UNIVERSIDAD PÚBLICA DE NAVARRA. DEPARTAMENTO DE CIENCIAS DE LA SALUD

Prevalencia de sobrepeso y obesidad en Navarra, 2004-2011. Factores asociados a la obesidad y su relación con la depresión

Tesis Doctoral

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Antonio Brugos Larumbe, Francisco Guillén Grima y Amelia Martí del Moral, directores de la presente Tesis Doctoral con título: Prevalencia de sobrepeso y obesidad en Navarra, 2004-2011. Factores asociados a la obesidad y su relación con la depresión

AUTORIZAN a presentar dicha Tesis Doctoral en la modalidad de compendio de publicaciones.

Fdo.: Antonio Brugos Larumbe Fdo.: Francisco Guillén Grima Fdo.: Amelia Martí del Moral

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A Lara,

porque cada sonrisa me da la vida

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LISTADO DE PUBLICACIONES

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1. Martin-Rodriguez E, Guillen-Grima F, Martí A, Brugos-Larumbe A. **Comorbidity associated with obesity in a large population: The APNA study**. Obes Res Clin Pract 2015; 9: 435-47.

2. Martin-Rodriguez E, Guillen-Grima F, Aubá E, Martí A, Brugos-Larumbe A. **Relationship between body mass index and depression in women: A 7-year prospective cohort study. The APNA study.** Eur Psychiatry 2016; 32: 55-60.

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ABREVIATURAS

OMS	Organización Mundial de la Salud
IMC	Índice de masa corporal
OR	Odds Ratio
SOPQ	Síndrome de ovario poliquístico
RR	Riesgo relativo
CVRS	Calidad de vida relacionada con la salud
TNF-α	Factor de necrosis tumoral
PCR	Proteína C reactiva
IL-6	Interleucina 6
EPOC	Enfermedad Pulmonar Obstructiva Crónica
LDL	Colesterol de baja densidad
VLDL	Colesterol de muy baja densidad
HDL	Colesterol de alta densidad
HR	Hazard Ratio
APNA	Atención Primaria de NAvarra

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I. INTRODUCCIÓN

1. OBESIDAD: DEFINICION, CLASIFICACIÓN Y EPIDEMIOLOGÍA

La obesidad es un problema sanitario de primera magnitud, en base a su alta frecuencia, las tendencias observadas en las últimas décadas [1] y las consecuencias que conlleva sobre morbilidad y mortalidad en la población que la sufre [2, 3]. Se trata de una enfermedad metabólica crónica de origen multifactorial cuya prevalencia en las últimas décadas se ha incrementado de forma alarmante alcanzando proporciones epidémicas [4]. Debido a su asociación con un amplio rango de enfermedades crónicas y al gran coste económico que ocasiona a todos los sistemas sanitarios, se ha convertido en uno de los problemas más importantes de salud pública, por lo que su estudio es una cuestión prioritaria para los profesionales sanitarios.

1.1. Definición y clasificación de la obesidad

El término "obesidad" se refiere al exceso de grasa. Según la Organización Mundial de la Salud (OMS), la obesidad y el sobrepeso se definen como una acumulación anormal o excesiva de grasa que puede ser perjudicial para la salud [5]. La obesidad conlleva una afectación física y psíquica de la persona, con patologías asociadas que limitan la esperanza de vida y deterioran la calidad de la misma, y que pueden determinar la proyección vital, social y laboral del individuo.

En función del porcentaje de grasa corporal, se definen los sujetos obesos como aquellos que presentan un porcentaje de grasa corporal por encima de los valores considerados normales, que son del 12-20% del peso corporal en los hombres y el 20-30% en las mujeres adultas [6, 7]. Sin embargo, los métodos empleados para medir directamente la grasa corporal no están disponibles en la práctica clínica diaria. Por esta razón, el método más utilizado para definir y clasificar la obesidad en el adulto es el **Indice de Masa Corporal** (IMC). Este parámetro proporciona una estimación de la grasa corporal suficientemente válida para fines clínicos. Se trata de un indicador simple de la relación entre el peso y la talla. Se calcula dividiendo el peso

de una persona en kilogramos por el cuadrado de su talla en metros (kg/m2). Proporciona la medida más útil del sobrepeso y la obesidad en la población, puesto que es la misma para ambos sexos y para los adultos de todas las edades. Sin embargo, esta estimación no es tan buena en niños, adolescentes o ancianos. Lo sobreestima en individuos musculosos (deportistas) y lo infravalora en personas con baja masa magra (ancianos). A pesar de ello, es el índice utilizado por la mayoría de estudios epidemiológicos y el recomendado por diferentes sociedades médicas y organizaciones de salud internacionales para el uso clínico dada su reproductibilidad, facilidad de utilización y capacidad de reflejar la adiposidad en la mayoría de la población.

La OMS ha propuesto una clasificación del grado de obesidad utilizando como criterio el IMC (**Tabla 1**).

Tabla 1. Clasificación de la obesidad según el IMC (OMS)

	IMC (kg/m^2)
Peso insuficiente	< 18,5
Normopeso	18,5-24,9
Sobrepeso	25,0-29,9
Obesidad	≥ 30
Obesidad tipo I	30,0-34,9
Obesidad tipo II	35,0-39,9
Obesidad tipo III	≥ 40

No existe un criterio uniforme para delimitar los intervalos de normopeso, sobrepeso y obesidad según los valores del IMC, y las clasificaciones pueden diferir ligeramente según la fuente consultada

Entre el IMC considerado normal (18,5-24,9 kg/m2) y el IMC que define obesidad (≥ 30 kg/m2) existe un amplio rango de sobrepeso (25 y 29,9 kg/m2) en el que se registra un exceso de grasa corporal y, con frecuencia, es un estadio transitorio hacia la obesidad. En este tramo se encuentra gran parte de la población española y reviste una notable importancia en la estrategia global de lucha contra este problema.

1.2. Epidemiología

La obesidad se considera como una de las epidemias del Siglo XXI. Esta afirmación, está siendo demostrada y confirmada con los estudios epidemiológicos más recientes [1]. El análisis del estatus ponderal de distintos estudios poblacionales realizados durante los últimos 35 años muestra un progresivo aumento del peso medio de las muestras [8].

La población española no escapa a esta pandemia mundial. En este sentido, los datos epidemiológicos de la evolución de las últimas décadas junto con los más recientes, reafirman que la obesidad es un problema de primera magnitud en España [9].

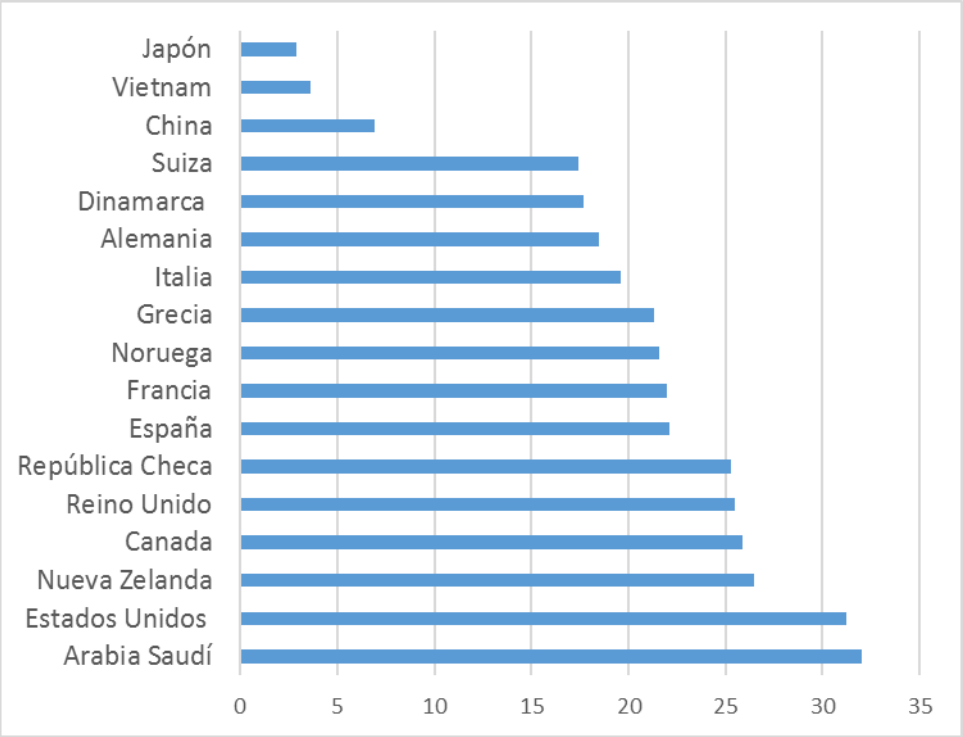
1.2.1. Epidemiologia de la obesidad a nivel mundial

En 2014, más de 1900 millones de adultos de 18 o más años tenían sobrepeso, de los cuales, más de 600 millones eran obesos. El 39% de las personas adultas de 18 o más años tenían sobrepeso, y el 13% eran obesas [5].

Existe una amplia heterogeneidad en la distribución de la prevalencia de obesidad a nivel mundial. La zona del Pacífico concentra la mayor proporción de personas con sobrepeso y obesidad en todo el mundo, según los datos correspondientes a 2014 que proporciona la OMS [10]. Países como las Islas Cook, Nauru, Palaos, Niue, Tonga y Samoa encabezan los rankings mundiales del índice de masa corporal, sobrepeso y obesidad por habitante. Se trata, en su mayor parte, de islas pobladas por unos pocos de miles de habitantes, entre los que predominan etnias polinesias.

Dentro de los países con mayor población, los que presentan las tasas más altas, superiores al 30%, son los Estados Unidos de América o Arabia Saudí, con prevalencias de 31,2% y 32% respectivamente (**Figura 1**). Tasas de entre el 20 y 30% se observan en algunos países de la comunidad europea como el Reino Unido (25,5%), Francia (22%) o España (22,1%), mientras que otros países europeos, como Dinamarca, Suiza o Italia, tienen tasas menores del 20% [10].

Figura 1. Prevalencia (%) de obesidad (IMC ≥ 30 kg/m^2) en adultos de ambos sexos en distintos países del mundo.



1.2.2. Epidemiología de la obesidad en España

Desde 1980, la obesidad se ha más que doblado en todo el mundo [5]. En España, la evolución de la prevalencia de obesidad según los datos de la Encuesta Nacional de Salud, se muestran en la **Tabla 2**. Se observa un progresivo y constante aumento en la prevalencia de obesidad, pasando del 7,8% en 1987 al 17% en 2012 [11]. Este aumento se observa para todos los grupos de edad y para ambos sexos [12-14]. Según los datos de la ENS-1987, la obesidad fue

levemente más prevalente en mujeres que en hombres y se mantuvo así hasta el 2001. En 2006, la obesidad es prevalente por igual en hombres y mujeres. Sin embargo, en el 2012 la prevalencia de obesidad en los hombres es mayor que en las mujeres.

Tabla 2. Prevalencia (%) de obesidad por sexo en población adulta española 1987-2012, según los datos de la Encuesta Nacional de Salud.

	1987	**1993**	**2001**	**2006**	**2012**
Total	7,8	9,9	12,8	16,4	17
Sexo					
Hombres	7,3	9,4	11,9	16,5	18
Mujeres	8,4	10,4	13,6	16,3	16

Uno de los datos más alarmantes se deriva del análisis de la evolución de la prevalencia de los distintos grados de obesidad. No sólo aumenta año a año la prevalencia de la obesidad, sino que la categoría en la que se ha observado un mayor incremento es la correspondiente al grado más extremo de la enfermedad, la denominada obesidad mórbida (IMC ≥ 40 kg/m^2). Así, el aumento de la prevalencia de obesidad durante el periodo 1993-2006, fue un 50% para obesidad grado I (IMC de 30-34,9 kg/m^2), del 110% para el grado II (IMC de 35-39,9 kg/m^2), y del 240% para obesidad mórbida (IMC ≥ 40 kg/m^2) [15]. Por tanto, en España está aumentando el número de personas con obesidad, pero especialmente el número y proporción de las que tiene grados extremos de exceso de peso, con lo que comporta de mayor gravedad, dificultades terapéuticas y enfermedades asociadas.

Recientemente se han realizado una serie de estudios epidemiológicos que nos ofrecen datos con medición directa de peso y talla en amplias muestras representativas de toda la población española, y esto supone un salto cualitativo muy importante para conocer mejor la

magnitud del problema. Actualmente disponemos de datos recientes de prevalencia de obesidad en España gracias a los estudios Enrica [16], dia@betes [17] y Darios [18]. Los resultados obtenidos en dichos estudios se resumen en la **Tabla 3**.

Tabla 3. Prevalencia (%) de sobrepeso y obesidad en España en mayores de 18 años.

Estudio	**Sobrepeso**	**Obesidad**
ENRICA	39,4	22,9
Di@bet.es	39,5	28,25
DARIOS	51	28

2. COMORBILIDAD ASOCIADA A LA OBESIDAD

La morbilidad y la mortalidad asociadas con el sobrepeso o la obesidad se conoce desde hace más de 2000 años [19]. El exceso de grasa corporal, particularmente de grasa visceral, incrementa el riesgo de padecer numerosas enfermedades [20, 21]. El aumento de este riesgo puede ser el resultado del efecto mecánico derivado de un mayor peso corporal o bien una consecuencia de las alteraciones metabólicas generadas por el exceso de grasa. Es importante destacar que las enfermedades asociadas a la obesidad son responsables de enormes costes sanitarios. Así, entre un 3% y un 7% del gasto sanitario total puede ser atribuido a la obesidad.

En la **Tabla 4** se resumen las comorbilidades más frecuentemente asociadas a la obesidad.

Tabla 4. Comorbilidades asociadas a la obesidad

Alteraciones cardiovasculares - Cardiopatía isquémica - Fibrilación auricular - Enfermedad cerebrovascular - Insuficiencia cardiaca congestiva	**Alteraciones digestivas** - Colelitiasis - Esteatosis hepática - Esteatohepatitis no alcohólica, cirrosis - Reflujo gastroesofágico, hernia de hiato
Alteraciones respiratorias - Disnea - Síndrome de apnea obstructiva del sueño - Asma bronquial	**Alteraciones musculo-esqueléticas** - Artrosis - Lesiones articulares - Deformidades óseas
Alteraciones metabólicas - Hipertensión arterial - Resistencia a la insulina y diabetes mellitus tipo 2 - Hiperuricemia - Dislipemia	**Alteraciones psicosociales** - Depresión - Discriminación social y laboral - Disminución de autoestima y calidad de vida - Trastornos del comportamiento alimentario
Alteraciones de la mujer - Disfunción menstrual - Síndrome de ovarios poliquísticos - Infertilidad	**Neoplasias** - Mujer: vesícula, mama y endometrio - Hombre: colón, recto y próstata

En una encuesta llevada a cabo en los Estados Unidos, aquellos individuos con sobrepeso u obesos tenían un mayor riesgo de hipertensión, hipercolesterolemia y diabetes mellitus comparados con individuos con normopeso [22]. El riesgo de hipertensión y diabetes mellitus

aumentaba con el incremento del IMC (Odds ratio (OR) ajustados de 2,6 a 4,8 para hipertensión y de 1,6 a 5,1 para diabetes mellitus en individuos con un IMC ≥ 25 kg/m^2). En varios estudios epidemiológicos, el riesgo de desarrollar una enfermedad crónica (colelitiasis, hipertensión, cardiopatía, cáncer de colon o ictus) se incrementa con el aumento del IMC [23].

El riesgo que sufre un paciente obeso de presentar comorbilidades es variable. La obesidad no influye de la misma manera en el desarrollo de las diferentes comorbilidades, predisponiendo más en unas que en otras. En la **Tabla 5** podemos ver el riesgo relativo de comorbilidades asociado a la obesidad. De acuerdo con ello, la diabetes tipo 2 y la dislipemia se presentan con una frecuencia tres veces mayor en obesos que en sujetos con normopeso y, sin embargo, algunos tipos de neoplasias o el síndrome del ovario poliquístico (SOPQ) se asocian con una frecuencia menor.

Tabla 5. Riesgo relativo (RR) de comorbilidades asociado a la obesidad.

Riesgo elevado (RR > 3)	**Riesgo moderado (RR =2-3)**	**Riesgo bajo (RR < 2)**
Diabetes mellitus tipo 2	Hipertensión arterial	Ciertos tipos de neoplasias
Resistencia a la insulina	Enfermedad coronaria	SOPQ
Dislipemias	Artrosis (rodilla)	Infertilidad
Colelitiasis	Hiperuricemia	Lumbagia
Hipoventilación		Elevado riesgo fetal

La obesidad no sólo genera un impacto sobre la morbimortalidad, sino también sobre la calidad de vida de aquellos que la padecen. La calidad de vida relacionada con la salud (CVRS) del obeso está afectada en al menos cuatro aspectos [24]:

- Problemas directamente relacionados con el exceso de grasa corporal, que condicionan tanto problemas físicos (alteración del rendimiento físico), como

mentales (alteración de la autoestima, depresión) o sociales (alteración de la relación con los demás, integración social, relaciones sexuales, etc.).

- Problemas relacionados con las complicaciones derivadas de la obesidad, como artropatías, diabetes mellitus, hipertensión arterial o arteriosclerosis.
- Problemas relacionados con el pronóstico vital y su percepción, como las expectativas de padecer en un futuro enfermedades cardiovasculares o hipertensión, por la concienciación que se tiene de la obesidad como factor de riesgo cardiovascular.
- Cambios de la CVRS ante los resultados de un tratamiento generalmente largo, de resultados lentos y con frecuentes recidivas.

Por todo ello, el clínico debe realizar un esfuerzo para determinar las enfermedades asociadas al exceso ponderal y, especialmente, las susceptibles de mejoría tras la pérdida de peso. Para ello, se sugiere dividir las comorbilidades en mayores y menores (**Tabla 6**), en función del riesgo vital o la repercusión en la calidad de vida [25].

Tabla 6. Comorbilidades mayores y menores de la obesidad

MAYORES	MENORES
Diabetes mellitus tipo 2	Colelitiasis
Hipertensión arterial	Reflujo gastroesofágico
Apnea del sueño	Esteatosis hepática
Enfermedad cardiovascular	Alteraciones menstruales
Osteartropatía severa en	Infertilidad
articulaciones de carga	Varices
Dislipemia	Hipertensión intracraneal benigna

Por tanto, la obesidad aumenta de forma significativa no sólo el riesgo de diabetes y de enfermedad cardiovascular, sino también de ciertos tipos de cáncer y otras enfermedades muy prevalentes, de tal manera que se ha convertido en la segunda causa de mortalidad prematura y evitable después del tabaco. Resulta por ello fundamental identificar y evaluar correctamente al paciente que presenta sobrepeso y obesidad, detectando y tratando de forma precoz las numerosas comorbilidades que acompañan a esta patología.

Entre las comorbilidades más importantes a destacar encontramos las siguientes:

2.1. Diabetes mellitus tipo 2

La diabetes mellitus tipo 2 se asocia estrechamente con obesidad en ambos sexos y en todos los grupos étnicos. Se ha constatado que el 80-95% de los casos de diabetes tipo 2 se pueden atribuir a la obesidad [26]. Existe un paralelismo perfecto entre el incremento de obesidad y el de diabetes tipo 2 en los últimos 30 años. La posibilidad de padecer diabetes tipo 2 aumenta paralelamente al incremento del IMC. Así, el riesgo de presentar diabetes tipo 2 es 40 veces mayor para las personas con un IMC > 35 kg/m² que para aquellas con un IMC < 23 kg/m^2 [27]. Además, el riesgo de diabetes mellitus tipo 2 se incrementa con el grado, duración de la obesidad y con la distribución de predominio central de la grasa corporal.

Esta clara asociación entre obesidad y diabetes mellitus tipo 2 ha sido demostrada por numerosos estudios epidemiológicos en diferentes zonas del mundo [28, 29]. En el estudio Nurses Health Study que incluyó a 114.281 enfermeras de Estados Unidos con un seguimiento de 14 años, el riesgo más bajo de diabetes se asoció a un IMC inferior a 22 kg/m^2, incrementándose gradualmente con el aumento de IMC [30]. De modo que el riesgo relativo de diabetes ajustado por la edad se incrementó 40 veces en mujeres con un IMC entre 31 y 32,9 kg/m^2 y hasta 93,2 veces en mujeres con un IMC superior o igual a 35 kg/m^2. Una relación similar se observó en los más de 51.000 hombres profesionales de la salud, participantes en el Health Professionals Follow-up Study [31]. En hombres, el riesgo más bajo se asoció con un IMC menor

a 24 kg/m^2 y el riesgo relativo de diabetes con IMC superior o igual 35 kg/m^2 fue 42 veces superior.

Otro factor, independientemente del grado de obesidad, es la distribución central de la grasa corporal que también es un factor de riesgo para el desarrollo de diabetes mellitus tipo 2. En un estudio realizado en japoneses americanos seguidos durante 6 a 10 años, la cantidad de grasa intraabdominal predijo la incidencia de diabetes tipo 2, independientemente de la adiposidad corporal total [32].

Los mecanismos implicados en el desarrollo de diabetes mellitus tipo 2 en individuos obesos susceptibles no son bien conocidos. La obesidad se asocia a un aumento de la resistencia a la insulina, desarrollándose la diabetes tipo 2 cuando la célula beta pancreática no puede satisfacer las demandas impuestas por este incremento de la insulinorresistencia. Los mecanismos propuestos para explicar cómo el exceso de tejido adiposo provoca resistencia a la insulina son a través del aumento en la secreción de citoquinas como el factor de necrosis tumoral (TNF-α) [33] y la resistina [34] o por la disminución de la adiponectina [35]. La combinación de una mayor producción hepática de glucosa y una disminución de su captación periférica favorecerían un estado de resistencia a la insulina que, a su vez, determinaría hiperglucemia.

2.2. Trastornos respiratorios asociados a la obesidad

Los efectos fisiopatológicos de la obesidad sobre la función pulmonar son múltiples y complejos, pero en general pueden considerarse dos grupos de factores patógenos:

- *Mecánicos*: El exceso de grasa comprime externa e internamente la cavidad torácica provocando el cierre de las pequeñas vías aéreas en las porciones declives del pulmón por el efecto presionante del contenido abdominal sobre la posición del diafragma. Esto da lugar a volúmenes pulmonares disminuidos y dinámicas pulmonares subóptimas. Se produce un marcado descenso –paralelo

al incremento del IMC- del volumen respiratorio forzado en el primer segundo, capacidad pulmonar total, volumen de reserva espiratorio y capacidad residual funcional. Cuando se compara con una persona de IMC de 20 kg/m^2, un paciente con IMC 30 kg/m^2 ha perdido el 66% de la capacidad residual funcional y el 70% del volumen de reserva espiratorio [36].

La consecuencia más directa de la obesidad sobre la función respiratoria es la aparición de disnea e intolerancia al ejercicio, resultado de la mayor carga de trabajo para mover un cuerpo obeso, a lo que se suma la adaptabilidad disminuida de la pared torácica y la fatiga de los músculos respiratorios.

- *Inflamatorios*: Existen una serie de cambios fisiopatológicos a nivel molecular. La proteína C reactiva (PCR), el TNF-α, la interleucina 6 (IL-6) y la leptina están elevados en el paciente obeso y pueden afectar a la reactividad de la vía aérea [37].

Todos estos cambios patológicos causados por la obesidad dan lugar a múltiples comorbilidades respiratorias, como el *asma*, la *apnea obstructiva del sueño*, el *síndrome de obesidad-hipoventilación* y la *hipertensión pulmonar* [38, 39].

2.2.1. Asma

El incremento simultáneo de la incidencia de obesidad y asma ha llevado a algunos investigadores a postular que el aumento de los casos de asma es consecuencia de la pandemia de obesidad. Diversos estudios sugieren que los pacientes con un IMC elevado presentan mayor riesgo de desarrollar asma [40, 41]. El riesgo de desarrollar asma se incrementa un 50% en la obesidad, aumentando la OR con el IMC, pero sin apreciarse diferencias entre hombre y mujeres.

El mecanismo por el que la obesidad puede ocasionar asma es probablemente multifactorial. El estado proinflamatorio encontrado en la obesidad probablemente contribuye

a la reactividad de la vía aérea. La elevación de TNF-α, IL-6 y/o PCR median el desarrollo de resistencia a glucocorticoides en el tratamiento del asma [42].

2.2.2. Enfermedad Pulmonar Obstructiva Crónica (EPOC)

La EPOC se caracteriza por la obstrucción progresiva e irreversible del flujo aéreo. Los efectos combinados de la obesidad y la EPOC contribuyen al deterioro de la función pulmonar. Ambas condiciones disminuyen el volumen expiratorio forzado, incrementan el estrés oxidativo pulmonar y sistémico e incrementan la inflamación a nivel local y sistémico.

La prevalencia de obesidad es notablemente mayor entre pacientes con EPOC en comparación con la población general, aunque puede variar dependiendo de la zona geográfica [37]. La aparición de la obesidad puede variar entre los fenotipos clínicos de la EPOC. Muchos estudios han demostrado que en la *EPOC temprana*, la obesidad se correlaciona positivamente con un aumento de la mortalidad. Pero "paradójicamente", los valores bajos de IMC se asocian con *estadios avanzados* de la EPOC [39, 43].

2.3. Dislipemia

La obesidad se asocia frecuentemente con un perfil lipídico aterogénico. Las alteraciones lipídicas asociadas a la obesidad más características son: elevación de las concentraciones séricas de colesterol de baja densidad (LDL), colesterol de muy baja densidad (VLDL) y triglicéridos, junto con una disminución de la concentración sérica de colesterol de alta densidad (HDL) [44, 45]. Estos cuatro cambios del metabolismo lipídico representan un incremento del riesgo aterogénico, siendo esta relación el mecanismo de unión mejor establecido entre la obesidad y la enfermedad cardiovascular [46].

Existe una correlación significativa entre fenómenos oxidativos e IMC, índice cintura/cadera y valores de lípidos y ácidos grasos libres, que explica la asociación entre la obesidad y la dislipemia.

Los datos del estudio NHANES-III [47] sobre dislipemia también reflejan la mayor prevalencia de hipercolesterolemia a medida que se incremente el IMC, especialmente en mujeres. La prevalencia de niveles bajos de HDL (< 35 mg/dL en varones y < 45 mg/dL en mujeres) también se relaciona con el IMC. Un cambio de 1 unidad en IMC implica un cambio de 0,69 mg/dL en HDL para mujeres y de 1,1 para varones. Además, los niveles de colesterol son más elevados en individuos con obesidad de predominio central.

2.4. Enfermedad cardiovascular

El exceso de peso es el factor de riesgo de enfermedad cardiovascular más prevalente. La asociación entre obesidad y enfermedad cardiovascular es compleja y no se limita a factores mediadores tradicionales como dislipemia y diabetes mellitus tipo 2. En los últimos años, diversos estudios han demostrado que la obesidad podría causar enfermedad cardiovascular mediante otros mecanismos como inflamación subclínica, disfunción endotelial, aumento del tono simpático y perfil lipídico aterogénico [48].

2.4.1. Insuficiencia cardiaca

La obesidad es un conocido factor de riesgo independiente de insuficiencia cardiaca. El riesgo de insuficiencia cardiaca se duplica en personas obesas, en comparación con aquellas con un IMC normal [49]. Varias cohortes de pacientes con insuficiencia cardiaca han revelado que un 15-35% de dichos pacientes son obesos y que un 30-60% tienen problemas de sobrepeso [50]. En el Framingham Heart Study durante un seguimiento de 14 años, por cada incremento de 1 kg/m^2 en el IMC, el riesgo de insuficiencia cardiaca aumentó en un 5% en hombres y 7% en mujeres [51].

2.4.2. Fibrilación auricular

La prevalencia de fibrilación auricular, al igual que la de obesidad, ha aumentado de manera significativa en los últimos años. El aumento en la prevalencia de fibrilación auricular podría atribuirse al envejecimiento de las poblaciones combinado con el mejor pronóstico de los pacientes con hipertensión, enfermedad coronaria e insuficiencia cardiaca, afecciones que aumentan el riesgo de fibrilación auricular [52]. Diversos estudios indican que la obesidad puede causar o favorecer la aparición de fibrilación auricular. Un metaanálisis reciente que incluyó 16 estudios con 123.249 pacientes, evaluó el impacto de la obesidad en la fibrilación auricular y demostró que los obesos tienen un 49% más de riesgo de fibrilación auricular en comparación con los individuos no obesos (RR 1,49; 95% IC 1,36-1,64) y que el riesgo se incrementa a medida que aumenta el IMC [53]. Otro estudio realizado con 18.290 individuos de mediana edad sugiere que el sobrepeso y la obesidad se asocian de forma independiente con un mayor riesgo de fibrilación auricular (Hazard Ratio (HR) 1,54 y HR 2,41 respectivamente) [54].

2.4.3. Hipertensión arterial

La prevalencia de hipertensión en individuos obesos es del 25 al 50%, mucho más alta que la de la población general, siendo el riesgo de hipertensión arterial 5 veces mayor en obesos. La obesidad es un factor de riesgo independiente e importante de hipertensión. El riesgo de hipertensión va en paralelo al grado de aumento de peso corporal [55].

Los datos del estudio NHANES-III [47] muestran que la prevalencia ajustada por la edad se incrementa progresivamente con el IMC. El riesgo relativo de hipertensión prácticamente se duplica (2,1 en varones y 1,9 en mujeres) en aquellos individuos con IMC > 30 kg/m2 respecto al grupo con IMC < 25 kg/m^2. Otros estudios, como el INTERSALT, observaron que un exceso de 10 kg de peso suponía un incremento de 3 mm de Hg en presión arterial sistólica y 2,3 mm en diastólica.

La pérdida de peso se asocia con descensos en los niveles de presión arterial. De manera que, por cada 1 kg de peso perdido la presión arterial sistólica y diastólica descienden

aproximadamente 1 mmHg. El estudio de *Framingham* demostró que el 79% de la hipertensión en varones y el 65% en las mujeres fue directamente resultado del exceso de peso [51]. El riesgo de padecer hipertensión arterial se correlaciona bien con el grado de exceso de peso y su distribución, siendo incluso un trastorno reversible a medida que se produce la pérdida ponderal.

Entre las posibles vías patogénicas encontramos [56]:

- Hiperreactividad del sistema nervioso simpático: la sobrealimentación se asocia a un aumento del tono simpático y a un aumento del nivel de noradrenalina, mientras que el ayuno produciría los efectos contrarios. Además, se sabe que la noradrenalina no es únicamente una sustancia presora, sino que también incrementa la reabsorción tubular de sodio, probablemente a través de la activación de los receptores betaadrenérgicos del aparato yuxtaglomerular.
- Hiperinsulinemia y resistencia insulínica: la hiperinsulinemia puede ejercer numerosos efectos que contribuyen al incremento de la tensión arterial debido a:
  - El efecto antrinatriurético de la insulina.
  - El incremento del sistema nervioso simpático.
  - A la proliferación del músculo liso vascular.
  - A las alteraciones del transporte iónico de la membrana.

2.5. Enfermedad renal

La obesidad se asocia con múltiples condiciones que causan compromiso de la función renal, como la hipertensión, la diabetes y el síndrome metabólico. Sin embargo, datos de varias cohortes sugieren que la obesidad se asocia de forma independiente con un riesgo elevado de enfermedad renal crónica [57, 58].

Los efectos renales de la obesidad en estudios experimentales sobre animales y humanos incluyen tanto adaptaciones estructurales como funcionales: aumento de la tasa de filtración glomerular, incremento del flujo sanguíneo renal mediado por vasodilatación de la arteriola aferente e hipertrofia renal. Las causas de estos cambios hemodinámicos podrían estar relacionados con un incremento de la reabsorción de sal en el asa de Henle.

2.6. Hiperuricemia

La hiperuricemia forma parte frecuentemente del síndrome metabólico. Existen numerosas evidencias de que los niveles elevados de ácido úrico se correlacionan con el grado de obesidad (los niveles de ácido úrico y el riesgo de desarrollar artritis gotosa se incrementan con el IMC) [59, 60]. Por un lado, una dieta rica en purinas incrementa la producción de ácido úrico; por otra, la hiperinsulinemia de la obesidad reduce la excreción renal de ácido úrico. Así, en el estudio epidemiológico realizado en Estados Unidos (*Normative Aging Study*) [59], se encontró una correlación positiva entre los niveles de ácido úrico e IMC, con el índice cadera/cintura, así como con los niveles de insulinemia de ayuno. Estos datos sugieren que la hiperuricemia está involucrada en el síndrome de resistencia insulínica-obesidad.

2.7. Afectación hepática y de la vesícula biliar

Los pacientes obesos presentan infiltración grasa del parénquima hepático de forma lineal a la ganancia de peso. Esta esteatosis puede elevar las transaminasas en obesidad mórbida.

La *colelitiasis* es la patología hepatobiliar más frecuentemente asociada con la obesidad. En el *Nurses Health Study* [30], la incidencia de la enfermedad aumentó progresivamente desde IMC de 24 a 30 kg/m^2 y de forma más intensa a partir de IMC 30 kg/m^2. Las mujeres con un IMC > 45 kg/m^2 tuvieron 7 veces más riesgo de colelitiasis en comparación con aquéllas cuyo IMC < 24 kg/m^2. El incremento de riesgo de colelitiasis en la población obesa puede parcialmente

explicarse por un recambio aumentado de colesterol relacionado con la grasa corporal total. El colesterol es excretado en la bilis, y su exceso de concentración incrementa la probabilidad de precipitación de cálculos de colesterol en la vesícula biliar.

2.8. Asociación con neoplasias

La *International Agency for Research on Cancer* en 2002 y la *World Cancer Research Fund* en 2007, sugieren que existe evidencia convincente de la relación entre obesidad y cáncer. Fundamentalmente, cáncer de esófago (adenocarcinoma), páncreas, colorectal, cáncer de mama en mujeres postmenopáusicas, endometrio, riñón y, probablemente, cáncer de vesícula [61].

Un estudio con 57 cohortes y alrededor de 900.000 participantes mostro que se observó un aumento del 10% del riesgo de muerte por cáncer en comparación con el 30% de mortalidad general, por cada 5 unidades de IMC [3].

2.8.1. Cáncer de colon

El IMC está relacionado con el cáncer de colon, pero mucho más débil en las mujeres que en los hombres. En el Health Professionals Follow-up Study [62] se observó una asociación significativa entre obesidad y cáncer de colon en hombres (46.349 varones sin cáncer al inicio del estudio y 18 años de seguimiento). Los autores estimaron que un 29,5% de todos los casos de cáncer de colon eran atribuibles a un IMC > 22,5 kg/m^2.

2.8.2. Cáncer de mama

La obesidad está directamente relacionada con la mortalidad por cáncer de mama, predominantemente en mujeres postmenopáusicas. Curiosamente, la obesidad esta inversamente relacionada con la incidencia de cáncer de mama en mujeres premenopáusicas, pero el "beneficio" desaparece a partir de 10 años de la menopausia. En las mujeres

postmenopáusicas la grasa es la principal fuente de estrógenos, el factor de riesgo modificable más importante para cáncer de mama en postmenopáusicas [63].

2.8.3. Cáncer de próstata

La asociación entre obesidad y cáncer de próstata es compleja. González Svatetz y colaboradores [64] sugieren que la obesidad se asocia con una mayor incidencia de cáncer de próstata. En un estudio prospectivo [65] se evaluó el efecto del IMC sobre la mortalidad por cáncer de próstata en 287.700 hombres seguidos durante 5-6 años. El RR de mortalidad por dicho tipo de cáncer fue de 1,46 y 2,12 para un IMC > 30,4 kg/m^2 y > 35 kg/m^2, respectivamente. Sin embargo, otros estudios no encuentran asociación entre IMC y cáncer de próstata [66]. La falta de evidencia puede deberse a la *asociación dual* entre el IMC y el desarrollo de cáncer de próstata. Recientes estudios sugieren que el IMC está inversamente relacionado con el riesgo de cáncer de próstata localizado y directamente asociado al riesgo de cáncer de próstata avanzado o de alto grado [67, 68].

2.8.4. Cáncer de pulmón

Existe una asociación inversa entre IMC y cáncer de pulmón (la obesidad es un factor protector) [69]. En un metaanálisis de estudios prospectivos observacionales [70] que evaluaba la incidencia de 20 tipos de tumores y la influencia que tenían en dicha incidencia un incremento del IMC (reportado o medido), se incluyeron 141 artículos que recogían 282.137 casos nuevos de cáncer. Se observaron asociaciones negativas en carcinoma de pulmón tanto en hombres como en mujeres (RR de 0.76 ($p<0.0001$) y 0.71 ($p<0.0001$)). Además, se observó que existía una asociación negativa independientemente de la existencia o no de hábito tabáquico.

2.9. Alteraciones musculoesqueléticas: Osteoartritis

La incidencia de osteoartritis está significativamente aumentada en pacientes con sobrepeso/obesidad. Este es uno de los problemas asociados a la obesidad que conlleva mayor gasto sanitario. La sobrecarga de las articulaciones por el exceso de peso conlleva un aumento

en la aparición de artrosis, especialmente de articulaciones lumbares y de miembros inferiores (rodillas, tobillos). La asociación entre obesidad y osteoartritis es mayor en mujeres que en hombres. El aumento del riesgo de osteoartritis en otras articulaciones que no soportan peso, sugiere que algunos factores patogénicos de la obesidad alteran el metabolismo del cartílago y el hueso, independientemente de la carga articular. Como los sujetos obesos tienen mayores concentraciones de marcadores inflamatorios, esta inflamación puede contribuir a la limitación funcional y a la progresión funcional en aquellos pacientes con osteoartritis, además de reducir el umbral del dolor [71, 72].

Por cada kilogramo de incremento de peso, el riesgo de desarrollar osteoartritis se incrementa entre un 9 y un 13%. Se ha calculado que la OR para la osteoartritis de rodilla con un IMC > 30 kg/m^2 es 6,9 cuando se compara con un grupo de referencia cuyo IMC está entre 20 y 24 kg/m^2. Un descenso en IMC de 2 o más puntos conlleva un descenso de 50% de riesgo de artrosis [73].

La pérdida de peso reduce los factores de riesgo para artrosis sintomática de la rodilla, y baja las citosinas y adipocinas proinflamatorias, que juegan un papel en la degradación del cartílago.

2.10. Alteraciones en la mujer

2.10.1. Infertilidad

La obesidad en mujeres favorece el desarrollo de irregularidades en la menstruación, anovulación e infertilidad. Se ha demostrado una asociación entre IMC elevado y estado de infertilidad, relacionada fundamentalmente con la disfunción ovulatoria [74, 75]. Además, la obesidad puede aumentar el riesgo de abortos involuntarios y poner en peligro el éxito de los tratamientos de reproducción asistida y el embarazo (cuando el IMC > 30 kg/m^2) [76].

Un análisis realizado en 597 mujeres diagnosticadas de infertilidad en siete clínicas de Estados Unidos y Canadá mostró que las mujeres obesas (IMC superior o igual a 27 kg/m^2) tenían

un riesgo relativo de infertilidad por anovulación de 3,1 comparadas con mujeres con normopeso [77]. Asimismo, el estudio de la cohorte del *Nurses´ Health Study* mostró que un IMC superior o igual a 32 kg/m^2 a los 18 años es un factor de riesgo para infertilidad por alteraciones ovulatorias, con un riesgo relativo de 2,7 comparado con mujeres con IMC de 20 kg/m^2 [78].

2.10.2. Síndrome de ovario poliquístico (SOPQ)

El SOPQ y la obesidad también se asocian frecuentemente. Aproximadamente un 50% de las mujeres con SOPQ tienen sobrepeso u obesidad y la mayoría de ellas tienen un fenotipo abdominal [79]. Los mecanismos patogénicos que asocian el exceso de grasa corporal y las alteraciones del sistema reproductor femenino no son bien conocidos. Las mujeres obesas, especialmente aquellas con obesidad abdominal, tienen resistencia a la insulina e hiperinsulinemia y este aumento de insulina a nivel del tejido ovárico puede favorecer el exceso de síntesis de andrógenos. También se ha visto en mujeres obesas menores cifras de las globulinas transportadoras de hormonas sexuales, de la hormona del crecimiento y de las proteínas transportadoras del IGF-I y un incremento de las concentraciones de leptina [80, 81].

2.10.3. Obesidad y gestación

La obesidad durante el periodo gestacional se ha asociado a un aumento del riesgo materno y fetal (**Tabla 7**) [82].

2.11. Salud mental

La relación entre obesidad y los trastornos más comunes de salud mental es compleja. Se ha intentado encontrar un perfil de personalidad característico de los obesos y determinar una mayor susceptibilidad a presentar trastornos de personalidad o sintomatología psiquiátrica, pero los resultados de los estudios realizados no muestran un patrón característico y en cambio apuntan a grupos de obesos que muestran una mayor susceptibilidad a presentar patología psiquiátrica.

Estudios realizados con población general sugieren que el sobrepeso y la obesidad están asociados significativamente con desordenes psiquiátricos específicos: *esquizofrenia*, *trastorno bipola*r, *depresión*, ansiedad, conductas suicidas y trastornos de personalidad [83, 84].

Tabla 7. Complicaciones en embarazo y parto asociadas a la obesidad

Gestacionales	**Intraparto**
▪ Diabetes gestacional ▪ Preeclamsia ▪ Prematuridad ▪ Parto postérmino ▪ Gestación múltiple ▪ Infección del tracto urinario ▪ Apnea obstructiva del sueño ▪ Aborto espontaneo	▪ Parto prolongado ▪ Parto inducido ▪ Parto por cesárea ▪ Problemas anestésicos ▪ Distocia de hombro ▪ Malpresentación ▪ Hemorragias
Posparto	**Perinatales**
▪ Infección ▪ Hemorragia ▪ Retraso o ausencia de lactancia	▪ Anomalías congénitas ▪ Macrosomía ▪ Muerte fetal ▪ Obesidad

3. OBESIDAD Y DEPRESION

Una de las comorbilidades asociadas a la obesidad más controvertida es la depresión.

La depresión es un trastorno mental frecuente que ha sido categorizado entre los trastornos psicológicos más prevalentes en la población general. Se calcula que afecta a 350 millones de personas en el mundo y es la principal causa mundial de discapacidad contribuyendo de forma muy importante a la carga mundial general de morbilidad [85]. La OMS estima que se convertirá en una de las tres principales causas de carga de la enfermedad en 2030 [86].

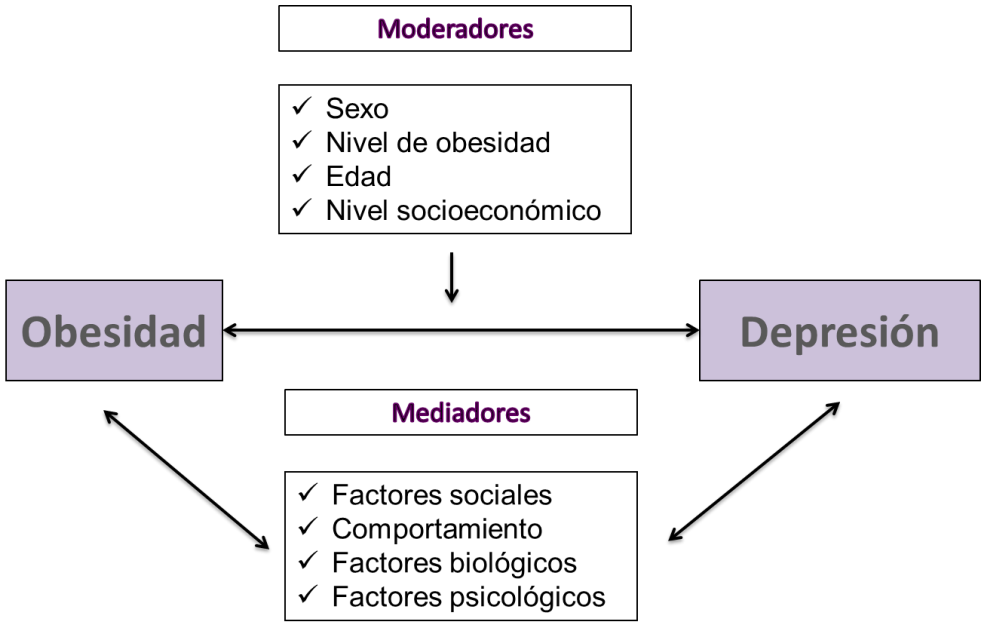
Tanto la depresión como la obesidad son dos patologías muy prevalentes a nivel mundial. Además, ambas patologías contribuyen de forma importante a la carga mundial de morbilidad. Por todo ello, es importante considerar ambas patologías y su posible asociación debido al importante coste económico que suponen para los sistemas sanitarios y a su implicación en la calidad de vida de los pacientes.

La asociación entre obesidad y depresión es compleja. Dicha asociación ha centrado muchas de las investigaciones de los últimos años. Sin embargo, los resultados obtenidos son inconsistentes. Aunque algunos autores consideran que no existe una clara asociación [87, 88], recientes estudios demuestran que existe una fuerte relación entre ambas patologías [89-92].

Los resultados de una revisión sistemática de estudios longitudinales apuntan hacia una **asociación bidireccional** entre la depresión y la obesidad [92]. Los autores concluyen que: "Las personas obesas tenían un 55% más de riesgo de desarrollar depresión a lo largo del tiempo, mientras las personas con depresión tenían un 58% más de riesgo de convertirse en obesas". En cuanto a la obesidad, en un meta-análisis que incluye 17 estudios (n = 204507) se demuestra que los individuos obesos son 1,18 veces más propensos a tener depresión que aquellos que no lo son, especialmente entre mujeres [90]. Por otra parte, diversos estudios prospectivos realizados en población adulta muestran que tener depresión al inicio de la cohorte predice una ganancia de peso durante el seguimiento [93-95].

Existen una serie de mecanismos que podrían explicar la posible asociación casual entre la obesidad y la depresión. La **Figura 2** muestra una visión general de esta compleja relación. Las *variables moderadoras* son aquellas que podrían influir en la dirección y/o fuerza de la relación entre las dos condiciones, mientras que las *variables mediadoras* ayudan a explicar esta asociación [96, 97]. Por otra parte, las alteraciones en el IMC y la depresión pueden tener mecanismos comunes: alteraciones neuroestructurales específicas [98], trastornos metabólicos [99] y/o factores inflamatorios [100, 101].

Figura 2. Modelo de la relación entre obesidad y depresión



Existen diversas teorías en cuanto a por qué la obesidad podría conducir a depresión en los adultos. Éstas hacen hincapié en el aumento de los problemas médicos y las restricciones de movilidad asociados a la obesidad que puede tener un impacto directo en el bienestar psicológico, y puede conducir a la depresión, trastornos de la alimentación, imagen corporal distorsionada y baja autoestima [102]. El obeso vive inmerso en una sociedad en que se prima como ideal de belleza la delgadez. Dentro de este marco los obesos sufren rechazo social y una valoración negativa por parte de la población general e incluso por los propios profesionales

sanitarios. El obeso es asociado a estereotipos negativos como indolente, falto de voluntad, comedor excesivo, poco atractivo social, sexual y laboralmente. En este ambiente "antigordura" el obeso se siente encerrado en un cuerpo que le resulta desagradable (a partir del rechazo que genera en los demás).

En cuanto a los mecanismos que pueden causar que aquellos adultos con depresión padezcan obesidad a lo largo del tiempo, existen menos estudios. Se ha sugerido que la mala salud mental puede conducir a un estilo de vida poco saludables y aumento del apetito. La combinación de un aumento del estrés junto con la baja adherencia a los programas de pérdida de peso, ingesta compulsiva, pensamientos negativos y la reducción del apoyo social, puede hacer que sea difícil para una persona deprimida evitar el aumento de peso [103].

Factores mediadores

Los principales factores de mediación relacionados con la obesidad y la depresión en adultos son:

a) Obesidad como causa de depresión
    - Factores relacionados con el *comportamiento*:
        - La dieta y la ingesta compulsiva
    - Factores *biológicos*:
        - Aumento de las tasas de enfermedad crónica (enfermedad cardiovascular, diabetes)
        - Dolor de cuerpo como consecuencia de la obesidad
        - Reducida actividad física
        - Problemas de sueño
        - Efectos secundarios de la medicación
        - Alteración en las concentraciones de hormonas

- Factores *psicológicos*:
  - Mala percepción de su salud
  - Baja autoestima
  - Preocupación por la imagen corporal
- Factores *sociales*:
  - Relacionados con el estigma del peso

b) Depresión como causa de obesidad

- Factores relacionados con el *comportamiento*:
  - Adopción de estilos de vida poco saludables
  - Desgaste de los programas de pérdida de peso
- Factores *biológicos*:
  - Efectos secundarios de la medicación
- Factores *psicológicos*:
  - Pocas expectativas en los intentos de pérdida de peso
- Factores *sociales*:
  - Falta de apoyo de familiares y amigos

Factores moderadores

Los siguientes factores pueden afectar la dirección y / o la fuerza de la relación entre la obesidad y la depresión en adultos.

a) Grado de obesidad

El grado de obesidad parece ser un factor de riesgo independiente para la depresión. Varios estudios han sugerido que la obesidad severa expone a los individuos a mayor riesgo de depresión [96, 104]. Se ha demostrado que las personas extremadamente obesas que buscan la cirugía bariátrica tienen una menor autoestima y mayores

puntuaciones de depresión que los individuos menos obesos que buscan intervenciones de pérdida de peso farmacológicos y de comportamiento [105].

b) Sexo

Se ha demostrado que el sexo modifica la asociación entre la obesidad y depresión. Algunos estudios demuestran una asociación positiva para las mujeres y, por el contrario, una relación negativa para hombres [92, 106, 107]. Las mujeres parecen estar más preocupadas por la obesidad que los hombres, y son de dos a tres veces más propensas a buscar tratamiento para bajar de peso [89]. Las mujeres experimentan una mayor insatisfacción con su peso que los hombres: de modo que a medida que aumenta la insatisfacción, aumenta el IMC. Además, las mujeres también experimentan más el estigma en relación con la obesidad y están bajo una mayor presión para ser delgada [104].

c) Nivel socioeconómico y nivel de educación

El nivel socioeconómico y el nivel de educación han sido identificados como factores de riesgo potencialmente importantes para el desarrollo de depresión en individuos obesos.

Los individuos de menor nivel socioeconómico pueden ser más propensos a experimentar depresión u obesidad. Un estudio reciente encontró que el impacto negativo de la obesidad en la calidad de vida fue mayor para las personas de niveles socioeconómicos más bajos [108]. Sin embargo, mientras que el estatus socioeconómico inferior está fuertemente asociado con un mayor riesgo de obesidad entre las mujeres, este patrón es menos clara para los hombres [109].

d) Otros factores

- Edad. Se considera a la edad como un factor moderador entre la obesidad y depresión. Las mujeres más jóvenes parecen tener un mayor riesgo de obesidad y depresión. Las personas mayores también pueden estar en mayor riesgo, ya

que los problemas de salud asociados con el envejecimiento pueden causar tanto ganancia de peso como depresión [110].

- Raza [111].

Por tanto, la asociación bidireccional entre obesidad y depresión ha sido destacada como una consideración importante para la práctica clínica. Se ha recomendado a los profesionales de la salud que deben controlar el peso de los pacientes depresivos y, del mismo modo, en pacientes con sobrepeso u obesidad, valorar el estado de ánimo. Esta sensibilización podría conducir a la prevención, detección temprana y el tratamiento conjunto de las personas en riesgo, y en última instancia, reducir la carga de ambas condiciones. Además, los profesionales deben animar a los pacientes a participar en comportamientos que ayudarán a mejorar, tales como el manejo del estrés, ejercicio y modificación del estilo de vida.

4. JUSTIFICACIÓN DE LAS PUBLICACIONES

Esta tesis doctoral es un compendio de las siguientes publicaciones:

1. Martin-Rodriguez E, Guillen-Grima F, Martí A, Brugos-Larumbe A. **Comorbidity associated with obesity in a large population: The APNA study**. Obes Res Clin Pract 2015; 9: 435-47. **Estudio 1**.

   El *primer objetivo* fue determinar la *prevalencia de sobrepeso y obesidad* en la población de Navarra que acude a los 7 centros de Atención Primaria. que pertenecen al estudio, en el año 2011. Como se ha comentado en el apartado 1 de esta introducción, la obesidad es una enfermedad cuya prevalencia ha aumentado de forma progresiva en las últimas décadas tanto a nivel mundial como en nuestro país. El objetivo fue determinar la prevalencia detectada en la práctica clínica y poder comparar nuestros resultados con otros estudios realizados en España. La trascendencia de este aumento alarmante de las tasas de obesidad, es su asociación con un amplio número de enfermedades crónicas, es decir, la comorbilidad que va asociada a ella. Por lo tanto, el *segundo objetivo* de este estudio fue estudiar la *comorbilidad asociada a la obesidad*, que como ha quedado demostrado en el apartado 2 de esta introducción, se trata de patologías crónicas y graves.

2. Martin-Rodriguez E, Guillen-Grima F, Aubá E, Martí A, Brugos-Larumbe A. **Relationship between body mass index and depression in women: A 7-year prospective cohort study. The APNA study.** Eur Psychiatry 2016; 32: 55-60. **Estudio 2.**

   Una de las comorbilidades más cuestionadas de la obesidad es su relación con la depresión. En los últimos años se ha observado un aumento progresivo de las dos patologías. Ambas condiciones tienen importantes implicaciones para los sistemas de salud en todo el mundo y representan una proporción significativa de la carga mundial

de la enfermedad. En concreto, la OMS cataloga la obesidad y la depresión como las principales enfermedades crónicas de la edad adulta.

El aumento de ambas enfermedades invita a pensar que existe una relación entre ambas. Como se ha comentado en el apartado 3 de esta introducción, mientras que algunos autores demuestran que existe una clara asociación entre ambas patologías, otros no encuentran dicha asociación. Debido a la falta de evidencia en los resultados publicados, el objetivo de este segundo trabajo fue evaluar la relación entre el IMC y la incidencia de depresión durante los 7 años de seguimiento en 20212 mujeres atendidas en los centros de salud pertenecientes al estudio. Además, se estimó el riesgo de desarrollar depresión a lo largo del seguimiento en función del IMC. El estudio se realizó con mujeres ya que parece que en éstas existe una relación positiva entre ambas patologías (como se ha explicado detalladamente en el apartado 3).

3. Martin-Rodriguez E, Martí A, Brugos-Larumbe A, Guillen-Grima F. **Prospective association between depression and overweight/obesity in a 7-year follow-up. The APNA study**. *Enviado, bajo revisión.* **Estudio 3**

Se ha descrito que la asociación entre la obesidad y la depresión es bidireccional (descrito en apartado 3). En el estudio 2 valoramos la asociación en una dirección, el riesgo de desarrollar depresión en función del IMC del individuo. En este tercer estudio, el objetivo fue valorar la otra dirección, es decir, examinar si las personas con depresión desarrollan o no sobrepeso u obesidad a lo largo del periodo de seguimiento.

II. OBJETIVOS

- O_1: Estimar la prevalencia de sobrepeso y obesidad en la población de Navarra que acude a los centros de Atención Primaria en el año 2011 (**Estudio 1**).
    - Comparar las prevalencias obtenidas en la práctica clínica con lo descrito en la bibliografía (**Estudio 1**).
- O_2: Estudiar la relación del sobrepeso y la obesidad con las comorbilidades asociadas y la depresión (**Estudio 1**)
    - Estudiar el efecto predictor del sobrepeso/obesidad sobre la depresión (**Estudio 2**).
    - Examinar la asociación entre depresión y sobrepeso/obesidad incidente (**Estudio 3**).

III. MATERIAL Y MÉTODOS

Para conseguir los objetivos anteriormente especificados, se desarrolló el estudio APNA (Atención Primaria de NAvarra).

1. POBLACIÓN DE ESTUDIO

La población APNA incluye a todos sujetos adultos (≥ 18 años) asignados a uno de los siete Centros de Atención Primaria de Navarra incluidos en el estudio (Azpilagaña, Burlada, Echavacoiz, Iturrama, San Jorge, Tafalla y Villava), entre el año 2004 y el 2011. Se realizó un muestreo de conveniencia para seleccionar los centros de salud participantes en el estudio. Se trata de siete centros de salud representativos de la población navarra, no existiendo diferencias con el resto de centros de salud de Navarra. El estudio comienza en el año 2004 ya que éste es el primer año que pudimos disponer del registro electrónico de la historia clínica. Consideramos el periodo de estudio de siete años apropiado para lograr nuestros objetivos.

Cuando un paciente acude a su centro de salud, sus datos demográficos y clínicos son recogidos en la historia clínica informatizada por su médico de atención primaria. De modo que, cada paciente tiene su historial clínico informatizado, que se actualiza cada vez que acude a su centro de salud. Cada paciente es considerado de manera individual, independientemente del número de veces que visite el centro de salud.

A partir de la historia clínica informatizada de Atención Primaria del Sistema Navarro de Salud, y después de suprimir la información personal, se obtuvo la base de datos. Ésta consta de 241714 pacientes (125135 mujeres y 116579 hombres).

Se excluyeron del estudio:

- Los sujetos asignados a los centros de salud incluidos en el estudio pero que no fueron atendidos en dichos centros: desplazados, fallecidos, …
- Todos los pacientes menores de 18 años, ya que el estudio se llevó a cabo con población adulta.

Por tanto, el tamaño final de la muestra es de 80019 sujetos el 31 de Diciembre de 2011 (40791 mujeres y 39228 hombres). Se comprobó que la población de 80019 sujetos era representativa del total de 241714 sujetos no existiendo diferencias significativas en cuanto a edad y sexo.

Este estudio fue aprobado por el Comité de Ética de la Universidad Pública de Navarra el 19 de Febrero de 2010.

2. VARIABLES ESTUDIADAS

Las variables incluidas en el estudio fueron:

- Edad
- Sexo
- Peso, en kilogramos
- Talla, en metros
- Diagnóstico de diversas enfermedades crónicas:
  - Intolerancia a la glucosa
  - Dislipemia
  - Ansiedad
  - Depresión
  - Trastorno mental severo, que incluye esquizofrenia y trastorno bipolar
  - Demencia
  - Insuficiencia cardiaca
  - Fibrilación auricular
  - Hipertensión arterial
  - Cáncer: pulmón, mama, colon y próstata
  - Asma

- Enfermedad Pulmonar Obstructiva Crónica
- Diabetes mellitus tipo 1 y tipo 2
- Insuficiencia renal
- Osteoartritis

Las variables de diagnóstico fueron recogidas de forma dicotómica, es decir, los sujetos tienen o no una determinada enfermedad. El diagnóstico de las diferentes patologías fue realizado por el médico de atención primaria.

3. DISEÑO DEL ESTUDIO

3.1. Estudio 1

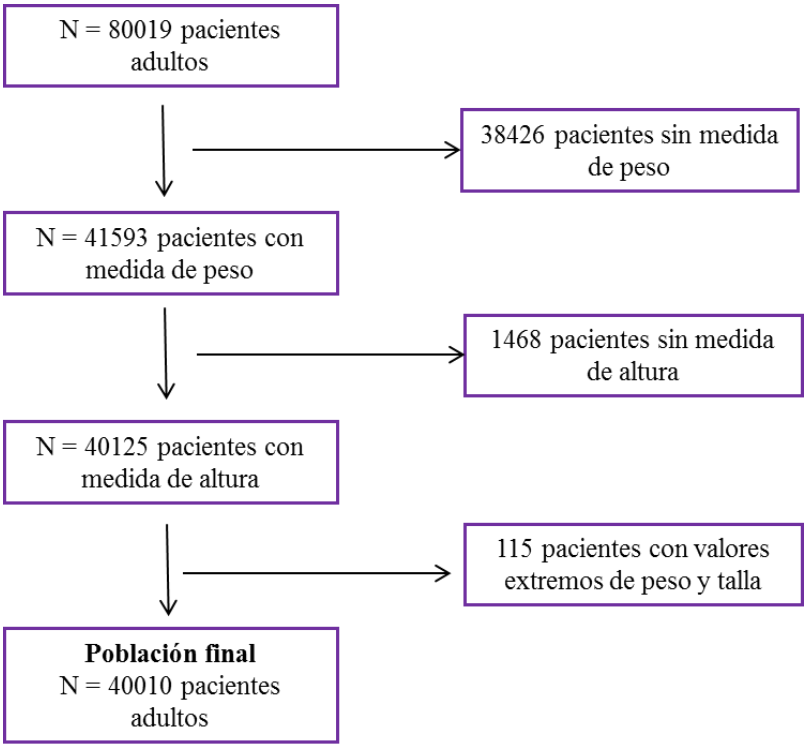
Para lograr los objetivos planteados se diseñó un **estudio descriptivo transversal**, seleccionando aquellos individuos que visitaron uno de los centros de salud en el año 2011.

En la **Figura 3** se muestra el diagrama de flujo en el que se detalla la selección de los individuos. La población final fue de 40010 pacientes, de los que 18988 fueron hombres y 21022 mujeres.

- *Variables incluidas en el estudio.* Se incluyeron todas las variables descritas en el apartado 2 de esta sección.
- *Sobrepeso y obesidad.* Para definir y clasificar el sobrepeso y la obesidad se calculó el IMC, basándonos en la clasificación de sobrepeso y obesidad propuesta por el comité de expertos de la OMS. Los pacientes fueron pesados y medidos durante la práctica clínica.
- *Análisis de sensibilidad.* Para demostrar que la muestra de 40010 sujetos era representativa de la muestra total de 80019 individuos y de la población navarra, se realizó un *análisis de sensibilidad.* Se ponderó nuestra población con la población navarra en términos de edad y sexo. Se observaron dos pequeñas diferencias, pero no fueron estadísticamente significativas. La

proporción de mujeres fue ligeramente mayor en la muestra de 40010 (53%) que en la de 80019 sujetos (51%). Además, la media de edad en la muestra de 40010 sujetos fue de 55 años y en la muestra de 80019 fue de 49 años. Estas pequeñas diferencias se pueden explicar porque las mujeres y las personas de mayor edad tienden a acudir con mayor frecuencia a los centros de salud.

Figura 3. Diagrama de flujo del estudio descriptivo transversal en una población de 40010 sujetos navarros. Estudio 1.



- *Análisis estadístico*
    - A partir de los datos de IMC, se calculó la prevalencia de sobrepeso y obesidad por sexo y grupos de edad, con sus respectivos intervalos de confianza. La

comparación de las proporciones fue realizada con el test chi-cuadrado. Valores de *p* menores que 0,05 se consideraron estadísticamente significativos.

- Para estudiar la asociación del sobrepeso y la obesidad con las diferentes comorbilidades se calcularon los OR ajustados por edad y sexo mediante una regresión logística, usando como pacientes de referencia aquellos con IMC < 25 kg/m^2.
- Los programas estadísticos empleados fueron el SPSS para Windows (versión 19.0) y EpiInfo (versión 6.04d).

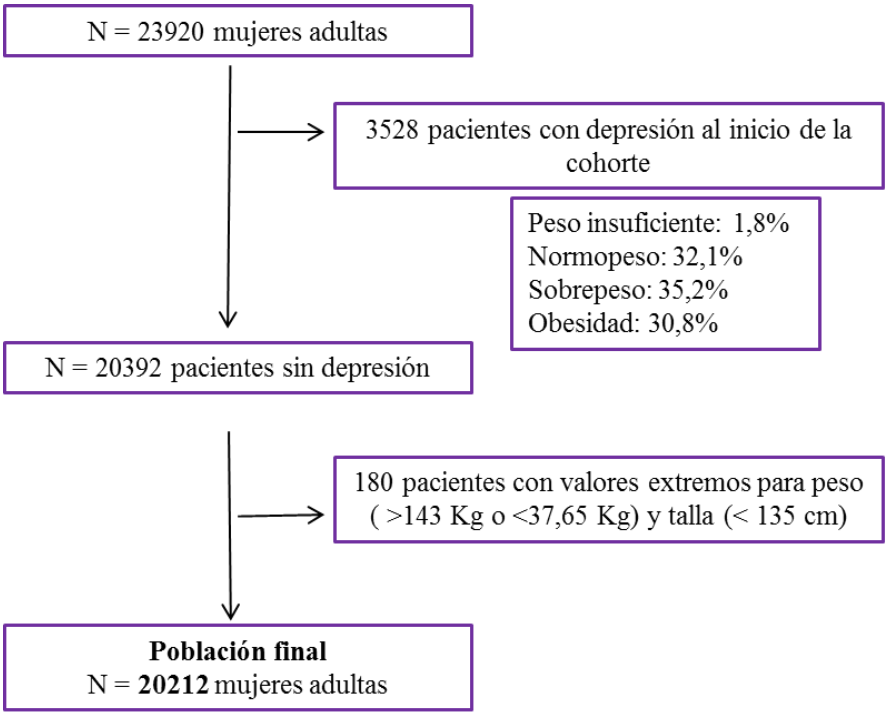
3.2. Estudio 2

Se realizó un estudio de **cohorte prospectivo**, con un periodo de seguimiento de 7 años (de 2004 a 2011). La cohorte APNA es una cohorte dinámica, es decir, a lo largo de los siete años de seguimiento, nuevos sujetos se incorporan a la cohorte mientras que otros dejan la cohorte.

El estudio se llevó a cabo con *mujeres*, que fueron seleccionadas como se muestra en la **Figura 4**. Para este estudio, se seleccionaron únicamente las mujeres que tenían datos de peso y talla registrados y se excluyeron del estudio aquellas mujeres con depresión al inicio de la cohorte. De modo que, nuestra población final para este segundo estudio fue 20212 mujeres.

- *Variables incluidas en el estudio.* Las variables consideradas en este segundo estudio fueron: sexo, edad, peso y talla al inicio de la cohorte, y diagnóstico de depresión durante el periodo de seguimiento.
- *Sobrepeso y obesidad.* Para definir y clasificar el sobrepeso y la obesidad se calculó el IMC, basándonos en la clasificación de sobrepeso y obesidad propuesta por el comité de expertos de la OMS. Los pacientes fueron pesados y medidos durante la práctica clínica.

Figura 4. Diagrama de flujo de una cohorte prospectiva de 20212 mujeres seguidas durante 7 años (de 2004 a 2007). Estudio 2.



- *Diagnóstico de depresión.* El diagnóstico de depresión fue efectuado por el médico de atención primaria. En nuestra cohorte, la depresión es diagnosticada clínicamente. En el Servicio Nacional de Salud la depresión es diagnosticada y tratada principalmente en los centros de atención primaria por el médico de atención primaria [112, 113]. La ley incluye entre las competencias obligatorias la siguiente: "Detectar precozmente y manejar las patologías del ámbito de la Salud Mental: depresión, ideación autolítica, ansiedad, trastorno de ansiedad social, conducta antisocial y trastorno por somatización" [114].

- *Análisis estadístico*
    - Se estimó la función de supervivencia mediante el método de Kaplan-Meier.
    - Se calculó la incidencia de depresión con sus intervalos de confianza.

- Mediante el análisis de regresión de Cox se calculó el riesgo de padecer depresión a lo largo del periodo de seguimiento en función del IMC inicial. El análisis fue ajustado por la edad. Se determinaron los HR con sus intervalos de confianza.
- Los programas estadísticos empleados fueron el SPSS para Windows (versión 19.0) y EpiInfo (versión 6.04d).

3.3. Estudio 3

Se realizó un estudio de **cohorte prospectivo dinámico**, con un periodo de seguimiento de 7 años (de 2004 a 2011).

La población de estudio fue de 91410 pacientes adultos. La selección de los pacientes se realizó según el diagrama de flujo que muestra la **Figura 5**. Debido a que los dos objetivos principales de este estudio requerían dos muestras de población diferentes, se diseñaron dos procedimientos independientes:

Análisis A. Estado de depresión inicial y riesgo de sobrepeso.

Para el análisis A, los pacientes fueron excluidos si tenían sobrepeso (IMC = 25,0-29,9 kg/m^2) al inicio de la cohorte. Un total de 79813 pacientes fueron incluidos para el presente análisis.

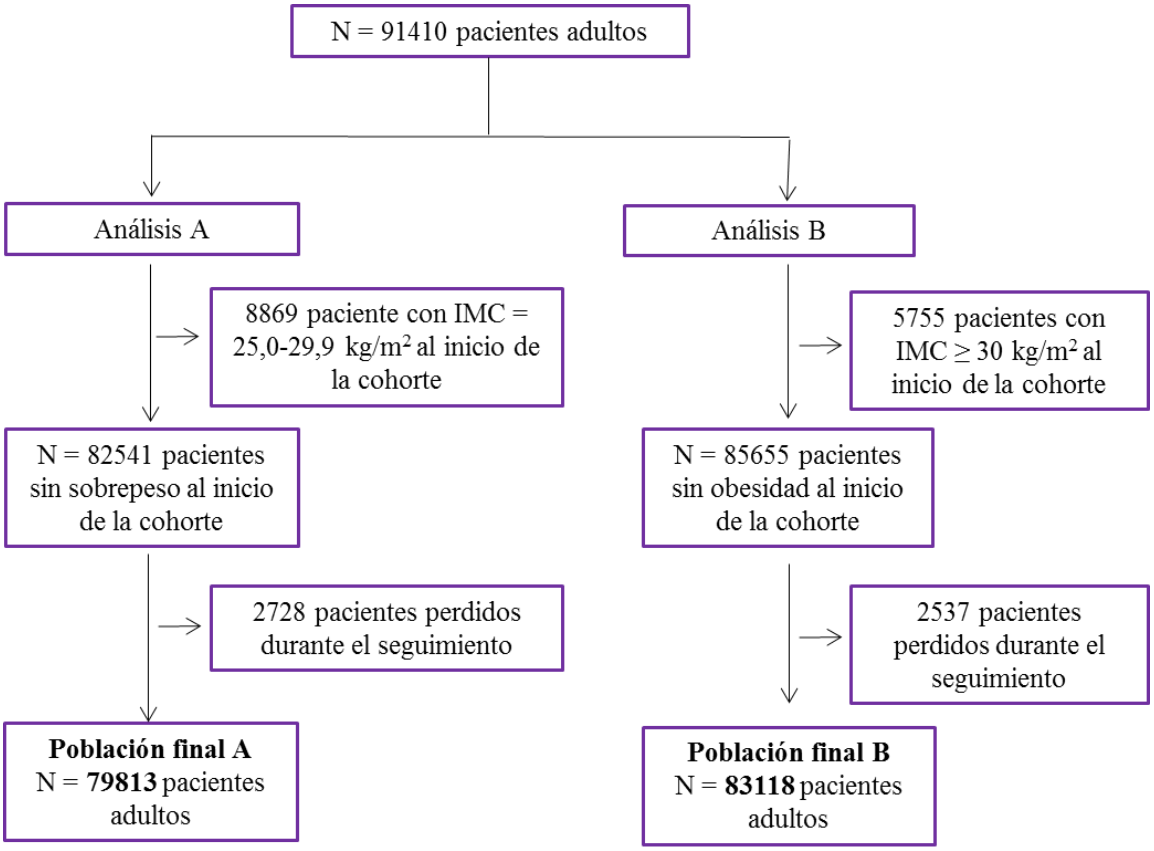
Análisis B. Estado de depresión inicial y riesgo de obesidad.

Para el análisis B, fueron seleccionados los pacientes sin obesidad al inicio de la cohorte (IMC < 30,0 kg/m^2). La población final fue de 83118 sujetos.

- *Variables incluidas en el estudio:* sexo, edad, diagnóstico de depresión al inicio de la cohorte, y peso y talla durante el periodo de seguimiento.
- *Sobrepeso y obesidad.* Para definir y clasificar el sobrepeso y la obesidad se calculó el IMC, basándonos en la clasificación de sobrepeso y obesidad propuesta por el comité de expertos de la OMS. Los pacientes fueron pesados y medidos durante la práctica clínica.

- *Diagnóstico de depresión.* El diagnóstico de depresión fue efectuado por el médico de atención primaria. En nuestra cohorte, la depresión es diagnosticada clínicamente [112, 113].

Figura 5. Diagrama de flujo de la población el Estudio 3.



- *Análisis estadístico*
    - Se estimó la función de supervivencia mediante el método de Kaplan-Meier.
    - Se calculó la incidencia de sobrepeso/obesidad con sus intervalos de confianza, por grupos de edad y estado de depresión inicial. Las proporciones fueron comparadas con el test Chi-cuadrado. Valores de *p* menores de 0,05 se consideraron estadísticamente significativos.
    - Mediante el análisis de regresión de Cox se calculó el riesgo de sufrir sobrepeso/obesidad a lo largo del periodo de seguimiento en función del estado

de depresión inicial. El análisis fue ajustado por la edad y sexo. Se determinaron los HR con sus intervalos de confianza.

- Los programas estadísticos empleados fueron el SPSS para Windows (versión 19.0) y EpiInfo (versión 6.04d).

IV. PUBLICACIONES

Obesity Research & Clinical Practice (2015) xxx, xxx–xxx

ELSEVIER

REVIEW

Comorbidity associated with obesity in a large population: The APNA study

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KEYWORDS
Obesity;
BMI;
Risk factors;
Comorbidity

Summary
Background: Overweight and obesity are major causes of comorbidities which can lead to further morbidity and mortality. The main objective of the present study was to estimate the comorbidity associated with obesity in 40,010 patients attending Primary Health Care Centres in Navarra.
Methods: It is a descriptive cross-sectional study. The association of overweight and obesity in different diseases was studied. Odds ratios (OR) adjusted for age and sex were calculated by unconditional logistic regression, using as reference patients with body mass index (BMI) lower than 25 kg/m^2.
Results: Increasing BMI is associated with glucose intolerance (OR: 1.07; 95% CI: 1.06–1.08), dyslipidemia (OR: 1.04; 95% CI: 1.03–1.04), hypertension (OR: 1.12; 95% CI: 1.12–1.13), type 2 diabetes (OR: 1.11; 95% CI: 1.10–1.11), kidney failure (OR: 1.04; 95% CI: 1.03–1.05), and osteoarthritis (OR: 1.06; 95% CI: 1.05–1.06). Moreover, all the degrees of obesity are associated with asthma (OR type I obesity: 1.33; OR type II obesity: 1.69; OR type III obesity: 1.75), heart failure (OR type I obesity: 1.68; OR type II obesity: 2.78; OR type III obesity: 4.35), and severe mental disorders (OR type I obesity: 2.02; OR type II obesity: 2.33; OR type III obesity: 2.50). Type II and morbid obesity are associated with chronic obstructive pulmonary disease and depression.

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Conclusion: Our study showed a positive association of the overweight and obesity with glucose intolerance, dyslipidemia, type 2 diabetes, hypertension, osteoarthritis, and kidney failure. An interesting point is the association of higher levels of BMI with depression.

Contents

Introduction

Obesity is a chronic metabolic disease of multifactorial origin whose prevalence in recent decades has been increasing at an alarming rate; it has been considered the XXI century epidemic [1]. The study of overweight and obesity is a priority question for health professionals, as it constitutes a major public health problem due to its association with serious chronic diseases and the economic cost of the health care systems [2,3].

Overweight and obesity are the fifth leading risks for global deaths [4]. At least 3.4 million adults die each year as a result of being overweight or obese. Although some studies indicate stabilization in the prevalence of obesity in some populations [5], it is still high in most developed countries. The United States is the country with the highest prevalence of overweight and obesity [6], while countries like Japan and Korea have the lowest prevalence values [7]. In Spain, as in other developed countries, the prevalence of overweight and obesity has risen substantially in the last years [8—10].

There are evidences linking overweight and obesity with a wide range of health problems. Being obese or overweight is associated with dyslipidemia, cardiovascular disease, type 2 diabetes, respiratory problems or several cancers [11—13]. The NHANES III study [14] concluded that subjects with a body mass index (BMI) $\geq 27\,kg/m^2$ have a 70% greater risk of obesity-related diseases.

The main objective of the present study was to estimate the comorbidity associated with obesity in 40,010 patients attending Primary Health Care Centres in Navarra.

Method

The APNA study (Atención Primaria de NAvarra) is a descriptive cross-sectional study. It was conducted in seven Primary Health Care Centres in Navarra: Azpilagaña, Burlada, Echavacoiz, Iturrama, San Jorge, Tafalla and Villava. The study population consists of all individuals who visited one of the seven centres in 2011. The patient data were collected electronically by the general practitioner during routine clinical practice. Each patient had their clinical history. If an individual visited a centre more than once in 2011, her clinical history

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was updated. We consider each patient individually, regardless of the number of times they visit your centre in 2011. The variables included were age, sex, weight (kilograms), height (meters) and diagnosis of several chronic diseases (glucose intolerance, dyslipidemia, anxiety, depression, severe mental disorder (bipolar disorder and schizophrenia), dementia, heart failure, atrial fibrillation, hypertension, lung cancer, breast cancer, prostate cancer, colon cancer, asthma, chronic obstructive pulmonary disease (COPD), type 1 and type 2 diabetes, kidney failure and osteoarthritis). One of the authors (ABL) has built a comprehensive Regional Registry with all this information after first deleting the personal data. This study was approved by the Ethical Committee of Public University of Navarra on February 19th 2010.

The population was 80,019 adult patients (39,228 males and 40,791 females). Patients were selected as shown in the flow chart (Fig. 1). Our final population was 40,010 adult patients (18,988 males and 21,022 females).

The Public Health Care System in Navarra provides medical assistance to almost 98% of the population. We corroborate that our sample of 40,010 subjects is representative of the 80,019 individuals sampled and of the entire Navarra census, in terms of age and sex. We also contrasted the 80,019 with the entire Navarra census and we found no statistical differences. We found two small differences although they were not statistical significant. The proportion of females to males was slightly higher in the 40,010 (53% females) than in the 80,019 (51% females) subjects. Similarly, average age was 55 years in the 40,010 while 49 years in the 80,019 subjects. We noted that elderly and females are slightly over represented because they tend to use medical services more frequently than other individuals. This supports the representative nature of our sample.

To define overweight and obesity in adults, we calculate the BMI (weight in kilograms divided by square of height in meters). Underweight was considered as BMI $< 18.5\,kg/m^2$, Normal Weight as BMI $18.5–24.9\,kg/m^2$, Overweight as BMI $25.0–29.9\,kg/m^2$, Type I obesity as BMI $30.0–34.9\,kg/m^2$, Type II obesity as BMI $35.0–39.9\,kg/m^2$, and Type III obesity (morbid) as BMI $\geq 40\,kg/m^2$, based on the classification of overweight and obesity proposed by the expert committee of WHO for adults.

Statistical analyses

Taking into account BMI data, the prevalence of overweight and obesity was calculated, with their confidence intervals, by sex and age group. Comparison of proportions was performed with Chi-square test. Test with a *p*-value less than 0.05 were considered statistically significant. The association of overweight and obesity in different diseases was studied. Odds ratio (OR) adjusted for age and sex were calculated by unconditional logistic regression, using as reference patients with BMI lower than $25\,kg/m^2$.

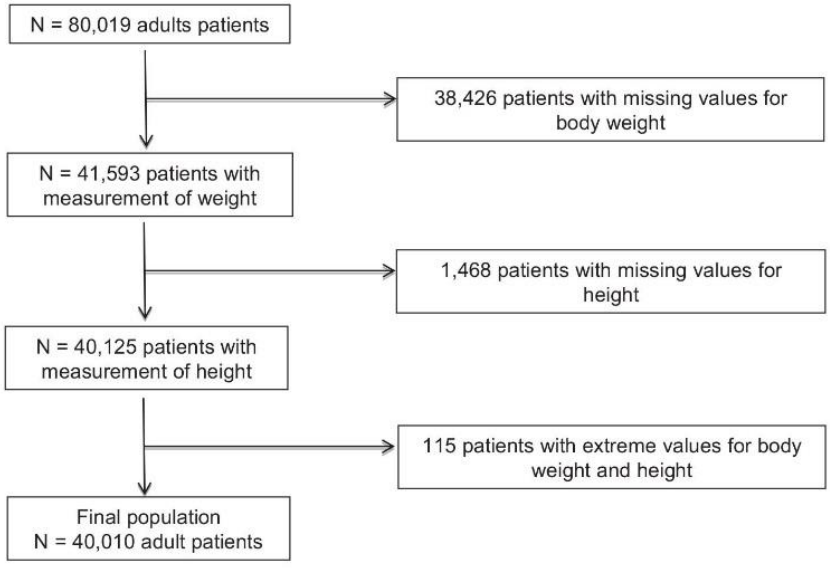

Figure 1 Flow chart of the APNA study population.

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In addition, a sensitivity analysis weighing our population with Navarra census, in terms of age and sex, was performed.

SPSS for Windows (version 19.0) and EpiInfo (version 6.04d) were the statistical programs used.

Results

Population characteristics

The study population includes individuals aged between 18 and 90 years (Table 1), with a mean age of 55.24 years. The age group with the highest number of individuals was 55–64 years. Mean BMI was $27.2 \pm 5.1\,kg/m^2$ ($27.7\,kg/m^2$ in males and $26.7\,kg/m^2$ in females). BMI increases progressively with age, with its maximum value in the age group of 65–74 years (BMI = $28.5\,kg/m^2$ (28.4–28.6)), a slight decrease was found in older subjects (≥75 years).

Prevalence of overweight and obesity

As shown in Table 2, the prevalence of overweight was 39.7% (39.2–40.1) (47.3% (46.6–48.0) in males and 32.8% (32.2–33.4) in females), and the prevalence of obesity was 25% (24.6–25.5) (25.9% (25.3–26.5) in males and 24.3% (23.7–24.9) in females).

The prevalence of overweight was higher in males than in females in all age groups (Fig. 2). The difference between males and females is statistically significant for all age groups except for subjects between 18 and 24 years ($p = 0.061$). In APNA study population, there are 10,019 obese subjects. As shown in Fig. 3, the prevalence of obesity increased with age and was higher in males than in females, except for those aged 65 years and older

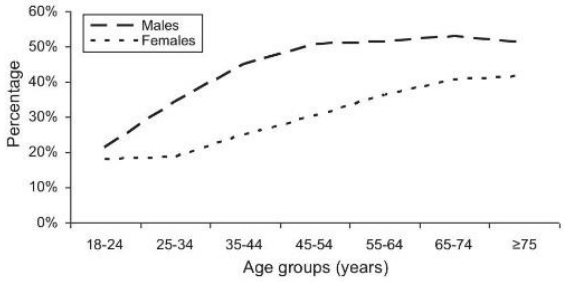

Figure 2 Prevalence of overweight for age group and sex in the APNA study.

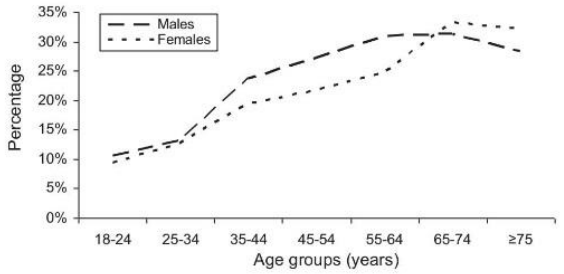

Figure 3 Prevalence of obesity for age group and sex in the APNA study.

in which obesity was more frequent in females. As for obesity, the difference was statistically significant for the age groups 35–44 years, 45–54 years, 55–64 years and ≥75 years ($p < 0.05$). The age groups 18–24 years ($p = 0.448$), 25–34 years ($p = 0.716$) and 65–74 years ($p = 0.084$) showed no statistically significant differences between males and females.

The prevalence of type I obesity was 18.1% (17.8–18.5), type II obesity was 5.1% (4.9–5.3) and morbid obesity was 1.8% (1.7–1.9)

Table 1 Characteristics of BMI by age group.

Age group (years)	*n*	BMI				
		Mean (95% CI)	SD	Median	25th quartile	75th quartile
Total	40,010	27.2 (27.1–27.2)	5.1	26.7	23.7	30.0
18–24	1620	23.5 (23.2–23.7)	5.1	22.3	20.0	25.9
25–34	5098	24.7 (24.5–24.8)	4.8	23.8	21.3	26.9
35–44	5251	26.6 (26.4–26.7)	5.4	25.7	22.8	29.3
45–54	6403	27.3 (27.1–27.4)	5.0	26.6	23.8	29.8
55–64	8018	27.8 (27.7–28.0)	4.9	27.3	24.5	30.4
65–74	7028	28.5 (28.4–28.6)	4.7	28.0	25.4	30.9
≥75	6592	28.2 (28.1–28.3)	4.8	27.8	25.1	30.7

CI, confidence interval; SD, standard deviation.

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Table 2 Prevalence of overweight and obesity in the APNA study in 2011, by sex and age groups.

	N	Underweight[a] % (95% CI)	Normal weight[b] % (95% CI)	Overweight[c] % (95% CI)	Type I obesity[d] % (95% CI)	Type II obesity[e] % (95% CI)	Type III obesity[f] % (95% CI)
Total	40,010	*1.7 (1.5–1.8)*	*33.6 (33.2–34.1)*	*39.7 (39.2–40.1)*	*18.1 (17.8–18.5)*	*5.1 (4.9–5.3)*	*1.8 (1.7–1.9)*
Males	18,988	0.8 (0.6–0.9)	26.1 (25.5–26.7)	*47.3 (46.6–48.0)*	*20.4 (19.8–21.0)*	*4.2 (3.9–4.5)*	*1.3 (1.2–1.5)*
18–24 years	719	6.7 (4.9–8.5)	61.5 (57.9–65.0)	21.3 (18.3–24.3)	6.3 (4.5–8.0)	2.5 (1.4–3.7)	1.8 (0.8–2.8)
25–34 years	2465	1.6 (1.1–2.1)	51.0 (49.1–53.0)	34.3 (32.4–36.1)	9.3 (8.2–10.5)	2.8 (2.2–3.5)	0.9 (0.6–1.3)
35–44 years	2606	0.6 (0.3–0.9)	30.5 (28.8–32.3)	45.1 (43.2–47.0)	17.1 (15.7–18.6)	4.4 (3.6–5.2)	2.2 (1.6–2.8)
45–54 years	3192	0.3 (0.1–0.5)	22.0 (20.5–23.4)	50.7 (48.9–52.4)	21.0 (19.6–22.4)	4.9 (4.1–5.6)	1.2 (0.8–1.6)
55–64 years	3930	0.2 (0.1–0.4)	17.6 (16.4–18.8)	51.3 (49.8–52.9)	25.3 (23.9–26.7)	4.3 (3.7–5.0)	1.2 (0.9–1.6)
65–74 years	3436	0.4 (0.2–0.7)	15.5 (14.3–16.7)	52.9 (51.2–54.5)	25.3 (23.9–26.8)	4.7 (4.0–5.4)	1.3 (0.9–1.6)
≥75 years	2640	0.4 (0.1–0.6)	20.1 (18.6–21.6)	51.1 (49.2–53.0)	23.4 (21.8–25.1)	3.9 (3.2–4.6)	1.0 (0.6–1.4)
Females	21,022	2.5 (2.3–2.7)	40.4 (39.8–41.1)	*32.8 (32.2–33.4)*	*16.1 (15.6–16.6)*	*5.9 (5.6–6.3)*	*2.3 (2.1–2.5)*
18–24 years	901	10.9 (8.8–12.9)	61.8 (58.7–65.0)	17.9 (15.4–20.4)	6.4 (4.8–8.0)	2.3 (1.4–3.3)	0.7 (0.1–1.2)
25–34 years	2633	6.6 (5.6–7.5)	61.9 (60.1–63.8)	18.7 (17.2–20.2)	8.2 (7.2–9.3)	3.4 (2.7–4.1)	1.2 (0.8–1.6)
35–44 years	2645	3.2 (2.5–3.8)	52.3 (50.4–54.2)	25.1 (23.5–26.8)	12.1 (10.9–13.4)	4.8 (4.0–5.6)	2.5 (1.9–3.1)
45–54 years	3211	1.5 (1.1–2.0)	46.2 (44.5–47.9)	30.5 (28.9–32.1)	13.2 (12.0–14.4)	6.2 (5.4–7.0)	2.4 (1.9–2.9)
55–64 years	4088	1.2 (0.8–1.5)	37.8 (36.3–39.3)	36.3 (34.8–37.8)	15.7 (14.6–16.8)	6.2 (5.5–7.0)	2.8 (2.3–3.4)
65–74 years	3592	0.8 (0.5–1.1)	25.3 (23.9–26.8)	40.7 (39.0–42.2)	22.6 (21.2–23.9)	7.7 (6.9–8.6)	2.9 (2.3–3.4)
≥75 years	3952	1.1 (0.7–1.4)	25.1 (23.7–26.4)	41.8 (40.3–43.3)	22.9 (21.6–24.2)	7.2 (6.4–8.0)	1.9 (1.5–2.4)

CI, confidence interval.
[a] Underweight: BMI < 18.5 kg/m^2.
[b] Normal weight: BMI 18.5–24.9 kg/m^2.
[c] Overweight: BMI 25.0–29.9 kg/m^2.
[d] Type I obesity: BMI 30.0–34.9 kg/m^2.
[e] Type II obesity: BMI 35.0–39.9 kg/m^2.
[f] Type III obesity: BMI ≥ 40 kg/m^2.

Association between overweight and obesity with studied diseases

BMI is associated with glucose intolerance (OR: 1.07; 95% CI: 1.06—1.08), dyslipidemia (OR: 1.04; 95% CI: 1.03—1.04), hypertension (OR: 1.21; 95% CI: 1.12—1.13), type 2 diabetes (OR: 1.11; 95% CI: 1.10—1.11), kidney failure (OR: 1.04; 95% CI: 1.03—1.05), and osteoarthritis (OR: 1.06; 95% CI: 1.05—1.06). As shown in Table 3, these six chronic diseases are certainly associated with overweight and obesity. In addition, all the degrees of obesity are associated with asthma (OR type I obesity: 1.33; OR type II obesity: 1.69; OR type III obesity: 1.75), atrial fibrillation (OR type I obesity: 1.24; OR type II obesity: 1.72; OR type III obesity: 2.34), heart failure (OR type I obesity: 1.68; OR type II obesity: 2.78; OR type III obesity: 4.35) and severe mental disorders (OR type I obesity: 2.02; OR type II obesity: 2.33; OR type III obesity: 2.50). Depression is associated with type II obesity (OR: 1.24; 95% CI: 1.09—1.42) and morbid obesity (OR: 1.28; 95% CI: 1.03—1.58). Type II and morbid obesity is also linked to COPD. Prostate cancer is only associated with type I obesity (OR: 1.39; 95% CI: 1.03—1.86). The APNA study has not found association between overweight/obesity with colon cancer and anxiety.

Sensitivity analysis

The prevalence of overweight and obesity in the population weighted is shown in Appendix A. This statistical weighting slightly decreased the prevalence of overweight and obesity. No differences in the trend of prevalence were found, comparing them with unweighted population. As shown in Appendix B, the association of overweight and obesity in the studied disease is the same in unweighted and weighted population. The sensitivity analysis proved the robustness of the results.

Discussion

The prevalence of overweight and obesity was 39.7% (39.2—40.1) and 25% (24.6—25.5) respectively in the APNA study population. These anthropometric data are registered from patients attending Primary Health Care Centres. Since, patients are not measured their height and weight every year, the results should be evaluated with some caution. Recently, there are two studies that estimated the prevalence of overweight and obesity population in Spain. If we compare our prevalence with other studies in the general population, the prevalence of overweight is similar to the reported values (39.4% (38.2—40.5)) in the ENRICA study [10]. But the prevalence of obesity is higher than those obtained (22.9% (21.9—23.8)) in the ENRICA study. Moreover, a higher prevalence of overweight and obesity was found in the DARIOS study [11] than in the APNA study. Unlike these studies, the data of the APNA study are collected in routine clinical practice. Within the group of obese, 18.1% are type I obese, 5.1% are type II obese and 1.8% are type III or morbid obese; similar data were observed in the ENRICA study.

With regard to sex, as in all European countries [15], overweight was higher in males than in females. In males, the prevalence was higher in the age group of 45—54 years and in females in the group older than 75 years, as reported in the ENRICA study. On the other hand, obesity in our study was more prevalent in males than in females except for over 75 years. The age group with the highest prevalence of obesity for both sexes was 65—74 years; contrary to results from the ENRICA study in which males aged 45—64 years old were more obese.

In the APNA study, from overweight to severe obesity are consistently associated with hypertension, glucose intolerance, type 2 diabetes, dyslipidemia, kidney failure and osteoarthritis. We found that the risk of hypertension increases progressively with higher levels of BMI [16—18]. The Nurses' Health Study showed that females who gained more than 25 kg in weight had a five-fold increase in the risk of hypertension, compared with females whose weight remained stable [19]. The APNA study found that each unit of higher BMI increases in 12% the risk of hypertension.

Glucose intolerance and type 2 diabetes are also associated with overweight and obesity and increases with the degree of BMI. The association between BMI and type 2 diabetes observed in our sample is concordant with studies from the literature [13,18,20,21]. The prevalence of type 2 diabetes in overweight and obesity was 11.5% and 25.2% respectively. It was higher in males than in females from overweight to type II obesity. Only in type III obesity the prevalence was higher in females. In the OBEDIA study [20] was obtained higher prevalence (17.8% for overweight and 34.8% for obesity). In that study, the prevalence was higher in males in all degrees of BMI $\geq 25\,kg/m^2$. The differences between APNA study and OBEDIA study may be because the OBEDIA study included patients from primary health care and specialized assistance, and the larger sample size.

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Table 3 Odds ratios (OR) for overweight and obesity and the studied diseases.

	N	OR (for each additional unit of BMI)[d] (95% CI)	OR Overweight[e] (95% CI)	OR Type I obesity[e] (95% CI)	OR Type II obesity[e] (95% CI)	OR Type III obesity[e] (95% CI)
Glucose intolerance	2935	1.07 (1.06–1.08)	**1.86 (1.67–2.08)**	**2.62 (2.32–2.95)**	**3.34 (2.84–3.92)**	**2.93 (2.27–3.79)**
Dyslipidemia	14,304	1.04 (1.03–1.04)	**1.66 (1.57–1.75)**	**1.67 (1.57–1.79)**	**1.58 (1.43–1.75)**	**1.27 (1.08–1.50)**
Anxiety	7775	1.00 (0.99–1.00)	0.99 (0.93–1.05)	0.93 (0.86–1.01)	0.96 (0.85–1.08)	0.94 (0.78–1.14)
Depression	4821	1.01 (1.01–1.02)	1.05 (0.97–1.13)	1.09 (1.00–1.20)	**1.24 (1.09–1.42)**	**1.28 (1.03–1.58)**
Severe mental disorder	372	1.06 (1.04–1.07)	1.21 (0.93–1.59)	**2.02 (1.51–2.71)**	**2.33 (1.55–3.51)**	**2.50 (1.37–4.58)**
Dementia	532	0.96 (0.94–0.98)	0.77 (0.62–0.94)	0.71 (0.55–0.92)	0.69 (0.45–1.06)	0.65 (0.30–1.41)
Heart failure	596	1.07 (1.05–1.08)	1.10 (0.87–1.38)	**1.68 (1.31–2.15)**	**2.78 (2.01–3.84)**	**4.35 (2.77–6.83)**
Atrial fibrillation	1510	1.04 (1.03–1.05)	0.99 (0.86–1.14)	**1.24 (1.06–1.45)**	**1.72 (1.37–2.15)**	**2.34 (1.67–3.30)**
Hypertension	12,813	1.12 (1.12–1.13)	**2.03 (1.90–2.17)**	**3.43 (3.18–3.70)**	**5.74 (5.12–6.45)**	**7.70 (6.43–9.22)**
Lung cancer[a]	92	0.96 (0.91–1.01)	0.66 (0.40–1.07)	0.40 (0.20–0.78)	0.32 (0.08–1.34)	0.55 (0.08–4.08)
Colon cancer	369	1.01 (0.99–1.03)	0.95 (0.73–1.24)	1.07 (0.79–1.44)	0.95 (0.57–1.59)	1.24 (0.57–2.71)
Prostate cancer[b]	459	1.02 (1.00–1.04)	1.21 (0.93–1.58)	**1.39 (1.03–1.86)**	1.19 (0.70–2.02)	0.70 (0.22–2.28)
Breast cancer[c]	380	0.99 (0.96–1.01)	0.70 (0.54–0.90)	1.04 (0.78–1.37)	0.93 (0.61–1.42)	0.81 (0.39–1.66)
Asthma	2267	1.03 (1.02–1.04)	1.06 (0.96–1.18)	**1.33 (1.17–1.50)**	**1.69 (1.42–2.02)**	**1.75 (1.34–2.29)**
COPD	1201	1.03 (1.01–1.04)	0.88 (0.75–1.03)	1.09 (0.91–1.29)	**1.93 (1.52–2.45)**	**1.89 (1.27–2.82)**
Type 1 diabetes	140	0.95 (0.91–0.99)	0.69 (0.47–1.02)	0.52 (0.29–0.91)	0.46 (0.17–1.28)	0.32 (0.04–2.30)
Type 2 diabetes	4455	**1.11** (1.10–1.11)	**1.81 (1.64–2.00)**	**3.13 (2.82–3.48)**	**5.03 (4.38–5.77)**	**8.42 (6.94–10.21)**
Kidney failure	1378	1.04 (1.03–1.05)	**1.41 (1.21–1.64)**	**1.55 (1.30–1.84)**	**2.03 (1.58–2.60)**	**2.69 (1.86–3.90)**
Osteoarthritis	6666	1.06 (1.05–1.06)	**1.35 (1.25–1.46)**	**1.82 (1.67–1.99)**	**2.38 (2.10–2.70)**	**2.74 (2.26–3.32)**

COPD, chronic obstructive pulmonary disease; BMI, body mass index. Bold values indicate that the association is statistically significant.

[a] OR adjusted for age, sex and smoking habits (smoker, non-smoker and former smoker).

[b] Only in males.

[c] Only in females.

[d] OR adjusted for age and sex.

[e] OR adjusted for age and sex. The reference used was patients with BMI < 25 kg/m^2.

Hypertension and type 2 diabetes increased linearly with higher BMI. With regard to dyslipidemia, Bays et al. [18] demonstrated that there was a significant trend towards higher prevalence of dyslipidemia as BMI increased. But when subjects are obese and morbidly obese (BMI $\geq$ 30 kg/m^2), the prevalence of dyslipidemia reaches its higher levels, and begins to decline. In the APNA study, the OR for dyslipidemia started to decline in subjects with BMI $\geq$ 35 kg/m^2.

There is also evidence that overweight and obesity may cause renal dysfunction and increased risk for chronic kidney disease [22,23]. In our study a significant risk for kidney failure was shown for different BMI range, from an OR of 1.41 for overweight to 2.69 for morbid obesity. In a cohort of over 11,000 healthy men, higher BMI was associated with an increased risk of incident chronic kidney disease [24]. In that study, a significant risk (OR 1.45) of developing chronic kidney disease was found when they compared subjects with BMI < 22.7 kg/m^2 with subjects with BMI > 26.6 kg/m^2.

With regard to the association of the BMI with osteoarthritis, our study found a significant association from an OR of 1.35 for overweight to an OR of 2.74 for severe obesity. Several studies have shown that the excess bodyweight, expressed as increased BMI, is associated with osteoarthritis risk [25–27]. Grotle et al. [26] reported that BMI > 30 kg/m^2 was significantly associated with osteoarthritis. Their results are slightly higher than ours. It could be that their sample size was smaller (1675 patients). Additionally, our study showed that the prevalence of the osteoarthritis in subjects with overweight and obesity was higher in females. Similar results were obtained by Jiang et al. [28], who found that the association was significantly stronger in females than in males.

Furthermore, obesity is recognized as the most important factor of cardiovascular risk [11,17,29]. It has been shown to be associated with atrial enlargement and ventricular diastolic dysfunction, both of which are risk factors for atrial fibrillation. Our results demonstrate that all degrees of obesity are associated with atrial fibrillation. A meta-analysis with 78,602 subjects reported that obese individuals have an associated 49% increased risk of developing atrial fibrillation compared to non-obese individuals [30]. Unlike our study, Thacker et al. [31] also found significant association in overweight, although the association of the atrial fibrillation with different degrees of obesity was lower than APNA study. These two studies had similar demographic characteristics: number of subjects, mean age and sex distribution.

With regard to heart failure, for every 1 kg/m^2 increment in BMI, the risk of heart failure increased 7%, adjusted for sex and age. Similar results were obtained in the Framingham Heart Study (for every 1 kg/m^2 increment in BMI, the risk of heart failure increased 5% in men and 7% in women) [32], during 14-year follow-up.

The overweight and obesity has been directly linked to the development of many cancers [33–35]. Our study evaluated the association of obesity with lung, colon, prostate and breast cancer.

First, as to lung cancer, our results found a protective association between type I obesity and lung cancer. According to Yang et al. [36], overweight and obesity were protective factors against lung cancer. Our study only found this protective association in subjects with BMI between 30 and 34.9 kg/m^2. The association of BMI with lung cancer is difficult to interpret, as the tobacco is the leading cause of lung cancer and is inversely related to BMI. We consider our population as a smoker or nonsmoker (including former smokers). As BMI increases, the number of smokers decreases. So smokers were 21.3% of the overweight subjects and 18.7% of morbidly obese. This is an interesting point for future research.

Moreover, unlike published in numerous studies [34,37,38], our study did not find an association between BMI and colon cancer. If the analysis is performed only adjusted for sex, a significant association with overweight and type I obesity is obtained. By including age in the multivariate analysis, we have no significant association. So we conclude that the age is a confounding factor.

With regard to prostate cancer, the association with BMI is complex. There are many studies that do not support an association between BMI and prostate cancer [39,40]. The lack of evidence can be due to a dual effect of BMI in prostate cancer development. Recent studies indicate that BMI is inversely associated with risk of localized prostate cancer and directly associated with risk of advanced prostate cancer [40–42]. Our study found an association between type I obesity and prostate cancer. The analysis was performed in all cases of prostate cancer, without measuring up the stage or severity. In future research, it would be interesting to consider the effect of BMI on localized and advanced prostate cancers.

The results of our study show a protective association of overweight with breast cancer. Recent studies established that the association between BMI and risk of breast cancer varied based on menopausal status. Cheraghi et al. [43] showed

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that increase in BMI during postmenopausal period can significantly increase the risk of breast cancer. The results of this meta-analysis showed that body mass index has no significant effect on the incidence of breast cancer during premenopausal period. Suzuki et al. [44] reported that overweight during premenopausal period would decrease the risk of breast cancer, while it might increase the risk of cancer during postmenopausal period. If we consider a menopausal status from 51 years, 73% of the overweight group was menopausal females (the mean age of overweight group was 60.6 years). Our study does not find the same association that the studies previously showed. It may be due to lower sample size.

Overweight and obese individuals are more likely to have respiratory symptoms than individuals with a normal BMI [45,46]. With regard to the association of the BMI with asthma, our study found a significant association in all degrees of obesity, from an OR of 1.33 for type I obesity to an OR of 1.75 for severe obesity. Several studies established that elevated BMI constitutes a risk factor for asthma in adults [47,48]. A meta-analysis [47] with 333,102 subjects reported an association between asthma and subjects with BMI $\geq$25 kg/m^2. This association was slightly higher than that obtained in our study. In addition, in this meta-analysis also found association in the overweight group.

Regarding the relation between obesity and COPD, our results showed significant association with type II and type III obesity. There are numerous works linking obesity to COPD [45,49,50]. These studies showed that there was a high prevalence of overweight and obesity in the early stages of COPD compared with the general population, but there was a paradox in that low BMI happens in patients with moderate to severe COPD. In our study, there is a lack of data on the degree of COPD.

Finally, there is evidence of the association between obesity and mental health [51]. We found significant association between severe mental disorder (bipolar disorder or schizophrenia) with all degrees of obesity. Each unit of higher BMI increases in 6% the risk of severe mental disorder. Gurpegui et al. [52] reported a significant association between subjects with BMI $\geq$25 kg/m^2 and severe mental disorder. This association was slightly higher than that obtained in our study. In addition, they also found association in the overweight group.

The depression was associated with type II and morbid obesity. Although there are studies that consider that there is not a clear association [53,54], recent studies find that there is a strong association between obesity and depression [55,56], being in agreement with the results obtained in our study. Obesity and depression are highly prevalent in today's society, so it is important to consider both diseases and their possible association due to major health cost and involvement in life quality. Unlike some studies reported [57,58], in our study an association between obesity and anxiety was not demonstrated.

Strengths and limitations

The main strength of our study is the large number of participants from several Primary Health Care Centres (40,010 patients). We corroborate that our sample of 40,010 subjects is representative of the 80,019 individuals sampled and of the entire Navarra census.

A limitation of the study is the high proportion of missing data (50%). The data are registered from patients attending in Primary Health Care Centres. Each year the patients are not measured and weighed. It would be advisable, as improvement of the quality of healthcare, that all the patients who come to a Primary Health Care Centres are weighed and measured.

We performed a sensitivity analysis whereby our population was weighted by age and sex of the Navarra census. The sensitivity analysis proved the robustness of the results.

In regarding the association of obesity with different studied types of cancer, due to the characteristics of our study, we found lower association.

In summary, the prevalence of overweight (40%) and obesity (25%) remains high being similar to the Spanish population data. The figures are higher in males than in females, except for the higher range of BMI (type II and type III obesity is more prevalent in females).

Our study showed a positive association of overweight and obesity with glucose intolerance, dyslipidemia, type 2 diabetes, hypertension, osteoarthritis and kidney failure. Moreover, all degrees of obesity were associated with cardiovascular diseases (atrial fibrillation and heart failure), respiratory problems (asthma) and severe mental disorder (bipolar disorder and schizophrenia). An interesting point is the association of higher levels of BMI with depression. It is important for health professionals to deal with the control and management of obesity, as it is associated with numerous health problems affecting mortality and life quality.

Conflict of interest

None.

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Appendix A. Prevalence of overweight and obesity in the APNA study in 2011 weighted by age and sex Navarra census

	N	Underweight[a] % (95% CI)	Normal weight[b] % (95% CI)	Overweight[c] % (95% CI)	Type I obesity[d] % (95% CI)	Type II obesity[e] % (95% CI)	Type III obesity[f] % (95% CI)
Total	40,010	*2.2 (2.1–2.4)*	*38.1 (37.6–38.6)*	*37.0 (36.6–37.5)*	*16.1 (15.8–16.5)*	*4.7 (4.5–4.9)*	*1.8 (1.6–1.9)*
Males	19,827	1.2 (1.0–1.3)	31.1 (30.4–31.7)	*44.3 (43.6–45.0)*	*18.0 (17.5–18.6)*	*4.0 (3.7–4.3)*	*1.4 (1.3–1.6)*
18–24 years	1721	6.7 (5.6–8.0)	61.5 (59.1–63.8)	21.3 (19.4–23.3)	6.3 (5.2–7.6)	2.5 (1.8–3.4)	1.8 (1.2–2.6)
25–34 years	3573	1.6 (1.2–2.1)	51.0 (49.4–2.7)	34.3 (32.7–35.9)	9.3 (8.4–10.3)	2.8 (2.3–3.4)	0.9 (0.6–1.3)
35–44 years	4307	0.6 (0.4–0.9)	30.6 (29.2–32.0)	45.1 (43.6–46.6)	17.1 (16.0–18.3)	4.4 (3.8–5.1)	2.2 (1.8–2.7)
45–54 years	3653	0.3 (0.1–0.5)	22.0 (20.6–23.3)	50.7 (49.0–52.3)	21.0 (19.7–22.4)	4.8 (4.2–5.6)	1.2 (0.9–1.7)
55–64 years	2776	0.2 (0.1–0.5)	17.6 (16.2–19.1)	51.3 (49.5–53.2)	25.3 (23.7–27.0)	4.3 (3.6–5.2)	1.2 (0.9–1.7)
65–74 years	1953	0.5 (0.2–0.7)	15.5 (1.9–17.2)	52.8 (50.6–55.1)	25.3 (23.4–27.3)	4.7 (3.8–5.7)	1.2 (0.8–1.9)
≥75 years	1844	0.4 (0.2–0.8)	20.1 (18.3–22.0)	51.1 (48.8–53.4)	23.4 (21.5–25.4)	3.9 (3.1–4.9)	1.0 (0.6–1.6)
Females	20,177	3.3 (3.0–3.5)	45.0 (44.3–45.7)	*29.9 (29.3–30.5)*	*14.3 (13.8–14.8)*	*5.4 (5.1–5.8)*	*2.1 (1.9–2.3)*
18–24 years	1646	10.9 (9.4–12.5)	61.8 (59.4–64.2)	17.9 (16.1–19.8)	6.4 (5.3–7.8)	2.3 (1.7–3.2)	0.7 (0.4–1.2)
25–34 years	3393	6.6 (5.8–7.5)	62.0 (60.3–63.6)	18.7 (17.4–20.1)	8.2 (7.3–9.2)	3.4 (2.8–4.1)	1.2 (0.9–1.6)
35–44 years	3949	3.2 (2.7–3.8)	52.3 (50.8–53.9)	25.1 (23.8–26.5)	12.1 (11.1–13.2)	4.8 (4.1–5.5)	2.5 (2.0–3.0)
45–54 years	3475	1.5 (1.2–2.0)	46.2 (44.5–47.9)	30.5 (29.0–32.1)	13.2 (12.1–14.4)	6.2 (5.4–7.0)	2.4 (1.9–2.9)
55–64 years	2750	1.2 (0.8–1.7)	37.8 (36.0–39.7)	36.3 (34.5–38.1)	15.7 (14.3–17.1)	6.2 (5.4–7.1)	2.4 (1.9–3.0)
65–74 years	2111	0.9 (0.5–1.4)	25.3 (23.5–27.3)	40.6 (38.5–42.8)	22.5 (20.8–24.4)	7.7 (6.6–9.0)	2.9 (2.2–3.7)
≥75 years	2853	1.1 (0.7–1.5)	25.1 (23.5–26.7)	41.8 (40.0–43.7)	22.9 (29.3–30.5)	7.2 (6.3–8.2)	2.0 (1.5–2.6)

CI, confidence interval.
[a] Underweight: BMI < 18.5 kg/m^2.
[b] Normal weight: BMI 18.5–24.9 kg/m^2.
[c] Overweight: BMI 25.0–29.9 kg/m^2.
[d] Type I obesity: BMI 30.0–34.9 kg/m^2.
[e] Type II obesity: BMI 35.0–39.9 kg/m^2.
[f] Type III obesity: BMI ≥ 40 kg/m^2.

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Appendix B. Odds ratios (OR) for overweight and obesity and the studied diseases weighted by age and sex Navarra census

	N	OR (for each additional unit of BMI)[d] (95% CI)	OR overweight[e] (95% CI)	OR Type I obesity[e] (95% CI)	OR Type II obesity[e] (95% CI)	OR Type III obesity[e] (95% CI)
Glucose intolerance	2265	1.07 (1.07–1.08)	**1.89 (1.67–2.14)**	**2.87 (2.51–3.29)**	**3.51 (2.93–4.21)**	**3.32 (2.51–4.40)**
Dyslipidemia	11,598	1.04 (1.04–1.05)	**1.74 (1.65–1.85)**	**1.80 (1.68–1.93)**	**1.72 (1.54–1.92)**	**1.35 (1.13–1.62)**
Anxiety	7694	1.00 (0.99–1.00)	0.99 (0.93–1.05)	0.94 (0.87–1.02)	0.96 (0.85–1.08)	1.01 (0.83–1.22)
Depression	4133	1.01 (1.01–1.02)	1.03 (0.95–1.12)	1.06 (0.96–1.17)	**1.23 (1.07–1.43)**	**1.29 (1.03–1.62)**
Severe mental disorder	363	1.06 (1.04–1.08)	1.23 (0.95–1.60)	**2.26 (1.70–2.98)**	**2.25 (1.48–3.41)**	**2.79 (1.57–4.93)**
Dementia	375	0.96 (0.94–0.99)	0.77 (0.60–1.00)	0.72 (0.53–0.97)	0.72 (0.43–1.19)	0.64 (0.25–1.64)
Heart failure	422	1.06 (1.05–1.08)	1.03 (0.79–1.35)	**1.61 (1.21–2.15)**	**2.68 (1.84–3.91)**	**3.79 (2.20–6.52)**
Atrial fibrillation	1043	1.04 (1.03–1.05)	1.03 (0.87–1.22)	**1.28 (1.06–1.55)**	**1.83 (1.39–2.40)**	**2.33 (1.53–3.53)**
Hypertension	9477	1.12 (1.12–1.13)	**2.08 (1.93–2.24)**	**3.62 (3.33–3.95)**	**6.22 (5.49–7.05)**	**8.18 (6.78–9.87)**
Lung cancer[a]	65	0.95 (0.90–1.01)	0.62 (0.35–1.08)	0.47 (0.22–0.98)	0.31 (0.06–1.74)	1.00 (0.17–5.69)
Colon cancer	254	1.01 (0.99–1.03)	0.93 (0.68–1.27)	1.04 (0.72–1.48)	0.89 (0.47–1.66)	1.15 (0.44–3.02)
Prostate cancer[b]	302	1.02 (0.99–1.05)	1.25 (0.90–1.73)	**1.43 (1.00–2.06)**	1.18 (0.61–2.29)	0.72 (0.17–3.10)
Breast cancer[c]	288	1.00 (0.97–1.02)	0.70 (0.52–0.93)	0.97 (0.70–1.34)	0.85 (0.51–1.40)	0.78 (0.34–1.81)
Asthma	2493	1.03 (1.02–1.04)	1.02 (0.92–1.12)	**1.29 (1.14–1.45)**	**1.56 (1.30–1.86)**	**1.93 (1.50–2.48)**
COPD	849	1.03 (1.01–1.04)	0.88 (0.73–1.06)	1.08 (0.88–1.33)	**2.06 (1.56–2.72)**	**1.82 (1.13–2.93)**
Type 1 diabetes	162	0.96 (0.93–1.00)	0.80 (0.56–1.16)	0.66 (0.39–1.10)	0.56 (0.22–1.43)	0.51 (0.11–2.40)
Type 2 diabetes	3244	1.12 (1.11–1.12)	**1.94 (1.73–2.18)**	**3.52 (3.11–3.98)**	**5.71 (4.86–6.70)**	**9.86 (7.94–12.23)**
Kidney failure	962	1.04 (1.03–1.06)	**1.41 (1.17–1.70)**	**1.56 (1.27–1.92)**	**1.99 (1.48–2.67)**	**2.81 (1.82–4.34)**
Osteoarthritis	4764	1.05 (1.05–1.06)	**1.29 (1.19–1.41)**	**1.76 (1.59–1.94)**	**2.31 (2.00–2.67)**	**2.70 (2.16–3.37)**

COPD, chronic obstructive pulmonary disease; BMI, body mass index. Bold values indicate that the association is statistically significant.

[a] OR adjusted for age, sex and smoking habits (smoker, non-smoker and former smoker).

[b] Only in males.

[c] Only in females.

[d] OR adjusted for age and sex.

[e] OR adjusted for age and sex. The reference used was patients with BMI < 25 kg/m^2.

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Original article

Relationship between body mass index and depression in women: A 7-year prospective cohort study. The APNA study

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ABSTRACT

Background: The association between body mass index (BMI) and depression is complex and controversial. The present study examined the relationship between BMI and new-onset depression during 7 years of follow-up in 20,212 adult women attending Primary Health Care Centres in Navarra, Spain.

Methods: The Atención Primaria de Navarra (APNA) study is a dynamic prospective cohort study. A total of 20,212 women aged 18–99 years (mean age: 50.7 ± 18.5 years) without depression at baseline were selected from 2004 to 2011. We estimated the incidence of depression. We used the Kaplan-Meier analysis to predict the survival curve. The risk of depression onset according to different measures of BMI at baseline was assessed using Cox regression analyses.

Results: During the 7 years of follow-up, depression appeared in 8.9% (95% CI 8.5–9.3). The highest rates of depression incidence at follow-up occurred in underweight and obese women (9.8% [95% CI 7.3–12.9] and 10.3% [95% CI 9.5–11.1] respectively). The distribution of depression incidence by weight category was U-shaped. The risk of depression increased over time with an observed Kaplan-Meier estimation of 6.67. After adjusting for age, underweight and obese women at baseline have increased risk of depression onset during the follow-up period compared with normal weight women (HR = 1.48, 95% CI = 1.09–2.00 and HR = 1.14, 95% CI = 1.01–1.29 respectively).

Conclusions: In this 7-year prospective study in the APNA women population, depression emerged in 8.9%. Being underweight or obese (not overweight) at baseline is significantly associated with future onset of depression.

1. Introduction

Obesity and depression are highly prevalent in women worldwide. They are an important public health problem that requires an affordable diagnosis and treatment at primary health care level.

Depression has a multifactorial etiology [1]; there are different physiopathological models of depression highlighting the roles of neurotransmitters, neurodegenerative, and inflammatory factors. These elements are modified by nutritional status, thus alterations in BMI and depression may share some mechanisms [2,3], since they are influenced by psychological elements.

The association between obesity and depression is complex and multifactorial. Some of the traits of obese subjects, such as low self-esteem, poor body image, maladaptive eating behaviors, exercise avoidance, medication, and hormonal and functional impairment, have been shown to also cause depression, which helps explaining the relationship between these two conditions [4]. Women appear to be at a higher risk of obesity and common mental health disorders than men. Furthermore, the mental health of women is

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more closely related to overweight and obesity than that of men [5].

The relationship between body mass index (BMI) and depression is controversial. Some studies showed that there is an association between underweight and depression [6,7], while others suggest the lack of a clear association between BMI and depression [8,9]. It is important to consider all BMI ranges (from underweight to obese) because underweight people may also have depressive symptoms due to their low self-esteem and negative body image.

In regard to obesity, a number of studies find obese individuals to be more likely to suffer from depression than non-obese individuals [10–12]. Moreover, in a meta-analysis of 17 community-based studies (n = 204,507), it is shown that obese people is 1.18 times more likely to have depression than those who were not obese, especially among women [13].

The main objective of the present study is to evaluate the relationship between BMI (from underweight and obesity) and depression onset during 7 years of follow-up in 20,212 women attending Primary Health Care Centres in Navarra. We examine the incidence of depression in underweight, normal weight, overweight and obese patients at baseline of the study. Interestingly, we estimate the risk of onset of depression over time according to BMI.

2. Methods

The Atención Primaria de Navarra (APNA) study is a multipurpose dynamic prospective cohort study, which was conducted in seven Primary Health Care Centres in Navarra (Azpilagaña, Burlada, Echavacoiz, Iturrama, San Jorge, Tafalla and Villava). The study population consists of all adults women (≥18 years) attending one of these seven centres. Navarra, has a registry of each patient's medical history collected electronically by the general practitioner during routine clinical practice. Every time a patient visits a Health Centre, his clinical register is updated. From these electronic data, one of the authors (ABL) has built a comprehensive database with all this information after deleting the personal information. A cross-sectional study within the APNA cohort has been published elsewhere [14]. The APNA cohort is dynamic, so that over the seven years, some new subjects were incorporated and others left the cohort. We followed up for 7 years (from 2004 to 2011). The variables considered in the study were sex, age, weight (kilograms) at baseline, height (meters) at baseline, and diagnosis of depression during the follow-up. This study was approved by the Ethical Committee of the Public University of Navarra on February 19th 2010.

The population was 23,920 adult women. Patients were selected as shown in the flow chart (Fig. 1). For this study, only patients free of depression at baseline were selected. The exclusion criteria was having depression at baseline. Our final population was 20,212 adult patients.

The diagnosis of depression was reported by a general practitioner [15,16]. In our cohort, depression has a clinical diagnostic. In the Spanish National Health Service, depression is diagnosed and treated mainly in Primary Health Care Centers by general practitioners. The law includes among the compulsory competences of general practitioners the following: "early detection and management of the following conditions in the field of mental health: depression, self-harm ideation, anxiety, social anxiety disorder, antisocial behavior and somatization disorder" [17].

To define overweight and obesity in adults, we calculate the BMI (weight in kilograms divided by the square of the height in meters). The patients were weighed and measured in a clinical setting. From the data of weight and height, BMI was calculated. Underweight was considered as BMI < 18.5 kg/m^2, normal weight as BMI 18.5–24.9 kg/m^2, overweight as BMI 25.0–29.9 kg/m^2 and obesity as BMI ≥ 30 kg/m^2, based on the classification of overweight and obesity proposed by the expert committee of WHO for adults [18].

2.1. Statistical analyses

Kaplan-Meier estimator was used to estimate the survival function. We selected women without depression and estimated the incidence of depression with their confidence intervals. The risk of depression onset according to different measures of BMI at baseline was assessed using Cox regression analyses. Analyses were adjusted for age. The proportional hazards (hazard ratios [HR] with 95% confidence intervals) were examined.

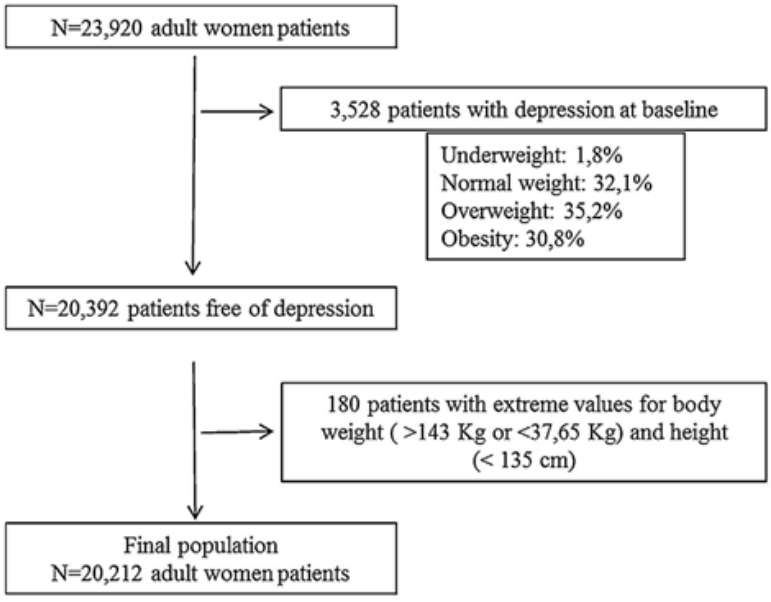

Fig. 1. Flow chart of the APNA population.

Table 1
Characteristics of the study population at baseline of the cohort by BMI categories.

Age group (years)	*n*	BMI categories (%, 95% CI)			
		Underweight *n* = 461	Normal weight *n* = 8310	Overweight *n* = 6622	Obesity *n* = 4819
Total	20,212	2.3 (2.1–2.5)	41.1 (40.4–41.8)	32.8 (32.1–33.4)	23.8 (23.3–24.4)
18–29	3403	6.4 (5.6–7.3)	63.2 (61.6–64.8)	18.4 (17.1–19.7)	12.0 (10.9–13.1)
30–39	2919	3.0 (2.5–3.8)	51.6 (49.7–53.4)	26.4 (24.8–28.0)	19.0 (17.6–20.5)
40–49	3280	1.7 (1.3–2.2)	45.5 (43.8–47.2)	31.0 (29.5–32.7)	21.8 (20.4–23.3)
50–59	3821	0.9 (0.6–1.2)	36.0 (34.5–37.6)	37.7 (36.2–39.2)	25.4 (24.0–26.8)
60–69	3040	0.7 (0.5–1.1)	24.4 (22.9–26.0)	40.9 (39.2–42.7)	34.0 (32.3–35.7)
≥70	3749	1.2 (0.9–1.6)	27.8 (26.4–29.3)	40.7 (39.1–42.2)	30.3 (28.9–31.9)

CI: confidence interval; BMI: body mass index.

SPSS for Windows (version 19.0) and EpiInfo (version 6.04d) were the statistical programs used.

3. Results

3.1. Population characteristics

The study population includes 20,212 women aged between 18 and 99 years, with a mean age of 50.7 ± 18.5 years. The age group with the highest number of individuals was 50-59 years. The prevalence of overweight and obesity at baseline was 32.8% (95% CI 32.1–33.4) and 23.8% (95% CI 23.3–24.4) respectively. As shown in Table 1, the frequency of overweight and obesity increased progressively with age, with its maximum value in the age group of 60–69 years. A slight decrease was found in older subjects (≥70 years). By contrast, the prevalence of underweight, 2.3% (95% CI 2.1–2.5), decreases with age, until age 70 when it starts increasing.

During the follow-up, depression appeared in 8.9% (95% CI 8.5–9.3) ($n = 1806$) of the initially non-depressed women. Thus, depression is more frequent in older subjects at baseline (Table 2). Furthermore, the risk of depression increases over time (Fig. 2), being the Kaplan-Meier estimation of 6.67 (95% CI 6.66–6.69).

Table 2
Incidence of depression by age group.

Age group (years)	*n*	No depression (%, 95% CI)	Depression (%, 95% CI)
Total	20,212	91.1 (90.7–91.5)	8.9 (8.5–9.3)
18–29	3403	95.6 (94.8–96.2)	4.4 (3.8–5.2)
30–39	2919	92.7 (91.6–93.6)	7.3 (6.4–8.4)
40–49	3280	91.7 (90.7–92.6)	8.3 (7.4–9.3)
50–59	3821	90.2 (89.2–91.2)	9.8 (8.8–10.8)
60–69	3040	89.7 (88.6–90.8)	10.3 (9.2–11.4)
≥70	3749	87.1 (86.0–88.2)	12.9 (11.8–14.0)

CI: confidence interval.

3.2. Incidence of depression by weight category

The highest rates for incidence of depression at follow-up were in underweight and obese women at baseline (9.8% [95% CI 7.3–12.9] and 10.3% [95% CI 9.5–11.1] respectively). Normal weight women had the lowest values (7.7% [95% CI 7.2–8.4]). The distribution of the incidence of depression by weight category was U-shaped (Fig. 3).

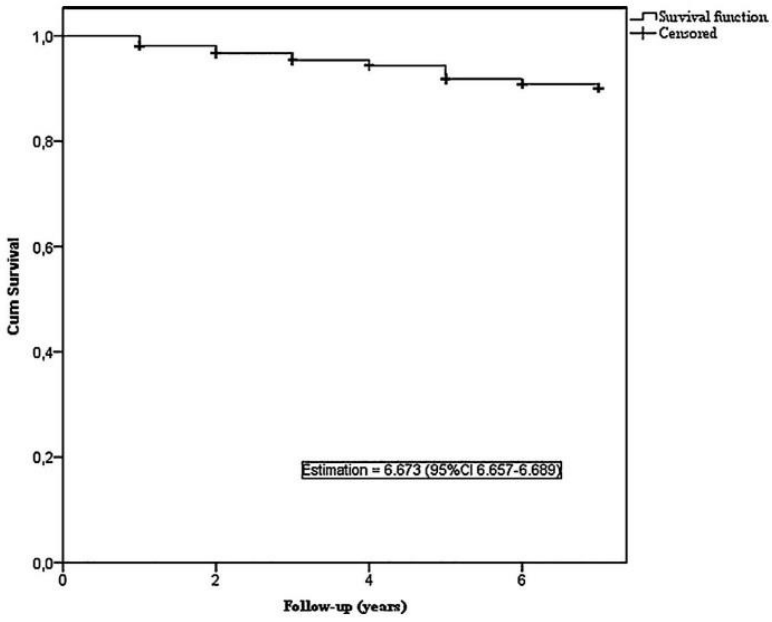

Fig. 2. Kaplan-Meier survival curve of time to depression onset.

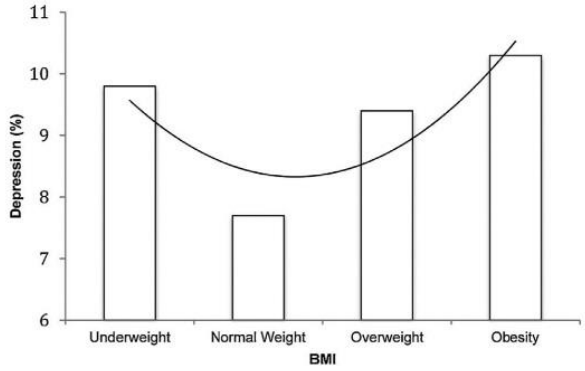

Fig. 3. U-curved association between BMI at baseline and new-onset depression.

3.3. Association between BMI and depression

Table 3 shows the results of Cox regression analyses assessing the risk of depression onset according BMI categories in non-depressed women at baseline. Compared with normal weight women, underweight and obese women were more likely to have depression onset during the 7 years of follow-up (HR = 1.48, 95% CI = 1.09–2.00 and HR = 1.14, 95% CI = 1.01–1.29 respectively). No significant association between overweight and depression onset was found (HR = 1.04, 95% CI = 0.93–1.16).

4. Discussion

After 7 years of follow-up, depression appeared in 8.9% (95% CI 8.5–9.3). The highest rates for incidence of depression were among underweight and obese women at baseline, which produced a U-shaped relationship between BMI and depression. Being underweight or obese at baseline is significantly associated with future onset of depression (HR = 1.48, 95% CI = 1.09–2.00 and HR = 1.14, 95% CI = 1.01–1.29 respectively).

The prevalence of overweight and obesity was 32.8% and 23.8% respectively in our population at baseline. Compared to the ENRICA study [19], we found similar values in the prevalence of overweight for the general population (32.5%), whereas the values we obtained for the prevalence of obesity were higher than previously reported (21.4%). Unlike the ENRICA study, our data were collected in routine clinical practice. Body weight tends to increase slightly but progressively as individuals age until it reaches a peak, after which it begins to decrease (≥70 years). In this respect, our results are consistent with the trend observed in French or German populations [20].

In this 7-year prospective study in the APNA women population, depression emerged in 8.9% of the initially non-depressed women. Worldwide, the number of people suffering from depression throughout his life is 8%–15% [21]. An epidemiological study carried out in different European countries including Spain (ESEMeD study) reported that the lifetime prevalence of depression in Spanish population was 10.6% while 12-month prevalence was 4.0% [22]. Serrano-Blanco et al. [23] conducted a study with patients of both sexes (n = 3815) in primary health care and they estimated that the prevalence of depression was 9.6%.

Table 3
Hazard ratios (HR) and 95% confidence intervals (CI) for incident depression by BMI at baseline, adjusted for age*.

		Depression	
	n	HR	95% CI
Underweight	461	1.48	1.09–2.00
Overweight	6622	1.04	0.93–1.16
Obesity	4819	1.14	1.01–1.29

*Normal weight status is the reference group when estimating the HR.

Moreover, we obtained that depression is more frequent in older subjects at baseline. Similar results were obtained by Bones-Rocha et al. [24], who found that the prevalence of poor mental health increases with age, being the highest among people over 65 years. There are environmental factors that explain the higher prevalence of depression in older adults, such as their tendency to isolation, family losses, retirement, neurobiological factors, chronic pain, loss of independence, drop in socioeconomic status and other physical problems [25].

Our study found a U-shaped relationship between BMI and depression, with higher incidence of depression observed in underweight (9.8%) and obese (10.3%) women at baseline. Several studies have shown a similar U-shaped association [7,26,27]. A large community-based study (n = 43,534) in Netherlands reported this association [7]. Carey et al. [26] conducted a cross-sectional survey among primary care patients in Australia (n = 4,058) and they reported the U-shaped association with the highest rates of depression observed among underweight and obese participants (24% and 23%, respectively). These values are higher than those obtained in our study. This difference may be explained by the smaller number of underweight participants in Carey et al.'s experiment (n = 21). Another limitation of these studies [7,26] compared to our work is that they use of self-reported data on BMI. A systematic review examined the relationship between self-reported and directly measured height and weight [28]. Overall, self-reported data show trends of under-reporting for weight and BMI and over-reporting for height. Our study examines the relationship of these two conditions over time.

In regard to the association of BMI with depression, our study found that being underweight and obese at baseline is significantly associated with future onset of depression among women. Our findings on the association between obesity and depression are consistent with previous longitudinal studies in adults [16,29–31]. A large study with extended follow-up periods (up to 16 years from 1994 to 2010) reported that being overweight or obese could predict the onset of depressive symptoms in middle-aged and older adults [29]. In the SUN project [32], childhood or young adult overweight/obesity was associated with an elevated risk for the development of adult depression. Both studies [29,32] found association between overweight and depression. By contrast, we found no association in overweight women (HR = 1.04; 95% CI = 0.93–1.16). Using data from the Nurse's Healthy Study, Pan et al. [30] shown that in women with no history of depression at baseline, obesity was associated with a moderately increased risk of depression onset at follow-up (OR, 1.10), whereas overweight was not associated with depression risk (OR, 1.00). We found that obese women are 14% more likely to have onset of depression. This small difference may be due to the different age populations. The mean age of our population is 50.7 years, while Pan et al. [30] performed their study with middle-aged and older women (mean age: 66.1 years).

There are several theories about why obesity might cause depression in adults. Increasing medical problems and mobility restrictions associated with obesity may have a direct impact on the psychological well-being. There are studies that evaluate the association factors such as low physical activity [33] or diet [34,35], with depression. Therefore, eating disorders, distorted body image, or low self-esteem can lead to depression [5]. There are several factors that influence the strength of the relationship between obesity and depression, such as sex, level of obesity or socioeconomic status. Sex has been consistently shown to modify the association between obesity and depression, with most studies demonstrating a positive relationship for women and a negative

one for men [11,12]. Regarding physiological pathways, alterations in the production proinflammatory cytokines or perturbations of cerebral endothelium could explain the association between obesity and depression [2,3,32].

Furthermore, we found that underweight women have higher risk of depression than normal weight women. Few studies have considered the relationship between underweight and depression [36–38]. Since most studies compare the prevalence of depression in obese vs. non-obese subjects. When underweight is not considered, the association between BMI and depression is weakened because the underweight group is at a higher risk of depression. In fact, a longitudinal study that evaluated the association between BMI and depression in a large representative sample, reported that the highest level of depressive symptoms was found among underweight subjects [27]. Ul-Haq et al. [37] found that being underweight was significantly associated with poorer mental health in women; however this association was not found significant in men. Mond et al. [38] reported that underweight women had significantly reduced mental health when compared to normal weight women. Their findings also suggest that underweight women are a vulnerable group, with an increased risk of impairment in both physical and mental health. The tobacco/alcohol consumption, underlying physical illnesses or psychological or biological factors may explain the association between underweight and depression.

Our results show a higher association in underweight women than in obese women. Of the 7726 women excluded at baseline because they had depression, 30.8% were obese. This may explain, in part, why we found a higher association between depression and underweight.

4.1. Strengths and limitations

The main strength of our study is the large number of participants from several Primary Health Care Centres ($n = 20,212$). This study examined the association of all BMI categories (from underweight to obesity) with depression in a large and representative sample. In addition, our study is a well-designed prospective cohort study that examines the relationship of these two conditions over 7 years of follow-up. Most of the published evidence is cross-sectional studies, which do not provide information on the temporal relationship between BMI and depression.

It is also important to consider that in our cohort, depression is diagnosed clinically. The most appropriate is to use a structured interview, but in the clinical practice this method is not cost-effective. Several screening questionnaires have been evaluated, although it has been reported that a simple question about depression has similar results than longer questionnaires [16].

Our cohort was performed only with women, so further research is needed to better explain the relationship between BMI and depression, which has been shown to be more consistent for women than for men.

Our analyses were only adjusted for age. There are other variables that can influence, besides body weight the onset of depression (medication use, chronic diseases, psychopathology, etc.). Due to the design of our study, we do not have this information. It would be interesting in future studies to consider these variables.

In summary, in this 7-year prospective study in the APNA women population, depression emerged in 8.9%. Our study found a U-shaped relationship between BMI at baseline and new-onset depression. Being underweight and obese (not overweight) at baseline is significantly associated with future onset of depression during the 7 years of follow-up (HR = 1.48 and HR = 1.14). Both obesity and depression account for a significant proportion of the global burden of disease, so it is important to consider both diseases and their possible association due to high socioeconomic cost and decreased quality of life.

Disclosure of interest

The authors have not supplied their declaration of competing interest.

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Prospective association between depression and overweight/obesity in a 7-year follow-up. The APNA study

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Abstract

Purpose: The present study examined the association between depression and new-onset overweight/obesity during 7 years of follow-up in patients attending Primary Health Care Centres in Navarra, Spain.

Methods: The APNA (Atención Primaria de Navarra) study is a dynamic prospective cohort study. A total of 91,410 adult subjects (≥ 18 years) were selected from 2004 to 2011. We estimated the incidence of overweight and obesity. We used the Kaplan-Meier analysis to predict the survival curve. The risk of overweight/obesity onset according to depression status at baseline was assessed using Cox regression analyses.

Results: During the 7 years of follow-up, overweight and obesity appeared in 14.1% (95% CI 13.8-14.3) and 7.6% (95% CI 7.4-7.8) respectively. The highest rates of overweight/obesity incidence at follow-up occurred in subjects with initial depression (18.8% (95% CI 17.5-20.1) and 11.7% (95% CI 10.8-12.7) respectively). The risk of overweight or obesity increases over time, being the Kaplan-Meier estimation of 6.46 and 6.71 respectively. Depressed patients at baseline have increased risk of overweight/obesity onset during the follow-up period compared with not depressed subjects (HR = 1.48, 95% CI = 1.09-2.00 and HR = 1.14, 95% CI = 1.01-1.29 respectively).

Conclusions: In this 7-year prospective study in the APNA population, overweight and obesity emerged in 14.1% and 7.6% respectively. Depressed subjects at baseline are significantly associated with future onset of overweight or obesity.

Key words: body mass index; depression; obesity; overweight; primary health care.

Prospective association between depression and overweight/obesity in a 7-year follow-up. The APNA study

Introduction

Depression and obesity are highly prevalent in worldwide. Depression is a common mental disorder that has been categorized among the most prevalent psychological disorders in the general population. It is the leading cause of disability worldwide. More than 350 million people of all ages suffer from depression [1]. The WHO estimates that it will become one of the three main causes of burden of disease in 2030 [2].

Obesity is a chronic metabolic disease of multifactorial origin whose prevalence in recent decades has been increasing at an alarming rate. In 2014, more than 1.9 billion adults were overweight. Of these over 600 million were obese [3]. There is evidence linking overweight and obesity with a wide range of health problems, such as, cardiovascular disease, type 2 diabetes, respiratory problems or several cancers [4, 5].

Taken together, depression and obesity account for a significant proportion of the global burden of disease, so it is important to consider their potential association due to their high economic costs and their involvement in quality of life. Furthermore, both disorders can currently be reliably diagnosed and treated by non-specialists as part of primary health care.

The relationship between depression and body mass index (BMI) is complex and multifactorial. Unhealthy lifestyles (smoking, alcohol consumption and being both socially and physically inactive), low self-esteem, poor body image, maladaptive eating behaviors, exercise avoidance, medication, and hormonal and functional impairment in adults, is associated with having a depressive disorder as well as with abnormal BMI [6-8]. It helps explaining the relationship between these two conditions. Moreover, alterations in BMI and depression may have common mechanisms: specific neurostructural alterations [9], metabolic disturbances [10] and inflammatory factors [11, 12].

This association has focused much research in recent years; however, the results from current studies are inconsistent. Recent evidence to suggest that depression is associated with BMI and vice versa [13-16], while some studies reported a negative association between depression and BMI [17,18].

There is evidence obesity is one of the most prevalent comorbidities of depression [15]. The prevalence of obesity is strongly elevated among subject suffering from depression [19]. Prospective studies in the adult population have found that baseline depression predicted weight gain at follow-up [20-22].

Therefore, the association between depression and overweight/obesity is controversial and it requires further investigation. The main objective of the present study is to examine the relationship between depression and overweight/obesity during 7 years of follow-up in subjects attending Primary Health Care Centres in Navarra. We examine the incidence of overweight/obesity according to baseline depression status. Interestingly, we estimate the risk of overweight/obesity onset according to depression status along 7-year of follow up.

Methods

The APNA (Atención Primaria de Navarra) study is a multipurpose dynamic prospective cohort study, which was conducted in Navarra, Spain. The study population consists of all adult patients (≥ 18 years) attending one of seven Primary Health Care Centres included in the study (Azpilagaña, Burlada, Echavacoiz, Iturrama, San Jorge, Tafalla and Villava) over a 7-year period (from 2004 to 2011). The APNA cohort is dynamic, so that over the seven years, some new subjects were incorporated and others left the cohort. Navarra, has a registry of each patient's medical history collected electronically by the general practitioner during routine clinical practice. Every time a patient visits a Health Centre, his clinical register is updated. From these electronic data, one of the authors (ABL) has built a comprehensive database with all this information after deleting the personal information [23]. Two studies (cross-sectional and

longitudinal) within the APNA cohort have been published elsewhere [23, 24]. This study was approved by the Ethical Committee of the Public University of Navarra on February 19th 2010.

The variables considered in the study were sex, age, diagnosis of depression at baseline, and weight (kilograms) and height (meters) during the follow-up. The diagnosis of depression was reported by a general practitioner. In our cohort, depression is diagnosed clinically [23]. To define overweight and obesity in adults, we calculate the BMI (weight in kilograms divided by the square of the height in meters). The patients were weight and measured during the clinical practice. From the data of weight and height, BMI was calculated. Underweight was considered as BMI <18.5 kg/m^2, Normal Weight as BMI 18.5-24.9 kg/m^2, Overweight as BMI 25.0-29.9 kg/m^2 and Obesity as BMI ≥ 30.0 kg/m^2, based on the classification of overweight and obesity proposed by the expert committee of WHO for adults [3].

The population was 91,410 adult patients. Patients were selected as shown in the flow chart (Figure 1). Because our two objectives required different population samples, we described analytic samples and procedures separately.

Analysis A. Baseline depression status and risk of overweight.

For the analysis A, patients were excluded if they were overweight (BMI = 25.0-29.9 kg/m^2) at baseline. After exclusion, a total of 79,813 patients were included in the current analysis.

Analysis B. Baseline depression status and risk of obesity.

For this study, only patients free of obesity at baseline (BMI < 30.0 kg/m^2) were selected. The final population for the analysis B was 83,118.

Statistical analyses

Survival curve was estimated using the Kaplan-Meier method. We selected individuals without obesity/overweight at baseline and estimated the incidence of obesity/overweight with their confidence intervals, by age groups and baseline depression status. Comparison of proportions was performed with Chi-square test. Test with a *p*-value less than 0.05 were considered

statistically significant. The risk of obesity/overweight onset according to depression status at baseline was assessed using Cox regression analyses. Analyses were adjusted for sex and age. The proportional hazards (Hazard Ratios (HR) with 95% confidence intervals) were examined.

SPSS for Windows (version 19.0) and EpiInfo (version 6.04d) were the statistical programs used.

Results

Analysis A. Baseline depression status and risk of overweight

Population Characteristics

The study population included 79,813 subjects (38,720 men and 41,093 women) aged between 18 and 105 years, with a mean age of 42.63 ± 16.88 years. The age group with the highest number of individuals was 18-29 years. The prevalence of depression at baseline was 5.5% (95% CI 5.3-5.6). As shown in Table 1, the frequency of depression increased progressively with age. The depression was more frequent in older subjects at baseline.

In this 7-year prospective study, overweight emerged in 14.1% (95% CI 13.8-14.3) (N=11,233). The incidence of overweight increased progressively with age (Figure 2), with its maximum value in the age group of 60-69 years. A slight decrease was found in older subjects (≥ 70 years). The incidence of overweight was higher in men than in women except for subjects ≥ 70 years, in which overweight was more frequent in women. The difference was statistically significant for all age groups ($p < 0.05$) between men and women.

Furthermore, the risk of overweight increases over time (Figure 3), being the Kaplan-Meier estimation of 6.46 (95% CI 6.45-6.47). In subjects without depression at baseline, men had more risk of overweight than women. Men with depression at baseline had also more risk of overweight than women depressed.

Incidence of overweight by baseline depression status.

As shown in Table 2, the highest rates for incidence of overweight at follow-up were in subjects with initial depression (18.8% (95% CI 17.5-20.1)).

Association between Depression and Overweight

Table 3 shows the results of Cox regression analyses assessing the risk of overweight onset according depression status in non-overweight patients at baseline. Depressed subjects were more likely to have overweight onset during the 7 years of follow-up (HR = 1.20, 95% CI = 1.12-1.29).

Depression in women represents an additional risk for overweight (HR = 1.22, 95% CI = 1.04-1.42). Moreover, in depressed subjects the higher the age of depression onset, the lower the risk of overweight (HR = 0.99, 95% CI =0.98-0.99).

Analysis B. Baseline depression status and risk of obesity

Population Characteristics

A total of 83,118 subjects (40,953 men and 42,165 women) aged between 18 and 105 years were included in the study. The mean age of the subjects was 43.22 ± 17.16 years. The age group with the highest number of individuals was 18-29 years. The prevalence of depression at baseline was 5.5% (95 % CI 5.4-5.7). The prevalence of depression increased progressively with age, being more frequent in older subjects at baseline (Table 1).

During the follow-up, obesity appeared in 7.6% (95% CI 7.4-7.8) (N=6,294) of the initially non-obese patients. As shown in Figure 2, the incidence of obesity increased progressively with age, with its maximum value in the age group of 60-69 years. The incidence of obesity was higher in men than in women in all age groups except for the age groups 18-29 and ≥ 70 years. The difference between men and women was statistically significant for all age groups ($p < 0.05$).

Moreover, as shown in Figure 3, the risk of obesity increases over time. The Kaplan-Meier estimation was 6.71 (95% CI 6.70-6.72). In subjects free of depression at baseline, men had more

risk of obesity than women. By contrast, women with depression had more risk of obesity than men depressed.

Incidence of obesity by baseline depression status.

Over 7 years of follow-up, the incidence of obesity was higher in patients with depression at baseline (11.7% (95% CI 10.8-12.7)) (Table 2).

Association between Depression and Obesity

As shown Table 3, depressed patients were more likely to have obesity onset during the 7 years of follow-up (HR = 1.27, 95% CI = 1.16-1.38). Depression in women represents an additional risk for obesity (HR = 1.41, 95% CI = 1.15-1.74). Moreover, in depressed patients, the higher the age of depression onset, the lower the risk of obesity (HR = 0.99, 95% CI =0.98-0.99).

Discussion

In this 7-year prospective study in the APNA population, overweight and obesity appeared in 14.1% and 7.6%, respectively. The highest rates for incidence of overweight/obesity were found in depressed subjects at baseline. Moreover, depression at baseline was significantly associated with future onset of overweight and obesity.

The prevalence of depression was 5.5% in our population at baseline. Worldwide, the number of people suffering from depression throughout his life is 8%-15% [25]. The ESEMeD study (European Study of the Epidemiology of Disorders) reported that prevalence in Spain is lower than in other European countries. The lifetime prevalence of depression in Spanish population is 10.6% while 12-month prevalence is 4.0% [26]. Unlike the APNA study, in the ESEMeD study, psychiatric diagnosis was made by training interviewers and this could have an impact on sensitivity or specificity. Moreover, individuals with mental illness could have more frequently rejected to participate in the survey. A study carried out in primary health care with patients of both sexes (N=3,815) found that the prevalence of depression was 9.6% [27]. Under-diagnosis is a problem in the management of depression that can account for differences in prevalence

values obtained in the different studies. WHO has identified several reasons such as: lack of resources, lack of trained health care providers and social stigma associated with mental disorders [1]. In Spain, 28% of patients with depression are not diagnosed in primary care [28]. Furthermore, the ESEMeD-Spain project showed that a sample of patients with depression, 59% did not attend either primary or specialized care in the previous year [29].

In APNA cohort, the depression is more frequent in older subjects at baseline. There are factors that explain the higher prevalence of depression in older adults: tendency to isolation, family losses, retirement, neurobiological factors, chronic pain, loss of independence, drop in socioeconomic status and other physical problems [30].

During the follow-up period, the incidence of overweight and obesity was higher in subjects with depression at baseline (18.8% and 11.7%, respectively). In regard to the association of depression with overweight/obesity, our study found that depression in subjects at baseline is significantly associated with future onset of overweight and obesity. Our findings on the association between depression and overweight/obesity are consistent with previous longitudinal studies in adults [14, 22, 31-33]. De Wit et al. [33], (N=2,447) showed that there is an association between depressive disorders and increase in body weight independent of lifestyle, health status, psychotropic medication use and socio-demographic factors (OR=1.66; 95% CI 1.30-2.46). A limitation of this study [33] was the relatively short follow-up period two years. A previous research [16] has demonstrated that baseline depression was associated with and increased risk of developing obesity (OR, 1.58; 95% CI, 1.33-1.87) after a follow-up period of 10 years, and the association between depression and overweight was null. A review [14] reported that a 53% of the reviewed studies found that depression was a significant predictor of obesity. In most of these studies, depression was found to increase risk for obesity, with *odds ratios* in the range of 2.0 to 3.0. The inconsistent results could be to the large heterogeneity of depression as well as to methodological variance across studies including sample selection, the length of follow-up, and the assessment of depression and obesity.

This relationship may vary by sex. Sex has been consistently shown to modify the association between obesity and depression, with most studies demonstrating a positive relationship for women and a negative one for men [13, 16]. Women appear to be at a higher risk of obesity and common mental health disorders than men. Furthermore, the mental health of women is more closely related to overweight and obesity than that of men [34, 35]. This is demonstrated in our study: women with depression were more likely to be overweight/obese than women without depression (HR = 1.22 and HR = 1.41, respectively). Moreover, among persons with depression, women were more likely to be obese than men. For all this, most research work is conducted only women. Using data from the Nurse's Healthy Study, Pan et al [31] showed that depression at the baseline period was associated with an increased risk of obesity at the follow-up period in baseline non-obese women (OR, 1.51; 95% CI 1.36-1.67). We found that depressed subjects are 27% more likely to have onset of obesity. This difference may be due to the different age populations.

There are several hypotheses about the link between depression and overweight/obesity in adults. Physiological or endocrinological pathways, such as those related to alterations in the production of proinflammatory cytokines or perturbations of cerebral endothelium, could explain the association between depression and obesity [9-12, 36].The depression is associated with dysregulation of the hypothalamic-pituitary-adrenal axis, which may be involved in the link between depression and obesity [37] Moreover, it is important to consider that several antidepressant medications promote an excess in body weight [38, 39]. Finally, depression may be associated with poor health behaviors: physical inactivity and poorer sleep quality, which could also lead to a higher body weight [40-42].

Strengths and Limitations

The main strength of our study is the large number of participants from several Primary Health Care Centres (79,813 subjects in the analysis A and 83,118 subjects in the analysis B). This study

examined the association of depression with overweight and obesity in a large and representative sample. Furthermore, our study is a well-designed prospective cohort study that examines the relationship of these two conditions over 7 years of follow-up. Most of the published evidence is cross-sectional studies, which do not provide information on the temporal relationship between depression and overweight/obesity.

It is also important to consider that in our cohort, depression is diagnosed clinically. The most appropriate is to use a structured interview, but in the clinical practice this method is not cost-effective. Several screening questionnaires have been evaluated, although it has been reported that a simple question about depression has similar results than longer questionnaires [43, 44].

Another strength of our work, compared with other published studies, is that the patients were weighed and measured in a clinical setting. Many research use of self-reported data on BMI. A systematic review examined the relationship between self-reported and directly measured height and weight [45]. Overall, self-reported data show trends of under-reporting for weight and BMI and over-reporting for height.

Our analyses were only adjusted for age and sex. There are other variables that can influence, besides depression the onset of overweight/obesity (medication use, chronic diseases, psychopathology, etc.). Due to the design of our study, we do not have this information. It would be interesting in future studies to consider these variables.

In summary, in this 7-year prospective study in the APNA population, overweight and obesity emerged in 14.1% and 7.6%, respectively. Our study found that depressed subjects at baseline are significantly associated with future onset of overweight and obesity during the 7 years of follow-up (HR = 1.20 and HR = 1.27). Both depression and obesity account for a significant proportion of the global burden of disease, so it is important to consider both diseases and their possible association due to high socioeconomic cost and decreased quality of life.

Ethical standards

The manuscript does not contain clinical studies or patient data.

Conflict of interest

The authors declare that they have no conflict of interest.

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Figure 1. Flow chart of the APNA population

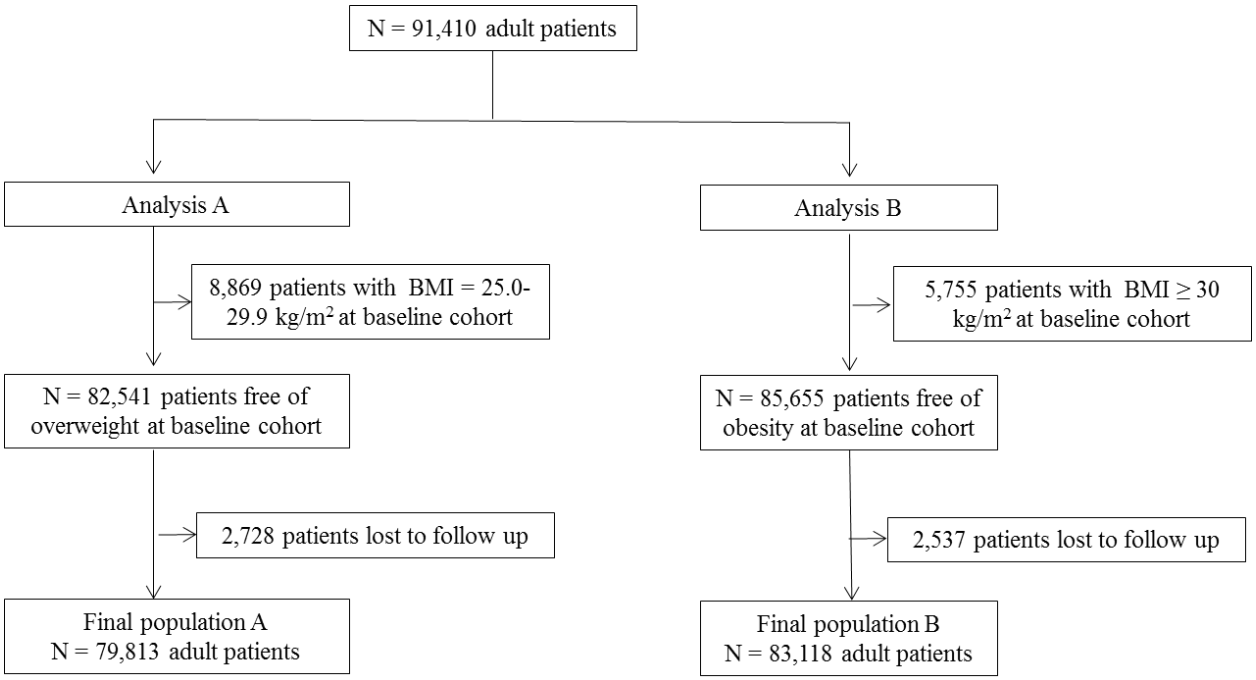


Figure 2. Incidence of overweight and obesity by age group

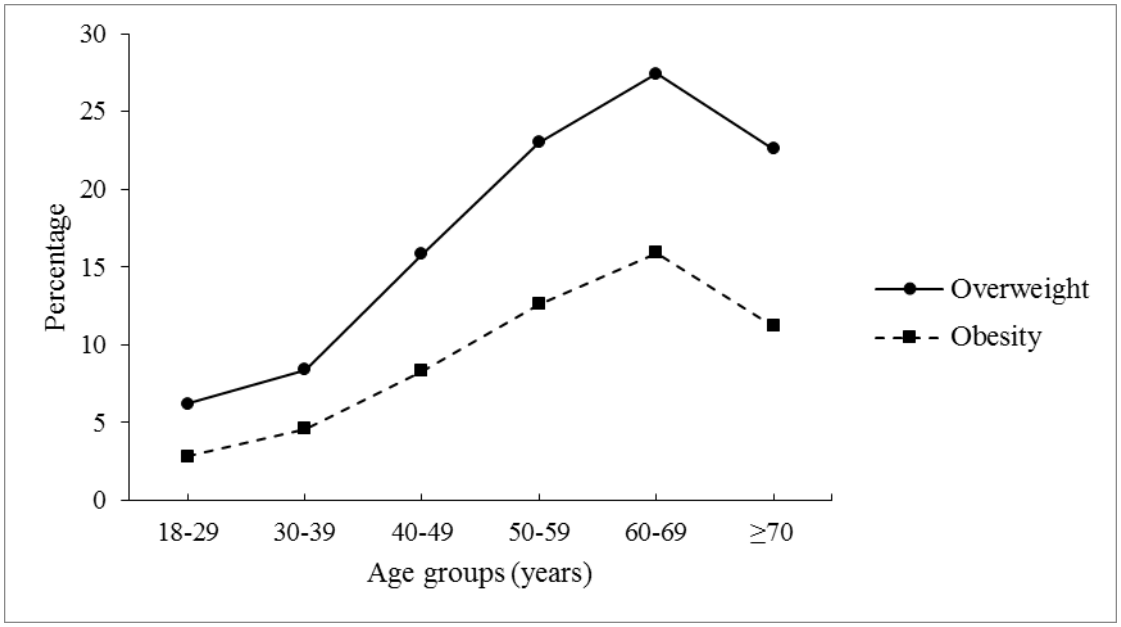
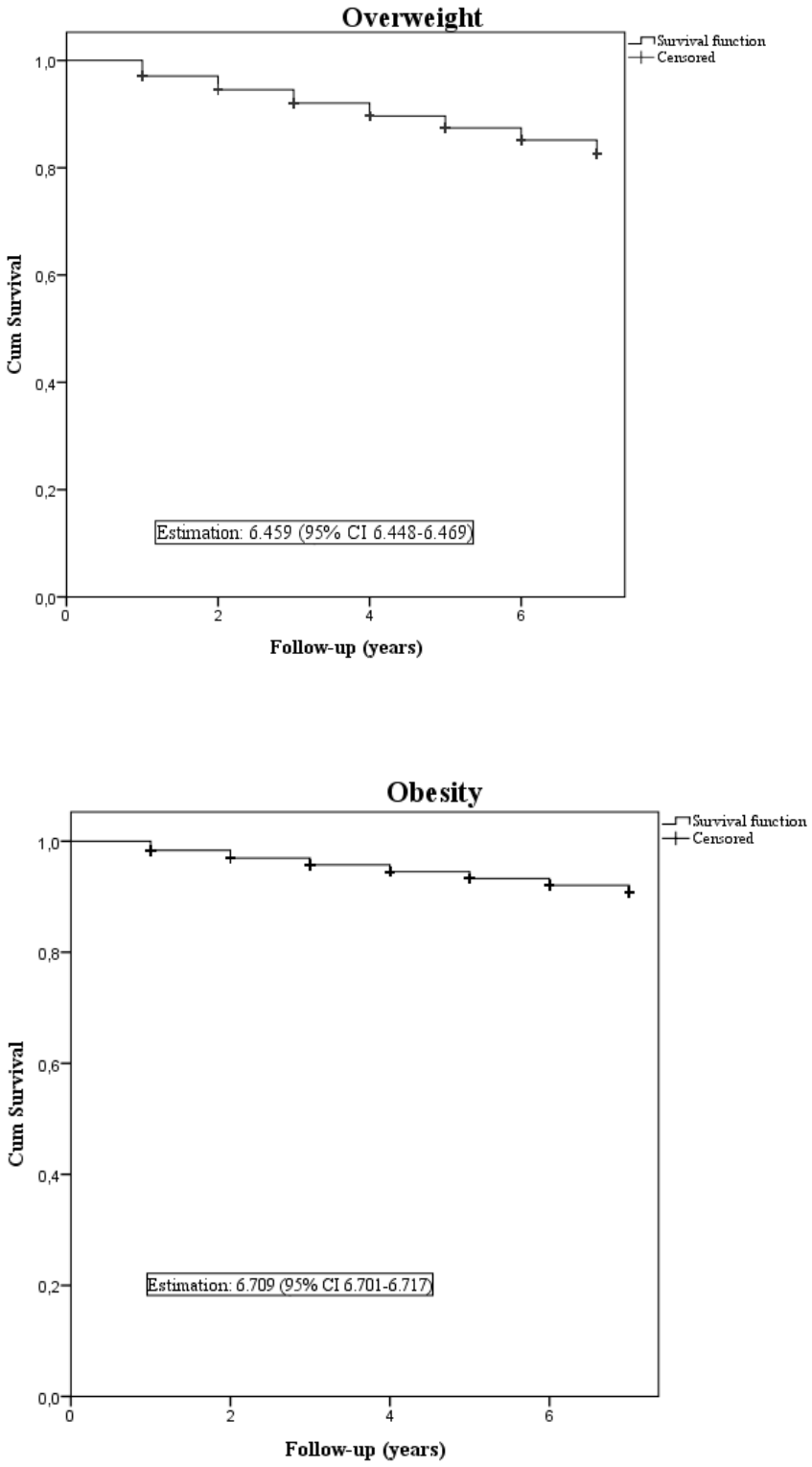


Figure 3. Kaplan-Meier survival curve of time to overweight and obesity onset



Table

Table 1. Characteristics of the study population at baseline cohort by depression status.

Age group (years)	Baseline depression status (%, 95% CI)					
	Analysis A			Analysis B		
	N	Not depressed	Depressed	N	Not depressed	Depressed
		N = 75,432	N = 4,381		N = 78,533	N = 4,585
Total	79,813	94.5 (94.4-94.7)	5.5 (5.3-5.6)	83,118	94.5 (94.3-94.6)	5.5 (5.4-5.7)
18-29	21,048	98.0 (97.8-98.2)	2.0 (1.8-2.2)	21,352	98.0 (97.8-98.2)	2.0 (1.8-2.2)
30-39	19,457	96.2 (95.9-96.5)	3.8 (3.5-4.1)	19,745	96.2 (96.0-96.5)	3.8 (3.5-4.1)
40-49	14,294	94.4 (94.0-94.8)	5.6 (5.2-6.0)	14,750	94.5 (94.1-94.9)	5.5 (5.1-5.9)
50-59	11,314	91.7 (91.2-92.2)	8.3 (7.8-8.8)	12,047	91.7 (91.2-92.2)	8.3 (7.8-8.8)
60-69	6,769	90.4 (89.6-91.1)	9.6 (8.9-10.4)	7,384	90.5 (89.9-91.2)	9.5 (8.8-10.1)
≥ 70	6,931	87.8 (87.0-88.5)	12.2 (11.5-13.0)	7,840	88.3 (87.6-89.0)	11.7 (11.0-12.4)

CI confidence interval

Table 2. Incidence of overweight and obesity by baseline depression status

	Overweight (%, 95% CI)	Obesity (%, 95% CI)
Total	14.1 (13.8-14.3)	7.6 (7.4-7.8)
Not depressed	13.8 (13.5-14.0)	7.3 (7.2-7.5)
Depressed	19.6 (18.4-20.8)	11.7 (10.8-12.7)

CI confidence interval

Table 3. Hazard Ratios (HR) and 95% confidence intervals (CI) for incident overweight and obesity by baseline depression status, adjusted for age and sex.

	Overweight (Analysis A)			Obesity (Analysis B)		
	N	HR	95% CI	N	HR	95% CI
Depression status						
Not depressed	75,432	1.00 (Ref)		78,533	1.00 (Ref)	
Depressed	4,381	1.20	1.12-1.29	4,585	1.27	1.16-1.38
Depression*Women		1.22	1.04-1.42		1.41	1.15-1.74
Depression*Age		0.99	0.98-0.99		0.99	0.98-0.99

V. CONCLUSIONES

1. La prevalencia de sobrepeso (**39,7%**) y obesidad (**25%**) continúa siendo elevada en Navarra. Nuestros resultados son similares a los publicados en otros estudios con población española, con la particularidad de que nuestros datos son recogidos durante la práctica clínica diaria en Navarra durante el año 2011.

2. Globalmente la prevalencia de sobrepeso y obesidad es mayor en varones que en mujeres, excepto para los niveles de obesidad II y III en los que las mujeres presentan cifras más altas.

3. Existe una asociación positiva del sobrepeso y la obesidad con la *intolerancia a la glucosa, dislipemia, diabetes mellitus tipo 2, hipertensión, insuficiencia renal y osteoartritis.* Además, todos los grados de obesidad están asociados con enfermedad cardiovascular (insuficiencia cardiaca y fibrilación auricular), problemas respiratorios (asma) y trastornos mentales severos (esquizofrenia y trastorno bipolar). Los niveles más elevados de IMC (obesidad tipo II y tipo III) están asociados con depresión.

4. Nuestro estudio encuentra una relación en forma de *U* entre el IMC de los sujetos al inicio del estudio y la incidencia de depresión a lo largo de los 7 años de seguimiento. Es decir, los individuos con peso insuficiente y con obesidad (valores más extremos de IMC) tienen una mayor incidencia de depresión. La incidencia de depresión detectada durante el periodo de seguimiento del estudio fue de 8,9%.

5. El ser obeso o tener peso insuficiente está asociado significativamente con el desarrollo de depresión a lo largo del tiempo (HR = 1,48 y HR = 1,14, respectivamente).

6. La depresión está significativamente asociada con el futuro desarrollo de sobrepeso y obesidad (HR = 1,20 y HR = 1,27). La incidencia detectada durante el periodo de seguimiento de sobrepeso fue de 14,1% y de obesidad de 7,6%.

7. En resumen, nuestro estudio constata la morbilidad asociada a la obesidad que junto con la alta prevalencia la convierte en un problema de salud de primer orden, lo que hace que se requiera un adecuado diagnóstico y tratamiento por parte los profesionales tanto de salud pública como de atención primaria y especializada. Particular importancia reviste la vinculación de la obesidad con la depresión, con la consiguiente disminución en la calidad de los pacientes que las padecen.

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VII. Anexo I

Factor de impacto de las revistas y áreas temáticas correspondientes a las publicaciones.

1. Martin-Rodriguez E, Guillen-Grima F, Martí A, Brugos-Larumbe A. Comorbidity associated with obesity in a large population: The APNA study. Obes Res Clin Pract 2015; 9: 435-47.

Revista: **Obesity Research & Clinical Practice**

Factor de impacto: (Q4) **1,177**

Área temática: **Nutrición** (62/77)

2. Martin-Rodriguez E, Guillen-Grima F, Aubá E, Martí A, Brugos-Larumbe A. Relationship between body mass index and depression in women: A 7-year prospective cohort study. The APNA study. Eur Psychiatry 2016; 32: 55-60.

Revista: **European Psychiatry**

Factor de impacto: (Q2) **3,439**

Área temática: **Psiquiatría** (40/140)