 2). However, with this scoring, which was suboptimal for the variability in our sample, those response was not linear.

4. Discussion

In this study, we found a consistent and inverse association between the CQI and the presence of subclinical atherosclerosis in femoral territories. However, this association was not shown in the carotid territories, probably because, at the age of the participants, subclinical atherosclerosis appears more frequently in femoral arteries. Nonetheless, CQI was also associated with lower atherosclerosis extension. Thus, our results suggest that consuming carbohydrates from whole grains instead of foods from refined

flours, those with a low glycemic index, consumed as a solid food, and associated with dietary fiber and reducing consumption of liquid carbohydrates and those with high glycemic index could potentially reduce the risk of subclinical atherosclerosis. These findings support the premise that the quality of dietary carbohydrates is likely to play an important role as a determinant of cardiovascular health.

Previously to the first definition of the CQI [22], its components had demonstrated significant clinical benefits in reducing the risk of CVD. In this sense, two meta-analyses [44,45] have shown that the consumption of dietary fiber, naturally present in fruit and vegetables, is inversely associated with the risk of coronary heart disease (CHD). Besides, other meta-analyses indicate that a high whole-grain intake has a protective effect against CHD [10], and it is associated with a reduced risk of all-cause mortality as well as CVD mortality [11]. Interestingly, the study of Steffen et al. [18] has shown a beneficial effect of whole-grains and both fruit and vegetable consumption on the risk of all-cause mortality and incident coronary artery disease, but not on ischemic stroke. Also, the study of Juan et al. [13] observed that the consumption of whole-grains was not associated with a reduction in ischemic stroke, although a high consumption of whole-grain cold breakfast cereal and bran decreased this risk. Finally, Livesey et al. [16], showed a relationship between the GI and CHD risk with a relative risk of 1.24 per each 10 U GI increase.

Several studies have assessed the effects of different components of the CQI in the development of atherosclerosis, when studying the early steps in the natural history of CVD. With regard to this, Mellen et al. [19] showed an inverse association between whole-grain intake and the carotid intima media thickness. Furthermore, Erkkilä et al. [17] demonstrated that the progression of coronary atherosclerosis was slowed down by a high intake of cereal fiber as well as whole-grain products in postmenopausal females, with established coronary artery disease. The association between the GI and atherosclerosis is more controversial. Some studies, like those carried out by Choi et al. [46] and Peng et al. [21], have shown a direct relationship between the GI and carotid stenosis, or coronary artery calcium. However, Goñi et al. [20] showed no association between the GI and the carotid intima media thickness. Likewise, Dearborn et al. showed no association between the GI and high-risk plaque features. In addition, the relationship between the GI and the maximum wall thickness was described as non-linear.

The association between CQI and atherosclerosis may stem from the effects that some quality aspects of dietary carbohydrates have on the traditional cardiovascular risk factors, although evidence is sparse beyond the diabetes realm. Two studies have shown how a high GI diet unfavorably affected CVD risk factors and therefore, the substitution of a high with a low GI dietary carbohydrates may reduce the risk of CVD [14,15]. Additionally, a recent systematic review and meta-analysis [47] concluded that the consumption of a high intake of dietary fiber or whole grains was associated with a reduced incidence of type 2 diabetes.

The study of Zazpe et al. [22] defined the CQI in literature for the first time, allowing scientist to compare participants with different carbohydrate quality intakes. This index has allowed to identify important associations in participants with high quality intake of carbohydrates. In the SUN project, among a Mediterranean cohort of 17,424 middle-aged adults, a higher CQI showed a significant inverse association with CVD incidence. This study also found that participants in the higher CQI and with more than 50% of energy intake coming from carbohydrates had the lowest risk of CVD [23]. In early stages of CVD development, the impact of a high adherence to CQI and specific cardiovascular risk factors have already been reported. The KNHANES survey showed an inverse association between a high CQI and the prevalence of traditional CVD risk factors like obesity and hypertension [25]. In addition, the PREDIMED-Plus randomized trial found that, after 12 months, improvements in CQI were strongly associated with concurrent favorable CVD risk factor changes, which persisted over time in overweight/obese adults with metabolic syndrome. Blood pressure, fasting blood glucose, and glycated hemoglobin, as well as triglycerides levels, all decreased as the CQI improved. Additionally, HDL-c levels showed significant increases as CQI changes improved [24]. However, the relationship between the CQI and subclinical atherosclerosis had not yet been studied, and presently there are no former studies focusing on femoral arteries.

Our findings extend the knowledge of the benefits of a high CQI on CVD events, showing benefits in the early stages of the atherosclerosis process. Atherosclerosis develops throughout our lifespan, from childhood to adulthood [48], and the quality of carbohydrates is already relevant from middle age onwards. The CQI association could be confirmed statistically with femoral plaques while only a mild association tendency appeared with carotid plaques. This is probably due to the age range of our sample, which is mainly composed of middle-aged men. When middle aged, subclinical atherosclerosis appears primarily in the femoral arteries, where, in addition, atherosclerosis is more strongly associated with known CVD risk factors [28,29].

Finally, this evidence provides grounds for specific recommendations on improving dietary carbohydrates quality in CVD primary prevention campaigns. CQI could also be used to inform about poor quality diets, to encourage specific qualitative changes in diets, as well as to monitor the success of these changes. Therefore, public health dietary recommendations should include improving the quality of dietary carbohydrates, rather than only limiting their intake quantity. In addition, it is worthwhile educating the general public to the benefits of food with high-quality carbohydrates, while at the same time, being able to identify this food.

Our study has several strengths, among which having been carried out with standardized protocols stands out. The study also used high-quality data collection methods to obtain information on subclinical atherosclerosis, both in femoral as well as carotid territories. However, it has also several limitations. First, the cross-sectional design does not allow to establish causality nor the temporality of the associations found, although in this case, dietary intake was not modified by the presence of subclinical disease. Second, our sample of females is too small to analyze separately, so we only included a middle-aged male sample. In addition, this is a sample of working men who all work in the same car assembly plant, thus, the results may not be directly generalized to other populations. Third, although the dietary assessment was conducted using FFQ by trained interviewers, we cannot rule out the presence of some misclassification [49]. However, the scientific literature supports that the FFQ is a feasible tool to evaluate food habits in epidemiological studies [34,50]. Fourth, even though we adjusted for the major potential confounders, residual confounding is still possible. Lastly, the use of the CQI could make the comparison with previous results difficult.

5. Conclusions

Our results suggest a protective effect of the consumption of high-quality carbohydrates on the presence of subclinical atherosclerosis in the femoral territory.

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Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2021.04.049.

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Association of beverage consumption with subclinical atherosclerosis in a Spanish working population

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Beverages play a substantial role meeting water, calorie, and nutrient requirements; however, they are presented as being major contributors to the current obesity epidemic. Although, the relationship between beverage consumption and metabolic risk factors for cardiovascular disease (CVD) in adults has been frequently studied, its association with subclinical atherosclerosis is of increased interest. We studied the association of beverage consumption with the presence of peripheral subclinical atherosclerosis among Spanish workers. We performed a cross-sectional study of 2089 middle-aged males, with a mean age of 50.9 (SD 3.9), and without CVD, carried out in the Aragon Workers' Health Study (AWHS). A food frequency questionnaire was used to measure beverage consumption of low-fat milk, coffee and tea (unsweetened), whole-fat milk, sugar-sweetened beverages, bottled fruit juice, artificially-sweetened beverages and 100% fruit juice. Atherosclerotic plaques were measured by ultrasound (in carotid arteries, and in femoral arteries). Atherosclerotic plaque was defined as a focal structure protruding ≥ 0.5 mm into the lumen, or reaching a thickness ≥ 50% of the surrounding intima-media thickness. As statistical analysis, we use logistic regression models, simultaneously adjusted for all beverage groups. As results, unsweetened coffee was the beverage most associated with peripheral subclinical atherosclerosis with an odds ratio (OR) of 1.25 (1.10–1.41), and 1.23 (1.09–1.40) 100g/day] for carotid, and femoral territories respectively. Moreover, subclinical atherosclerosis was positively associated with whole-fat milk [OR 1.10 (1.02–1.18) 100 g/day] in the femoral territory. The association was protective for low-fat milk in the carotid territory [OR 0.93 (0.88–0.99) 100g/day]. There was also a protective association with bottled fruit juices in the femoral territory [0.84 (0.74–0.94) 100g/day]. Our results suggest a detrimental association with the consumption of coffee, as well as with whole-fat milk and the presence of subclinical atherosclerosis. Therefore, an element of prudence excluding water and low-fat milk, must be applied when recommending beverage consumption.

Abbreviations

ARIC study	Atherosclerosis Risk in Communities study
ASBs	Artificially sweetened beverages
AWHS	Aragon Workers' Health Study
BMI	Body Mass Index
CAC	Coronary artery calcium
CEICA	Clinical Research Ethics Committee of Aragon
CHD	Coronary Heart Disease

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CHS	Coronary Heart Study
CVD	Cardiovascular Disease
FFQ	Food Frequency Questionnaire
FHS	Framingham Heart Study
HDL-c	High-Density Lipoprotein Cholesterol
LDL-c	Low-Density Lipoprotein Cholesterol
METs	Metabolic Equivalents
OR	Odds Ratio
RR	Relative Risk
SD	Standard Deviation
SSBs	Sugar sweetened beverages
TG	Triglycerides

Atherosclerosis is the pathological process that causes most cardiovascular disease (CVD). Lifestyle related factors, such as smoking, lack of physical activity, or an unhealthy diet are involved in its etiology[1–4].

As part of the diet, beverages play a substantial role in meeting water requirements, and are an important source of calories as well as nutrients[4,5]. However, they are suspected of being one of the major contributors to the current obesity epidemic[6]. Thus, caloric free beverages -especially water- or those only containing beneficial nutrients, should be the primary beverages consumed[4,7].

Current recommendations about the consumption of low-fat or fat-free dairy products rather than regular-fat[4,8] have been questioned by different studies. Results regarding whole milk consumption are inversely associated with coronary arterial calcium progression especially in males[9]. They have been also associated with better cardiovascular profile such as lower systolic and diastolic blood pressure, and triglycerides (TG) levels, or higher high-density lipoprotein cholesterol (HDL-c), compared with non-consumption[10].

Coffee might be related to delaying the atherosclerotic process in carotid arteries[11]. Furthermore, some studies have found a reduced risk of stroke with regular coffee intake[12], while others have found an increased coronary heart disease (CHD) risk with a consumption of over 2 cups/day of espresso coffee[13], but its consumption was not associated with a worse profile for plasma lipid concentrations.

The role of fruit juices is also the object of debate, even in the International Dietary Guidelines[4,7], due to its reduced nutritional and fibre content and its higher caloric density, compared to whole fresh fruit. Instead, recent studies have found positive associations with a moderate intake of 100% fruit juice and pure fruit juice with lower risk of CVD, CHD, and stroke[14,15].

Sugar sweetened beverages (SSBs) contain added caloric sweeteners such as sucrose, high sucrose corn syrup, or fruit-juice concentrates, and they are the largest contributors to added sugar intake[16]. Consumption of SSBs have also been shown to affect cardiovascular health[17] with an increased risk of stroke, and myocardial infarction[18]. Conversely, artificially sweetened beverages (ASBs) have been proposed as a potential replacement for SSBs, but there is still scarce evidence on the benefits of this exchange[6,19,20].

Although the relationship between beverage consumption and metabolic risk factors for CVD in adults has been frequently studied, the interest of the association between beverages and subclinical atherosclerosis is growing rapidly. Thus, we aim to study the association of non-alcoholic beverage consumption with the presence of subclinical atherosclerosis in the carotid and the femoral arteries.

Materials and methods

Study design and population. This cross-sectional analysis was carried out in a subsample of the Aragon Workers' Health Study (AWHS), whose design and methodology have been previously described[21]. Briefly, the AWHS is a prospective cohort based on the annual physical examinations of 5678 workers belonging to an automobile assembly plant from Spain, with the aim of determining the risk factors for metabolic abnormalities and subclinical atherosclerosis. Between 2011 and 2014, a subgroup of 2616 participants aged 39–59 and free from CVD at baseline, attended extensive clinical examinations including subclinical atherosclerosis imaging, as well as an interview with questionnaires on diet, and lifestyles. We excluded females due to the small number (n = 132), and those with missing data on subclinical atherosclerosis (n = 316), and CVD risk factors (n = 79). The final sample comprised 2089 males (see Supplemental Fig. 1). The study was approved by the Clinical Research Ethics Committee of Aragon (CEICA). All participants provided written informed consent.

Data collection. *Diet assessment.* Habitual diet during the preceding year of the interview was assessed using a semi-quantitative food frequency questionnaire (FFQ) previously validated in Spain[22]. This questionnaire is the updated version of the original FFQ, which collects information of 136 food items instead of the 118 food items initially contained, considering nine frequencies from "never or almost never" to "more than six times a day". The updated version incorporates highly consumed foods in Spain and was designed to adapt to the Spanish diet and its evolution. The reproducibility and relative validity of this FFQ was assessed in the Predimed-Plus population, finding good reproducibility and a relative validity similar to those of FFQ used in other prospective studies[23].

Consumption of milk (whole fat, semi-skimmed, and fat-free), decaffeinated coffee, caffeinated coffee and tea, 100% orange juice and other 100% fruit juices (with and without pulp, or from concentrate), bottled fruit juices (with and without added sugars), diet soda, and other artificially sweetened drinks, soft drinks, and milkshakes, were expressed in grams per day. Red, rosé, and white wine, beer and distillated drinks were expressed into daily grams of ethanol.

The semi-skimmed and the fat-free milks were combined into the category of "*low-fat milk*". Unsweetened coffee, decaffeinated coffee, and tea were grouped to create a *"coffee and tea"* category. The "*whole fat milk*" category included just this item. A "*sugar-sweetened beverages*" category was created by summing up the other soft drinks, and milkshakes. Consumption of 100% orange juice and other 100% fruit juices were grouped to create a "*100% fruit juices*" category, while bottled fruit juices were grouped in a separate category as *"bottled fruit juices"*. In addition, the "*artificially sweetened beverages*" category included diet soda as well as artificially sweetened drinks.

Atherosclerosis imaging. The presence of plaques in the carotid and femoral arteries was assessed using a Philips IU22 ultrasound system (Philips Healthcare, Bothell, WA). Ultrasound images were acquired with linear high-frequency 2-dimensional probes (Philips Transducer L9-3, Philips Healthcare), using the Bioimage Study protocol for the carotid arteries[24], as well as a specifically designed protocol for the femoral arteries[25]. Inspection sweeps were obtained on the right and left side of the carotid (common, internal, external, and bulb) as well as on the femoral territories. Plaque was defined as a focal structure protruding ≥ 0.5 mm into the lumen, or reaching a thickness ≥ 50% of the surrounding intima-media thickness. All measurements were analyzed using electrocardiogram gated frames corresponding to the end-diastole (R-wave)[26].

Sociodemographic, clinical, and biological data. The main factory occupation is designed to allow for continuous car manufacturing, so workers are distributed in fixed shifts or rotating shifts. In night and rotating shifts (90% of the sample) most of the workers had elementary school education and belonged almost entirely to the manual labor workforce.

Age, sex, clinical, and laboratory data were obtained in the annual medical examination performed in the factory, including clinical data, BMI, blood pressure, medical history, and the current use of medication. Laboratory measurements were performed on blood samples collected in fasting conditions (> 8 h). Fasting serum glucose, TG, total cholesterol, and high-density lipoprotein cholesterol (HDL-c) were measured by spectrophotometry (Chemical Analyzer ILAB 650, Instrumentation Laboratory). Low-density lipoprotein cholesterol (LDL-c) levels were calculated using the Friedewald equation when TG were lower than 400 mg/dl. Arterial blood pressure was measured after a 5 min rest period with an OMRON M10-IT digital blood pressure monitor (OMRON Healthcare Co. Ltd., Japan), and we recorded the average of 3 consecutive automatic readings. Smoking habit was categorized as current smoking if the participant reported having smoked in the last year, former smoking if the participant had smoked at least 50 cigarettes in his lifetime, but not in the last year, and never smoking. Ever smoking (current and former) versus never smoking was used in the main analysis.

Arterial hypertension was defined as having systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg, or self-reported use of antihypertensive medication[27]. Dyslipidemia was defined as having total cholesterol ≥ 240 mg/dl, or LDL-c ≥ 160 mg/dl, or HDL-c < 40 mg/dl, or self-reported use of lipid-lowering drugs[28]. Diabetes was defined as fasting plasma ≥ 126 mg/dl or self-reported treatment with hypoglycemic medication[27].

We assessed physical activity using the validated Spanish version[29] of the questionnaire on the frequency of engaging in physical activity used in the Nurses' Health Study[30] and in the Health Professionals' Follow-up Study[31]. A metabolic cost was assigned to each activity using the Ainsworth's compendium for physical activities[32]. We computed the volume of activity performed by each participant, and it was multiplied by the time the participant reported practicing it. Summing up all activities, we obtained a value of overall weekly METs-h.

Statistical methods. For descriptive porpoises, the mean of each beverage group was calculated including for those participants without consumption. The percentage of participants who did not consume was also reported.

The association between beverages and the presence of atherosclerotic plaques in carotid arteries (right and/or left, accounted jointly as one circulatory affected territory), and femoral arteries (right and/or left, accounted jointly as one circulatory affected territory) was examined using logistic regression. Separate analyses for each beverage group as well as mutually adjusted analyses taking into account all groups were performed. Models were adjusted for age, BMI, smoking status (ever smoker or never smoker), alcohol consumption (gr/day), hypertension, dyslipidemia, diabetes, and total METs-h/week.

The association of beverage groups with the presence of atherosclerosis was estimated using Odds Ratios (OR) and calculated in two ways: as 100 g per day of the beverage, which is a normative amount habitually used in nutritional epidemiology that allows for comparation with other studies; and per Standard deviation (SD) of consumption, reported as a log OR, in order to understand what beverage had a stronger association with the presence of atherosclerosis when considering its actual variation in the sample.

To better assess the relative importance of each beverage group on health, we translated ORs to years of arterial aging by dividing the coefficient of each beverage group by the coefficient of age, obtained in the same regression model.

The confounding variables were previously selected from those that in past research on diet and subclinical atherosclerosis had influenced the results, and those variables of dietary interest that historically may be potential confounders.

P values below 0.05 were considered statistically significant. R statistical software (v. 4.1.3) was used for the analysis.

Ethical approval. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the central Institutional Review Board of Aragón (CEICA) (PI07/09).

Results

Descriptive analysis, beverage consumption and the percentage of participants without consumption. The 2089 participants had a mean age of 50.9 (SD: 3.9), and a mean BMI of 27.6 (SD: 3.3) kg/m^2. Participants were ever-smokers in 77.1%, 37.4% had hypertension, 49.2% dyslipidemia, and 5.6% diabetes.

The beverage groups most frequently consumed were low-fat milk, coffee and tea (95% of consumption in this group was coffee), whole milk, and SSBs. There was a substantial number of participants who did not consume a specific beverage group, except for coffee. Within the rest of beverage groups, there was no consumption by at least one third of the participants in the sample (Table 1).

Association between 100 g/d of beverages consumed and the presence of plaques in peripheral arteries. The beverage most strongly associated with peripheral subclinical atherosclerosis was coffee [OR, 1.25 (1.10, 1.41), and 1.23 (1.09–1.40) per 100 g/day] for carotid, and femoral territories respectively. Moreover, subclinical atherosclerosis was associated with whole-fat milk consumption [OR 1.10 (1.02–1.18) per 100 g per day] in the femoral territory. On the contrary, low-fat milk showed a protective association [OR 0.93 (0.88–0.99) per 100 g/day] in the carotid territory. Bottled fruit juices also showed a protective association [0.84 (0.74–0.94) per 100 g/day] in the femoral territory (Table 2).

Association per standard deviation of beverages consumed and the presence of plaques in peripheral arteries. When studying the change per one SD, coffee was again the most influential group for peripheral subclinical atherosclerosis, with an absolute log OR per SD of 0.17 (0.08, 0.26), and 0.16 (0.06, 0.26) for the carotid, and the femoral territories respectively. The corresponding estimates for whole-fat milk obtained an absolute log OR of 0.12 (0.02, 0.22) for the femoral territory (Supplemental Table 1). Additionally, low-fat milk was −0.13 (−0.23, −0.03) for the carotid territory and bottled fruit juices were −0.14 (−0.24, −0.05) for the femoral territory.

Component	Beverage consumption	
	Mean (SD) of gr/day	Percentage without consumption [count]
1. Low-fat milk (semi-skimmed)	155.6 (185.3)	39.5 [825]
2. Coffee and tea (unsweetened decaffeinated coffee, caffeinated coffee, and tea)	127.3 (76.7)	3.2 [67]
3. Whole-fat milk	68.5 (133.3)	66.4 [1387]
4. Sugar-sweetened beverages (soft drinks or milkshakes)	67.3 (128.3)	43.5 [909]
5. Bottled fruit juices	40.7 (82.5)	59.4 [1240]
6. Artificially sweetened beverages (diet soda or artificially sweetened drinks)	20.2 (84.4)	87.0 [1817]
7. 100% fruit juice (100% orange juice or other 100% fruit juice)	14.1 (43.6)	77.1 [1611]

Table 1. Beverage consumption and the percentage of participants without consumption, among middle-aged men in the AWHS (N = 2089). Values are mean (standard deviation) or % [number]. Mean was computed including those without consumption.

Association per 100gr				
	Carotid plaques OR (95%CI)		Femoral plaques OR (95%CI)	
Participants (N = 2089)	Separated analysis	Mutually adjusted analysis	Separated analysis	Mutually adjusted analysis
Low-fat milk (semi-skimmed)	0.94 (0.89, 0.99)*	0.93 (0.88, 0.99)*	1.01 (0.96, 1.07)	1.03 (0.98, 1.09)
Coffee and tea	1.23 (1.09, 1.39)***	1.25 (1.10, 1.41) ***	1.25 (1.10, 1.41)***	1.23 (1.09, 1.40)**
Whole-fat milk	1.05 (0.98, 1.12)	1.00 (0.93, 1.08)	1.10 (1.02, 1.18)*	1.10 (1.02, 1.18)*
Sugar-sweetened beverages	1.08 (1.00, 1.16)*	1.07 (1.00, 1.15)	1.08 (1.01, 1.17)*	1.08 (1.00, 1.17)
Bottled fruit juices	1.01 (0.90, 1.13)	1.01 (0.90, 1.13)	0.84 (0.75, 0.94)**	0.84 (0.74, 0.94)**
Artificially sweetened beverages	1.02 (0.91, 1.13)	1.03 (0.92, 1.15)	0.99 (0.89, 1.11)	1.00 (0.90, 1.12)
100% Fruit juice	1.01 (0.82, 1.25)	1.05 (0.84, 1.29)	0.94 (0.76, 1.17)	0.95 (0.76, 1.17)

Table 2. Association between 100 g/d of beverages consumed and the presence of plaques in peripheral arteries among participants in the AWHS. AWHS, Aragon Workers' Health Study; OR, odds ratio; CI, confidence interval. N, total number of participants. Asterisks denote *P* value: ***$p \leq 0.001$, **$p \leq 0.01$, *$p \leq 0.05$. †Adjusted for age, BMI, smoking status (ever smoker or never smoker), alcohol consumption (gr/day), hypertension, dyslipidemia, diabetes and total METs-h/week. The mutually adjusted analysis included all beverage groups simultaneously in the same regression model.

Association between 100 g/d and per standard deviation of beverages consumed and arterial aging. In the model with all the beverage groups mutually adjusted, the consumption of 100 g per day of coffee represented more than 2 years of arterial aging, both, for the carotid and femoral territories. The consumption of 100 g/day of whole milk aged femoral arteries about 1 year, while femoral arteries looked 1.9 years younger per 100 g/day of bottled fruit juice consumed. Additionally, the consumption of 100 g/day of low-fat milk prevented aging of carotid arteries about 0.7 years (Table 3). Considering the global influence in the sample, one SD of coffee consumption aged the arteries by 1.7 years, while bottled fruit juice prevented 1.5 years of aging in the femoral arteries, and low-fat milk prevented 1.3 years of aging in carotid arteries (Supplemental Table 2).

Discussion

In this large epidemiological study, we found a consistent association between the consumption of coffee and the presence of subclinical atherosclerosis for the carotid as well as the femoral territories. Furthermore, we found a pernicious association for whole-fat milk in the femoral territory. In addition, a protective association was found for low-fat milk in the carotid territory, and for bottled fruit juice in the femoral territory. Thus, our results suggest that avoiding drinking coffee and consuming low-fat milk are options, which are not linked to negative outcomes and could potentially reduce the risk of subclinical atherosclerosis among middle-age men who were initially free of CVD.

Our results about low-fat milk and whole milk are in accordance with current international recommendations[4,8], suggesting the benefit of consuming low-fat instead of whole milk. Nevertheless, current studies have reported inconsistent results about the harmful association of whole milk consumption and the development of CVD. On one hand, the study by Hidaka et al. has observed that low- and free-fat milk were associated with a reduction in atherogenic lipoprotein profile evidenced by lower plasma triglycerides and phospholipid levels, as well as being beneficial for TG/HDL-c and TG/LDL-c ratios[33]. On the other hand, as previously mentioned, the study of Sun et al. has observed that whole milk consumption improved cardiometabolic profile by lowering systolic and diastolic blood pressure, TG, as well as increasing HDL-c levels[10].

Coffee is the most popular and widely consumed non-alcoholic beverages in the world[4], and its role has been described to be beneficial on CVD incidence. Habitual coffee intake (more than three cups/day), has been shown to reduce the risk of heart failure on the Framingham Heart Study (FHS), the Cardiovascular Heart Study (CHS), and the Atherosclerosis Risk in Communities (ARIC) study[34]. Stevens et al. used machine learning based on random forest analysis to identify potential risk factors associated with CHD, stroke, and heart failure in the FHS. These results were later validated in the CHS and ARIC. Compared with those with no coffee consumption, the risk of heart failure was reduced respectively by 31% (HR, 0.69 [95% CI, 0.55–0.87]; $p < 0.001$) and by 29% (HR, 0.71 [95% CI, 0.58–0.89]; $p < 0.001$) in participants drinking 2 or 3 cups/day[34]. Moreover, Miranda et al.[35], have reported that coffee intake decrease the odds for subclinical atherosclerosis measured by coronary artery calcium, among never smokers[35]. After stratifying by smoking status, the analysis revealed a lower OR for coronary calcification (CAC > 100) in never smokers who drank more than 3 cups/day [OR: 0.37 (95% CI, 0.15–0.91)], whereas among current and former smokers, the intake of coffee was not significantly associated with coronary artery calcium. Finally, a meta-analysis by Kim et al.[36] has found that long-term coffee intake was inversely and significantly associated with CVD related mortality, with the lowest relative risk (RR) at intakes of 2.5 cups/day[36].

However, not all previous studies report in the same direction. In accordance with our results, Grioni et al. found that consumption over 2 cups/day of Italian-style coffee was associated with increased risk of CHD [HR:1.37 (95% CI 1.03–1.82) for > 2–4 cups/day and 1.52 (95% CI 1.11–2.07) for over 4 cups/day (p trend < 0.001) compared to reference (< 1 cup/day)]. Coffee intake was not associated with plasma lipid changes[13] in their study. It is important to highlight that differences in coffee elaboration and composition across southern Europe and other parts of the world may be responsible for the discrepancies. Indeed, consumption of unfiltered boiled coffee was associated with unfavourable changes in the lipid profile, and may cause a slight but significant rise in systolic blood pressure[37–39]. These unfavourable associations were mitigated with filtered coffee consumption, which is associated with a reduction of cardiovascular and general mortality, when compared to unfiltered coffee[40,41].

Association per 100gr—Arterial aging		
Participants (N = 2089)	**Carotid plaques Log OR (95%CI)**	**Femoral plaques Log OR (95%CI)**
Low-fat milk (semi-skimmed)	− 0.7 years or -9 months *	0.3 years or 4 months
Coffee and tea	2.3 years or 27 months ***	2.1 years or 26 months **
Whole-fat milk	0.0 years or 1 months	0.9 years or 11 months *
Sugar-sweetened beverages	0.7 years or 8 months	0.8 years or 9 months
Bottle fruit juices	0.1 years or 1 months	− 1.9 years or − 22 months **
Artificially sweetened beverages	0.3 years or 3 months	0.0 years or 0 months
100% Fruit juice	0.5 years or 6 months	− 0.6 years or − 7 months

Table 3. Association between 100 g/d of beverages consumed and arterial aging among participants in the AWHS. AWHS, Aragon Workers' Health Study; OR, odds ratio; CI, confidence interval. N, total number of participants. Asterisks denote P value: ***$p \leq 0.001$, **$p \leq 0.01$, *$p \leq 0.05$. †Adjusted for age, BMI, smoking status (ever smoker or never smoker), alcohol consumption (gr/day), hypertension, dyslipidemia, diabetes and total METs-h/week.

Apart from that, we cannot rule out the selection of the sample when studying older participants, instead of, in our case, where participants were middle-age men and free for CVD. With the available information, it still must be said that coffee consumption remains a question of debate within the scientific community.

So far, there is some controversy on the effect of fruit juice consumption. Our results suggest a reduction of subclinical atherosclerosis with bottled fruit juice consumption. In accordance with this, the study by Scheffers et al. showed that, compared with no consumption, up to 7 glasses/week of pure fruit juice consumption (defined as 100% fruit juice that can be both, fresh juice and bottled juice from concentrate) was significantly associated with reduced risk of CVD and CHD; and consumption of 1–4 and 4–8 glasses/week was significantly associated with a lower risk of stroke[15]. Furthermore, a recent meta-analysis by D'Elia et al. observed a non-linear inverse dose–response relationship between 100% fruit juice consumption and the risk of stroke (up to 200 ml/day), compared with no consumption, probably mediated by the decrease in blood pressure[14]. On the contrary, a recent meta-analysis of Pan et al.[42] reported a significant association of 100% fruit juice intake with CVD mortality among highest category versus lowest category of 100% fruit juice consumption[42]. However, in our study we could not identify the effect produced by bottled fruit juice with or without added sugars. Thus, it may be necessary to know the composition of bottled fruit juice, such as type of fruit, added or artificially sugars, antioxidants, elaboration process, etc., in order to correctly evaluate these associations in the future.

In line with our results, the consumption of SSBs and ASBs have already been demonstrated to have harmful effects on cardiovascular health[43]. Consumption of SSBs was associated with increased risk of CVD, CHD, or stroke[18,43,44]. For example, results of a meta-analysis by Narain et al.[18] suggest a greater risk of stroke (RR 1.13, 95% CI 1.02–1.24) and myocardial infarction (RR 1.22, 95% CI 1.14–1.30) with a one-serving per day increase in SSB consumption. When they evaluate high vs. low SSB consumption, the results suggest that there was a greater risk of myocardial infarction (RR 1.19, 95% CI 1.09–1.31). Moreover, their results suggest only a greater risk of stroke (RR 1.08, 95% CI 1.03–1.14) with a one serving per day increase in ASB consumption. When evaluating high vs. low consumption of ASB, there was a significantly greater risk of stroke (RR 1.14, 95% CI 1.04–1.26) and vascular events (RR 1.44, 95% CI 1.02–2.03)[18]. These results are in accordance with the study by Koning et al.[44] in which an association between SSB consumption and CHD was found[44]. Additionally, results from the meta-analysis by Yin et al.[43] suggest that 1 serving/day increment in SSB and ASB consumption was associated with an 8% and 7% CVD incidence and mortality, respectively.

Traditionally, diet quality has been based on solid food. However, beverages could play an important role in the onset and development of CVD. One of the main strengths of our study is that all beverages habitually consumed were considered. In addition, the "Mutually Adjusted Analysis" shows the results after adjusting the model for the rest of the beverages, eliminating the confusion that some beverages may exert on others. Additionally, the analyses were adjusted for traditional cardiovascular risk factors. Finally, the use of standardized protocols and high-quality data collection methods to obtain information on subclinical atherosclerosis stand out. Nevertheless, it has also several limitations. First, the cross-sectional design does not allow to establish causality nor the temporality of the associations found, although in this case, dietary intake was not modified by the presence of the subclinical disease, which was unknown by the participant. Second, our sample of females is too small to be analyzed separately. In addition, our sample comprised working males, all of whom worked in the same car assembly plant, as such, the results may not be directly generalized to the general population. Third, although the dietary assessment was conducted using FFQ by trained interviewers, we cannot rule out the presence of some misclassification[45]. However, the scientific literature supports that the FFQ is a feasible tool to evaluate food habits in epidemiological studies[46,47]. Fourth, even though we adjusted for the major potential confounders, residual confounding is still possible. Finally, other modifiers of the association between beverages consumption and subclinical atherosclerosis have not been considered.

In summary, prudence must be used when interpreting our findings and when making recommendation for CVD primary prevention. Excluding water and low-fat milk, the consumption of the other beverages within our study still require further debate, specifically when considering coffee consumption. While this debate remains, coffee consumption among middle-age men should not be encouraged.

Conclusion

Our results suggest that, among middle-age men free from CVD, there was a detrimental association between the consumption of coffee and the presence of subclinical atherosclerosis. Moreover, a protective association of low-fat milk on the presence of subclinical atherosclerosis in carotid territories was observed.

Data availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending on request from the corresponding author. The data are not public due to ethical reasons.

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Author contributions
The authors' contributions were as follows—A.M.C.: interpretation of data and drafting the manuscript. M.L.: analysis of data, and critical revision of the manuscript. P.G.C.: study concept and critical revision of the manuscript. B.M.F. study concept and design, interpretation of data, and drafting of the manuscript. J.A.C., E.J., R.S.R.: revision of the manuscript for intellectual content. A.M.C., M.L., P.G.C., B.M.F., J.A.C., E.J., and R.S.R. read and approved the final manuscript.

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Competing interests
The authors declare no competing interests.

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Clinical Research Article

Low-Quality Carbohydrate Intake Is Associated With a Higher Prevalence of Metabolic Syndrome: The AWHS Study

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Abstract

Context: The relationship between carbohydrate quality intake and metabolic syndrome (MetS) is of growing interest.

Objective: We aimed to assess the association between the adherence to a dietary carbohydrate quality index (CQI) with the occurrence of MetS in a Spanish cohort of working adults.

Methods: A cross-sectional study was conducted of 2316 middle-aged men, aged 50.9 (SD 3.9) years, with no previous cardiovascular disease, and pertaining to the Aragon Workers' Health Study (AWHS) cohort. Diet was collected with a 136-item semiquantitative food-frequency questionnaire. The CQI (range 4-15) was based on: dietary fiber intake, a low glycemic index, the ratio of whole grains/total grains, and the ratio of solid carbohydrates/total carbohydrates. The higher the CQI, the healthier the diet. MetS was defined by using the harmonized National Cholesterol Education Programme–Adult Treatment Panel III (NCEP-ATP III) definition. The associations across 3-point categories of the CQI and the presence of MetS were examined using logistic regression.

Results: An inverse and significant association between the CQI and MetS was found. Fully adjusted odds ratios (ORs) for MetS risk among participants in the 10- to 12-point category (second highest CQI category) was 0.64 (95% CI, 0.45-0.94), and in the 13- to 15-point category (highest category) was 0.52 (95% CI, 0.30-0.88), when compared with the 4- to 6-point category (lowest category). Participants with 10 to 12 and 13 to 15 points on the CQI showed a lower risk of hypertriglyceridemia: OR 0.61 (95% CI, 0.46-0.81), and 0.48 (95% CI, 0.32-0.71) respectively.

Conclusion: Among middle-aged men, a higher adherence to a high-quality carbohydrate diet is associated with a lower prevalence of MetS. Triglyceridemia is the MetS component that contributed the most to this reduced risk.

Key Words: carbohydrates, metabolic syndrome, triglycerides, carbohydrate quality index

Abbreviations: AWHS, Aragon Workers' Health Study; CQI, carbohydrate quality index; CVD, cardiovascular disease; FFQ, food frequency questionnaire; GI, glycemic index; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; MetS, metabolic syndrome; OR, odds ratio; RR, relative risk; TGs, triglycerides.

The prevalence of metabolic syndrome (MetS) is on the rise worldwide, becoming a public health concern (1). MetS is a condition that includes a cluster of risk factors, such as high waist circumference, high blood pressure, atherogenic dyslipidemia, and high plasma glucose. MetS has been linked to the development of type 2 diabetes mellitus and cardiovascular diseases (CVDs) (2, 3). The increase in the occurrence of MetS has been attributed to the rise in obesity, which in turn is associated with a sedentary lifestyle (1) as well as with poor dietary habits (4, 5). Therefore, efforts to prevent MetS in the public health arena have focused on promoting healthy lifestyles, including a healthy diet (2, 6).

A high-quality carbohydrate diet is now considered to be healthy and favorable. Thus, improving the quality of carbohydrate intake seems to be more beneficial than reducing their quantity (7). Carbohydrate quality is a multidimensional entity that integrates several parameters and, as such, these parameters could act in a synergetic way (7, 8). Traditionally, there are some

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dietary parameters that were used to assess carbohydrate quality, such as fiber intake, whole-grain consumption, the glycemic index (GI), or the glycemic load. It has been shown that a higher intake of fiber and whole grain is associated with a lower risk of MetS (9-11), while the consumption of refined grain is positively associated with MetS (11). In the same way, a high dietary GI increases the risk of MetS (12, 13).

In recent years, authors have assessed the overall carbohydrate quality within a dietary pattern by elaborating a single index, known as the carbohydrate quality index (CQI). The first definition of the CQI was performed by Zazpe et al (14), allowing scientists to compare participants with different quality and quantity of carbohydrate intake, as well as to describe the role of carbohydrates as a group in disease development. High scores in this index are associated with lower cardiometabolic risk factors, such as obesity (15, 16), high waist circumference (17), high glycated hemoglobin A_{1c} (18), and hypertension (15), which eventually could result in the occurrence of MetS. High CQI scores have also been associated with lower subclinical atherosclerosis (19) and CVD (20). Nevertheless, the scarce evidence about the association between the CQI and the occurrence of MetS have shown mixed results (15, 21). Therefore, we aim to study the association between the adherence to the CQI and the occurrence of MetS in a well-characterized Spanish sample of working adults.

Materials and Methods

Study Design and Population

This is a cross-sectional study carried out with a subsample from the Aragon Workers' Health Study (AWHS), whose design and methodology have been previously described (22). The AWHS is a prospective cohort with the aim to characterize risk factors for metabolic abnormalities and subclinical atherosclerosis, by performing annual physical examinations of 5678 workers belonging to an automobile assembly plant from Spain. Between 2011 and 2014, a total of 2617 participants aged 39 to 59 years and free from CVD at baseline, attended extended examinations that included an interview with questionnaires on diet and lifestyles. We excluded women due to their small number (n = 132), and those with missing data on diet or on the components of MetS (n = 169). The final sample comprised 2316 men (Supplementary Fig. S1) (23). The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the clinical research ethics committee of Aragon (CEICA) (PI07/09). All participants provided written informed consent.

Data Collection

Diet assessment and carbohydrate quality index calculation

The habitual diet over the year preceding the interview was assessed using a semiquantitative food frequency questionnaire (FFQ) previously validated in Spain (24). This questionnaire collects data on the frequency of the consumption of 136 food items, considering 9 frequencies from "never or almost never" to "more than six times a day." Additionally, dietary energy, macronutrient, and micronutrient intake were derived by using Spanish food composition tables (25, 26).

We calculated the CQI (19) to assess an overall index for carbohydrate quality, considering the following components: 1) dietary fiber intake (g/d); 2) the GI; 3) whole-grain/total grain ratio; 4) and solid carbohydrate/total carbohydrate ratio. Dietary fiber intake was calculated according to the Spanish food composition tables. GI was calculated as a weighted GI that was based on the GI for each individual food that was obtained from Spanish food composition tables (25, 26), and using a previously defined formula (15). Whole-grain consumption was estimated as the sum of "whole bread consumption," "integral cereal consumption," and "whole wheat cookie consumption." Total grain intake was calculated by summing up all types of grains, defined as the intake of whole grains, refined grains, and their products (including refined bread, refined breakfast cereal, white rice, refined pasta, pizza, and different biscuits, as well as pastry products). Liquid carbohydrates were calculated by summing up carbohydrates ingested from sugar-sweetened beverages and fruit juice. Solid carbohydrates accounted for the carbohydrate content from the rest of the foods.

Each component contributed to the score as follows (14): 1) For dietary fiber intake, participants were categorized into quartiles, and points were assigned from 1 to 4. Higher fiber intake increases the final score. 2) For GI, participants were categorized into quartiles, but points were assigned in reverse, from 4 to 1. Lower GI values increase the final score. 3) For the ratio of whole grains/total grains, participants were categorized into 3 groups. Those with no whole-grain consumption received 1 point, and the rest were divided into 2 equally sized groups and received 2 and 3 points. Thus, this component was categorized into 3 groups based on the low variability consumption of whole grains in the sample. Higher ratios increase the final score. 4) For the ratio of solid carbohydrate/total carbohydrate, participants were categorized into quartiles, and points were assigned from 1 to 4. Higher ratios increase the final score (Table 1).

Finally, the CQI was constructed by summing up all the component scores (ranging from 4 to 15). We classified participants into four 3-point intervals of this final score. Higher CQI values mean better quality of the carbohydrate consumed (see Table 1).

Metabolic syndrome definition

MetS was diagnosed, according to the modified National Cholesterol Education Program—Adult Treatment Panel III definition (NCEP-ATP III) (2), when participants met at least 3 of the following 5 criteria: elevated waist circumference (≥102 cm), elevated fasting blood glucose (≥100 mg/dL or receiving antidiabetic drugs), elevated blood pressure (systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg, or receiving antihypertensive drugs), elevated serum triglycerides (TGs) (≥150 mg/dL or being on drug treatment for hypertriglyceridemia), and reduced serum high-density lipoprotein cholesterol (HDL-c) (<40 mg/dL).

Sociodemographic, clinical, and biological data

Age, type of work (blue collar or white collar), physical examination, as well as laboratory data were obtained during the annual medical examination by using standardized procedures.

The physical examination included height, weight, waist circumference, and blood pressure measurements. Medical history and the current use of medication were also collected. Waist circumference was obtained by using a flexible, nonextendible measuring tape (GulicK model 67 109) that was verified and revised monthly vs another tape calibrated every 3 years. The measurements were taken in the middle point between the iliac crest and the lowest point of the costal margin on the midaxillary line in a horizontal plane (parallel to the

Table 1. Components and algorithm used to calculate the carbohydrate quality index

Components of CQI	Index range (points) (4-15)	Scores according to groups of component (cutoff points)			
Dietary fiber intake, g/d	1-4	G1 = 1 (0-20.1)	G2 = 2 (20.1-24.4)	G3 = 3 (24.4-29.3)	G4 = 4 (29.3-max)
Glycemic index	1-4	G1 = 4 (0-48.8)	G2 = 3 (48.8-51.9)	G3 = 2 (51.9-54.0)	G4 = 1 (54.0-max)
Ratio of whole grains/total grains	1-3	G1 = 1 0	G2 = 2 (0, 0.246]	G3 = 3 (0.246-max)	
Ratio of solid carbohydrates/total carbohydrates	1-4	G1 = 1 (0-0.947)	G2 = 2 (0.947-0.977)	G3 = 3 (0.977-0.996)	G4 = 4 (0.996-max)

Abbreviations: CQI, carbohydrate quality index; G, group; Max, maximum.

Table 2. Baseline characteristics of Aragon Workers' Health Study participants according to carbohydrate quality index categories

		Carbohydrate quality index				
N = 2316	**Mean**	**4-6 points (lowest quality) n = 334**	**7-9 points n = 1039**	**10-12 points n = 745**	**13-15 points (highest quality) n = 198**	***P* for trend**
Age, y	50.9 (3.9)	50.4 (4.2)	51.0 (3.9)	51.1 (3.8)	51.0 (3.6)	.058
Type of work, white collar % (n)	12.0 (277)	10.8 (36)	10.3 (107)	14.4 (107)	13.6 (27)	.028
BMI	27.9 (3.5)	27.6 (3.6)	27.9 (3.5)	28.0 (3.4)	27.9 (3.5)	.292
Waist circumference, cm	98.0 (9.3)	97.5 (9.2)	98.4 (9.3)	97.9 (9.4)	97.2 (8.9)	.623
Systolic blood pressure, mm Hg	125.6 (14.0)	125.1 (13.9)	126.0 (13.7)	124.9 (14.2)	126.3 (15.3)	.980
Diastolic blood pressure, mm Hg	82.7 (9.5)	82.8 (9.5)	83.0 (9.2)	82.3 (9.6)	83.0 (10.1)	.570
Total cholesterol, mg/dL	220.1 (36.3)	220.1 (39.3)	218.7 (34.6)	222.1 (36.5)	219.7 (38.2)	.351
HDL-c, mg/dL	52.8 (11.4)	51.7 (10.7)	51.7 (10.9)	54.5 (11.8)	54.6 (12.1)	<.001
Non–HDL-c, mg/dL	167.2 (35.0)	168.4 (38.2)	167.0 (33.3)	167.6 (35.4)	165.1 (37.4)	.511
LDL-c, mg/dL	137.9 (31.4)	137.4 (34.2)	137.2 (30.6)	138.8 (30.7)	139.3 (33.4)	.285
Triglycerides, mg/dL	151.8 (98.9)	157.1 (91.0)	155.7 (108.1)	146.8 (88.6)	140.9 (97.5)	.013
Fasting glucose, mg/dL	98.0 (17.8)	96.7 (16.1)	97.9 (18.7)	98.2 (16.9)	99.4 (18.9)	.094
Ever-smokers, % (n)	76.7 (1776)	78.4 (262)	77.9 (809)	74.5 (555)	75.8 (150)	.126
Physical activity, total METs-h/wk	32.3 (23.0)	27.6 (20.8)	31.8 (22.2)	34.9 (24.5)	33.4 (23.9)	<.001
Hypertension, % (n)	38.7 (896)	36.2 (121)	39.0 (405)	38.5 (287)	41.9 (83)	.308
Dyslipidemia, % (n)	49.4 (1145)	49.7 (166)	48.7 (506)	49.5 (369)	52.5 (104)	.546
Diabetes, % (n)	5.8 (135)	4.5 (15)	6.0 (62)	5.5 (41)	8.6 (17)	.167

Values are mean (SD) or % (number). *P* value for trend from unadjusted regression models.
Abbreviations: BMI, body mass index; HDL-c, high-density lipoprotein cholesterol, LDL-c, low-density lipoprotein cholesterol; MET, metabolic equivalent; Non–HDL-c: non–high-density lipoprotein cholesterol.

ground), at the end of a nonforced exhale, with arms relaxed along the body and the legs slightly apart.

Laboratory data were obtained from fasting blood samples (>8 hours). Total cholesterol, HDL-c, TGs, and serum glucose were measured by spectrophotometry (Chemical Analyzer ILAB 650, Instrumentation Laboratory). Low-density lipoprotein cholesterol (LDL-c) was calculated using the Friedewald equation when TGs were lower than 400 mg/dL.

Lifestyles were obtained by interview. Participants were categorized as ever-smokers if they were "current smokers" (they reported having smoked in the last year) or "former smokers" (they had smoked at least 50 cigarettes in their lifetime, but not in the last year).

We assessed physical activity using the validated Spanish version (27) of the frequency of engaging in physical activity questionnaire, used in the Nurses' Health Study (28) and in the Health Professionals Follow-up Study (29). A metabolic value was assigned to each activity using the Ainsworth's compendium for physical activities (30), and was multiplied by the times the participant reported practicing it. We obtained a value for overall weekly metabolic equivalents-h by summing up all the activities.

Hypertension was defined as having systolic blood pressure greater than or equal to 140 mm Hg, or diastolic blood pressure greater than or equal to 90 mm Hg, or self-reported use of antihypertensive medication (31). Diabetes was defined as fasting plasma greater than or equal to 126 mg/dL or self-reported treatment with hypoglycemic medication (31). Dyslipidemia was defined as having total cholesterol greater than or equal to 240 mg/dL, or LDL-c greater than or equal to 160 mg/dL, or HDL-c less than 40 mg/dL, or self-reported use of lipid-lowering drugs (3).

Statistical Methods/Analysis

The CQIs were categorized into 4 groups (4-6, 7-9, 10-12, and 13-15 points) and the association of MetS was examined by

Table 3. Nutritional baseline characteristics of Aragon Workers' Health Study participants according to carbohydrate quality index categories

		Carbohydrate quality index				
N = 2316	Overall	4-6 points (lowest quality) n = 334	7-9 points n = 1039	10-12 points n = 745	13-15 points (highest quality) n = 198	*P* for trend
Total energy, kcal/d	2915.1 (731.3)	2814.5 (618.9)	2973.8 (738.2)	2909.1 (775.2)	2799.9 (669.5)	.570
Carbohydrates, g/d	333.0 (107.3)	334.2 (90.2)	344.3 (111.0)	324.9 (110.9)	302.3 (90.6)	<.001
Protein, g/d	108.5 (25.4)	101.2 (21.8)	109.0 (25.7)	110.2 (25.8)	112.2 (25.8)	<.001
Total fat, g/d	111.2 (29.0)	106.1 (24.8)	112.5 (29.2)	112.0 (30.4)	110.1 (28.5)	.116
Monounsaturated fatty acids, g/d	50.8 (13.7)	48.4 (11.3)	51.4 (13.8)	51.5 (14.4)	49.4 (13.9)	.17
Polyunsaturated fatty acids, g/d	18.4 (6.7)	17.6 (6.3)	18.8 (6.7)	18.3 (6.8)	18.6 (6.5)	.363
Saturated fatty acids, g/d	32.5 (10.8)	31.9 (9.5)	33.1 (10.8)	32.3 (11.2)	31.2 (10.8)	.247
Trans-saturated fatty acids, g/d	.9 (0.5)	0.9 (0.4)	0.9 (0.5)	0.8 (0.5)	0.7 (0.5)	<.001
Alcohol intake, g/d	21.2 (19.8)	16.8 (17.6)	21.2 (19.1)	23.0 (21.3)	21.6 (20.4)	<.001
Dietary fiber, g/d	25.5 (8.0)	19.4 (4.0)	23.9 (6.7)	28.2 (7.9)	34.2 (8.3)	<.001
Glycemic index	50.8 (4.7)	54.2 (2.0)	52.1 (3.5)	48.8 (4.9)	45.5 (4.5)	<.001
Solid carbohydrates, g/d	320.6 (103.9)	308.6 (84.2)	331.0 (107.5)	316.8 (108.8)	299.8 (89.7)	.091
Liquid carbohydrates, g/d	12.4 (15.8)	25.6 (20.7)	13.2 (14.8)	8.1 (12.2)	2.5 (3.9)	<.001
Whole grains, g/d	28.5 (61.6)	0.6 (4.8)	6.9 (29.6)	44.9 (66.7)	127.3 (92.1)	<.001
Total grains, g/d	282.6 (137.2)	284.0 (119.5)	298.1 (142.1)	268.8 (138.2)	251.4 (124.8)	<.001

Values are mean (SD) or % (number). *P* value for trend from unadjusted regression models.

using logistic regression. The models were adjusted for age, type of work, body mass index derived from the weight and height of a person in kg/m^2, smoking status, physical activity (total metabolic equivalents-h/week), hypertension, dyslipidemia, diabetes, total energy intake, protein intake, total fat intake, and alcohol intake. The same analyses were performed for MetS criteria separately. R statistical software (ver. 4.1.3) was used, and *P* values below .05 were considered statistically significant.

Results

The sample included 2316 men with a mean age of 50.9 (SD 3.9). Compared with individuals in the lowest CQI category, participants in the highest CQI category had higher concentrations of HDL-c, lower concentrations of TGs, and exerted more physical activity (Table 2).

Concerning diet, participants with higher CQI consumed fewer carbohydrates and trans-fatty acids, while consuming more protein and alcohol than participants with lower CQI. (Table 3).

The prevalence of MetS among participants was 27.5% (636 cases). The prevalence of the diagnosis criteria were 32.0% for elevated waist circumference, 37.3% for elevated fasting glucose, 57.1% for elevated blood pressure, 37.8% for elevated TGs, and 9.5% for reduced HDL-c.

Our results show a significant inverse association between the adherence to the CQI and the occurrence of MetS. Compared with participants in the lowest CQI category (4-6 points), those in the highest CQI category (13-15 points) had a lower prevalence of MetS (23.7% vs 27.5%). The fully adjusted odds ratios (OR) for MetS among participants with 10 to 12 points was 0.64 (95% CI, 0.45-0.94), and among those with 13 to 15 points was 0.52 (95% CI, 0.30-0.88), when compared with those in the 4- to 6-point CQI category (*P* for trend <.001) (Table 4, Fig. 1). Participants in both the 10- to 12-point category and the 13- to 15-point category also showed a lower risk of hypertriglyceridemia: OR = 0.61 (95% CI, 0.46-0.81) and 0.48 (95% CI, 0.32-0.71), respectively, when compared with those in the 4- to 6-point category (*P* for trend <.001) (see Table 4, Fig. 2). No significant association was found for the rest of MetS components (see Table 4).

Discussion

In this large epidemiological study, we found an inverse association between the adherence to the CQI and the occurrence of MetS. Therefore, consuming a diet rich in high-quality carbohydrates is associated with a lower risk of MetS among middle-aged Mediterranean working men who were free of CVD. This association was mainly driven by the hypertriglyceridemia component. These findings support that the quality of dietary carbohydrates is likely to play an important role in cardiometabolic health.

In the latest research, the isolated CQI components showed considerable clinical benefits in reducing the risk of MetS. More in particular, a study performed with 1301 adult cancer survivors (9) showed that as fiber intake increases the risk of MetS decreases (9). Moreover, a meta-analysis conducted with 14 observational studies, both cross-sectional and cohort studies (11), suggested that whole-grain consumption was negatively associated with MetS, whereas refined grain consumption was positively associated (11). Likewise, a meta-analysis that assessed whether a high GI or glycemic load contributed to the development of MetS (12) showed that a high vs a low dietary GI (but not glycemic load) was associated with an increased risk of MetS. Finally, the consumption of sugar-sweetened beverages, as an example of liquid carbohydrates, is suggested to increase the risk of MetS. In fact, meta-analyses by Malik et al (32) and Narain et al (33) reported that the consumption of sugar-sweetened beverages was associated

Table 4. Association between carbohydrate quality index and metabolic syndrome, as well as metabolic syndrome criteria in Aragon Workers' Health Study participants

	Carbohydrate quality index				
Participants (N = 2316)	4-6 points (lowest quality) OR (95%CI) n = 334	7-9 points OR (95% CI) n = 1039	10-12 points OR (95% CI) n = 745	13-15 points (highest quality) OR (95% CI) n = 198	*P* for trend[b]
MetS diagnosis, % (n)	27.5% (n = 92)	30.0% (n = 312)	24.8% (n = 185)	23.7% (n = 47)	
Age-adjusted	Ref.	1.08 (0.82-1.43)	0.83 (0.62-1.11)	0.78 (0.52-1.17)	.0384
Multivariable-adjusted[a]	Ref.	1.00 (0.71-1.41)	0.64 (0.45-0.94)	0.52 (0.30-0.88)	<.001
Waist circumference criterion for MetS, % (n)	30.5% (n = 102)	33.6% (n = 349)	31.0% (n = 231)	29.8% (n = 59)	
Age-adjusted	Ref.	1.12 (0.855-1.46)	0.99 (0.745-1.31)	0.94 (0.63-1.37)	.624
Multivariable-adjusted[a]	Ref.	0.98 (0.655-1.47)	0.73 (0.477-1.13)	0.72 (0.40-1.31)	.0556
Fasting blood glucose criterion for MetS, % (n)	35.6% (n = 119)	37.0% (n = 384)	37.7% (n = 281)	40.4% (n = 80)	
Age-adjusted	Ref.	1.01 (0.782-1.32)	1.04 (0.796-1.37)	1.18 (0.82-1.70)	.239
Multivariable-adjusted[a]	Ref.	0.96 (0.073-1.28)	0.96 (0.071-1.29)	1.03 (0.07-1.54)	.918
Blood pressure criterion for MetS, % (n)	56.0% (n = 187)	58.4% (n = 607)	56.0% (n = 417)	56.1% (n = 111)	
Age-adjusted	Ref.	1.04 (0.807-1.34)	0.93 (0.714-1.22)	0.94 (0.66-1.35)	.384
Multivariable-adjusted[a]	Ref.	1.01 (0.715-1.43)	0.83 (0.573-1.20)	0.71 (0.41-1.19)	.0416
Triglyceride criterion for MetS, % (n)	42.8% (n = 143)	39.9% (n = 415)	34.4% (n = 256)	30.8% (n = 61)	
Age-adjusted	Ref.	0.88 (0.68-1.13)	0.69 (0.53-0.90)	0.59 (0.40-0.85)	<.001
Multivariable-adjusted[a]	Ref.	0.81 (0.62-1.06)	0.61 (0.46-0.81)	0.48 (0.32-0.71)	<.001
HDL-cholesterol criterion for MetS, % (n)	9.3% (n = 31)	11.5% (n = 120)	7.0% (n = 52)	8.6% (n = 17)	
Age-adjusted	Ref.	1.273 (0.85-1.96)	0.73 (0.46-1.18)	0.92 (0.48-1.68)	.0215
Multivariable-adjusted[a]	Ref.	1.538 (0.98-2.47)	0.88 (0.53-1.48)	0.95 (0.47-1.88)	.0376

Abbreviations: HDL, high-density lipoprotein; MetS, metabolic syndrome; N, total number of participants; OR, odds ratio; Ref., reference.
[a]Adjusted for age, type of work (blue collar or white collar), body mass index, smoking status (ever smoker or never smoker), physical activity (total metabolic equivalents-h/wk), hypertension, dyslipidemia, diabetes, total energy, protein intake, total fat intake, and alcohol intake.
[b]*P* for trend is calculated using carbohydrate quality index as a continuous variable.

with an increment of 20% and 46% in the risk of developing MetS, respectively. This may be plausible because liquid from carbohydrates, as in sugar-sweetened beverages, are suggested to produce less satiety than an equivalent amount of carbohydrates coming from solid food (34).

The association between CQI and MetS may stem from quality aspects of dietary carbohydrates on traditional metabolic risk factors. For example, 2 studies performed with adults from Korea (15) and Spain (35) showed a significant inverse association between CQI and the incidence of overweight/obesity (15, 35) as well as with hypertension (15). However, another study conducted in the Framingham Offspring cohort (17) showed that a higher CQI was only marginally associated with a small increase in waist circumference, suggesting that CQI does not strongly influence waist circumference. These results are in accordance with the PREDIMED-Plus randomized trial by Martínez-González et al (7), which was conducted among participants at high risk for CVD. After 12 months of follow-up, improvements in CQI were favorably associated with CVD as well as with improvements in MetS components. Thus, improvements in CQI lead to a reduction in body weight, waist circumference, systolic and diastolic blood pressure, fasting blood glucose, glycated hemoglobin A_{1c}, TGs, and to increments in HDL-c (7), even among those who already had MetS.

The association between the adherence to the CQI and MetS has also been previously assessed in a representative sample composed of 12 027 adults from Korea (15). The association did not reach statistical significance when comparing extreme sex-specific quintiles of the CQI after adjustment for confounders, although central estimates were always protective. In a recent study conducted with 850 participants living in Iran and collected through the health system (21), no association between CQI and MetS was found after using a modified version of the CQI. Discrepancy in results may stem from differences in the MetS definition (eg, cutoff points for abdominal obesity were modified in Korean adults to account for their phenotype), also differences among countries in food consumption (eg, in the Iranian sample no consumption of whole grain was accounted for, which made the investigators eliminate this component from the index), the selection of the samples (eg, our sample was made up only of men), or the few number of events.

The biological mechanisms underlying the association between carbohydrate quality and MetS could be related to insulin resistance, impaired glucose metabolism, increased inflammation, weight gain and obesity, and reduced fiber intake.

Low-quality carbohydrate diets are practically based on high amounts of carbohydrate from refined sources, such as liquid carbohydrates, white bread, white rice, refined flours, and a high amount of added sugars (36). These diets show a lower consumption of proteins and fats, which are associated with an adverse effect on total mortality (36). A high consumption of refined carbohydrates is usually accompanied by a high dietary GI and glycemic load content (21, 36).

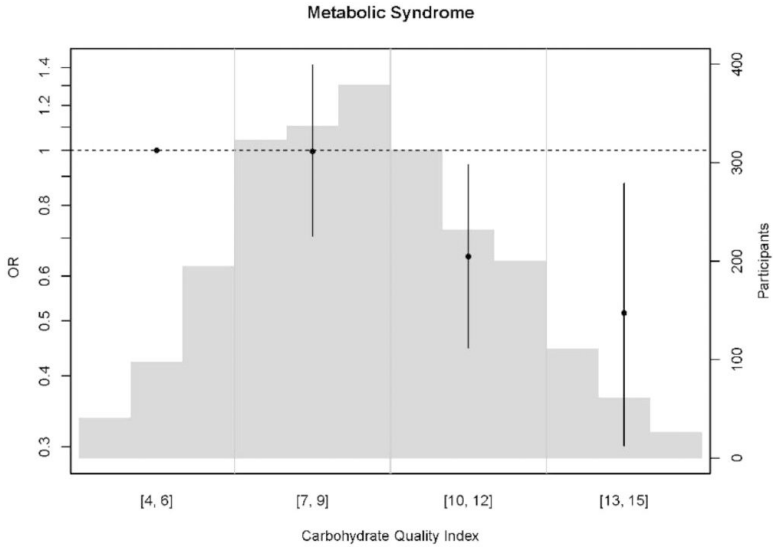

Figure 1. Odds ratios (OR) (95% CI) for metabolic syndrome according to carbohydrate quality index categories. Adjusted for age, type of work (blue collar or white collar), body mass index, smoking status (ever smoker or never smoker), physical activity (total metabolic equivalents-h/wk), hypertension, dyslipidemia, diabetes, total energy, protein intake, total fat intake, and alcohol intake.

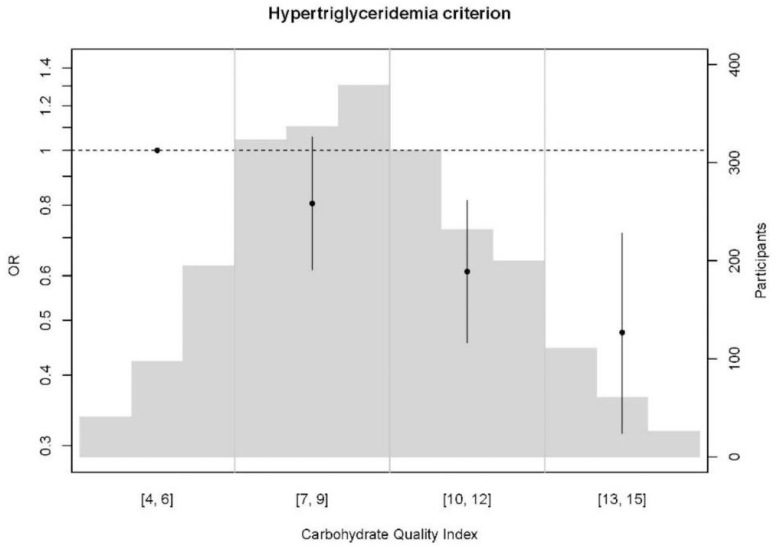

Figure 2. Odds ratios (OR) (95% CI) for the triglyceride criterion of the MetS according to carbohydrate quality index categories. Adjusted for age, type of work (blue collar or white collar), body mass index, smoking status (ever smoker or never smoker), physical activity (total metabolic equivalents-h/wk), hypertension, dyslipidemia, diabetes, total energy, protein intake, total fat intake, and alcohol intake.

Refined carbohydrates, especially those with a high GI, increase digestion and absorption of food, leading to rapid spikes in blood sugar levels, causing an overproduction of insulin and a suppression of free fatty acid levels (37). A counter-regulatory hormone response is triggered, reducing reactive hypoglycemia and enhancing the secretion of free fatty acids to levels above those observed after consumption of low GI meal (37, 38). Moreover, low-quality carbohydrates are characterized by their low dietary fiber content, making satiety signals in the body less effective (39). Over time, the abrupt changes in circulating concentrations of glucose and free fatty acids that trigger failures in satiety perception could increase

food intake and decrease insulin sensitivity, leading to inflammation, obesity, dyslipidemia, hypertriglyceridemia, and insulin resistance (40, 41). Moreover, a low-quality carbohydrate diet is characterized by a high consumption of liquid carbohydrates. Beverages with carbohydrates are easily digestible, providing less satiety signals to the body, but considerably increase daily caloric intake, promoting the previous mentioned mechanisms (42, 43).

Our findings extend the knowledge of the benefits of a high-quality carbohydrate diet on the occurrence of MetS. Our findings are relevant from a public health point of view, since dietary recommendations should include improving the quality of dietary carbohydrates, rather than only limiting their intake in quantity. Improvements in dietary habits should involve high-quality carbohydrate consumption, increments in the consumption of fruit and vegetables, a reduction in the consumption of sugar-sweetened beverages, as well as in the consumption of carbohydrates that are quick and easy to digest, such as liquid carbohydrates, refined grains, or those coming from ultraprocessed food. Therefore, it is relevant to communicate to the public the importance of the quality of carbohydrates over quantity. However, it is also desirable to replicate these analyses in other populations, whether Mediterranean or not, and in longitudinal cohort studies.

Strengths and Limitations

Our study has several strengths, such as the use of standardized protocols and high-quality data collection methods to obtain information on MetS, as well as our relatively large sample size. However, it also has several limitations. First, the cross-sectional design does not allow us to establish causality, nor the temporality of the associations. Second, our sample of women was too small to be analyzed separately, and therefore results were obtained only among men. In addition, our sample comprised working men, all of whom worked in the same car assembly plant; as such, the results may not be directly generalized to the general population. Third, although the dietary assessment was conducted using an FFQ and carried out by trained interviewers, we cannot rule out the presence of some degree of misclassification (44). However, the scientific literature supports that the FFQ is a valid tool to evaluate food habits in epidemiological studies (25, 45). Fourth, even though we adjusted for the major potential confounders, residual confounding may persist.

In short, this study provides grounds for specific recommendations on improving dietary carbohydrate quality as the primary prevention of MetS. The CQI could also be used to inform the general public about a poor-quality diet, which in turn may result in dietary qualitative changes. The CQI could also be useful in monitoring these changes.

Conclusion

Our results suggest that there is a protective association between the consumption of high-quality carbohydrates and the presence of MetS and hypertriglyceridemia among middle-aged men free of CVD.

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Author Contributions

The authors' contributions were as follows—A.M.C.: interpretation of data and drafting of the manuscript. M.L.: analysis of data and critical revision of the manuscript. P.G.C.: study concept and critical revision of the manuscript. B.M.F.: study concept and design, interpretation of data, and drafting of the manuscript. J.A.C., N.C.G., and V.M.B.: revision of the manuscript for intellectual content. A.M.C., M.L., P.G.C., B.M.F., J.A.C., N.C.G., and V.M.B. read and approved the final manuscript.

Disclosures

None.

Data Availability

Data described in the manuscript, code book, and analytic code will be made available on request pending on request from the corresponding author. The data are not public due to ethical reasons.

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6

Discusión global

El estilo de vida y en definitiva todos los componentes que lo modulan y definen, parecen jugar un papel clave y de vital importancia en la disminución de la probabilidad de padecer diferentes enfermedades no transmisibles que se desarrollan a lo largo de la vida, como pueden ser la ECV, la aterosclerosis subclínica o el SM.

En el ámbito de la investigación acerca de los estilos de vida y su influencia en las enfermedades no transmisibles, el compendio de publicaciones que conforman la presente Tesis Doctoral, ha contribuido a mejorar el conocimiento acerca de la relación entre la alimentación y este tipo de enfermedades. Las dimensiones de la muestra, la rigurosidad en la recogida de datos y la disponibilidad de múltiples variables han permitido obtener información valiosa y ampliar el conocimiento científico, generando nuevas hipótesis que puedan ser confirmadas en un futuro con otro tipo de estudios de diseño prospectivo.

La alimentación y, en concreto, la calidad de los carbohidratos consumidos es uno de los pilares fundamentales del estilo de vida y que, sin duda, como hemos podido comprobar en los diferentes manuscritos que componen esta Tesis Doctoral y en la literatura científica, influye en la salud de las personas (44,79,80). Así pues, nuestros resultados sugieren que el consumo de hidratos de carbono procedentes de cereales integrales, aquellos con un índice glucémico bajo, consumidos como alimentos sólidos, y asociados a fibra dietética podrían reducir potencialmente el riesgo de aterosclerosis subclínica y de SM. Estos resultados apoyan la premisa de que la calidad de los hidratos de carbono de la dieta puede desempeñar un papel importante como factor determinante de la salud cardiovascular y metabólica.

Las dietas con carbohidratos de baja calidad se basan prácticamente en cantidades elevadas de carbohidratos procedentes de fuentes refinadas, como los carbohidratos líquidos, el pan blanco, el arroz blanco, las harinas refinadas y una gran cantidad de

azúcares añadidos (81). Estas dietas presentan un menor consumo de proteínas y grasas, que se asocian a un impacto adverso sobre la mortalidad total (81). Un elevado consumo de hidratos de carbono refinados suele ir acompañado de un elevado índice glucémico y carga glucémica de la dieta (81,82).

Además de los anteriores, los mecanismos biológicos que subyacen a la asociación entre la calidad de los hidratos de carbono y el SM podrían estar relacionados con la resistencia a la insulina, el deterioro del metabolismo de la glucosa, el aumento de la inflamación, el aumento de peso y la obesidad, y la reducción de la ingesta de fibra.

Los hidratos de carbono refinados, especialmente los que tienen un IG elevado, aceleran la digestión y la absorción de estos principios inmediatos, lo que provoca picos rápidos en los niveles de glucosa en sangre, causando una sobreproducción de insulina y una supresión de los niveles de ácidos grasos libres (83). Esto, a su vez, desencadena una respuesta hormonal contrarreguladora que reduce el descenso reactivo de glucosa y aumenta la secreción de ácidos grasos libres si se comparan con los observados tras el consumo de una comida con IG bajo (83,84). Además, los hidratos de carbono de baja calidad se caracterizan por su bajo contenido en fibra dietética, lo que hace que las señales de saciedad en el organismo sean menos eficaces (85). Con el tiempo, los cambios bruscos en las concentraciones circulantes de glucosa y ácidos grasos libres, al desencadenar fallos en la percepción de la saciedad, podrían aumentar la ingesta de alimentos, además de disminuir la sensibilidad a la insulina, provocando inflamación, obesidad, dislipidemia e hipertrigliceridemia (86,87). Además, una dieta alta en hidratos de carbono se caracteriza por un elevado consumo de hidratos de carbono líquidos, normalmente en forma de SSB. Esta elevada ingesta de bebidas azucaradas ha demostrado tener efectos perjudiciales en la salud cardiovascular, afectando tanto al riesgo de padecer SM como aterosclerosis subclínica.

En primer lugar, el consumo de SSB conduce al aumento de peso, la dislipidemia, así como la resistencia a la insulina debido al alto contenido de azúcar añadido y su elaboración común con diferentes variedades de fructosa. Las calorías adicionales que se consumen con las bebidas carbonatadas no suelen compensarse con una menor ingesta de energía procedente de alimentos sólidos ni con un aumento del gasto energético, lo que a su vez conduce a un aumento de peso. Las SSB, como formas de hidratos de carbono

líquidos, producen menos saciedad que la cantidad equivalente de hidratos de carbono procedentes de alimentos sólidos, ya que son fácilmente digeribles (88). Además, el consumo excesivo de SSB aumenta la lipogénesis secundaria al metabolismo hepático de la fructosa (59,89). Asimismo, la fructosa es metabolizada por el hígado, lo que provoca dislipidemia (90) e hiperuricemia inducida por el hígado, propiciando el desarrollo de resistencia a la insulina (58,91). Por último, la elevada carga glucémica tras el consumo de SSB promueve la liberación de citocinas proinflamatorias en respuesta a la hiperglucemia (92). Todos estos mecanismos biológicos llevan al aumento de riesgo de padecer no solo SM, sino también aterosclerosis subclínica, dando lugar a posibles eventos cardiovasculares futuros.

Tradicionalmente, la calidad de la dieta se ha basado únicamente en los alimentos sólidos. Sin embargo, las bebidas pueden jugar un rol importante en el establecimiento y desarrollo de la ECV. No obstante, no debemos sólo enfocarnos en el efecto que las bebidas azucaradas tienen sobre la salud cardiometabólica. Otras bebidas como la leche, los zumos, o el café, pueden modular la funcionalidad correcta de nuestro organismo, actuando como agentes beneficiosos o perjudiciales cuando hablamos de salud cardiovascular.

Así pues, nuestros resultados sugieren que evitar el consumo de café y de leche entera podrían reducir potencialmente el riesgo de aterosclerosis subclínica. Como alternativas, consumir agua o leche baja en grasa, que no están vinculadas a resultados negativos, podrían beneficiar la salud cardiovascular. Sin embargo, algunas de estas evidencias no están exentas de controversia, como es el caso de la evidencia acerca del café.

El café es la bebida no alcohólica más popular y más consumida en el mundo (51), y se ha descrito su papel beneficioso sobre la incidencia y mortalidad de las ECV, así como sobre el desarrollo de aterosclerosis subclínica. Sin embargo, existen evidencias similares a la nuestra al estudiar el efecto del café de tipo italiano, donde se encontró un efecto perjudicial del mismo (93). Es importante destacar que las diferencias en la elaboración y composición del café en el sur de Europa y en otras partes del mundo pueden ser responsables de las discrepancias. De hecho, el consumo de café hervido sin filtrar se asoció a cambios desfavorables en el perfil lipídico, y puede causar un ligero, pero significativo aumento de la presión arterial sistólica (94–96). Estas asociaciones

desfavorables se atenuaron con el consumo de café filtrado, que se asocia a una reducción de la mortalidad cardiovascular y general, en comparación con el café sin filtrar (94–96). Con la información disponible, todavía hay que decir que el consumo de café sigue siendo una cuestión de debate dentro de la comunidad científica. Por ello, mientras persista este debate, no debe fomentarse el consumo de café entre los hombres de mediana edad.

Todas las evidencias recogidas en la presente Tesis Doctoral y la evidencia presente en la literatura justifican la importancia del cambio de paradigma en cuanto a la alimentación, más allá del beneficio de la dieta mediterránea. La calidad de los componentes de la dieta, especialmente en el grupo más consumido, ha demostrado impactar en el metabolismo y favorecer el desarrollo de múltiples patologías.

Sin dejar de lado otras recomendaciones proporcionadas por las autoridades sanitarias, como la reducción de sal (97), de azúcar (98) o del consumo de carne roja (99), estas deberían de incidir en cambios dietéticos basados en consumir grupos alimentarios de mejor calidad. Las mejoras en los hábitos dietéticos deben implicar un consumo de hidratos de carbono de alta calidad, un aumento del consumo de frutas y verduras, una reducción del consumo de bebidas azucaradas, así como del consumo de hidratos de carbono de digestión rápida y fácil, como los hidratos de carbono líquidos, los cereales refinados o los procedentes de alimentos ultraprocesados. Por lo tanto, merece la pena educar al público en general sobre los beneficios de los alimentos con carbohidratos de alta calidad y, al mismo tiempo, ser capaz de identificar estos alimentos.

Para ello, la creación de un índice de calidad de carbohidratos ha surgido como una herramienta útil para ser empleada en estudios epidemiológicos, y poder estimar la calidad de los carbohidratos consumidos y su proporción con relación a la dieta global. Este índice permite fortalecer el conocimiento sobre la relación entre el consumo de carbohidratos de baja calidad y su efecto en la salud cardiometabólica. A futuro, sería ideal poder transformar esta herramienta válida en investigación, en un cuestionario individual que pudiera ofrecer información al público general acerca de la calidad de su alimentación y la adherencia al consumo de carbohidratos de elevada calidad.

Sin duda, en la actualidad, la investigación sobre cómo los estilos de vida influyen en el desarrollo de enfermedades no transmisibles, es de vital importancia, y por ello este

campo se encuentra en pleno desarrollo. Serán las futuras investigaciones las que vayan aportando nuevo conocimiento al respecto, a través del cual sin duda conseguiremos mejorar la salud y calidad de vida de las personas.

La presente Tesis Doctoral presenta fortalezas, así como diferentes limitaciones observadas en los diferentes proyectos y manuscritos. En primer lugar, la revisión sistemática con metaanálisis, presenta la fortaleza de haber explorado por separado la asociación entre el consumo de bebidas azucaradas y el riesgo de síndrome metabólico, sin incluir aquellos estudios en los que el consumo de bebidas edulcoradas podría influir en los resultados. En segundo lugar, también se actualizó la evidencia científica mediante la inclusión de artículos originales omitidos en metaanálisis anteriores. En tercer lugar, se excluyeron los estudios con datos incompletos, clasificaciones erróneas o errores en el análisis de los datos, así como los estudios de baja calidad metodológica. En cuarto lugar, otra potente fortaleza consistió en el empleo de una metodología adecuada basada en las recomendaciones del Manual Cochrane para Revisiones Sistemáticas de Intervenciones (Cochrane Handbook for Systematic Reviews of Intervention) y las directrices PRISMA para realizar el metaanálisis, así como para informar de los resultados. En quinto lugar, otra fortaleza radica en la forma en la que se evaluaron la calidad metodológica de los estudios incluidos y el riesgo de los diferentes tipos de sesgos, a través de diferentes herramientas validadas y adecuadas a sus diferentes diseños metodológicos. En sexto lugar, se mostraron datos sobre estudios transversales y de cohortes, realizando análisis separados para cada tipo de diseño. Por último, se proporcionaron explicaciones para los resultados obtenidos gracias a los estudios prospectivos, los cuales nos aportaban estimaciones de riesgo más débiles.

El metaanálisis también cuenta con algunas limitaciones. Quizá la principal consiste en que la mayoría de los estudios incluidos fueron transversales, lo que impidió establecer una relación temporal entre el consumo de bebidas azucaradas y la aparición de SM, aunque los análisis separados, según su diseño, atenuaron esta limitación. En segundo lugar, los resultados muestran un alto grado de heterogeneidad entre los estudios. Esta heterogeneidad podría estar relacionada con las diferencias en la medición de la exposición, los criterios de diagnóstico de síndrome metabólico, la duración de los periodos de seguimiento y el ajuste por factores de confusión, aunque la asociación fue positiva en todos los estudios de cohortes incluidos. Además, este metaanálisis está

limitado por las pruebas existentes. Se observó una escasez de estudios de cohortes prospectivos, lo que también dio lugar a un sesgo de publicación confirmado por los test adecuados. Por último, el número de raciones no fue comparable en todos los estudios, lo que probablemente derivó en una subestimación de la asociación.

El proyecto AWHS presenta varias fortalezas que sitúan al proyecto como un referente en su campo de investigación. Sin embargo, presenta algunas limitaciones, siendo necesario tenerlas en cuenta a la hora de interpretar los diferentes resultados obtenidos a través del mismo.

Como una de las principales fortalezas de los estudios derivados del proyecto AWHS cabe remarcar el relativamente elevado tamaño de la cohorte original de la que surgen los distintos estudios incluidos en la presente Tesis Doctoral. Por otro lado, el proyecto destaca en el empleo de protocolos estandarizados y métodos de recogida de datos de alta calidad para obtener información acerca de diversas variables de interés, como pueden ser la aterosclerosis subclínica (tanto en el territorio femoral como en el carotídeo), el SM, la alimentación, o el nivel de actividad física y sedentarismo. En el ámbito de la alimentación, que es el que compete en los estudios realizados, la recogida de datos se llevó a cabo con cuestionarios dietéticos validados y realizados por personal formado para ello, siendo tanto el personal como las herramientas muy minuciosas a la hora de recoger una amplia variedad de alimentos y bebidas que pudieran ser empleados en los estudios. Por otro lado, cabe destacar el empleo de variados métodos estadísticos para conseguir la información más adecuada en cada caso, intentando disminuir los posibles factores de confusión ajustando siempre por los principales factores de riesgo tanto cardiovasculares, de presencia de síndrome metabólico, o de estilos de vida, y componentes de dieta que puedan influir en los resultados.

Como se ha indicado en anteriores apartados, el proyecto AWHS surgió con el objetivo de evaluar las diferentes trayectorias de los factores de riesgo cardiovascular tradicionales y emergentes, y su asociación con las anomalías metabólicas y la aterosclerosis subclínica en la población española de mediana edad y libre de cualquier ECV clínica. Sin embargo, la muestra del proyecto se ha compuesto de 5678 trabajadores de la misma planta de ensamblaje de automóviles, en la que la mayoría de ellos son hombres y de raza caucásica, siendo la muestra de mujeres demasiado pequeña como para poder analizarla y extraer

asociaciones. Sin duda este hecho limita la validez externa de los resultados de investigación, haciendo que tan solo sean aplicables a la población de sexo masculino y de raza caucásica.

A su vez, también cabe destacar que algunas de las mediciones y variables registradas en el proyecto fueron autorreportadas por los participantes y que, aunque las entrevistas a través de las cuales fueron obtenidos esos datos fueron efectuadas por personal investigador entrenado para ello, el uso de información autorreportada puede estar sujeto a sesgos debido a la subjetividad y al grado de colaboración que cada participante presenta. Las variables evaluadas a través de esta metodología y que se utilizan en alguno o varios estudios que forman parte de esta Tesis Doctoral son el nivel educativo, el patrón alimentario, y el consumo de diferentes sustancias como el tabaco o el alcohol.

Por otro lado, dado que el tiempo de seguimiento de la cohorte debe ser elevado para poder apreciar cambios longitudinales en las variables observadas, hasta poder contar con un tiempo significativo, se han ido realizando estudios de diseño transversal, con un corte temporal concreto, como es el caso de los tres estudios llevados a cabo para la presente Tesis Doctoral. Por ello, estas investigaciones no permiten establecer la causalidad ni la temporalidad de las asociaciones encontradas en todos ellos. Para atenuar este efecto, se escogieron patologías cuya existencia fuera desconocida por el paciente por ser no sintomáticas, lo que disminuye la posibilidad de que el participante modificase los hábitos dietéticos por el hecho de padecerla.

Por último, aunque los investigadores del proyecto AWHS mantienen una alta calidad metodológica en sus investigaciones, es posible que a pesar de su esfuerzo puedan existir algunos factores confusores residuales que hagan que la magnitud del efecto mostrado en los estudios no sea del todo correcta.

7

Conclusiones

Artículo 1. Las conclusiones del metaanálisis, basados en los resultados de 14 estudios epidemiológicos de base poblacional de alta calidad y que incluían a un total de 91.625 adultos, muestran una relación positiva entre el consumo de bebidas azucaradas y el riesgo de padecer el SM. Los resultados de los estudios transversales muestran que los adultos en la categoría más alta de consumo tenían un 35% más de riesgo de padecer el SM en comparación con los de la categoría más baja de consumo. El resultado correspondiente de los estudios longitudinales fue un 18% más de riesgo de incidencia de SM; si bien se identificó sesgo de publicación. En el futuro, es deseable la publicación de más estudios que evalúen la asociación prospectiva. Mientras tanto, las autoridades de salud pública deben prestar atención a la aplicación de estrategias públicas generales para desalentar el consumo de bebidas azucaradas y promover hábitos saludables que reduzcan los factores de riesgo asociados al síndrome metabólico.

Artículo 2. Entre los varones de mediana edad, un consumo de hidratos de carbono de alta calidad se asocia con una menor prevalencia de aterosclerosis subclínica de la arteria femoral en comparación con un consumo inferior, lo que indica una relación precoz entre la calidad de los hidratos de carbono y el desarrollo de enfermedad cardiovascular. Nuestros hallazgos amplían el conocimiento de los beneficios de un elevado CQI en los eventos cardiovasculares, mostrando beneficios en las primeras etapas del proceso de aterosclerosis.

Artículo 3. Entre los hombres de mediana edad libres de enfermedad cardiovascular, existe una asociación perjudicial entre el consumo de café y la presencia de aterosclerosis subclínica. Además, se observó una asociación protectora de la leche desnatada sobre la presencia de aterosclerosis subclínica en los territorios carotídeos. Sin embargo, dada la discrepancia entre la comunidad científica con determinadas bebidas, debe actuarse con prudencia a la hora de interpretar nuestros resultados y de formular recomendaciones para la prevención primaria de la ECV. Excluyendo el agua y la leche desnatada, el consumo

de las otras bebidas de nuestro estudio todavía requiere un debate más profundo, específicamente cuando se considera el consumo de café. Mientras se mantenga este debate, no debe fomentarse el consumo de café entre los hombres de mediana edad.

Artículo 4. Existe una asociación protectora entre el consumo de hidratos de carbono de alta calidad y la presencia de síndrome metabólico e hipertrigliceridemia entre los hombres de mediana edad libres de enfermedad cardiovascular. Este estudio proporciona fundamentos para recomendaciones específicas sobre la mejora de la calidad de los hidratos de carbono de la dieta como prevención primaria del SM. El CQI también podría utilizarse para informar al público en general sobre una dieta de mala calidad, lo que a su vez podría dar lugar a cambios cualitativos en la dieta. El CQI también podría ser útil para supervisar estos cambios.

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Apéndice

A continuación, se refiere el factor de impacto, área temática y posición en el ranking del ISI Journal of Citation Reports (JCR) 2022, de las revistas correspondientes a las publicaciones que se recogen en la presente Tesis Doctoral, así como la contribución de la doctoranda a cada artículo publicado.

Tabla 2: Características de las revistas donde se enmarcan los artículos pertenecientes a la Tesis Doctoral

Artículos publicados

Artículo	Revista	Factor de impacto (JCR 2022)	Contribución de la doctoranda
I	Clinical Nutrition Nutrition & Dietetics – Science Citation Index Expanded: 14/88 – Q1	6.3	Búsqueda bibliográfica, interpretación de análisis estadísticos, redacción y revisión crítica del manuscrito aprobación de la versión final para su publicación.
II	Nutrients Nutrition & Dietetics – Science Citation Index Expanded: 17/88 – Q1	5.9	Concepción inicial y diseño del estudio, búsqueda bibliográfica, realización e interpretación de análisis estadísticos, redacción y revisión crítica del manuscrito aprobación de la versión final para su publicación.
III	Scientific Reports Multidiciplinary Sciences – Science Citation Index Expanded: 22/73 – Q2	4.6	Búsqueda bibliográfica, interpretación de análisis estadísticos, redacción y revisión crítica del manuscrito aprobación de la versión final para su publicación.

IV	The Journal of Clinical Endocrinology & Metabolism Endocrinology & metabolism – Citation Index Expanded: 31/145 – Q1	5.8	Búsqueda bibliográfica, interpretación de análisis estadísticos, redacción y revisión crítica del manuscrito aprobación de la versión final para su publicación.

Anexos

Los anexos presentados previamente se muestran en esta sección por orden de aparición.

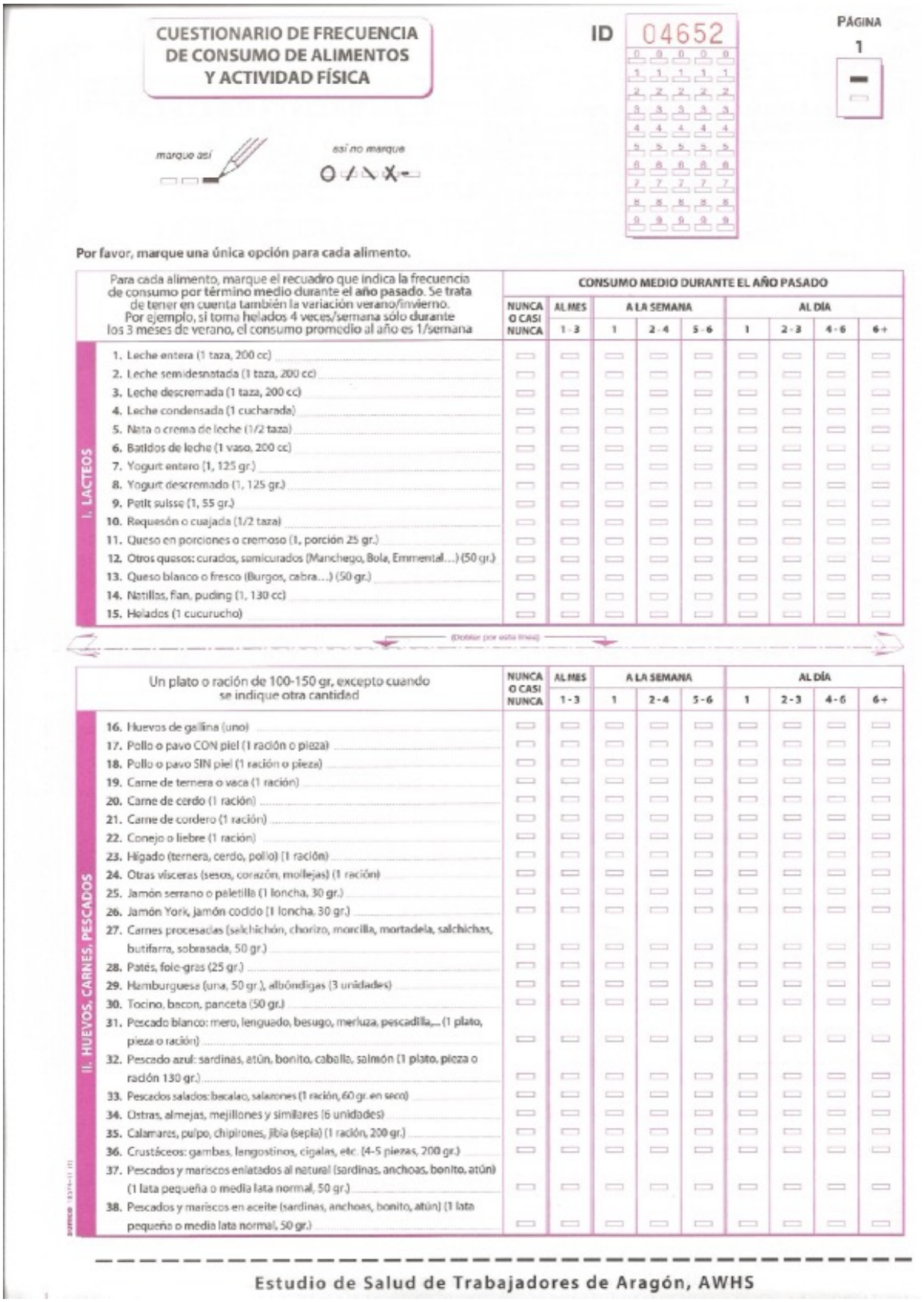
Anexo 1: Cuestionario de frecuencia de consumo de alimentos.

Anexo 2: Cuestionario de frecuencia de realización de actividad física.

Anexo 3: Aprobación del Comité Ético de Investigación Clínica de Aragón.

Anexo 4: Consentimiento informado para participantes del estudio AWHS.

Anexo 1: Cuestionario de frecuencia de consumo de alimentos.



CUESTIONARIO DE FRECUENCIA DE CONSUMO DE ALIMENTOS Y ACTIVIDAD FÍSICA

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PÁGINA 1

marque así — así no marque

Por favor, marque una única opción para cada alimento.

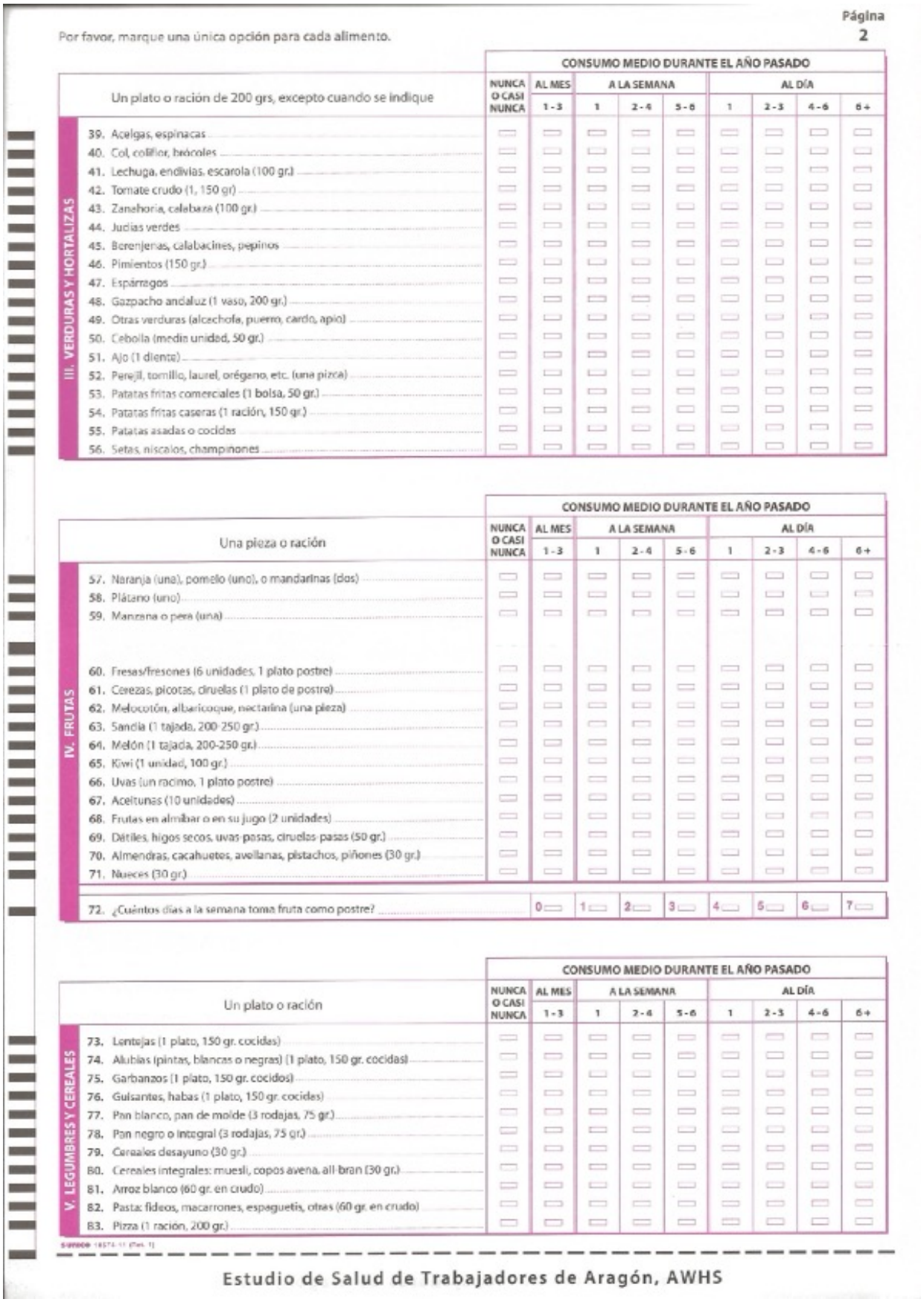
Para cada alimento, marque el recuadro que indica la frecuencia de consumo por término medio durante el año pasado. Se trata de tener en cuenta también la variación verano/invierno. Por ejemplo, si toma helados 4 veces/semana sólo durante los 3 meses de verano, el consumo promedio al año es 1/semana	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1-3	1	2-4	5-6	1	2-3	4-6	6+
I. LACTEOS									
1. Leche entera (1 taza, 200 cc)									
2. Leche semidesnatada (1 taza, 200 cc)									
3. Leche descremada (1 taza, 200 cc)									
4. Leche condensada (1 cucharada)									
5. Nata o crema de leche (1/2 taza)									
6. Batidos de leche (1 vaso, 200 cc)									
7. Yogurt entero (1, 125 gr.)									
8. Yogurt descremado (1, 125 gr.)									
9. Petit suisse (1, 55 gr.)									
10. Requesón o cuajada (1/2 taza)									
11. Queso en porciones o cremoso (1, porción 25 gr.)									
12. Otros quesos: curados, semicurados (Manchego, Bola, Emmental....) (50 gr.)									
13. Queso blanco o fresco (Burgos, cabra....) (50 gr.)									
14. Natillas, flan, puding (1, 130 cc)									
15. Helados (1 cucurucho)									

(Doblar por esta línea)

Un plato o ración de 100-150 gr, excepto cuando se indique otra cantidad	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1-3	1	2-4	5-6	1	2-3	4-6	6+
II. HUEVOS, CARNES, PESCADOS									
16. Huevos de gallina (uno)									
17. Pollo o pavo CON piel (1 ración o pieza)									
18. Pollo o pavo SIN piel (1 ración o pieza)									
19. Carne de ternera o vaca (1 ración)									
20. Carne de cerdo (1 ración)									
21. Carne de cordero (1 ración)									
22. Conejo o liebre (1 ración)									
23. Hígado (ternera, cerdo, pollo) (1 ración)									
24. Otras vísceras (sesos, corazón, mollejas) (1 ración)									
25. Jamón serrano o paletilla (1 loncha, 30 gr.)									
26. Jamón York, jamón cocido (1 loncha, 30 gr.)									
27. Carnes procesadas (salchichón, chorizo, morcilla, mortadela, salchichas, butifarra, sobrasada, 50 gr.)									
28. Patés, foie-gras (25 gr.)									
29. Hamburguesa (una, 50 gr.), albóndigas (3 unidades)									
30. Tocino, bacon, panceta (50 gr.)									
31. Pescado blanco: mero, lenguado, besugo, merluza, pescadilla,... (1 plato, pieza o ración)									
32. Pescado azul: sardinas, atún, bonito, caballa, salmón (1 plato, pieza o ración 130 gr.)									
33. Pescados salados: bacalao, salazones (1 ración, 60 gr. en seco)									
34. Ostras, almejas, mejillones y similares (6 unidades)									
35. Calamares, pulpo, chipirones, jibia (sepia) (1 ración, 200 gr.)									
36. Crustáceos: gambas, langostinos, cigalas, etc. (4-5 piezas, 200 gr.)									
37. Pescados y mariscos enlatados al natural (sardinas, anchoas, bonito, atún) (1 lata pequeña o media lata normal, 50 gr.)									
38. Pescados y mariscos en aceite (sardinas, anchoas, bonito, atún) (1 lata pequeña o media lata normal, 50 gr.)									

Estudio de Salud de Trabajadores de Aragón, AWHS

Anexo 1: Cuestionario de frecuencia de consumo de alimentos.



Página 2

Por favor, marque una única opción para cada alimento.

	Un plato o ración de 200 grs, excepto cuando se indique	CONSUMO MEDIO DURANTE EL AÑO PASADO								
		NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
			1-3	1	2-4	5-6	1	2-3	4-6	6+
III. VERDURAS Y HORTALIZAS	39. Acelgas, espinacas									
	40. Col, coliflor, brócoles									
	41. Lechuga, endivias, escarola (100 gr.)									
	42. Tomate crudo (1, 150 gr)									
	43. Zanahoria, calabaza (100 gr.)									
	44. Judías verdes									
	45. Berenjenas, calabacines, pepinos									
	46. Pimientos (150 gr.)									
	47. Espárragos									
	48. Gazpacho andaluz (1 vaso, 200 gr.)									
	49. Otras verduras (alcachofa, puerro, cardo, apio)									
	50. Cebolla (media unidad, 50 gr.)									
	51. Ajo (1 diente)									
	52. Perejil, tomillo, laurel, orégano, etc. (una pizca)									
	53. Patatas fritas comerciales (1 bolsa, 50 gr.)									
	54. Patatas fritas caseras (1 ración, 150 gr.)									
	55. Patatas asadas o cocidas									
	56. Setas, níscalos, champiñones									

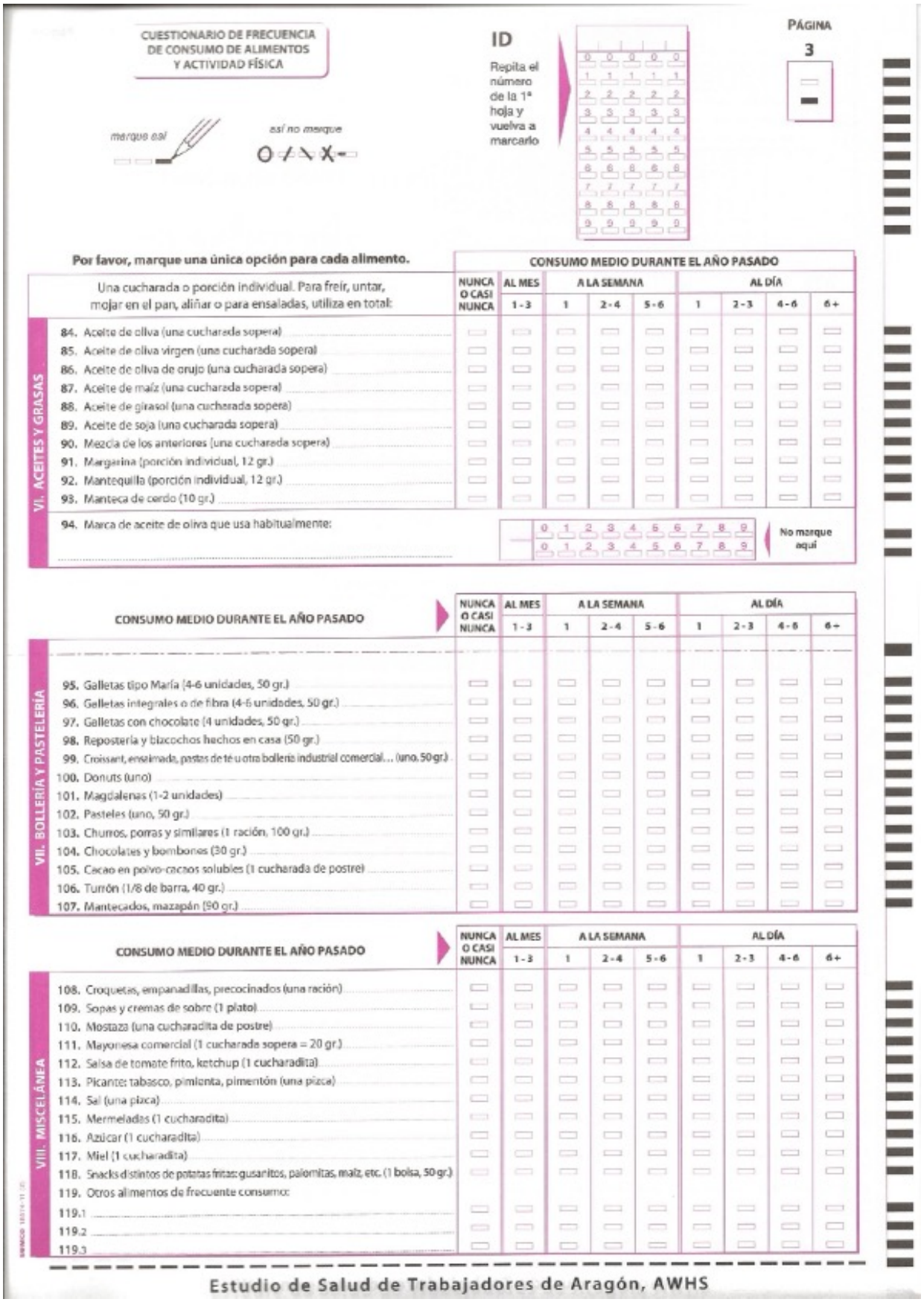
	Una pieza o ración	CONSUMO MEDIO DURANTE EL AÑO PASADO								
		NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
			1-3	1	2-4	5-6	1	2-3	4-6	6+
IV. FRUTAS	57. Naranja (una), pomelo (uno), o mandarinas (dos)									
	58. Plátano (uno)									
	59. Manzana o pera (una)									
	60. Fresas/fresones (6 unidades, 1 plato postre)									
	61. Cerezas, picotas, ciruelas (1 plato de postre)									
	62. Melocotón, albaricoque, nectarina (una pieza)									
	63. Sandía (1 tajada, 200-250 gr.)									
	64. Melón (1 tajada, 200-250 gr.)									
	65. Kiwi (1 unidad, 100 gr.)									
	66. Uvas (un racimo, 1 plato postre)									
	67. Aceitunas (10 unidades)									
	68. Frutas en almíbar o en su jugo (2 unidades)									
	69. Dátiles, higos secos, uvas pasas, ciruelas pasas (50 gr.)									
	70. Almendras, cacahuetes, avellanas, pistachos, piñones (30 gr.)									
	71. Nueces (30 gr.)									

	72. ¿Cuántos días a la semana toma fruta como postre?	0	1	2	3	4	5	6	7

	Un plato o ración	CONSUMO MEDIO DURANTE EL AÑO PASADO								
		NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
			1-3	1	2-4	5-6	1	2-3	4-6	6+
V. LEGUMBRES Y CEREALES	73. Lentejas (1 plato, 150 gr. cocidas)									
	74. Alubias (pintas, blancas o negras) (1 plato, 150 gr. cocidas)									
	75. Garbanzos (1 plato, 150 gr. cocidos)									
	76. Guisantes, habas (1 plato, 150 gr. cocidos)									
	77. Pan blanco, pan de molde (3 rodajas, 75 gr.)									
	78. Pan negro o integral (3 rodajas, 75 gr.)									
	79. Cereales desayuno (30 gr.)									
	80. Cereales integrales: muesli, copos avena, all bran (30 gr.)									
	81. Arroz blanco (60 gr. en crudo)									
	82. Pasta: fideos, macarrones, espaguetis, otras (60 gr. en crudo)									
	83. Pizza (1 ración, 200 gr.)									

Estudio de Salud de Trabajadores de Aragón, AWHS

Anexo 1: Cuestionario de frecuencia de consumo de alimentos.



CUESTIONARIO DE FRECUENCIA DE CONSUMO DE ALIMENTOS Y ACTIVIDAD FÍSICA

ID

Repita el número de la 1ª hoja y vuelva a marcarlo

PÁGINA 3

marque así

así no marque

Por favor, marque una única opción para cada alimento.

CONSUMO MEDIO DURANTE EL AÑO PASADO

Una cucharada o porción individual. Para freír, untar, mojar en el pan, aliñar o para ensaladas, utiliza en total:	NUNCA O CASI NUNCA	AL MES 1-3	A LA SEMANA 1	A LA SEMANA 2-4	A LA SEMANA 5-6	AL DÍA 1	AL DÍA 2-3	AL DÍA 4-6	AL DÍA 6+
VI. ACEITES Y GRASAS									
84. Aceite de oliva (una cucharada sopera)									
85. Aceite de oliva virgen (una cucharada sopera)									
86. Aceite de oliva de orujo (una cucharada sopera)									
87. Aceite de maíz (una cucharada sopera)									
88. Aceite de girasol (una cucharada sopera)									
89. Aceite de soja (una cucharada sopera)									
90. Mezcla de los anteriores (una cucharada sopera)									
91. Margarina (porción individual, 12 gr.)									
92. Mantequilla (porción individual, 12 gr.)									
93. Manteca de cerdo (10 gr.)									
94. Marca de aceite de oliva que usa habitualmente:									

No marque aquí

CONSUMO MEDIO DURANTE EL AÑO PASADO

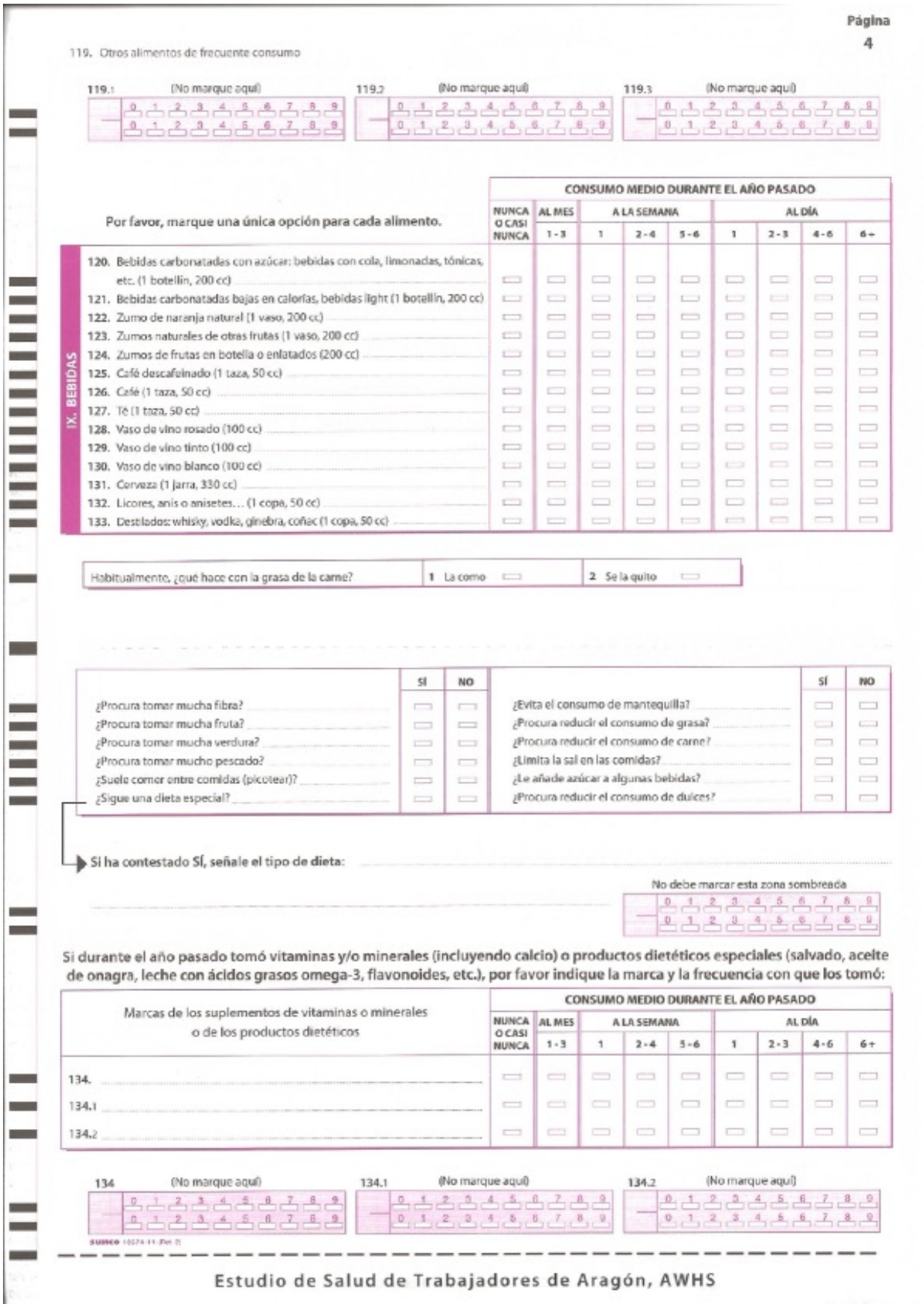
	NUNCA O CASI NUNCA	AL MES 1-3	A LA SEMANA 1	A LA SEMANA 2-4	A LA SEMANA 5-6	AL DÍA 1	AL DÍA 2-3	AL DÍA 4-6	AL DÍA 6+
VII. BOLLERÍA Y PASTELERÍA									
95. Galletas tipo María (4-6 unidades, 50 gr.)									
96. Galletas integrales o de fibra (4-6 unidades, 50 gr.)									
97. Galletas con chocolate (4 unidades, 50 gr.)									
98. Repostería y bizcochos hechos en casa (50 gr.)									
99. Croissant, ensaimada, pastas de té u otra bollería industrial comercial... (uno, 50 gr.)									
100. Donuts (uno)									
101. Magdalenas (1-2 unidades)									
102. Pasteles (uno, 50 gr.)									
103. Churros, porras y similares (1 ración, 100 gr.)									
104. Chocolates y bombones (30 gr.)									
105. Cacao en polvo-cacaos solubles (1 cucharada de postre)									
106. Turrón (1/8 de barra, 40 gr.)									
107. Mantecados, mazapán (50 gr.)									

CONSUMO MEDIO DURANTE EL AÑO PASADO

	NUNCA O CASI NUNCA	AL MES 1-3	A LA SEMANA 1	A LA SEMANA 2-4	A LA SEMANA 5-6	AL DÍA 1	AL DÍA 2-3	AL DÍA 4-6	AL DÍA 6+
VIII. MISCELÁNEA									
108. Croquetas, empanadillas, precocinados (una ración)									
109. Sopas y cremas de sobre (1 plato)									
110. Mostaza (una cucharadita de postre)									
111. Mayonesa comercial (1 cucharada sopera = 20 gr.)									
112. Salsa de tomate frito, ketchup (1 cucharadita)									
113. Picantes: tabasco, pimienta, pimentón (una pizca)									
114. Sal (una pizca)									
115. Mermeladas (1 cucharadita)									
116. Azúcar (1 cucharadita)									
117. Miel (1 cucharadita)									
118. Snacks distintos de patatas fritas: gusanitos, palomitas, maíz, etc. (1 bolsa, 50 gr.)									
119. Otros alimentos de frecuente consumo:									
119.1									
119.2									
119.3									

Estudio de Salud de Trabajadores de Aragón, AWHS

Anexo 1: Cuestionario de frecuencia de consumo de alimentos.



Página 4

119. Otros alimentos de frecuente consumo

119.1 (No marque aquí) | 119.2 (No marque aquí) | 119.3 (No marque aquí)

IX. BEBIDAS

Por favor, marque una única opción para cada alimento.

	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1-3	1	2-4	5-6	1	2-3	4-6	6+
120. Bebidas carbonatadas con azúcar: bebidas con cola, limonadas, tónicas, etc. (1 botellín, 200 cc)									
121. Bebidas carbonatadas bajas en calorías, bebidas light (1 botellín, 200 cc)									
122. Zumo de naranja natural (1 vaso, 200 cc)									
123. Zumos naturales de otras frutas (1 vaso, 200 cc)									
124. Zumos de frutas en botella o enlatados (200 cc)									
125. Café descafeinado (1 taza, 50 cc)									
126. Café (1 taza, 50 cc)									
127. Té (1 taza, 50 cc)									
128. Vaso de vino rosado (100 cc)									
129. Vaso de vino tinto (100 cc)									
130. Vaso de vino blanco (100 cc)									
131. Cerveza (1 jarra, 330 cc)									
132. Licores, anís o anisetes... (1 copa, 50 cc)									
133. Destilados: whisky, vodka, ginebra, coñac (1 copa, 50 cc)									

Habitualmente, ¿qué hace con la grasa de la carne? 1 La como ☐ 2 Se la quito ☐

	SÍ	NO		SÍ	NO
¿Procura tomar mucha fibra?	☐	☐	¿Evita el consumo de mantequilla?	☐	☐
¿Procura tomar mucha fruta?	☐	☐	¿Procura reducir el consumo de grasa?	☐	☐
¿Procura tomar mucha verdura?	☐	☐	¿Procura reducir el consumo de carne?	☐	☐
¿Procura tomar mucho pescado?	☐	☐	¿Limita la sal en las comidas?	☐	☐
¿Suele comer entre comidas (picotear)?	☐	☐	¿Le añade azúcar a algunas bebidas?	☐	☐
¿Sigue una dieta especial?	☐	☐	¿Procura reducir el consumo de dulces?	☐	☐

Si ha contestado SÍ, señale el tipo de dieta: .....

No debe marcar esta zona sombreada

Si durante el año pasado tomó vitaminas y/o minerales (incluyendo calcio) o productos dietéticos especiales (salvado, aceite de onagra, leche con ácidos grasos omega-3, flavonoides, etc.), por favor indique la marca y la frecuencia con que los tomó:

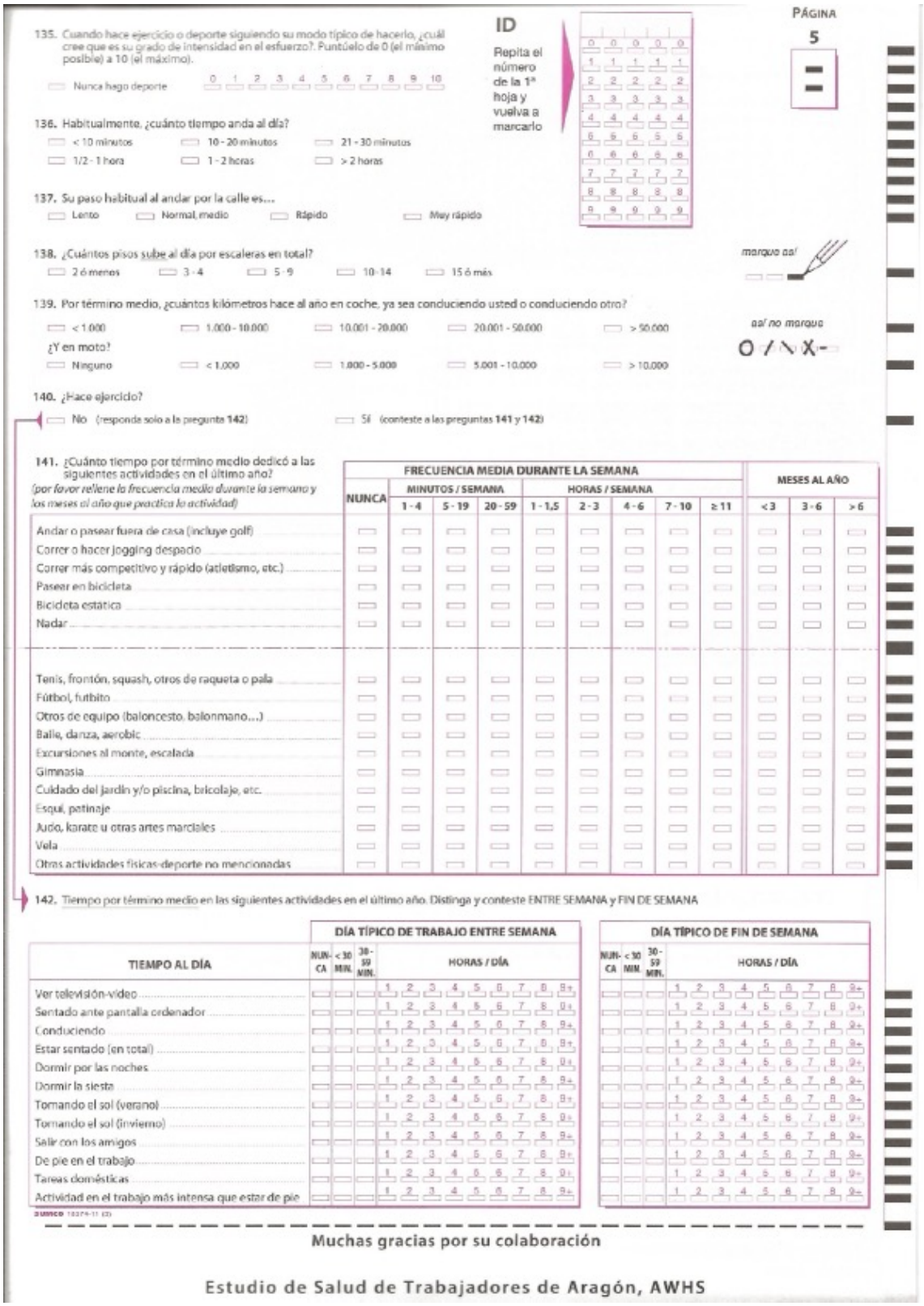
Marcas de los suplementos de vitaminas o minerales o de los productos dietéticos	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1-3	1	2-4	5-6	1	2-3	4-6	6+
134.									
134.1									
134.2									

134 (No marque aquí) | 134.1 (No marque aquí) | 134.2 (No marque aquí)

SUMCO 10074-11 (Rev.3)

Estudio de Salud de Trabajadores de Aragón, AWHS

Anexo 2: Cuestionario de frecuencia de realización de actividad física.



135. Cuando hace ejercicio o deporte siguiendo su modo típico de hacerlo, ¿cuál cree que es su grado de intensidad en el esfuerzo? Puntúelo de 0 (el mínimo posible) a 10 (el máximo).

Nunca hago deporte 0 1 2 3 4 5 6 7 8 9 10

ID

Repita el número de la 1ª hoja y vuelva a marcarlo

PÁGINA 5

136. Habitualmente, ¿cuánto tiempo anda al día?

< 10 minutos | 10 - 20 minutos | 21 - 30 minutos
1/2 - 1 hora | 1 - 2 horas | > 2 horas

137. Su paso habitual al andar por la calle es...

Lento | Normal, medio | Rápido | Muy rápido

138. ¿Cuántos pisos sube al día por escaleras en total?

2 ó menos | 3 - 4 | 5 - 9 | 10 - 14 | 15 ó más

marque así

139. Por término medio, ¿cuántos kilómetros hace al año en coche, ya sea conduciendo usted o conduciendo otro?

< 1.000 | 1.000 - 10.000 | 10.001 - 20.000 | 20.001 - 50.000 | > 50.000

¿Y en moto?

Ninguno | < 1.000 | 1.000 - 5.000 | 5.001 - 10.000 | > 10.000

así no marque

140. ¿Hace ejercicio?

No (responda solo a la pregunta **142**) | Sí (conteste a las preguntas **141** y **142**)

141. ¿Cuánto tiempo por término medio dedicó a las siguientes actividades en el último año?
(por favor rellene la frecuencia media durante la semana y los meses al año que practica la actividad)

	NUNCA	FRECUENCIA MEDIA DURANTE LA SEMANA: MINUTOS / SEMANA 1 - 4	5 - 19	20 - 59	HORAS / SEMANA 1 - 1,5	2 - 3	4 - 6	7 - 10	≥ 11	MESES AL AÑO < 3	3 - 6	> 6
Andar o pasear fuera de casa (incluye golf)												
Correr o hacer jogging despacio												
Correr más competitivo y rápido (atletismo, etc.)												
Pasear en bicicleta												
Bicicleta estática												
Nadar												
Tenis, frontón, squash, otros de raqueta o pala												
Fútbol, futbito												
Otros de equipo (baloncesto, balonmano...)												
Baile, danza, aerobic												
Excursiones al monte, escalada												
Gimnasia												
Cuidado del jardín y/o piscina, bricolaje, etc.												
Esquí, patinaje												
Judo, karate u otras artes marciales												
Vela												
Otras actividades físicas-deporte no mencionadas												

142. Tiempo por término medio en las siguientes actividades en el último año. Distinga y conteste ENTRE SEMANA y FIN DE SEMANA

TIEMPO AL DÍA	DÍA TÍPICO DE TRABAJO ENTRE SEMANA: NUNCA	< 30 MIN.	30 - 59 MIN.	HORAS / DÍA 1 2 3 4 5 6 7 8 9+	DÍA TÍPICO DE FIN DE SEMANA: NUNCA	< 30 MIN.	30 - 59 MIN.	HORAS / DÍA 1 2 3 4 5 6 7 8 9+
Ver televisión-video								
Sentado ante pantalla ordenador								
Conduciendo								
Estar sentado (en total)								
Dormir por las noches								
Dormir la siesta								
Tomando el sol (verano)								
Tomando el sol (invierno)								
Salir con los amigos								
De pie en el trabajo								
Tareas domésticas								
Actividad en el trabajo más intensa que estar de pie								

Muchas gracias por su colaboración

Estudio de Salud de Trabajadores de Aragón, AWHS

Anexo 3: Aprobación del Comité Ético de Investigación Clínica de Aragón.

GOBIERNO DE ARAGON
Departamento de Salud y Consumo

COMITÉ ÉTICO DE INVESTIGACIÓN
CLÍNICA DE ARAGÓN (CEICA)
Avda. Gómez Laguna, 25 planta 3
50009 Zaragoza

Dña. María González Hinjos, Secretaria del Comité Ético de Investigación Clínica de Aragón,

CERTIFICA

Que el proyecto de investigación titulado "**Aragón Workers Health Study"**

Investigador Principal: **Dr. Jose Antonio Casasnovas Lenguas.**

Ha sido evaluado por este Comité y tras la revisión de la documentación aportada, este CEIC resuelve **AUTORIZAR** la realización del estudio, según consta en el acta 09/2007, de 16 de mayo de 2007, y en este sentido se informa al Investigador Principal del proyecto.

Lo que firmo en Zaragoza, a 23 de mayo de 2007.

DIPUTACIÓN GENERAL DE ARAGÓN
DEPARTAMENTO DE SALUD Y CONSUMO
COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA DE ARAGÓN

María González Hinjos

Anexo 3: Aprobación del Comité Ético de Investigación Clínica de Aragón.

GOBIERNO DE ARAGON
Departamento de Salud y Consumo

COMITÉ ÉTICO DE INVESTIGACIÓN
CLÍNICA DE ARAGÓN (CEICA)
Avda. Gómez Laguna, 25 planta 3
50009 Zaragoza

LISTA DE MIEMBROS DEL COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA DE ARAGÓN

Dra. María González Hinjos, Secretaria del Comité Ético de Investigación Clínica de Aragón,

CERTIFICA

Que en la reunión de este Comité celebrada el día 16 de abril de 2007 estuvieron presentes las siguientes personas:

- Carlos Aibar Remón; Médico. Servicio de Medicina Preventiva y Salud Pública. Hospital Clínico Universitario Lozano Blesa. Profesional Sanitario experto en epidemiología clínica.
- Marina Heredia Ríos; Representante de las Organizaciones de Consumidores y Usuarios.
- Gabriel Hernández Delgado; Médico. Servicio de Radiología. Hospital Universitario Miguel Servet. Representante de Comisión de Investigación.
- Angela Idoipe Tomás; Farmacéutica. Servicio de Farmacia. Hospital Universitario Miguel Servet. Farmacéutica de Hospital.
- María Jesús Lallana Álvarez. Farmacéutica de Atención Primaria de Zaragoza Sector III.
- Cesar Loris Pablo; Médico. Servicio de Pediatría. Hospital Universitario Miguel Servet. Presidente del Comité. Representante de Comisión de Investigación.
- Jesús Magdalena Belio; Médico. Centro de Salud de Azuara. Médico con labor asistencial y representante del Comité de Ética Asistencial del Área de Atención Primaria II y V.
- Javier Perfecto Ejarque; Médico. Centro de Salud Arrabal. Médico con labor asistencial.
- Susana Torrente Gari; Jurista. Centro de Estudios Sociales. Licenciada en Derecho ajena a la profesión sanitaria.
- María González Hinjos; Farmacéutica. Secretaria del Comité Ético de Ensayos Clínicos.

Lo que firmo en Zaragoza, a 23 de mayo de 2007

DIPUTACIÓN GENERAL DE ARAGÓN
DEPARTAMENTO DE SALUD Y CONSUMO
COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA

Firmado: María González Hinjos

DNV
ACREDITADO POR ENAC

Anexo 4: Consentimiento informado para participantes del estudio AWHS.

HOJA DE INFORMACIÓN PARA EL TRABAJADOR

Naturaleza del proyecto

Aragón, al igual que otras sociedades desarrolladas, está sufriendo una epidemia de sobrepeso y de obesidad, que conlleva un riesgo mayor para desarrollar diabetes, síndrome metabólico, enfermedad cardiovascular, cáncer, enfermedades hepáticas, respiratorias y músculo-esqueléticas. Sin embargo no afecta por igual a todas las personas, algunas están más predispuestas que otras. Sabemos que los factores genéticos y ambientales (como el estilo de vida) pueden influir en el desarrollo futuro de la enfermedad.

El Aragón Workers Health Study es el estudio de salud de trabajadores de Aragón, el **objetivo** de este estudio es conocer mejor cómo se desarrolla la enfermedad cardiovascular, la obesidad, la diabetes, la hipertensión. Saber cuales son los hábitos de vida y los factores genéticos que nos protegen y los que hacen que progrese la enfermedad y nos lleven a sufrir angina de pecho, infarto de miocardio, claudicación de extremidades, infarto o hemorragia cerebral, etc.

Nuestro propósito es lograr una prevención cardiovascular más eficaz, centrándola sobre los trabajadores más predispuestos o con mayor riesgo de sufrir la enfermedad.

Este estudio está promovido conjuntamente por el departamento de Salud y Consumo del **Gobierno de Aragón** y por la fundación Centro Nacional de Investigaciones Cardiovasculares. Los investigadores responsables de este estudio pertenecen al Instituto Aragonés de Ciencias de la Salud (I+CS), a la Universidad de Zaragoza, al Centro Nacional de investigaciones cardiovasculares (CNIC) y al Servicio Aragonés de la Salud (SALUD).

En qué consiste la participación

Solicitamos su consentimiento informado para que usted nos autorice a:

- **Acceder a los datos clínicos** que se han recogido en su reconocimiento médico de su empresa, de forma totalmente anónima y exclusivamente con fines de investigación.

- **Utilizar los restos de sangre**, suero , plasma y orina que son desechados tras el análisis de sangre de su reconocimiento médico para realizar en esos restos los análisis bioquímicos y genéticos que nos permitan encontrar marcadores que nos indiquen de forma temprana su riesgo de enfermedad cardiovascular.

- **Realizar distintas técnicas de imagen indoloras**, no invasivas y sin riesgos a trabajadores más predispuestos a enfermar, para poder detectarles lesiones iniciales de enfermedad aterosclerótica en sus arterias, y poder así aplicarle la mejor prevención cardiovascular posible.

Anexo 4: Consentimiento informado para participantes del estudio AWHS.

Qué hacen los investigadores con las muestras de sangre

Las muestras de sangre recogida se procesarán en el laboratorio de General Motors de Figueruelas.

Se separará y guardará en pequeños contenedores parte de suero, plasma, orina y sangre. De las células sanguíneas se extraerá el material genético (el DNA) necesario.

Estas muestras se congelarán y guardarán en un banco de muestras por si en un futuro surgen nuevas líneas de investigación. Este material podrá ser compartido con otros grupos de investigación, procedimiento que siempre se hará bajo las normas de seguridad y confidencialidad necesarias y con autorización previa del comité científico del estudio, la dirección del Instituto Aragonés de Ciencias de la Salud (I+CS) y el Centro Nacional de Enfermedades Cardiovasculares (CNIC) que además serán los responsables de la custodia de dichas muestras.

En todos los aspectos referidos a la conservación y destrucción de las muestras recogidas y almacenadas, aseguramos el cumplimiento de la ley 14/2007 de investigación biomédica.

Qué hacen los investigadores con los datos que recogen

Los datos se guardan en ficheros, en bases de datos informatizadas. Estos ficheros identifican a cada participante con un código, por tanto no contienen ni su nombre ni otro dato que permita identificarle a ningún miembro del equipo investigador. Por lo tanto la comunicación de resultados tendrá que ser a través de su médico de empresa, que es quien únicamente conoce ese código.

Finalmente los resultados derivados de estos análisis se publican en revistas científicas. Estos datos no se utilizarán para otra finalidad que no sea la descrita y para su uso se seguirá siempre: su voluntad, la normativa vigente respecto a protección de datos de carácter personal y en general a la ética en la investigación científica.

Los resultados de los análisis de sangre, tanto de los habituales, como de los especiales y de DNA, así como los resultados de las exploraciones de imagen, serán entregados directamente al Servicio de Prevención de Riesgos Laborales de General Motors Figueruelas, para que sea su médico de empresa el que le transmita la información confidencial a cada trabajador.

Beneficios y riesgos de participar en el estudio

El beneficio del estudio para la sociedad es **profundizar en el conocimiento de la enfermedad cardiovascular** y así intentar encontrar herramientas (marcadores) para detectar la enfermedad antes de que provoque síntomas, para mejorar su prevención y tratamiento,

Anexo 4: Consentimiento informado para participantes del estudio AWHS.

detectando a las personas que tienen más riesgo de padecer enfermedad cardiovascular: infarto de miocardio, angina, infarto cerebral etc.

A corto plazo no se prevé que los resultados obtenidos del estudio puedan beneficiar directamente al individuo participante, aunque esperamos obtener estas herramientas diagnósticas útiles a partir de los tres años de iniciado el estudio. Por ello, es probable que usted pueda salir beneficiado de unas novedosas e incruentas técnicas de imagen para el diagnóstico de enfermedad que aún no ha producido síntomas y un conocimiento más profundo sobre sus metabolismo, hábitos de vida y, por tanto, sobre su riesgo cardiovascular.

Los riesgos para los participantes del estudio son inexistentes.

Garantía de participación voluntaria

Si a pesar de todo decide no participar, su atención por el personal médico de la factoría General Motors España Figueruelas no se verá afectada en nada, Además, en el caso que usted acepte participar, ha de saber que se puede retirar **en cualquier momento sin tener que dar explicaciones,** simplemente diciéndoselo a un miembro del equipo médico de General Motors. Su muestra será retirada del banco de almacenamiento y sus datos clínicos eliminados.

En el caso de que se jubilara de forma ordinaria o debido a una incapacidad podría continuar en el estudio, asumiendo completamente el equipo de investigación todos los procedimientos que se realizaran.

Muchas gracias por su tiempo y atención.

EL EQUIPO MEDICO INVESTIGADOR

Anexo 4: Consentimiento informado para participantes del estudio AWHS.

HOJA DE CONSENTIMIENTO INFORMADO

PROYECTO: Estudio de la salud de los trabajadores de Aragón

Yo, ...

(nombre y apellidos)

He leído la hoja de información que se me ha entregado.
He podido hacer preguntas sobre el estudio.
He recibido suficiente información sobre el estudio.

He hablado con: ....
.....

(nombre y apellidos de la persona que ha explicado este consentimiento investigador)

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:
1) cuando quiera
2) sin tener que dar explicaciones
3) sin que esto repercuta en mis cuidados médicos
Presto libremente mi conformidad para participar en el estudio.

Doy mi conformidad para participar en este estudio cuyos procedimientos y objetivos se me han explicado.

He recibido una copia firmada de este Consentimiento Informado.

Fecha:

Firma del participante :

He explicado la naturaleza y el propósito del estudio al paciente mencionado

Fecha:

Firma del Investigador:

Anexo 4: Consentimiento informado para participantes del estudio AWHS.

Deseo dejar de participar en este estudio desde la fecha indicada en adelante, aunque el equipo investigador podrá utilizar los datos clínicos y las muestras que hasta ahora habían recogido.

Fecha:

Firma del participante:

Deseo dejar de participar en este estudio y, por lo tanto, deberán destruirse las muestras biológicas almacenadas, así como los datos clínicos aportados para este estudio hasta el momento.

Fecha:

Firma del participante: