UNIVERSIDAD DE MURCIA

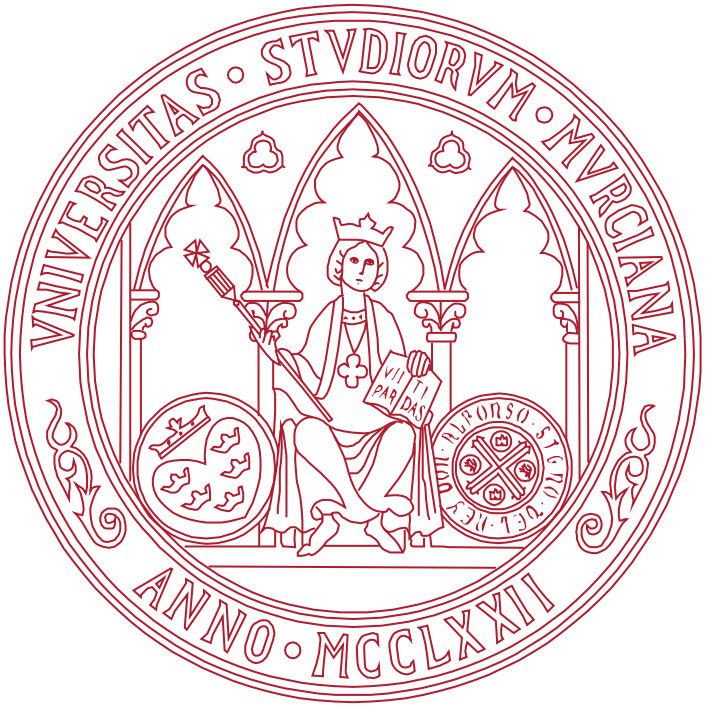
ESCUELA INTERNACIONAL DE DOCTORADO

Genetic and Environmental Factors Involved in Sleep Quality

Factores Genéticos y Ambientales Implicados en la Calidad de Sueño

D. Juan José Madrid Valero

2019



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FACULTAD DE PSICOLOGÍA

Genetic and environmental factors involved in sleep quality

Factores genéticos y ambientales implicados en la calidad de sueño

Director: Dr. Juan Ramón Ordoñana Martín

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MURCIA

D. Juan Ramón Ordoñana, profesor titular del Departamento de Anatomía humana y Psicobiología de la Universidad de Murcia, director de la Tesis Doctoral de Juan José Madrid Valero,

AUTORIZA

La presentación de dicha Tesis Doctoral, titulada "Genetic and environmental factors involved in sleep quality" realizada por D. Juan José Madrid Valero, bajo mi inmediata dirección y supervisión, en la Facultad de Psicología, en la modalidad de compendio de publicaciones, siendo las mismas:

Madrid-Valero, J. J., Martínez-Selva, J. M., Ribeiro do Couto, B., Sánchez-Romera, J. F., & Ordoñana, J. R. (2017). Age and gender effects on the prevalence of poor sleep quality in the adult population. *Gac Sanit*, *31*(1), 18-22. doi:10.1016/j.gaceta.2016.05.013

Madrid-Valero, J. J., Martínez-Selva, J. M., & Ordoñana, J. R. (2017). Sleep quality and body mass index: a co-twin study. *J Sleep Res, 26*(4), 461-467. doi:10.1111/jsr.12493

Madrid-Valero, J. J., Sanchez-Romera, J. F., Gregory, A. M., Martinez-Selva, J. M., & Ordonana, J. R. (2018). Heritability of sleep quality in a middle-aged twin sample from Spain. *Sleep, 41*(9). doi:10.1093/sleep/zsy110

Madrid-Valero, J. J., Ordoñana, J. R., Klump, K. L., & Burt, S. A. (2018). Children Sleep and Antisocial Behavior: Differential Association of Sleep with Aggression and Rule-Breaking. *J Abnorm Child Psychol*. doi:10.1007/s10802-018-0480-0

E INFORMA

Que las revistas, en las que han sido publicadas, están indizadas en el *Journal Citation Reports*, constituyendo en su conjunto una unidad científica, que es presentada para la obtención del grado de Doctor con mención de *Doctorado Internacional* por la Universidad de Murcia.

Firmado,

Dr. Juan Ramón Ordoñana

En Murcia, a 11 de febrero de 2019

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La presente Tesis Doctoral ha sido posible gracias a la financiación de la Fundación Séneca, Agencia de Ciencia y Tecnología de la Región de Murcia a través de la ayuda “Contratos predoctorales de formación del personal investigador(19814/FPI/15)” incluida en el “Programa de Talento Investigador y su Empleabilidad” del Plan de Actuación de la Fundación Séneca para 2015

‘‘Ningún descubrimiento se
haría ya si nos contentásemos
con lo que sabemos’’

(Lucio Anneo Séneca)

Agradecimientos

En primer lugar, me gustaría expresar mi más sincero agradecimiento a la Fundación Séneca, por la confianza que ha depositado en mí financiado este proyecto y las estancias de investigación.

Gracias a mi director Juan Ramón Ordoñana Martín por haberme formado como investigador, por ser un ejemplo, por su entusiasmo, por haberme enseñado casi todo lo que sé sobre investigación y sobre todo por haberme recibido con los brazos abiertos.

A mis compañeros del departamento de Anatomía Humana y Psicobiología con los que he tenido el privilegio de trabajar: Francisca González, Juan Francisco Sánchez, José María Martínez, Juan Pedro Sánchez y Bruno Ribeiro. De manera muy especial a la Dra. Eduvigis Carrillo, por ser uno de los apoyos más importantes durante este periodo y por sus valiosos consejos.

A todos los compañeros de la Facultad de Psicología. En especial a la Dra. María Rubio que sin duda ha sido un apoyo fundamental durante todo este periodo y a la que admiro como investigadora.

A mis compañeros de la Asociación de Jóvenes Investigadores de la Universidad de Murcia. En especial a David, Gabi y Ana.

A la doctora Alexandra Burt, por acogerme durante mi estancia en la Michigan State University.

De manera muy especial, gracias a Rod y Kim Friesen por hacer que mi estancia en Michigan fuera una experiencia única, por todo vuestro apoyo y ayuda, todo el cariño que me demostrasteis y hacer que me sintiera como en casa. A todos los amigos que hice en Michigan y que hicieron que mi estancia fuera especial: Paola, Josué, Garrett, Emma y Ping. A Alessia Baldaccini, por todo tu apoyo durante mi estancia.

A la Dra. Alice Gregory, que hizo que mi estancia en la Goldsmiths University of London fuera una experiencia maravillosa y que supuso un salto de calidad en mi carrera investigadora. Gracias por ser un ejemplo a seguir, una de las mejores investigadoras, por todo tu entusiasmo y por ser una persona maravillosa.

A todos mis compañeros de la Goldsmiths University con los que tuve el placer de compartir mi tiempo y lugar de trabajo. En especial, a Teemu Toivainen quien ha sido mi apoyo principal en Londres y un buen amigo. A Robert Chapman, por ser una persona excelente y de la que he aprendido mucho. A Helen Spray por todos los ratos que compartimos y todo lo que aprendí contigo. A mis amigos de Londres, en especial Roberto Amarelo por ser una persona maravillosa y por todos los buenos momentos que pasamos en Londres. A Andrea Costa por ser uno de mis mejores amigos en Londres y con quien compartí muy buenos momentos durante mi estancia.

A la doctora Louise Arsenault, por haberme acogido durante mi estancia en el King's College de Londres y ayudarme a crecer como investigador.

A todos mis amigos y familia que me habéis apoyado durante esta etapa y a los que, por desgracia, ya no están.

A Marta, por todo tu apoyo y porque juntos hemos compartido momentos inolvidables.

A mi padre, por estar siempre a mi lado, por haberme ayudado en los momentos más difíciles de este periodo, por haberme enseñado muchas cosas y por estar siempre cuando te necesito.

A mi madre, por haberme ayudado desde el principio, por tu apoyo incondicional, por todos los sacrificios, por confiar en mí y porque sin ti esto no habría sido posible.

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LIST OF ABBREVIATIONS

AIC	Akaike's information criterion
BMI	Body Mass Index
CBCL	Child Behaviour CheckList
CBT-I	Cognitive Behavioural-Therapy for Insomnia
DZ	Dizygotic
EEG	Electroencephalogram
GWAS	Genome-Wide Association Studies
MSUTR	Michigan State University Twin Registry
MTR	Murcia Twin Registry
MZ	Monozygotic
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
REM	Rapid-Eye-Movement
RGM	Registro de Gemelos de Murcia
TBED-C	Twin Study of Behavioral and Emotional Development in Children

RESUMEN

La calidad de sueño es un aspecto fundamental para nuestra salud general y funcionamiento cognitivo. En las últimas décadas se han producido cambios en nuestra sociedad que sin duda han tenido un impacto significativo en nuestra calidad de sueño. Cada vez somos más conscientes de la importancia del sueño para nuestra salud y, por lo tanto, cada vez prestamos más atención a la calidad del mismo. Actualmente, el sueño se considera uno de los pilares fundamentales para la salud general, a la altura del ejercicio físico y la dieta.

Frases como “ya dormiré cuando esté muerto” o “el sueño es una pérdida de tiempo” cada vez tienen un menor calado en nuestra sociedad.

Esta tesis doctoral partió con el objetivo de investigar las influencias genéticas y ambientales implicadas en la calidad de sueño. Para ello hace uso de diversas metodologías, incluyendo estudios epidemiológicos clásicos y análisis de genética cuantitativa, y tiene como recurso principal los registros de gemelos. Los estudios que componen esta tesis doctoral han sido publicados en revistas indizadas en repertorios internacionales con índice de impacto. En estos estudios se puede comprobar la complejidad de la calidad de sueño y su importancia para la salud del individuo.

Esta tesis se ha realizado gracias a la participación de los gemelos del Registro de Gemelos de Murcia (RGM) y del Registro de Gemelos de la Universidad Estatal de Michigan, siendo un claro ejemplo de la versatilidad de este tipo de registros ya que, en esta tesis doctoral, se han llevado a cabo diversos estudios con metodologías diferentes.

Como se ha mencionado anteriormente, la calidad de sueño tiene un impacto notable en la salud y calidad de vida del individuo y depende de múltiples factores. La población española cuenta con características únicas como son la costumbre de echar la siesta, una franja horaria desplazada con respecto a la hora solar, o unos horarios de comidas retrasados en comparación con otros países de su entorno, que la hacen diferente de las demás poblaciones. Sin embargo, los datos disponibles sobre prevalencia en población española eran escasos y no actualizados. Por tanto, el estudio 1 [Madrid-Valero, J. J., Martínez-Selva, J. M., Ribeiro do Couto, B., Sánchez-Romera, J. F., & Ordoñana, J. R. (2017). Age and gender effects on the prevalence of poor sleep quality in the adult population. *GacSanit*, 31(1), 18-22. doi:10.1016/j.gaceta.2016.05.013], se dirigió a conocer cómo es la calidad de sueño en la población española y qué efecto tienen factores

como la edad, el sexo o el estatus menopáusico sobre la misma. Para ello, se utilizó una muestra representativa de la población de la Región de Murcia que puede ser comparable a la población española. Esta muestra estuvo formada por 2144 participantes en el RGM. La muestra del RGM está compuesta tanto por varones como mujeres en edad adulta (rango de edad 43-71 años). Para medir la calidad de sueño se utilizó el conocido índice de calidad de sueño de Pittsburgh que nos permite conocer tanto la calidad de sueño global del sujeto, como los diferentes componentes de la calidad de sueño (por ejemplo, duración y latencia). En este estudio se comprobó que un alto porcentaje de la población en esta franja de edad (38,2%), presenta una pobre calidad de sueño, es decir, una puntuación mayor de 5 puntos en el índice de calidad de sueño de Pittsburgh. Además, se comprobó que las mujeres tenían casi el doble de probabilidad de presentar una pobre calidad de sueño respecto a los varones. La edad fue otro factor fundamental para la calidad de sueño. En este sentido, se encontró una asociación significativa donde la calidad de sueño empeora progresivamente según aumenta la edad. Este patrón de empeoramiento fue más estable en mujeres que en hombres. Por último, este estudio también constató que el estatus menopáusico no tiene un efecto significativo sobre la calidad de sueño en la población estudiada. En conjunto, estos resultados ponen de manifiesto que existe una alta proporción de la población española que presenta una pobre calidad de sueño y que existen notables diferencias en función del sexo y la edad.

El estudio 2 [Madrid-Valero, J. J., Sanchez-Romera, J. F., Gregory, A. M., Martinez-Selva, J. M., & Ordonana, J. R. (2018). Heritability of sleep quality in a middle-aged twin sample from Spain. *Sleep*, 41(9). doi:10.1093/sleep/zsy110], trata de dar respuesta al porqué de las diferencias individuales en calidad de sueño, estudiando los factores genéticos y ambientales implicados en la misma. El concepto de heredabilidad nos informa de qué proporción de las diferencias fenotípicas en una población dada se

deben a factores genéticos y qué proporción a factores ambientales. Por lo tanto, el concepto de heredabilidad es un estadístico y puede cambiar de una población a otra. Los estudios de este tipo que se habían llevado a cabo, se habían realizado habitualmente en poblaciones con características diferentes a la población española y ninguno de ellos había utilizado una muestra de adultos de ambos sexos. Por tanto, el objetivo principal de este estudio fue determinar las influencias genéticas y ambientales en población española y ver, si existían diferencias en la distribución de la varianza en función del sexo. Nuestros resultados mostraron que un porcentaje sustancial de la varianza en calidad de sueño (34%) se debe a factores genéticos, siendo el resto debido a factores ambientales no compartidos. Además, no se encontraron diferencias de sexo. Todos los componentes del índice de calidad de sueño de Pittsburgh mostraron estar influidos por factores genéticos (30-45%), excepto eficiencia del sueño. El ambiente compartido sólo tuvo un efecto significativo para el componente "eficiencia del sueño" (20%). Este estudio, añade información novedosa sobre los fundamentos de la calidad de sueño en población española, constatando que la calidad de sueño está significativamente influida por factores genéticos y que la distribución de esta varianza no difiere en función del sexo.

El estudio 3 [Madrid-Valero, J. J., Martínez-Selva, J. M., & Ordoñana, J. R. (2017). Sleep quality and body mass index: a co-twin study. *J Sleep Res*, 26(4), 461-467. doi:10.1111/jsr.12493] por su parte tuvo como objetivo estudiar la relación que existe entre la calidad de sueño y el índice de masa corporal, variable fundamental para la salud general y estrechamente relacionada con variables psicológicas como la ansiedad o la depresión. Esta relación había sido estudiada anteriormente, pero focalizándose en la duración de sueño, uno de los componentes principales de la calidad de sueño. Sin embargo, la calidad es un concepto más amplio que engloba diferentes aspectos del sueño como son: eficiencia, latencia y duración entre otros. Estudios previos han demostrado

que existe una estrecha relación entre la calidad de sueño y el índice de masa corporal. Sin embargo, la direccionalidad y causalidad de esta relación es confusa. Para estudiar esta relación, se utilizó un diseño caso-control con gemelos, que nos permite altos niveles de control para posibles variables de confusión (incluyendo factores genéticos). La muestra fue la misma que para el estudio anterior, 2150 sujetos pertenecientes al RGM. Cuando se estudió la influencia del índice de masa corporal sobre la calidad de sueño, se comprobó como en la muestra total existía una relación significativa. Sin embargo, esta relación perdió robustez y significación cuando se seleccionaron gemelos discordantes para calidad de sueño. Por el contrario, cuando se estudió la influencia de la calidad de sueño sobre el índice de masa corporal, la relación permaneció significativa en todas las condiciones incluyendo gemelos monocigóticos discordantes para índice de masa corporal. Estos resultados confirman la estrecha relación que existe entre la calidad de sueño y el índice de masa corporal y además apuntan a una posible direccionalidad de la misma donde la calidad de sueño tiene un efecto significativo sobre el índice de masa corporal pero no al revés.

El último estudio que compone esta tesis, el estudio número 4 [Madrid-Valero, J. J., Ordoñana, J. R., Klump, K. L., & Burt, S. A. (2019). Children Sleep and Antisocial Behavior: Differential Association of Sleep with Aggression and Rule-Breaking. J Abnorm Child Psychol, 47(5), 791-799. doi:10.1007/s10802-018-0480-0], se centra en estudiar la relación existente entre diferentes características del sueño y el comportamiento antisocial en niños. En concreto este estudio se dirigió a estudiar las influencias genéticas y ambientales subyacentes a la relación entre diferentes características del sueño y dos dimensiones del comportamiento antisocial (agresividad y ruptura de las normas). Para ello se utilizó una muestra del registro de gemelos de la Universidad Estatal de Michigan. Esta muestra estuvo formada por 1030 pares de

gemelos con edades comprendidas entre los 6 y los 12 años. Las características de sueño y las dos dimensiones del comportamiento antisocial se evaluaron mediante el cuestionario Child Behavior Checklist. Este estudio corroboró la fuerte asociación que existe entre el sueño y el comportamiento antisocial en niños, encontrando puntuaciones muy superiores tanto en agresividad como en ruptura de las normas en aquellos niños que presentan problemas de sueño con tamaños del efecto entre el 0.25 y 0.77. Todos los fenotipos estudiados (las seis variables de sueño y las dos dimensiones del comportamiento antisocial) mostraron una fuerte influencia genética (65% para agresividad, 53% para ruptura de las normas y entre 62% y 89% para las diferentes características de sueño). Sin embargo, el patrón de relaciones encontrado fue diferente para cada una de las dimensiones del comportamiento antisocial y las distintas variables de sueño. Se encontró un importante solapamiento genético entre las diferentes medidas de sueño y agresividad, mientras que en el caso de la dimensión de ruptura de las normas este solapamiento genético fue de menor magnitud y no significativo en la mayoría de los casos. Por el contrario, la correlación ambiental entre las diferentes variables de sueño y las dos dimensiones del comportamiento antisocial fueron siempre de menor magnitud y no significativas en la mayoría de los casos. Estos resultados, ponen de manifiesto la importancia de la relación entre el sueño y los problemas de conducta en niños. Además, estos resultados ponen de relieve que existe un importante solapamiento genético entre la agresividad y diferentes características de sueño, mientras que en el caso de la ruptura de las normas este solapamiento genético es mucho menor.

En conjunto, estos cuatro estudios aportan, de manera general, información novedosa sobre la calidad de sueño y, de forma particular, sobre las influencias genéticas y ambientales de la misma; dando respuesta a cómo es la calidad de sueño de la población española y el porqué de las diferencias individuales. Además, se estudió la asociación que

existe entre la calidad de sueño y variables relacionadas con la salud y el comportamiento en poblaciones de diferentes lugares geográficos y rangos de edad.

En resumen, estos estudios resaltan la importancia del sueño para nuestra salud general. En la primera parte de este trabajo, se constata que en la población española hay un elevado porcentaje de personas que padecen una pobre calidad de sueño y que la edad y el sexo son factores fundamentales a la hora de explicar estos resultados. La segunda parte se dirigió a determinar qué papel juegan los factores genéticos y ambientales a la hora de explicar las diferencias individuales en calidad de sueño. Los factores genéticos tuvieron una influencia significativa, aunque menor que los factores ambientales. Se constató además que, a pesar de las diferencias existentes entre hombres y mujeres en calidad de sueño, los factores genéticos implicados no difieren significativamente entre sexos. En la última parte de esta tesis se estudia la relación de la calidad de sueño con el índice de masa corporal (estudio 3) y con el comportamiento antisocial (estudio 4). En ambos casos se encuentra una fuerte relación.

Estos resultados nos permiten tener un conocimiento mayor sobre la calidad de sueño y, particularmente, cuál es la situación en nuestro país. Tener un conocimiento más preciso sobre su etiología nos permitirá diseñar tratamientos y programas de prevención más efectivos que puedan mejorar la calidad de sueño de los pacientes y por tanto su calidad de vida.

Esta tesis doctoral ha sido desarrollada en la Facultad de Psicología de la Universidad de Murcia y gracias a los Registros de Gemelos de Murcia y de la Universidad Estatal de Michigan. Las estancias cortas de investigación realizadas en otros centros de investigación, tanto en Europa como fuera de ella, han permitido al autor realizar un trabajo mucho más completo, extenso y riguroso y han sido parte fundamental

de su formación como investigador. Estas colaboraciones han quedado plasmadas en algunos de los artículos que componen esta tesis doctoral o relacionados con la misma. Además, de esas estancias cortas de investigación han surgido colaboraciones que han dado lugar a otros estudios que actualmente se encuentran en fase de revisión o preparación para ser publicados.

INTRODUCTION

This doctoral thesis started with the aim of deepening in the knowledge about sleep quality and its relationship with variables related to general health. Sleep is one of the most important factors in our health, comparable to diet or physical activity. Sleep is related to almost every single psychological variable and it is essential for both physical and psychological health.

The importance of a good sleep quality is finally receiveng the attention that it deserves. This message have had an impact into the population and people are more concerned about their sleep and statements such as "sleep is a waste of time" or "I will sleep when I am dead" are less popular now. This can be noticed, for example, in the increasing availability of sleep measuring devices which have become very popular.

This interest can also be noticed in the scientific literature. Researchers are more and more interested in sleep and the treatment of sleep disorders and difficulties, focused on sleep have demonstrated to be effective and efficient, while having an additional impact on other variables such as depression or anxiety (Morin et al., 2015).

Sleep is essential for the correct functioning of our body and brain (Walker, 2017), but there is not a unique answer to why we sleep. This thesis is obviously not aimed to answer every question about sleep but to shed some light upon the complexity of sleep determinants and their relationship —specifically regarding the genetic and environmental influences on sleep quality.

Genetic factors explain a substantial proportion of the individual differences in sleep characteristics (Barclay & Gregory, 2013). However, heritability is a population statistic and may vary across different samples (Visscher, Hill, & Wray, 2008). In line with this, Spain has specific characteristics that make Spanish population unique; and a behavioral genetic approach can be useful to address these special characteristics. Moreover, studying sleep using a behavioural genetic approach also allow us to understand the role of the environment since these designs tell us as much about the environment as genetics (Plomin, DeFries, Knopik, & Neiderhiser, 2016).

The use of a twin sample allows us to disentangle the role of genetic and environmental influences in sleep phenotypes, but a twin sample, if populaton-based, can also be used as a representative sample of the reference population. This work is divided into three main parts, in the first one, participants were treated as individuals subjects rather than twins, whereas in the second and third they were treated as twins. The first part aimed to know how is sleep quality in the Spanish population, which has some differential characteristics from other populations typically studied, such as the behaviour of siesta, a time zone displaced with respect to solar time, or later meal times. The goal of the second part of this work was to estimate the genetic and environmental influences on sleep quality in the Spanish population and also test for possible sex differences in the variance distribution. The third part was aimed to study the relationship between sleep and two relevant variables for general health and behaviour such as body mass index or antisocial behaviour.

List of publications included:

- **Madrid-Valero, J. J**., Martínez-Selva, J. M., Ribeiro do Couto, B., Sánchez-Romera, J. F., & Ordoñana, J. R. (2017). Age and gender effects on the prevalence of poor sleep quality in the adult population. *GacSanit*, *31*(1), 18-22. doi:10.1016/j.gaceta.2016.05.013

  Impact Factor (JCR): 1.581

- **Madrid-Valero, J. J**., Sanchez-Romera, J. F., Gregory, A. M., Martinez-Selva, J. M., & Ordonana, J. R. (2018). Heritability of sleep quality in a middle-aged twin sample from Spain. *Sleep, 41*(9). doi:10.1093/sleep/zsy110

  Impact Factor (JCR): 4.571

- **Madrid-Valero, J. J**., Martínez-Selva, J. M., & Ordoñana, J. R. (2017). Sleep quality and body mass index: a co-twin study. *J Sleep Res, 26*(4), 461-467. doi:10.1111/jsr.12493

  Impact Factor (JCR): 3.433

- **Madrid-Valero, J. J**., Ordoñana, J. R., Klump, K. L., & Burt, S. A. (2019). Children Sleep and Antisocial Behavior: Differential Association of Sleep with Aggression and Rule-Breaking. J Abnorm Child Psychol, 47(5), 791-799. doi:10.1007/s10802-018-0480-0

  Impact Factor (JCR): 3.406

This document is organised as follows: Chapter 1 is a general section displaying a review of the scientific literature, in order to support and justify the design of our research. Chapter 2 lists the objectives of this work. Chapter 3 contains the methodology that was used in the different studies that compose this thesis. After that, in Chapter 4, a brief abstract of the main results is presented; and in Chapter 5, the published studies are attached. Finally, Chapter 6 includes the conclusions of this work and puts them in relation with the aforementioned objectives, and Chapter 7 contains a summary of this doctoral thesis.

CHAPTER 1: BACKGROUND AND THEORETICAL FRAMEWORK

1.1. What is sleep and why we sleep?

Researchers —including Francis Crick or Sigmund Freud have tried to answer this question. However, sleep remains as one of the biggest biological mysteries (Walker, 2017).

Although it could seem counterintuitive, sleep is defined as a behaviour (Carlson, 2010). Behavioural sleep characteristics include: 1) stereotyped posture; 2) absence or decrease of voluntary body movements; 3) poor response to external stimuli and 4) limited duration and reversibility of that state (Ramos, 1996). Defining sleep as a behaviour has two relevant implications from a psychological perspective. The first one is that, as a behaviour, sleep is susceptible to be modified. For example, Cognitive Behavioural-Therapy for Insomnia (CBT-I) is often the treatment of choice for treating the most common sleep disorder, insomnia (Morin et al., 2015). The other relevant implication is that it is influenced by genetic factors— just like any behaviour/psychological trait (Plomin et al., 2016).

Sleep, in its various forms, is universal among all the species (Cirelli & Tononi, 2008). Human behaviours are subject to natural selection in the same way physical features are, and so is sleep. Despite sleep being a behaviour that exposes the organism to several risks such as being vulnerable to predators, natural selection has not been able to get rid of it (Carlson, 2010), and some species have developed very extraordinary alternative mechanisms, such as hemispheric sleep in dolphins (Branstetter, Finneran, Fletcher, Weisman, & Ridgway, 2012).

Sleep is such an essential function for life that, contrary to eating or drinking, we cannot force ourselves not to sleep, and, inevitably after a few days, we will end up sleeping. The best proof that sleep is essential for our lives is that total sleep deprivation ends up with the death of the organism, as studies on sleep deprivation in rats show (Rechtschaffen, Bergmann, Everson, Kushida, & Gilliland, 1989, 2002). Another dramatic example is fatal familial insomnia which is a rare autosomal dominant hereditary disorder, which causes persistent insomnia, ataxia, and memory problems that worsen progressively until the subject dies (Lugaresi et al., 1986).

Those are extreme examples of the importance of sleep. However, there are plenty of other relevant examples of the importance of sleep for our health. Short sleep/poor sleep and sleep disorders have been associated with a plethora of negative physical consequences such as higher risk of mortality (Amagai et al., 2004; Kripke, Garfinkel, Wingard, Klauber, & Marler, 2002; Y. Li et al., 2014), higher body mass index (BMI) (Bjorvatn et al., 2007; Cappuccio et al., 2008; Watson, Buchwald, Vitiello, Noonan, & Goldberg, 2010; Watson et al., 2012), hormonal and biochemical changes (Massar, Liu, Mohammad, & Chee, 2017; Spiegel, Leproult, et al., 2004; Spiegel, Tasali, Penev, & Van Cauter, 2004), type 2 diabetes (Cappuccio, D'Elia, Strazzullo, & Miller, 2010a; Gangwisch et al., 2007), hypertension (Wang et al., 2015), chronic pain (Karaman et al., 2014; Marty et al., 2008) and even cancer (Owens et al., 2016).

There is also a wide variety of negative psychological consequences associated to sleep disturbances such as depression and anxiety (Jansson-Fröjmark & Lindblom, 2008; Ohayon & Roth, 2003; Royuela & Macías, 1997a), poor school adjustment (Williams, Nicholson, Walker, & Berthelsen, 2016), peer victimisation (van Geel, Goemans, & Vedder, 2016), attention-deficit/hyperactivity disorder (Gregory, Agnew-Blais, Matthews, Moffitt, & Arseneault, 2017), altered cognitive functioning (Kronholm et al., 2009), negative cognitive bias (Gobin, Banks, Fins, & Tartar, 2015), behavioural problems (Hoedlmoser, Kloesch, Wiater, & Schabus, 2010) and aggression (Gregory & O'Connor, 2002) among others.

Although sleep remains as one of the biggest biological mysteries there are a wide variety of functions that have been associated to sleep (Krueger, Frank, Wisor, & Roy, 2016):

- Immune functions: sleep is related with our immunological system. There is a corpus of knowledge supporting that sleep or sleep loss affects our immunological system (Imeri & Opp, 2009). Indeed, it seems to be a bidirectional relationship between sleep and immunity. For example, prolonged sleep deprivation can lead to chronic systemic low-grade inflammation (Besedovsky, Lange, & Haack, 2019).
- Caloric use: for every organism the homeostatic balance of energy is essential. During sleep the metabolic rate is lower than wakefulness and body and brain temperatures are regulated at a lower level (Krueger et al., 2016).
- Restores brain energy: available research has pointed out that sleep has an essential function to provide energy stores to the brain. In other words, during wakefulness energy stores of the brain are consumed and restored during sleep (Scharf, Naidoo, Zimmerman, & Pack, 2008).
- Glymphatic function: Another function that have been linked with sleep is related to the glymphatic system. The glymphatic system main function is to clean toxin and other brain products from the central nervous system since sleep promote cleaning processes (Krueger et al., 2016).
- Cognitive functions: sleep is related with all our cognitive functions. Sleep deprivation has negative effects for our performance and an adequate sleep-wakefulness pattern is essential for our correct cognitive functioning. During sleep memory consolidation processes occur and learnings during wakefulness are integrated as well (Carlson, 2010). Additionally, the worsening in cognitive performance is recovered after

sleep, showing that adequate performance of our cognitive functions is somehow dependent of sleep (Rosa, Bonnet, & Warm, 1983).

- Connectivity function: It has also been suggested that sleep is related with the brain plasticity function. However, this relationship is not simply unidirectional and sleep effects may vary depending on certain factors such as circuits under examination, age of the organism, or the kind of stimuli (Frank & Cantera, 2014).

Those are several functions related to sleep. Different theories have tried to address the functionality of sleep from an evolutionary perspective. For example, the *homeostatic theory of sleep regulation* states that the principal function of sleep is to provide rest and recovery to the organism. It has also been proposed that sleep would meet an adaptive function — *adaptive theory of sleep*. Animals exhibit different sleep needs and in different times. For example, some species such as bats can hunt in certain hours and for a limited amount of time in order to not to be exposed to predators, while other species such as elephants have longer periods of wakefulness which allow them to consume large quantities of food needed to maintain their large bodies. Therefore, different species have various wake-sleep cycles that could be beneficial for the survival of the organism (Lambert, 2017).

Given the highly relevant functions of sleep, the maladjustment of sleep organization/structure/system produces dysfunctions and disturbances which may potentially affect our health negatively. Actually, there is a high prevalence of sleep problems in the population (Ohayon, 2002), to the point that they are becoming a global epidemic (Chattu et al., 2018; Stranges, Tigbe, Gómez-Olivé, Thorogood, & Kandala, 2012), involving a high burden for society in terms of both direct and indirect costs (Daley, Morin, LeBlanc, Grégoire, & Savard, 2009; Hillman et al., 2018; Ozminkowski,

Wang, & Walsh, 2007). The average time of sleep duration in the population is decreasing and that could be due to factors such as the change to a 24/7 society (i.e. a society where stimuli are available all the time, especially in the business field), shift works, artificial lights, mobile phones and internet among others (Hale & Guan, 2015; Kronholm et al., 2008; Rowshan Ravan, Bengtsson, Lissner, Lapidus, & Björkelund, 2010). The way that we consume technology has changed and it has a relevant impact in our sleep patterns (Shochat, 2012). That makes sleep epidemiology a fascinating and rapidly growing field (Ferrie, Kumari, Salo, Singh-Manoux, & Kivimäki, 2011).

In that sense psychological therapies have shown to be a good strategy to treat sleep problems cost-effectively (Reynolds & Ebben, 2017). CBT-I is the treatment of choice for insomnia (Morin et al., 2015). It is typically carried out by a trained psychologist or other mental health trained clinician in four to six individual or group sessions. In these sessions the professional gives guidance to the patient about how to change sleep habits, sleep schedules and thinking patterns (Morin et al., 2015). CBT-I has shown to be an effective treatment for insomnia (Trauer, Qian, Doyle, Rajaratnam, & Cunnington, 2015) and its effects are well maintained over time (Morin, Colecchi, Stone, Sood, & Brink, 1999; Morin et al., 2015).

1.2. Neurobiology of sleep and circadian rhythms

There are different rhythms controlling our basic functions. These rhythms can be classified in circadian, ultradian, or infradian depending on the periodicity (around, less or more than 24h respectively). Sleep is a circadian rhythm with a period cycle of about 24 hours. Different structures are involved in this process. One of the most important structures for sleep is the suprachiasmatic nucleus, which is the brain area implicated in the regulation of the circadian rhythms (Carlson, 2010). The suprachiasmatic nucleus

receives stimulation from light via tracts extending from the retina (Lambert, 2017). Although, light is the most powerful *Zeitgeber* (German word for time-giver) blind people also exhibit these rhythms (Sack, Brandes, Kendall, & Lewy, 2000). However, there are many more *Zeitgebers* in our contemporary society such as the alarm clock, city sounds, meal times, or other members of the family that help us to regulate our sleep cycle (Lambert, 2017).

Melatonin is another important factor involved in the regulation of sleep rhythm. Melatonin is a hormone secreted by the pineal gland, the secretion of melatonin increases in darkness and decreases when we are exposed to light. When melatonin increases, wakefulness is less likely; therefore, melatonin is considered a sleep facilitator (Lambert, 2017). Melatonin has been used as potential treatment for certain sleep disorders (e.g. insomnia) or jet-lag (Alston, Cain, & Rajaratnam, 2019).

1.3. Sleep stages

Sleep in humans is divided into several stages with different characteristics. During wakefulness, a normal electroencephalogram (EEG) shows 2 basic patterns of activity: alpha and beta. The alpha activity is associated with a state of relaxation whereas the beta activity is associated with a state of alertness (Carlson, 2010).

EEG signal activity during sleep can be used to identify five sleep stages:

- Stage 1: this stage is a transition from wakefulness to sleep. In this stage brain activation decreases and theta activity in the EEG begins. This stage has a duration of around ten minutes.
- Stage 2: this stage is characterized by an irregular EEG that includes periods of theta activity. In this stage there are sleep spindles and K-complexes. Sleep spindles are sudden bursts of oscillatory brain activity;

and K-complexes are large waves that react to external stimuli while sleeping. While spindles can appear in other sleep stages, the K-complexes appears only in stage 2. Some researchers think that these mechanisms are involved in keeping the subject asleep.

- Stage 3 and 4: There is not a clear difference between stages 3 and 4, and the threshold between them is blurred, so as the National Sleep Foundation combined them in just one phase. In these stages the EEG shows delta activity. They are referred to as 'deep sleep', when the awakening is more difficult.
- Rapid-Eye-Movement (REM) sleep. REM sleep is the last stage and it is characterised by a desynchronised EGG activity. It is also called paradoxical sleep since beta activity appears in the EGG, which is typical of wakefulness or stage 1.

The set of stages is called sleep cycle and it takes around 90 minutes which includes a REM period of 20-30 minutes. In each cycle all the stages are repeated except stage one. In a normal period of eight hours typically 4-5 sleep cycles occur (Carlson, 2010; Ramos, 1996).

1.4. Sleep quality

Buysse et al.,(1989) describe sleep quality as a complex phenomenon that is difficult to define and measure objectively. The term sleep quality is widely used in clinical practice. However, there are some difficulties in describing what sleep quality is. It could be defined as a set of measures such as: sleep duration, awakenings, sleep latency, sleep efficiency and sleep disturbances (Buysse et al., 1989; Krystal & Edinger, 2008). Sleep quality is not related directly with quantity and self-reported quality does not

correlate well with Polysomnography (PSG) defined sleep (Moul et al., 2002). Whether the meaning of sleep quality for subjects with insomnia is the same for subjects without insomnia has also been studied. The results showed that the meaning of sleep quality and variables involved are broadly similar for both groups (Harvey, Stinson, Whitaker, Moskovitz, & Virk, 2008).

1.5. Sleep measures

PSG is considered the gold-standard measure for sleep. It consists of a set of measures such as electroencephalography (brain activity), electrooculography (ocular movements), electromyography (muscular activity) and electrocardiography (hearth rhythms) (Carlson, 2010). Polysomnography produces a set of objective measures that informs us about sleep pattern and changes during sleep with high accuracy. Nevertheless, this measures have a limited role in the clinical practice and should not replace a thorough clinical evaluation (Reite, Buysse, Reynolds, & Mendelson, 1995).

Another objective measure of sleep is actigraphy, in which a device is usually placed on the wrist and records the activity and movements of the subject. Therefore, its main limitation is the difficulty to discriminate between sleep and wakefulness periods without any movement (Ancoli-Israel et al., 2003; Sadeh, 2011). Actigraphy is a useful tool for the evaluation of sleep in healthy subjects and in patients who may suffer from certain sleep disorders such as advanced sleep phase syndrome, delayed sleep phase syndrome, and shift work disorder (Morgenthaler et al., 2007). Actigraphy is also indicated to evaluate the efficacy of clinical interventions. However, when it comes to clinical diagnosis it should be combined with other measures (objective or subjective) (Sadeh, 2011).

There are a wide variety of self-reported instruments that have shown good psychometric properties and are widely used in research and clinical practice. These instruments allow us to conduct studies with large samples while other, more-objective, measures, such as PSG, would make the study unfeasible due to the high costs and complex logistics involved. The following questionnaires are the most commonly used for research and clinical purposes:

- "Epworth Sleepiness Scale" (ESS): it is used to evaluate daytime sleepiness (Johns, 1991).
- "The Pittsburgh Sleep Diary": it is a useful tool for the quantification of subjectively reported sleep and waking behaviour (Monk et al., 1994).
- Pittsburgh Sleep Quality Index (PSQI): it is the most commonly used questionnaire for assessing sleep quality (Buysse et al., 1989).
- "Insomnia Severity Index" (ISI) questionnaire: It is commonly used to evaluate insomnia (Bastien, Vallières, & Morin, 2001).
- Another way to evaluate insomnia is by using the criteria from the diagnosis manual DSM-V (American Psychiatric Association, 2013).
- Sleep Timing Questionnaire: It is an alternative to sleep diaries for evaluating total time of sleep and circadian rhythms (Monk et al., 2003).
- Questionnaires for evaluating chronotype and individual preferences are the "Morningness-Eveningness Questionnaire" (MEQ) (Horne & Ostberg, 1976) and the Munich Chronotype Questionnaire (MCTQ) (Roenneberg, Wirz-Justice, & Merrow, 2003).
- There are also different questionnaires to assess symptoms of sleep apnoea such as: the STOP-BANG questionnaire (Chung, Abdullah, & Liao, 2016) or the BERLIN questionnaire (Netzer, Stoohs, Netzer, Clark, & Strohl, 1999).

1.6. Age and sleep

Age is a key variable for sleep quality. Sleep needs are different across the life span, which is represented by the fact that, in general, the number of sleeping hours we

need decreases with age. For example, new-borns typically need around 14-17h, infants 12-15h, adults 7-9h and older adults 7-8h (Hirshkowitz et al., 2015).

Sleep quality decreases with age in both sexes (Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). Both studies using objective and subjective measures have shown that sleep quality worsens with age while increasing the frequency of sleep disturbances (Buysse et al., 1991). Advancing age is associated with lower sleep duration, less sleep efficiency and more awakenings during sleep (Carrier, Monk, Buysse, & Kupfer, 1997). Moreover, studies using the PSQI found that the subjective perception of sleep quality decreases parallelly (Asghari, Farhadi, Kamrava, Ghalehbaghi, & Nojomi, 2012) and that the prevalence of poor sleep quality in older people can be as high as 64% (Park, Yoo, & Bae, 2013). Consequently, the prevalence of insomnia also increases with age (Atalay, 2011; Ohayon, 2002).

The age-related sleep worsening is in part due to the phase advance that typically occurs around the age of 40, which consists on going to bed earlier and waking up earlier as well (Carrier, Paquet, Morettini, & Touchette, 2002). Additionally, with increasing age, a set of changes in the brain activity during sleep would contribute to a higher vulnerability of the functioning of the sleep-wake cycle. The analysis of the EEG spectral activity reveals a progressive reduction of the slow (0.25-4.75 Hz) and fusiform spectral density. Additionally, the high frequency cortical activity increases, above 18 Hz, which can be interpreted as an elevated cortical arousal. Taken together, this indicates a gradual vulnerability of the regulation system of the sleep-wake rhythm (Carrier, Land, Buysse, Kupfer, & Monk, 2001; Myers & Badia, 1995).

1.7. Sex and sleep

Women generally report poorer sleep quality and greater sleep problems than men (Middelkoop, Smilde-van den Doel, Neven, Kamphuisen, & Springer, 1996). A meta-analysis of sex differences in the prevalence of insomnia found that women are 1.41 times more likely to suffer from insomnia than men (Krystal, 2003; Ohayon, 2002; Zhang & Wing, 2006). But not all studies found the same results. For example, one study found that women had a poorer sleep quality than men when sleep quality was assessed by subjective method whereas men had a poorer sleep quality when sleep quality was assessed by objective methods (van den Berg et al., 2009). Hence, it has been suggested that the correspondence between self-reported sleep quality and objective measures of sleep quality may differ between men and women (Vitiello, Larsen, & Moe, 2004). Scientific literature has constantly found that women are more prone to complain about their sleep than men across the life span (Bixler, Vgontzas, Lin, Vela-Bueno, & Kales, 2002; Ohayon, 2002).

One relevant variable that could underlie these differences is menopause. During the menopause hormonal changes occur, that could affect sleep quality negatively (Kravitz et al., 2008; Xu et al., 2011). It has been found that postmenopausal women have a loss of circadian robustness and a worsening of sleep quality in comparison with premenopausal women (Gómez-Santos et al., 2016). Other factors such as comorbid conditions (e.g. depression) could also explain this association (Pengo, Won, & Bourjeily, 2018).

1.8. Associations between sleep and psychopathology, behaviour and health related variables

A good sleep quality is essential for the correct functioning of our general health (Irwin, 2015). This section reviews the associations between sleep quality and psychological and physical variables, with special attention to behavioural genetic studies.

1.8.1. Sleep and depression and anxiety

There is a strong relationship between depression and poor sleep. In fact, sleep complaints are one of the criteria for the diagnosis of major depressive disorder (American Psychiatric Association, 2013). Depression often co-occurs with symptoms of insomnia or poor sleep quality (Riemann & Voderholzer, 2003; Royuela & Macías, 1997a).

Several studies have shown that insomnia and depression are strongly correlated (L. Li, Wu, Gan, Qu, & Lu, 2016). For example, in a longitudinal study people with depression were 2,28 times more likely to develop insomnia; moreover, insomnia was related to risk of future depression (3.5 times more likely) (Jansson-Fröjmark & Lindblom, 2008). Furthermore, a meta-analysis of longitudinal studies found a two-fold risk to develop depression for people with insomnia (Baglioni et al., 2011). Finally,

Alvaro et al. (2013), in a systematic review, concluded that there seems to be a bidirectional relationship between insomnia and depression.

Studies using different variables have also found significant relationships between sleep and depression. For example, Kaneita et al. (2009) found a significant association between sleep quality and poor mental health. Another longitudinal study with adolescents found a significant bidirectional relationship between those traits (Meijer, Reitz, Deković, van den Wittenboer, & Stoel, 2010). Sleep duration has also been linked to depression. In a recent meta-analysis both short and long sleep duration were associated with an increased risk to suffer depression in adults (Zhai, Zhang, & Zhang, 2015).

A similar picture can be found for anxiety. Several studies have found a significant association between insomnia and anxiety (Jansson-Fröjmark & Lindblom, 2008; Johnson, Roth, & Breslau, 2006), and also between sleep quality and anxiety (Gregory, Buysse, et al., 2011; Kaneita et al., 2009; Meijer et al., 2010; Royuela & Macías, 1997a).

As we will see later, these three phenotypes (i.e., sleep quality, depression and anxiety) are substantially influenced by genetic underpinnings (i.e. typically around 30-40% of the variance) (Barclay, Eley, Buysse, Archer, & Gregory, 2010; Gasperi, Herbert, Schur, Buchwald, & Afari, 2017; Hettema, Neale, & Kendler, 2001; Nivard et al., 2015; Partinen, Kaprio, Koskenvuo, Putkonen, & Langinvainio, 1983; Sullivan, Neale, & Kendler, 2000). Consequently, some studies have also investigated the genetic factors

underlying these associations. For example, a large genetic overlap (genetic correlations above .5) has been found between insomnia and depression/anxiety (Gehrman et al., 2011; Gregory et al., 2016; Lind et al., 2017). Likewise, other studies report substantial genetic overlap between sleep quality and depression/anxiety, both in young adults (Gregory, Buysse, et al., 2011) and adults (Gasperi et al., 2017).

1.8.2. Antisocial behaviour and conduct problems

Sleep is also related to behavioural problems (Denis et al., 2017). Short sleep duration and sleep difficulties are related to reduced academic performance, psychopathology, poor school adjustment, behavioural disinhibition and peer victimisation in children, among other adverse consequences (Dahl & Lewin, 2002; Dimitriou, Le Cornu Knight, & Milton, 2015; van Geel et al., 2016; Williams et al., 2016).

A similar picture can be found for adults. For example, one study in young men reported that those subjects with shorter sleep duration had higher scores on anger and hostility (Taub, 1977). Moreover, Lindberg et al., (2003) found a differential distribution of the sleep stages between habitually violent offenders and healthy controls. Not all the studies found a significant association between aggression and sleep duration (Shin et al., 2005). However, as Kamphuis et al., (2012) stated in their review, not only sleep quantity but also sleep quality should be taken into account to analyse this relationship.

Although further research is needed to understand the role of sleep in conduct problems (especially in adults), the results points to a significant relationship between these variables.

1.8.3. Sleep and health related variables

Short sleep duration is associated with higher BMI in both children and adults (Cappuccio et al., 2008). A higher BMI is also associated with insomnia, apnoea and poor sleep quality (Bjorvatn et al., 2007; Hung et al., 2013; Kim, 2015; Moraes et al., 2013; Sivertsen, Pallesen, Sand, & Hysing, 2014; Tatone-Tokuda et al., 2012; Watson et al., 2010; Watson et al., 2012).

Previous studies have suggested that impaired sleep may result in increases in BMI through different factors such as increases in sympathetic nervous activity (Spiegel, Leproult, & Van Cauter, 1999), a decrease in leptin levels, an increase in ghrelin levels, or an increase in appetite and hunger (Spiegel, Tasali, et al., 2004).

Despite the well-established relationship between sleep quality and BMI, the directionality of this relationship is not fully known. In that sense, informative genetic designs and longitudinal studies are needed to elucidate the directionality of this relationship.

Sleep quality is also associated with cognitive functioning (Lo, Groeger, Cheng, Dijk, & Chee, 2016) or academic performance (Mirghani, Mohammed, Almurtadha, & Ahmed, 2015). Both sleep quality and duration have been associated with mortality risk. Hublin et al. (2007) reported in different studies with the same sample an increased risk of mortality for subjects in the upper and lower extremes of the sleep duration distribution and also in participants with poorer sleep quality (Hublin, Partinen, Koskenvuo, & Kaprio, 2011). Nevertheless, the scientific literature shows mixed results regarding mortality for subjects with long/short sleep duration or insomnia (Cappuccio, D'Elia, Strazzullo, & Miller, 2010b; T. Z. Liu et al., 2017; Lovato & Lack, 2019). A possible

explanation for these associations is the possibility that there is mediation by other illnesses and disorders that have not been studied within the research studies.

Pain is another variable that has been linked to poor sleep quality (Andreucci, Campbell, & Dunn, 2017; Finan, Goodin, & Smith, 2013). Moderate but significant phenotypic correlations have been found between these two phenotypes (0.23 - 0.36), Moreover, a substantial genetic overlap have been found between these two traits (rA=0.69; 0.33) in samples of adult twins (Gasperi et al., 2017; Pinheiro et al., 2018).

1.9. Genetic and environmental influences on sleep

There is a wide inter-individual variability in sleep characteristics which is obviously due to both genetic and environmental influences over sleep related neurobiological processes (Hublin, Partinen, Koskenvuo, & Kaprio, 2013). Analysing the relative weight of both factors in normal and altered sleep has long been one of the main aims of behaviour genetics researchers, both for the intrinsic value of such knowledge and for being a first step in the pursuit of the identification of specific genes related to sleep characteristics. In this sense, twin studies have been classically used as a methodological resource in this area of research for they allow to disentangle the role of both genetic and environmental factors in sleep (Barclay & Gregory, 2013).

1.9.1. Sleep quality

Regarding the heritability of sleep quality, in a study asking participants —adults of both sexes— how they would rate their sleep quality with different options (i.e., good, fairly good, fairly poor, poor or could not say) a heritability estimate of 44% was found (Partinen et al., 1983). Heath et al. (1990) also assessed sleep quality in 4 sub-cohorts, ranging from 18 to 88 years of age, and found a moderate but significant heritability (32%).

Other studies have estimated the genetic influences on sleep quality using the PSQI (Buysse et al., 1989). For example, Genderson et al. (2013), using the PSQI index in a sample of middle-aged male twins, found a heritability of 34%, while non-shared environment accounted for 66% of the variance. In the same study, the heritability estimate was found similar (31%), when sleep quality was dichotomized using a cutoff point for poor sleep (i.e., PSQI≤5 or PSQI>5); that is, subjects with poor or adequate sleep quality. A similar value of heritability (37%) for the PSQI global index was found in another adult population (Gasperi et al., 2017).

The genetic influences on sleep quality have also been studied in other stages of the life span. The heritability value found in adolescents and young adults was similar, although slightly higher than that found in adults. For example, genetic influences accounted for 43% of the variance in young adults (Barclay, Eley, Buysse, Archer, et al., 2010) and 41% in adolescents (Taylor, Gregory, Freeman, & Ronald, 2015).

Despite the well-known differences between men and women, to the best of our knowledge, there are no studies that have investigated specifically if there is a sex-limitation effect producing different distribution of the variance in males and females. It is also important to highlight that different means do not necessarily imply differences in the genetic influences.

Additionally, the possibility of a changing heritability due to variations in social habits has not been explored. There is, for instance, a lack of comparative research between different cultural conditions regarding sleep. As discussed previously, some populations (i.e. Mediterranean or Chinese) have their own cultural characteristics and unique behaviours that make them different from the samples where these studies have been typically carried out (e.g., Northern European countries and USA).

Regarding the different components of sleep quality, according to the PSQI, a moderate proportion of the variance is also explained by genetic factors in most cases. Barclay et al., (2010) found heritability values ranging from 0 to 47% for the different dimensions of the PSQI in young adults. In adults, and Genderson et al., (2013) reported heritability values for the components of the PSQI questionnaire ranging from 23 to 34%, in adults. However, in this study no genetic factors were found for the component "use of sleeping medication".

Furthermore Barclay et al., (2010) also tested the genetic overlap between the different components of the PSQI. They found a moderate phenotypic correlation among the PSQI components that could be substantially accounted for by genetic correlation. Most of the genetic correlations among components of PSQI were above .69 (Barclay, Eley, Buysse, Rijsdijk, et al., 2010). These results reinforce that components of PSQI are distinguishable dimensions, if strongly correlated, of sleep quality.

These results highlight the role of genetic factors in explaining the inter-individual variability in sleep quality.

1.9.2. Sleep duration

Sleep duration is the most frequently studied dimension of sleep quality. That is partly due to its ease to be measured: commonly using a single question. There are several studies that have estimated the genetic and environmental influences on sleep duration. For example, in the aforementioned study by Partinen et al., (1983) the heritability of sleep duration was estimated at 44%, which is the same as the value they found for sleep quality.

Other studies have found somewhat lower results regarding the genetic influences on sleep duration in adults, ranging from 27 to 31% (R. Liu et al., 2012; Watson et al., 2010). Genderson et al., (2013) found that 29% of the sleep duration variance was attributable to genetic factors in adults. However other authors found no genetic influences on sleep duration for young adults (Barclay, Eley, Buysse, Rijsdijk, et al., 2010). Butkovic et al., (2014) estimated the broad sense heritability for sleep duration at 63%.

There are also studies in children and adolescents that have estimated the heritability for sleep duration. For example, in children aged 12, additive genetic influences accounted for 65% of the variance (Sletten et al., 2013). However, a different pattern of results was found in infants, where shared-environment had the higher value (63%) and genetic influences were moderate (26%) (Fisher, van Jaarsveld, Llewellyn, & Wardle, 2012). Another study estimated the genetic and environmental influences on night sleep duration at several age points finding that genetic influences accounted for 47, 20, 58 and 54% of the variance at 6, 18, 30 and 48 months respectively (Touchette et al., 2013). Interestingly, the higher value for shared-environment was at 18mo which is similar to the one found in the study by Fisher et. al., (2012).

The stability of the genetic and environmental influences on sleep duration was tested with a time delay of 15 years, finding that genetic effects are very stable over this time period (Hublin et al., 2013).

1.9.3. Chronotype

Three main chronotypes have been identified in the human species: morning-type, evening-type, or a mix of both chronotypes (Horne & Ostberg, 1976; Kerkhof, 1985). These two kinds of chronotypes (i.e. morning and evening) would represent the extremes

of a continuum. People with morning chronotypes tends to wake up early and go to bed early too and their peak of productivity is located during the morning. On the other hand, the evening-type is associated with a peak of productivity during the evening and tend to go to bed later and wake up later as well (Horne & Ostberg, 1976; Kerkhof, 1985).

This characteristic of sleep is also influenced by genes and around one-half of the variation is due to genetic factors (Koskenvuo, Hublin, Partinen, Heikkilä, & Kaprio, 2007; Toomey, Panizzon, Kremen, Franz, & Lyons, 2015). Moreover, physiological processes such as the secretion of cortisol which has a peak before the awakening is also influenced by genetic factors which affect the sleep cycle (Elder, Wetherell, Barclay, & Ellis, 2014; Linkowski et al., 1993). Thus, the genetic and environmental influences of circadian rhythms related to sleep were studied finding that for cyclic measures (i.e. mesor, acrophase, amplitude, percentage of rhythmicity, the Rayleigh test, and circadian function index) genetic factors accounted by 40-72% of the variance (Lopez-Minguez et al., 2016). Wrist temperature, which is a good marker to assess the circadian system, has also been studied using a behavioural genetic approach. It was found that cyclic variation in temperature is also substantially influenced by genetic factors, with heritability for the different measures ranging from 46 to 70% (Lopez-Minguez, Ordoñana, Sánchez-Romera, Madrid, & Garaulet, 2015). This rhythmicity associated to sleep has a behavioural expression in the patterns of night-time and diurnal sleep, such that taking siesta appears also to be dependent on genetic factors, with a heritability of 65% (Lopez-Minguez, Morosoli, Madrid, Garaulet, & Ordoñana, 2017).

1.9.4. Insomnia

Insomnia is one of the most common sleep disorders and has a high population prevalence (Morin et al., 2015). The genetic influences on insomnia have been studied in

several samples. In adults, the heritability value for insomnia have been reported in a range between 20 to 55% (Drake, Friedman, Wright, & Roth, 2011; Hublin et al., 2011; Lind, Aggen, Kirkpatrick, Kendler, & Amstadter, 2015; Watson, Goldberg, Arguelles, & Buchwald, 2006). Substantial genetic influences for this trait were also found in children, adolescents and young adults (Barclay, Gehrman, Gregory, Eaves, & Silberg, 2015; Gehrman et al., 2011; Gregory et al., 2016; Taylor et al., 2015).

1.9.5. Other sleep disorders

There are only a handful of studies that have investigated the genetic and environmental influences on sleep apnoea. For example, a pioneering study in adults found a higher concordance for snoring in MZ (0.67) than DZ (0.50) twins (Ferini-Strambi et al., 1995), and another study in a middle-aged sample found a heritability of 52% for disruptive snoring (Desai, Cherkas, Spector, & Williams, 2004). However, in elderly people, a lower value (23%) for self-reported snoring was found (Carmelli, Bliwise, Swan, & Reed, 2001). The heritability of the apnea-hypopnea index (i.e., number of apnea and hypopnea events per hour of sleep) has also been studied finding heritability values ranging from 23 to 37% in adults (de Paula et al., 2016; Patel, Larkin, & Redline, 2008). Furthermore, a recent study, in an adult population, suggested that airway structures and head postures could be under strong genetic control (Kang, Sung, Song, & Kim, 2018). Despite sleep apnoea being a common sleep disorder with prevalence ranging from 9 to 38% in the general adult population (Senaratna et al., 2017) there are no studies about the genetic and environmental influences in young people.

Different studies have also estimated the heritability of other sleep related disorders. For example, in a sample of adult twins a 52% of the variance in rest leg syndrome was attributable to genetic factors (Desai et al., 2004). Narcolepsy also showed

a substantial genetic influence with estimates of 35 and 39% for narcolepsy-like symptoms for male and female respectively (Kaprio, Hublin, Partinen, Heikkilä, & Koskenvuo, 1996). Sleep walking is also influenced by genetic factors. However, there are large differences regarding the genetic influences between men and women. Hublin et al., (1997) found a heritability of 36% for women and 80% for men. Sleep talking and bruxism also showed substantial genetic influences (Hublin, Kaprio, Partinen, & Koskenvuo, 1998a, 1998b).

However, heritability is a statistic and it may vary from one population to another (Visscher et al., 2008). In that sense, some populations (e.g., Spain) have unique features, such us the displaced time zone, the practice of siesta, late bedtimes and meal schedules that should be taken into account when conducting twin studies about sleep since they could influence the relative impact of genetic and environmental underpinnings of these traits. Moreover, other type of studies such as meta-analyses of twin studies should be carried out in order to synthesize the available results and check for possible heterogeneity among studies.

1.10. Molecular genetics studies

Heritability provides essential information about the relative weight of general genetic factors on inter-individual phenotypic variation. However, it is not informative regarding which specific genes and through which pathways genetics influence sleep-related traits. In the last years, molecular genetics studies are beginning to analyse and complete this puzzle. Heritability estimates using SNP-based heritability have found lower values than twin studies. For example, around 10% for sleep duration and sleepiness and ranging from 7 to 20% for insomnia (Dashti et al., 2019; Jansen et al.,

2019; Lane et al., 2017). Those values are notably lower than those from twin studies, which are another example of the so called missing heritability (Manolio et al., 2009; Mayhew & Meyre, 2017). Recent Genome-Wide Association Studies (GWAS) (with 113,006 and 1,331,010 participants respectively) have found several genes and loci associated with insomnia (Hammerschlag et al., 2017; Jansen et al., 2019). These studies have explored gene-sets and pathways involved in different measures related to sleep, such as insomnia or sleep duration, and are detecting an increasing number of loci implicated (Dashti et al., 2019; Doherty et al., 2018; Jansen et al., 2019; Jones et al., 2016; Lane et al., 2017; Nishiyama et al., 2019). Other GWAS have also identified variants that contribute to self-reported sleep duration, excessive day time sleepiness and chronotype (Jones et al., 2016; Lane et al., 2017; Lane et al., 2016). Consistent replications for sleep duration and insomnia in PAX-8, VRK2 or MEIS-1 have been found (Dashti et al., 2019; Doherty et al., 2018; Jones et al., 2016; Lane et al., 2017). Furthermore, these studies found strong genetic correlations between insomnia and psychiatric (e.g. major depression or anxiety disorder) and metabolic traits.

Given the large number of genes with small effect involved, recent techniques such as polygenic risk scores (PRS) have been developed to deepen in this question. PRSs are scores that summarize the effect of multiple genes, each with a tiny effect, assigning a value according to the specific variants contained in an individual's genome (Choi, Mak, & O'Reilly, 2018). These scores could help us develop prevention programs, tailored

interventions and more effective treatments. For example, in a recent study, Dashti et al., (2018) found a U-shaped relationship between sleep duration and asthma, depression, hypertension, insomnia, obesity, apnoea and type-2 diabetes where both short and long sleepers had an increased risk for suffering these health problems.

CHAPTER 2: OBJECTIVES

Chapter one has exposed a general vision about the state of the art regarding sleep from a behavioural genetic perspective. However, the literature review leaves some research questions that must be addressed. This thesis is composed of four studies aimed modestly to give some answers that could help fill the gap in scientific knowledge about the role of genetics in sleep.

This thesis is composed of four studies which have been published in indexed journals with impact factor. These studies are included in chapter 5.

As previously stated, all human traits/behaviours are influenced by genetic factors and sleep is not an exception. Sleep is one of the most important behaviours for our health and the main purpose of this doctoral thesis is to deepen in the knowledge about sleep quality and its underpinnings in order to answer the following research questions:

- "how is sleep quality in the Spanish population?";
- "to what extent are the differences in sleep quality due to genetic factors?";
- "how does sleep quality relate to relevant variables for health and behaviour?".

The starting point of this work was to study the sleep quality in the Spanish population since the literature review identified a scarcity of updated studies about the frequency and characteristics of different levels of sleep quality. Therefore, our first objective was to estimate the prevalence of poor sleep quality in a representative sample of the adult Spanish population (Ordoñana et al., 2018). We also tested the role of age and sex and the effect of menopause on sleep quality (Madrid-Valero, Martinez-Selva, Ribeiro do Couto, Sanchez-Romera, & Ordonana, 2017).

The second part of this work was aimed to estimate the genetic and environmental influences on sleep quality and its components. From our previous publication, we established that age and sex have a significant impact on sleep quality. Therefore, we estimated the genetic and environmental influences on sleep quality controlling for age effects and testing for possible sex differences on the distribution of the variance (Madrid-Valero, Sanchez-Romera, Gregory, Martinez-Selva, & Ordonana, 2018).

The third part was aimed to study the relationships between sleep quality and different measures related to health (i.e., BMI) and behaviour (i.e. antisocial behaviour). The first publication of this part was also carried out in the Murcia Twin Registry (MTR). This work studied the relationship between sleep quality and BMI using a co-twin design in order to test causality and directionality of this association (Madrid-Valero, Martínez-Selva, & Ordoñana, 2017).

The second study of this part was carried out at the Michigan State University Twin Registry (MSUTR) with a children sample. This study investigated the association between two measures of antisocial behaviour (i.e., rule-breaking and aggression) and different measures of sleep (Madrid-Valero, Ordoñana, Klump, & Burt, 2019).

In summary, this doctoral thesis deepens in the knowledge about genetic and environmental factors underlying sleep quality in the Spanish population, which has differential characteristics from the populations where this kind of studies have typically been carried out; and in the genetic relationships between sleep and relevant health and behavioural traits. This work followed an integrative approach using different methodologies in order to study sleep quality from a comprehensive standpoint.

The aforementioned general objectives were addressed in these specific research objectives:

Section 1: Sleep quality in the adult population.

Study 1: Age and gender effects on the prevalence of poor sleep quality in the adult population (Madrid-Valero, Martinez-Selva, et al., 2017).

1. To estimate the prevalence of poor sleep quality in Spanish adult population.
2. To investigate the role of age, sex and menopausal status on sleep quality.

Section 2: Genetic and environmental influences.

Study 2: Heritability of sleep quality in a middle-aged twin sample from Spain (Madrid-Valero et al., 2018).

1. To estimate the genetic and environmental influences on sleep quality in the Spanish population.
2. To test for sex differences in the distribution of the variance.
3. To estimate the genetic and environmental influences on the components of sleep quality.

Section 3: Associations between sleep quality and other variables.

Study 3: Sleep quality and body mass index: a co-twin study (Madrid-Valero, Martínez-Selva, et al., 2017).

1. To test for possible causal paths between sleep quality and body mass index.
2. To shed light on the directionality of this relationship controlling for genetic factors.

Study 4: Children sleep and antisocial behavior: differential association of sleep with aggression and rule-breaking (Madrid-Valero et al., 2019).

1. To study the association between different measures of sleep and two dimensions of antisocial behaviour (i.e., rule-breaking and aggression).
2. To estimate both individual variance and sources of covariance among aggressive behaviour or rule-breaking behaviour, and each sleep variable.
3. To test for possible differences in the associations between the sleep variables and each of the dimensions of antisocial behaviour.

CHAPTER 3: METHOD

The methodology used in this doctoral thesis was subject to the objectives of each study. In this section the samples, instruments, variables and study designs are described. Twin registries have been the main research resource for this work. Twin samples, especially when population-based, allow us to use participants either as individuals forming a representative sample or as twins to perform informative genetic designs.

3.1. Participants

Participants for this doctoral thesis come from two different samples. The first sample (sample 1) is composed of participants from the MTR (Ordoñana et al., 2006; Ordoñana et al., 2013), which are adults aged between 43 and 71 years. The second sample (sample 2) is composed of twins aged between 6 and 12 years from the MSUTR (Burt & Klump, 2013). Sample 1 was used for Study 1 (Madrid-Valero, Martinez-Selva, et al., 2017), Study 2 (Madrid-Valero et al., 2018) and Study 3 (Madrid-Valero, Martínez-Selva, et al., 2017) whereas sample 2 was used for Study 4 (Madrid-Valero et al., 2019).

In the following sections the main characteristics of these samples will be shown as well as the variables and instruments used.

3.1.1. Sample 1: Murcia Twin Registry

MTR is a population-based twin registry which means that the participants are a representative sub-sample of the population of origin (Ordoñana et al., 2018). The MTR is the only twin registry of this kind in Spain and it has unique characteristics in comparison with other twin registries.

The MTR was established in 2006 under the support of the University of Murcia and the Regional Health Authority and it is coordinated by the Faculty of Psychology (Human Anatomy and Psychobiology department). Its main aim is to focus on the genetic and environmental influences on variables related to health and health-related behaviours (Ordoñana et al., 2013).

Participants in the MTR are people born from multiple births between 1940 and 1966 (2281 participants). Currently a new data collection is ongoing and subjects born

between 1967 and 1976 are being collected. Additionally, the MTR has also data from about 100 university twin pairs.

The participation in the MTR is voluntary and subject to informed consent (annex 1). Inclusion criteria for the registry are: pairs with both members alive at the time of incorporation, residence in the Region of Murcia, and no conditions or disability that may limit their voluntary participation. The MTR, and specifically the research project this thesis is based upon, has been approved by the Research Ethics Committee of the University of Murcia (annex 2).

The sample for studies 1, 2 and 3 was composed of around 2, 150 subjects (differences in total sample between studies are due to missing data for the key variables involved in each analysis).

- Study 1 (Madrid-Valero, Martinez-Selva, et al., 2017): 2, 144 participants composed the sample, which was 45.3% male (N=971), and had a mean age of 53.7 (SD=7.3). For this study, participants were treated in all the analyses as individuals rather than twins. Therefore, no categorisation was made based on zygosity.
- Study 2 (Madrid-Valero et al., 2018). In this study we used almost the same number of participants (N=2, 150). Nevertheless, the design of this study was a classical twin study with MZ twins (32.7%) and DZ twins (67.3%).
- Study 3 (Madrid-Valero, Martínez-Selva, et al., 2017). As in the previous two studies, a sample of 2,150 subjects was used. The co-twin analyses followed a sequential process where first, the total sample was analysed.

Subsequently, all discordant pairs for sleep quality (N=316) or BMI (N=430) were analysed and finally stratified by zygosity.

3.1.2. Sample 2: Michigan State University Twin Registry

This sample was composed of 2,060 twin children from 1,030 families participants in the MSUTR (Burt & Klump, 2013; Klump & Burt, 2006). Specifically, this sample belongs to the Twin Study of Behavioral and Emotional Development in Children (TBED-C). The TBED-C has two different subsamples. The first one is composed of 1,056 twins recruited from across lower Michigan (USA). The other sample, "at risk", contains 1,004 twins from families that reside in modest or disadvantaged neighborhoods in the same recruitment area.

In order to be included in the MSUTR neither twin could have a physical or cognitive impairment that would interfere in the assessment. Ethics approval was provided by the Michigan State University. Parent(s) were requested for an informed consent for both their children and themselves and twins provided informed assent.

The participation in the two different sub-samples was 62% and 56% for the population based and the "at risk" sample. These rates of participation are similar or better than other twin registries (Baker, Barton, & Raine, 2002; Hay, McStephen, Levy, & Pearsall-Jones, 2002). Both sub-samples were representative, as it was checked via a brief questionnaire screen administered to nearly 85% of non-participating families (Burt & Klump, 2013).

This sample was 51.3% male with a mean age of 8.06 years (range 6-11.96; SD=1.45). The ethnicity was White non-Hispanic (81.7%), African-American (9.5%), Native American (1.1%), Asian (0.8%), Latinx (0.7%) and other (6.2%).

In Study 4 (Madrid-Valero et al., 2019), a classical twin design was used with 426 MZ twins pairs and 604 DZ twin pairs. In this study both univariate and bivariate models were used to estimate the genetic and environmental influences and also sources of covariance between phenotypes.

3.2. Main variables

The key variables for the different studies were:

- Study 1 (Madrid-Valero, Martinez-Selva, et al., 2017) described prevalence of sleep quality and analysed the influence of age and sex on such prevalence. Sleep quality was measured by means of the PSQI questionnaire (Buysse et al., 1989). Frequencies of the components of sleep quality were also described making use of the different sub-scales of the PSQI. Finally, the effect of menopause on sleep quality was also tested.
- Study 2 (Madrid-Valero et al., 2018) performed a classical twin design. Genetic and environmental influences on the PSQI index and its components were estimated. The key variables were PSQI total score and its elements: 1) subjective sleep quality, 2) sleep latency, 3) sleep duration, 4) habitual sleep efficiency, 5) sleep disturbances, 6) use of sleeping medication and 7) daytime dysfunction. Zygosity information was also used in order to separate MZ and DZ twin pairs.
- Study 3 (Madrid-Valero, Martínez-Selva, et al., 2017), used again data from the PSQI index. In this study, the relationship between sleep quality and BMI was studied. BMI data was obtained by means of self-report in all male and 40.6% of

the female participants, whereas for the rest of the sample BMI was obtained by a blinded research assistant who collected objectively measured weight and height. Zygosity was ascertained by DNA test in 338 twin pairs. For the rest of the sample zygosity was established by a 12-item questionnaire that classifies twins in accordance to DNA markers in nearly 96% of the cases (Ordoñana et al., 2013).

- Study 4 (Madrid-Valero et al., 2019) measured different sleep phenotypes. This set of variables were measured through the individual items from the Children Behaviour CheckList (CBCL) (Achenbach & Rescorla, 2001). These items refer to: "Sleep less than most kids"; "Nightmares"; "Overtired without good reason"; "Sleep more than most kids during day and/or night"; "Talks or walks in sleep"; and "Trouble sleeping" (0 = never, 1 = somewhat or sometimes true, 2 = often/mostly true). Items were dichotomized. Two dimensions of antisocial behaviour were also measured using two sub-scales of the CBCL (Achenbach & Rescorla, 2001): rule-breaking and aggression. Zygosity was ascertained using a standard 5-item questionnaire that assesses within-pair physical similarity and is over 95% accurate when compared to DNA (Peeters, Van Gestel, Vlietinck, Derom, & Derom, 1998).

3.3. Instruments

3.3.1. Pittsburgh Sleep Quality Index

PSQI was the main instrument for the first 3 studies. It is a widely used questionnaire for measuring sleep quality (Buysse et al., 1989). The PSQI has seven subscales which cover the main components of sleep quality: 1) subjective sleep quality, 2) sleep latency, 3) sleep duration, 4) habitual sleep efficiency, 5) sleep disturbances, 6)

use of sleeping medication, and 7) daytime dysfunction. Scores range from 0 to 3 for each of the sub-scales and all together yield a global score which ranges from 0 to 21. Higher scores represent poorer sleep quality. Subjects with a global PSQI >5 are categorised as subjects with poor sleep quality (Buysse et al., 1989).

This questionnaire has a validated Spanish version (Royuela & Macías, 1997b), which is the one used in the MTR (annex 3). The PSQI has good psychometric properties, high correlations with objective measures, and has previously shown a validated single-factor scoring structure (Boudebesse et al., 2014; Carpenter & Andrykowski, 1998; Raniti, Waloszek, Schwartz, Allen, & Trinder, 2018). In the MTR sample, the Cronbach's alpha was .73 for the global score.

Moreover, this questionnaire also allows us to know different characteristics of sleep such as: usual bed time, usual awakening time, the average sleep hours during the last month and reasons of awakening during sleep.

3.3.2 Child Behavior Checklist

The CBCL is a well-known and validated instrument for assessing aggressive and rule-breaking antisocial behaviours (Achenbach & Rescorla, 2001). It has two sub-scales: one for aggression, which has 18 items (e.g., "attacks people", "bullied", "cruel", "gets in fights") and other for rule-breaking, which has 17 items (e.g., "breaks rules"," cheat or lie", "no guilt", 'steals'). Cronbach's alpha in sample 2 for aggression and rule-breaking sub-scales was .88 and .65 respectively.

The CBCL also has several questions about sleep. These questions have been previously used to measure sleep characteristics in children (Gregory & O'Connor, 2002; Pirinen, Kolho, Simola, Ashorn, & Aronen, 2010). CBCL sleep items have shown adequate convergent validity with validated sleep measures and may be useful

individually when assessing specific facets of sleep functioning, especially with items such as “trouble sleeping” (Becker, Ramsey, & Byars, 2015; Gregory, Cousins, et al., 2011).

3.3.3 Other measures

3.3.3.1 Zygosity

For Sample 1, zygosity was ascertained by DNA test in 338 twin pairs. For the rest of the sample zygosity was established by a 12-item questionnaire which has an agreement with DNA markers in nearly 96% of the cases (Ordoñana et al., 2013).

Sample 2 zygosity was ascertained using a standard 5-item questionnaire that assesses within-pair physical similarity and is over 95% accurate when compared to DNA (Peeters et al., 1998).

3.3.3.2 BMI

Body weight was valued in barefoot subjects wearing light clothes, using a digital scale accurate to the nearest 0.1 kg (TANITA BC-420 MA; Tanita Corporation of America, Arlington Heights, Il, USA). Height was determined using a portable stadiometer (rank, 0.14–2.10). These data were used to calculate the BMI according to the following formula: weight (kg)/height $(m)^2$.

3.3.3.3 Depression/Anxiety

Anxiety/depression was measured with the depression/anxiety dimension of the EuroQol (EQ-5D) health questionnaire. This questionnaire requires participants to respond to five health domains (mobility, selfcare, usual activities, pain or discomfort, and anxiety or depression) (Rabin & de Charro, 2001). Participants were asked to answer

a single question that best described them on that day, with answers classified as “I am not anxious or depressed, “I am moderately anxious or depressed,” or “I am extremely anxious or depressed.”

3.3.4 Sociodemographic measures

The protocol questionnaire of the MTR (annex 3) includes a wide variety of sociodemographic measures such as: age, sex. Other measures were also assessed. Educational attainment was reported ranging from illiterate to University-High degree. Smoking was also evaluated; participants were divided into two different categories: 1) ex or never smoker; 2) current regular smoker. Regarding physical activity; Participants were asked to choose, among the following options, the one that best described their engagement in leisure physical activity: (1) “I do not practice exercise. My leisure time is mostly sedentary (reading, watching TV, movies, etc.)”; (2) “Some sport or physical activity occasionally (walking, gardening, soft gym, light efforts, etc.)”; (3) “Regular physical activity several times a month (tennis, jogging, swimming, cycling, team sports, etc.)”; (4) “Physical training several times a week”.

3.3.5 Summary table of main variables included in each study

	Study 1	**Study 2**	**Study 3**	**Study 4**
PSQI	✓	✓	✓	
PSQI Sub-scales	✓		✓	
CBCL (Sleep and Antisocial behaviours				✓
Age	✓	✓	✓	✓

Sex	✓	✓	✓	✓
Zygosity		✓	✓	✓
BMI		✓		
Depression/Anxiety		✓		
Educational attainment		✓		
Smoking		✓		
Physical activity		✓		

3.4 Analyses and design

Although this work uses twin samples for all the studies, the type of analysis varies from one study to other thanks to the versatility of twin registries. This section shows a brief summary of the main methods used.

3.4.2 Descriptive statistics and regression analyses

Descriptive analyses inform, in all the studies, about the characteristics of the sample (e.g., age, sex, mean/percentage value for the key variables). Study 1 (Madrid-Valero, Martinez-Selva, et al., 2017) uses logistic regression analyses in order to analyse the effect of age and gender on sleep quality (PSQI global score and PSQI sub-scales).

3.4.3 Co-twin control study

The co-twin control design is a sequential analysis where firstly the total sample is analysed, then discordant twin pairs (one of the members of the pair shows the outcome whilst the other one not), and finally the analyses of discordant pairs are stratified by zygosity. The co-twin control design allows for a high level of control for confounders,

especially in the last condition (i.e., MZ), since genetics and early shared environment are controlled. This kind of designs are an elegant and useful tool to study causal links between variables when experimental designs are not possible (e.g., for ethical reasons) (Vitaro, Brendgen, & Arseneault, 2009).

The logic of the co-twin designs can be summarized as follows. If the risk factor (in Study 2: sleep quality or BMI) causes the outcome (e.g., a disorder) then the likelihood of having the disorder for those subjects exposed to the risk factors should be similar in the whole sample and in the DZ and MZ discordant twins. On the other hand, if the relationship is not causal but due to confounding factors from shared environment, then the relationship will be significant in the whole sample but will lose significance in discordant pairs. Finally, if the relationship is due to genetic factors common to the predictor and the outcome, then the association will be significant in the general population but it will in turn become weaker and non-significant in MZ twin pairs, since they share 100% of their segregate DNA. The magnitude of these results depends on the degree of genetic influence (Kendler et al., 1993).

3.4.4 Behaviour genetics and twin studies

Behavioural genetics is a relatively new field of research. During the last decades there have been remarkable contributions from this discipline to psychology. One of the most important contributions has been the recognition of genetic influences to explain psychological traits or disorders (Knopik, Neiderhiser, DeFries, & Plomin, 2017; Turkheimer, 2000). This field has grown rapidly, as it can be seen in the progressive increase in the number of publications (Ayorech et al., 2016). Behavioural genetics has a wide variety of research strategies and designs such as adoption and twin studies, which are commonly known as quantitative genetics (Knopik et al., 2017). Twin studies are a

biological experiment which allows us to analyse to what extent variation in a phenotype is influenced by genetic factors. In that sense, twin registries have proved to be a wonderful tool for research since they are useful not only to separate genetic and environmental factors but also causal inference, multivariate genetic correlations or gene-environment interplay (Odintsova et al., 2018). As we have stated before, the main resource for this doctoral thesis has been twin registries, especially the MTR.

Twin studies make use of the difference between MZ twins (who share 100% of their segregating DNA) and DZ twins (who share on average 50% of their segregating DNA) and the fact that both share the same early environment to a similar extent. Therefore, if MZ are more similar than DZ twins in a trait, then we can conclude that this trait should be influenced by genetic factors. After decades of research, scholars have declared 4 laws in behavioural genetics (Chabris, Lee, Cesarini, Benjamin, & Laibson, 2015; Turkheimer, 2000): 1) "All human behavioural traits are heritable"; 2) "the effect of being raised in the same family is smaller than the effect of genes"; 3) "a substantial portion of the variation in complex human behavioural traits is not accounted for by the effects of genes or families"; and 4) "genetic effects are produced by a large number of genetic variants with a very small effect". Polderman et al., (2015) conducted a meta-analysis of the heritability of human traits virtually for all twin studies in the past 50 years. They found an average heritability value of 49% across all traits.

There is a recent important concern in Psychology about the replication of the studies (Ioannidis, 2005; Moonesinghe, Khoury, & Janssens, 2007). However, twin studies have some particularities that deserve to be addressed. Firstly, there is less publication bias in behavioural quantitative genetics since low and high heritability values would be equally interesting. Secondly, twin samples are usually larger in comparison

with other kinds of studies. Finally, it is difficult to find a variable in psychology that could explain 50% of the variance by itself as it happened on average for genetic influences (Plomin et al., 2016). Therefore, effect sizes are usually big.

3.4.4.1 Twin method

Classical twin designs make use of the difference between MZ and DZ twins to decompose the variance into genetic and environmental factors. Those components of the variance are: additive genetic influences (A) which are the sum of allelic effects across all loci; non-additive genetic influences (D) which refer to non-additive genetic effects, such as genetic dominance and epistasis, common-shared environment (C), which are the influences that make twin pairs raised in the same family similar to each other; and non-shared environment (E), which refers to the effects that make family members less alike (Neale & Cardon, 1992; Verweij, Mosing, Zietsch, & Medland, 2012).

In a classical twin design with twins reared together it is not possible to estimate C and D at the same time. C and D are negatively correlated (while C influences *increase* the DZ correlation relative to the MZ correlation, D *decreases* the DZ correlation relative to the MZ correlation). In order to calculate C and D in the same model, an extended model is needed (e.g., extended family designs) to satisfy the requirements of degrees of freedom for the analysis (Neale & Cardon, 1992; Verweij et al., 2012). Therefore, the selection of C or D in the different models is made based on the within-pair correlations patterns for MZ and DZ twins. Typically C is selected when the DZ twin correlation is greater than half of the MZ twin correlation and D is selected when the DZ twin correlation is less than half of the MZ correlation (Neale & Cardon, 1992; Verweij et al., 2012).

Univariate models allow us to estimate the extent of the genetic influence on a phenotype. This type of model was used in Study 2 (Madrid-Valero et al., 2018). In addition, in Study 4 (Madrid-Valero et al., 2019), multivariate models were used to estimate both individual variance and sources of covariance, in order to estimate the extent of the genetic and environmental overlap between phenotypes. In other words, these models allow us to know to what extent genes influencing one of the phenotypes are also influencing the other phenotype. For both univariate and multivariate models, nested models were tested in order to check if anyone of the variance components (i.e., A, C/D) could be dropped without a significant worsening of the model fit. The fit of the different models and submodels was checked using the likelihood-ratio chi-square test and Akaike's information criterion (AIC) (Akaike, 1987). In saturated models, assumptions of twin designs were tested in order to test for possible differences in means and variances between the different groups: MZ/DZ twins and twin order.

CHAPTER 4: MAIN RESULTS

In this section the main results of this doctoral thesis are summarized, while the complete findings can be consulted in more detail in Chapter 5. The obtained results reinforce the importance of sleep for health and also deepen in the knowledge about the genetic and environmental influences on sleep quality in a population where no studies of this kind had been previously carried out.

- Study 1: The objective of the first study was to describe sleep quality in the Spanish adult population. A high prevalence of poor sleep quality was found. Four out of ten (38.2%) participants in the study reported a poor sleep quality (PSQI score > 5). Our results also showed that women are more likely than men to have poor sleep quality (OR: 1.88; 95%CI: 1.54 to 2.28). Meanwhile, the prevalence of poor sleep quality stands at 30.1% for men it goes up to 44.6% for women. On the other hand, no differences were found for sleep duration. Almost the same value was found for sleep duration in men and women: 6.42 hours (SD=1.3) and 6.43 hours (SD=1.4) respectively. Menopausal status was tested as a possible relevant variable to explain the sex differences found, but the effect did not have any significant effect on sleep quality. There is a worsening of sleep quality in women between 45 and 50 years but the increase in sleep problems occurred for all groups of women regardless the menopausal status. Regarding age, a direct and significant relationship was found. In other words, sleep quality gets worse as age increases (OR: 1.05; 95%CI: 1.03 to 1.06). To sum up, this study found a high prevalence of poor sleep quality among the Spanish adult population. Furthermore, remarkable sex differences were found in sleep quality between men and women (e.g., women are more likely to use sleeping medication, experience sleep disturbances or have longer sleep latency). Finally, this study also highlights that age has a significant impact on sleep quality (Madrid-Valero, Martinez-Selva, et al., 2017).
- Study 2: In this study we aimed to disentangle the role of genetic and environmental factors on sleep quality. A classical twin design was performed to estimate the variance components. Regarding the PSQI global score, the best fit was provided by an AE model, where 34% of the variance was attributable to

genetic factors and the rest to non-shared environmental factors. In order to test for sex differences a sex-limitation model was also fitted but no differences between men and women were found. Regarding the components of sleep quality, substantial genetic influences (ranging from 30 to 45%) were found in all of them except for sleep efficiency. For sleep efficiency the variance was explained mainly by non-shared environmental factors (80%) and the rest (20%) by shared environment (Madrid-Valero et al., 2018).

- Study 3: This Study aimed to investigate the relationship between sleep quality and BMI. Those subjects with overweight/obesity showed poorer sleep quality than subjects with lower BMI ($\bar{x}$= 5.32; SD: 4.0 and $\bar{x}$= 4.62; SD: 3.7, respectively). In order to test causality and the directionality of the association, a double co-twin control design was performed. When BMI was taken as the outcome, its association with sleep quality was significant in all conditions: total sample (b = 0.098; 95% CI: 0.046, 0.150; *P*< 0.001), all discordant pairs (b = 0.173; 95% CI: 0.082, 0.263; *P*< 0.001), DZ discordant twins (b = 0.174; 95% CI: 0.067, 0.282;*P* = 0.002) and MZ discordant twins (b = 0.173; 95% CI: 0.001, 0.345; *P* = 0.050). However, when the outcome was sleep quality, the association with BMI showed a different pattern of results. As expected, the association in the total sample was similar (b = 0.075; 95% CI: 0.035, 0.115; *P*< 0.001). However, the analyses for discordant pairs on sleep quality yielded to non-significant results in all conditions: all discordant twin pairs (b = 0.021; 95% CI: -0.043, 0.086; *P* = 0.508), DZ twins (b = 0.028; 95% CI:-0.059, 0.114, *P* = 0.526) and MZ twins (b = 0.001; 95% CI: -0.094, 0.096; *P* = 984). This pattern of results suggests a causal influence of sleep quality on BMI, but not to the contrary. In summary, this study confirms the relationship between sleep quality and BMI, and points out to a

possible directional relationship where sleep quality has a significant impact on BMI (Madrid-Valero, Martínez-Selva, et al., 2017).

- Study 4: The fourth work of this doctoral thesis studied the relationship between a set of sleep variables and antisocial behaviour. Unlike the other studies, this one was carried out in a different sample, this time composed of children between 6 and 12 years. Our results showed that both aggression and rule-breaking are strongly related to sleep. All sleep variables were significantly associated with both rule-breaking (Cohen's effect ranged from 0.25 to 0.64) and aggression (Cohen's effect ranged from 0.28 to 0.77). The univariate models showed that all sleep variables (i.e., 'sleep less than most kids'; 'nightmares'; 'overtired'; 'sleep more than most kids'; 'talks or walks' and 'trouble sleeping' are under substantial genetic influence. The best fitting model for the sleep variables was and AE model, except for 'sleep more than most kids' where and ADE model provided the best fit. In summary, all these phenotypes were highly heritable ranging from 62 to 89%. Interestingly, we found a different pattern of associations between each sleep variable and the two dimensions of antisocial behaviour. Regarding aggression and sleep variables, the phenotypic correlations ranged from 0.15 to 0.42 and all the genetic correlations were significant ranging from 0.27 to 0.64. However, the environmental correlations were all non-significant except for 'sleep more than most kids' (−0.47, 95% CI: -0.70, -0.16). By contrast, for rule-breaking only two genetic correlations were significant: 'sleep more than most kids' (0.40, 95% CI: 0.25, 0.57) and 'trouble sleeping' (0.46, 95% CI: 0.18, 0.84) (Madrid-Valero et al., 2019).

All in all, these studies deepen in the complexity of sleep and specifically on sleep quality. This doctoral thesis sheds light on the underpinnings of sleep quality and the relationship with other variables. Furthermore, this work addressed these questions in populations with unique characteristics.

CHAPTER 5: PUBLICATIONS

5.1. List of publications

This doctoral thesis is based on the following studies published in journals indexed in the Science/Social Science Citation Index.:

- **Madrid-Valero, J. J.**, Martínez-Selva, J. M., Ribeiro do Couto, B., Sánchez-Romera, J. F., & Ordoñana, J. R. (2017). Age and gender effects on the prevalence of poor sleep quality in the adult population. *GacSanit, 31*(1), 18-22. doi:10.1016/j.gaceta.2016.05.013

- **Madrid-Valero, J. J.**, Martínez-Selva, J. M., & Ordoñana, J. R. (2017). Sleep quality and body mass index: a co-twin study. *J Sleep Res, 26*(4), 461-467. doi:10.1111/jsr.12493

- **Madrid-Valero, J. J.**, Sanchez-Romera, J. F., Gregory, A. M., Martinez-Selva, J. M., & Ordonana, J. R. (2018). Heritability of sleep quality in a middle-aged twin sample from Spain. *Sleep, 41*(9). doi:10.1093/sleep/zsy110

- **Madrid-Valero, J. J**., Ordoñana, J. R., Klump, K. L., & Burt, S. A. (2019). Children Sleep and Antisocial Behavior: Differential Association of Sleep with Aggression and Rule-Breaking. J Abnorm Child Psychol, 47(5), 791-799. doi:10.1007/s10802-018-0480-0

During the process of writing this thesis, the candidate has also participated in additional research. Although not oriented to the specific topic of this dissertation, they are indirectly related and have contributed greatly to the training process to become a PhD:

- Ordoñana, J. R., Sánchez Romera, J. F., Colodro-Conde, L., Carrillo, E., González-Javier, F., **Madrid-Valero, J. J**., . . . Martínez-Selva, J. M. (2018). [The

Murcia Twin Registry. A resource for research on health-related behaviour]. GacSanit, 32(1), 92-95. doi:10.1016/j.gaceta.2016.10.008

- Pinheiro, M. B., Morosoli, J. J., Ferreira, M. L., **Madrid-Valero, J. J.**, Refshauge, K., Ferreira, P. H., & Ordoñana, J. R. (2018). Genetic and Environmental Contributions to Sleep Quality and Low Back Pain: A Population-Based Twin Study. Psychosom Med, 80(3), 263-270. doi:10.1097/PSY.0000000000000548

- Lopez-Minguez, J., Dashti, H. S., **Madrid-Valero, J. J.**, Madrid, J. A., Saxena, R., Scheer, F. A., . . . Garaulet, M. (2018). Heritability of the timing of food intake. ClinNutr.. doi:10.1016/j.clnu.2018.03.002

- Perach, R., Allen, C. K., Kapantai, I., **Madrid-Valero, J. J.**, Miles, E., Charlton, R. A., & Gregory, A. M. (2018). The psychological wellbeing outcomes of nonpharmacological interventions for older persons with insomnia symptoms: A systematic review and meta-analysis. Sleep Med Rev, 43, 1-13. doi:10.1016/j.smrv.2018.09.003

- Carvalho-E-Silva, A. P. M. C., Harmer, A. R., Pinheiro, M. B., **Madrid-Valero, J. J**., Ferreira, M., Ordoñana, J. R., & Ferreira, P. H. (2019). Does the heritability of chronic low back pain depend on how the condition is assessed? Eur J Pain. doi:10.1002/ejp.1448

- **Madrid-Valero, J. J.,** Ronald, A., Shakeshaft, N., Schofield, K., Malanchini, M., Gregory, A. M. (In Press). Sleep quality, insomnia and internalising difficulties in adolescents: insights from a twin study. SLEEP

5.2. Study 1

Age and gender effects on the prevalence of poor sleep quality in the adult population

Juan J. Madrid-Valero[a], José M. Martínez-Selva[a,b], Bruno Ribeiro do Couto[a,b], Juan F. Sánchez-Romera[b,c] and Juan R. Ordoñana[a,b]

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Abstract.

Objective: Sleep quality has a significant impact on health and quality of life and is affected, among other factors, by age and sex. However, the prevalence of problems in this area in the general population is not well known. Therefore, our objective was to study the prevalence and main characteristics of sleep quality in an adult population sample. Methods: 2,144 subjects aged between 43 and 71 years belonging to the Murcia (Spain) Twin Registry. Sleep quality was measured by self-report through the Pittsburgh Sleep Quality Index (PSQI). Logistic regression models were used to analyse the results. Results: The prevalence of poor sleep quality stands at 38.2%. Univariate logistic regression analyses showed that women were almost twice as likely as men (OR: 1.88; 95% confidence interval [95%CI]: 1.54 to 2.28) to have poor quality of sleep. Age was directly and significantly associated with a low quality of sleep (OR: 1.05; 95%CI: 1.03 to 1.06). Conclusions: The prevalence of poor sleep quality is high among adults,

especially women. There is a direct relationship between age and deterioration in the quality of sleep. This relationship also appears to be more consistent in women.

Publication:

Madrid-Valero, J. J., Martínez-Selva, J. M., Ribeiro do Couto, B., Sánchez-Romera, J. F., & Ordoñana, J. R. (2017). Age and gender effects on the prevalence of poor sleepquality in the adult population. *GacSanit, 31*(1), 18-22.doi:10.1016/j.gaceta.2016.05.013

5.3. Study 2

Heritability of sleep quality in a middle-aged twin sample from Spain

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Abstract

Study Objectives: Sleep quality is associated with health throughout the life span, which is particularly salient in middle-age and older adulthood. Sleep quality appears to be influenced by both genetic and environmental factors. However, there is still limited information about genetic influences on sleep quality in middle-aged adults, and particularly in those from certain geographical locations. We estimated the magnitude of genetic and environmental influences on sleep quality in a representative sample of middle-aged Spanish twins.

Methods: The sample comprised 2150 individuals born between 1939 and 1966, who participate in the Murcia Twin Registry. To estimate the heritability of sleep quality variables, we performed univariate analyses for the global score on the Pittsburgh sleep quality index and for each of its components.

Results: We found moderate but significant heritability (34%) for sleep quality. The genetic variance of the components of the Pittsburgh index ranged from 30 to 45 per cent, except for sleep efficiency for which no genetic influence could be detected. In summary,

there was a moderate genetic influence on most dimensions of sleep quality in a sample of adult male and female twins. Shared environment influences were not found.

Conclusions: This study adds new information regarding the underlying determinants of sleep quality by providing heritability estimates in a middle-aged population-based representative sample from a geographical location that has not been included in studies of this type previously. This could provide a reference point for future research regarding sleep research in middle-age.

Publication:

Madrid-Valero, J. J., Sanchez-Romera, J. F., Gregory, A. M., Martinez-Selva, J. M., & Ordonana, J. R. (2018). Heritability of sleep quality in a middle-aged twin sample from Spain. *Sleep*, *41*(9). doi:10.1093/sleep/zsy110

5.4. Study 3

Sleep quality and body mass index: a co-twin study

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Abstract.

There is a consistent relationship between body mass index and sleep quality. However, the directionality and possible confounding factors of this relationship are unclear. Our aim is to confirm the association between sleep quality and body mass index, independent of possible genetic confounding, as well as to provide some indirect inferences about the directionality of this association. The co-twin study design was used to analyse the body mass index–sleep relationship in a sample of 2150 twins. We selected two parallel sub-samples of twins discordant for body mass index (n = 430 pairs), or discordant for sleep quality (n = 316 pairs). Sleep quality and body mass index showed an inverse relationship (b = 0.056, P = 0.032) in the global sample. When twins discordant for body mass index were selected, this association maintained a similar effect size and statistical significance, at all levels of the case–control analysis (all discordant pairs b = 0.173, P < 0.001; dizygotic twins b = 0.174, P = 0.002; monozygotic twins b = 0.173, P = 0.050). Nevertheless, when twin pairs were selected on the basis of their discordance for sleep quality, the association between body mass index and sleep quality appeared weaker and lost significance (b = 0.021, P = 0.508). The analyses including only dizygotic (b = 0.028, P = 0.526) or monozygotic (b = 0.001, P = 0.984) pairs produced similar non-significant

results. Our results confirm the relationship between sleep quality and body mass index, even after applying high levels of control, including genetic factors. Moreover, this study suggests a possible directionality of this relationship, such that sleep quality would strongly affect body mass index, while the opposite would be less robust and consistent in nonclinical samples.

Publication:

Madrid-Valero, J. J., Martínez-Selva, J. M., & Ordoñana, J. R. (2017). Sleep quality and body mass index: a co-twin study. *J Sleep Res, 26*(4), 461-467. doi:10.1111/jsr.12493

5.5. Study 4

Children Sleep and Antisocial Behavior: Differential Association of Sleep with Aggression and Rule-Breaking

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Abstract

There is a strong relationship between sleep and behavioral problems. These findings are often interpreted via environmental explanations, such that poor sleep directly exacerbates or causes symptoms of aggression and behavior problems. However, there are other possible explanations, such that the genes predicting poor sleep also predict aggression or rule-breaking. The current study sought to elucidate the origin of this relationship. The sample was composed of 1030 twin pairs (426 monozygotic and 604 dizygotic). The sample was 51.3% male with a mean age of 8.06 years (range 6–11.96; SD = 1.45). Aggression, rule-breaking and sleep were assessed through the Child Behavior Checklist (CBCL). We fitted bivariate Cholesky genetic models to the data, decomposing the variance within, and the covariance among, aggression, rule-breaking, and sleep functioning into their genetic and environmental components. Genetic correlations between all sleep variables and aggression were significant and moderate to large in magnitude, but mostly small and non-significant between sleep and rule-breaking. We did not find evidence of a causal or environmental relationship between the

majority of sleep variables and aggression, but rather clear evidence of genetic pleiotropy. However, the pattern of associations between rule-breaking and sleep measures was less consistent. Aggression and rule-breaking appear to be differentially associated with sleep.

Publication:

Madrid-Valero, J. J., Ordoñana, J. R., Klump, K. L., & Burt, S. A. (2019). Children Sleep and Antisocial Behavior: Differential Association of Sleep with Aggression and Rule-Breaking. J Abnorm Child Psychol, 47(5), 791-799. doi:10.1007/s10802-018-0480-0

CHAPTER 6: CONCLUSIONS

As stated previously, this doctoral thesis has addressed sleep quality using different methodologies and approaches. This work has 3 distinct, well differentiated parts which followed a logic course, answering these questions: “How is sleep quality in the Spanish population?; to what extent differences in sleep quality are due to genetic factors? and how does sleep quality relate with other variables?. In the first part, the prevalence of poor sleep quality was estimated in the Spanish population. The second part was aimed to study the underpinnings of the individual differences in sleep quality.

Finally, the third part was addressed to study the relationship between sleep quality and two different variables relevant for health and behaviour. All in all, these results highlight the importance and complexity of human sleep.

Despite sleep becoming an important concern in our society there were no studies about prevalence in the Spanish population. Study 1 (Madrid-Valero, Martinez-Selva, et al., 2017) found that the prevalence of poor sleep quality is quite high. Furthermore, sleep duration in this sample is lower on average than the 7-9 hours recommended for the National Sleep Foundation. In order to do that, a representative sample of the Spanish adult population was used. This study also found that the prevalence of poor sleep quality is much higher in women than in men. Furthermore, the reasons for having a poor sleep quality differ between men and women. Women usually mentioned partner snoring/noises or a care-giver role as important sources of sleep disturbance whereas men usually mentioned shift working or the emergence of age-related diseases (e.g. respiratory or prostatic). Age was another relevant factor for sleep quality. In this study it was found that sleep quality worsens with age. However, menopausal status did not have a significant impact on sleep quality per se since the same worsening was found at this age range regardless of menopausal status. As we have seen before, sleep problems are related to a plethora of negative adverse consequences and it involves a high burden for the society in terms of absenteeism, drugs and associated diseases.

The comparison with other studies is difficult due to the scarcity of studies in the Spanish general population. Results from outside Spain are consistent with ours finding, similar average scores of PSQI in different age ranges (Asghari et al., 2012; Knutson, Rathouz, Yan, Liu, & Lauderdale, 2006; Park et al., 2013). These results are also consistent with a poorer sleep quality in women than in men as it has been consistently

found across the literature (Ohayon & Sagales, 2010; Uhlig, Sand, Odegård, & Hagen, 2014; Zhang & Wing, 2006). Although menopausal status has been linked with the high prevalence of sleep problems in women (Xu et al., 2011), in our sample the effect of menopause was completely overshadowed by age. Age has been also linked to a worsening in the sleep quality (Ohayon et al., 2004), and our results are consistent with these findings showing that poor sleep quality worsens with age. This association appears to depend on evolutive changes occurring during adult life, which involve increasing vulnerability of the regulatory system of the sleep-wake rhythm (Carrier et al., 2002).

Therefore, the second part, Study 2 (Madrid-Valero et al., 2018) aimed to deepen into the knowledge about the underpinnings of sleep quality. The use of a large sample of adult twins allowed us to develop a classical twin design and also a sex-limitation analysis to test for possible sex differences in the variance distribution. The use of this design (sex-limitation) was motivated by the significant differences in the prevalence of poor sleep quality between men and women.

Our results showed that a high proportion of the variance in sleep quality —about one third, is explained by genetic factors. These results agree with previous research despite the unique environmental influences of the Spanish population. Moreover, no differences were found between males and females. These results are similar from those using different populations such as adolescents (Taylor et al., 2015), young adults (Barclay, Eley, Buysse, Archer, et al., 2010) or adults (Genderson et al., 2013). Despite the differences in the prevalence of poor sleep quality between men and women, the distribution of the variance was similar among them. To the best of our knowledge there are no studies that have reported differences in the heritability of sleep quality.

Regarding the components of sleep quality, all components showed a significant genetic influence except sleep efficiency. About 30-45% of the variance is explained by genetic factors whereas for sleep efficiency the common-shared environment has a significant effect although variance was mainly explained by environmental factors. These results are comparable with other studies in young adults (Barclay, Eley, Buysse, Rijsdijk, et al., 2010) ranging from 0.21 to 0.47 and in adults (Genderson et al., 2013) ranging from 0.23 to 0.34. However, we found that the best fitting model for "use of sleeping medication" was an AE model whereas Genderson et al., (2013) found a CE model. This discrepancy could be due to the use both men and women make in our sample as opposed to the cited study. Additionally, we did not find significant genetic influences for the component "efficiency".

These results highlight the importance of genetic factors to explain the individual differences in sleep quality. However, the main source of variation for sleep quality and its components were of environmental origin.

Further research, such as meta-analytic studies, is needed to corroborate these results and looking for possible moderators.

The last part of this doctoral thesis, examined the association between sleep and two different variables. In Study 3 (Madrid-Valero, Martínez-Selva, et al., 2017), the association between sleep quality and BMI was tested in a co-twin design. The relationship between sleep quality and BMI was confirmed in a large sample of adult twins. These results highlight the importance of an adequate sleep quality for our general health. A poorer sleep quality was associated with a higher BMI.

In addition, the directionality of this relationship was tested and the results suggested that, rather than a bidirectional relationship, sleep quality appears to influence

BMI whereas the reverse relationship is less clear. Our results confirm the strong relationship between poor sleep quality and BMI (Hung et al., 2013; Kim, 2015). Using a co-twin study, it was possible to test this relationship controlling for genetic and early common-shared environment and this relationship appears to be independent. Regarding the directionality of this association our results chimes with the previous literature. Thus, Seegers et al. (2011) found that short sleep duration influence BMI in a longitudinal study with preadolescents. Another study found that short sleep duration predicted future weight gain and incident obesity in women (Patel, Malhotra, White, Gottlieb, & Hu, 2006). Although a mutual influence cannot be completely discarded, our study extends the results to sleep quality since most of the studies were focused on sleep duration and reinforce the idea that disturbed sleep has a significant impact on BMI.

Finally, Study 4 (Madrid-Valero et al., 2019) examined the relationship between sleep and antisocial behaviour in a sample of children twins.

A strong relationship between different sleep characteristics and two dimensions of antisocial behaviour was found. Results showed that children with sleep problems have much higher levels of aggression and rule-breaking than children with an adequate sleep. These results are consistent with the previous studies in which sleep disturbances were associated with an increased probability of physical and verbal aggression, hostility and anger (Gregory & O'Connor, 2002; Randler & Vollmer, 2013; Sivertsen et al., 2015). To the best of our knowledge there are no studies that have investigated the relationship between sleep disturbances and these two measures of antisocial behaviour. Our results support the presence of common genetic pathways between poor sleep and aggression in children. On the other hand, the genetic overlap between sleep disturbances and rule-breaking was lower. These results highlight that the relationship between sleep

disturbances and aggression is more genetic in origin than the relationship between sleep disturbances and rule-breaking. Possible future research should address the identification of possible environmental factors or mediators that are influencing both sleep and antisocial behaviour.

To sum up, this doctoral thesis has studied sleep quality using different methodologies and different samples. The importance of sleep in different areas can be noticed across all these studies. Additionally, this doctoral thesis emphasizes sleep as a modifiable behaviour which has a wide variety of consequences in different fields. Treating sleep difficulties could improve other areas such as psychological disorders. Psychological treatments have shown to be an effective treatment choice and future research should investigate the effects of psychological sleep treatments in other areas. Further research should also expand these results using new methods such as molecular genetic designs.

CHAPTER 7: GLOBAL SUMMARY

Sleep quality is an essential variable for our health and cognitive functioning. Recent changes in our society have had a significant impact in our sleep quality and we are more and more aware about the importance of sleep for our health, which is at the same level as physical activity or diet. Therefore, sleep is nowadays getting more attention. Unhelpful attitudes such as “I will sleep when I am dead” or “sleep is a waste of time” have less and less impact in our society.

This doctoral thesis started with the objective of researching the genetic and environmental influences involved in sleep quality, and highlights the complexity of this phenotype and its importance for health and behaviour. To do so, this work uses several methodologies based on the resources provided by two twin registries: the MTR and the MSUTR. In that sense, it is a clear example of the versatility of twin registries. The studies that comprise this doctoral thesis have been published by journals indexed in international scientific repositories with impact factor.

Sleep quality has a significant impact in people's health and quality of life. Spanish population has unique characteristics such as siesta, use of a time zone displaced with respect to the sun, or later meal and bed times. However, data available about prevalence in the Spanish population was scarce and not updated. Therefore, Study 1 [Madrid-Valero, J. J., Martínez-Selva, J. M., Ribeiro do Couto, B., Sánchez-Romera, J. F., & Ordoñana, J. R. (2017). Age and gender effects on the prevalence of poor sleep quality in the adult population. *GacSanit*, 31(1), 18-22. doi:10.1016/j.gaceta.2016.05.013] addressed how sleep quality is among Spanish population and what effect factors such as age, sex or menopausal status have on such quality. To do so, a representative sample of the Spanish population was used. This sample was composed of 2144 participants of the Murcia Twin Registry. This sample comprises middle-aged (range 43-71) males and females. In order to measure sleep quality, the well-known PSQI questionnaire was used, which allowed us to ascertain both global sleep quality and each of its components (e.g., duration or latency). This Study found that a high percentage of the Spanish population (38,2%) has poor sleep quality (i.e., a score >5 points in the PSQI). In addition, women were almost twice as likely as men to have poor sleep quality. Age was another essential factor to explain sleep quality, as sleep quality worsens progressively as age increases. This pattern of worsening was

more stable for women than for men. All in all, these results show that there is a high prevalence of poor sleep quality in the Spanish population and that there are important differences due to sex and age.

Study 2 [Madrid-Valero, J. J., Sanchez-Romera, J. F., Gregory, A. M., Martinez-Selva, J. M., & Ordonana, J. R. (2018). Heritability of sleep quality in a middle-aged twin sample from Spain. *Sleep*, 41(9). doi:10.1093/sleep/zsy110] addressed the aetiology of the differences in sleep quality. Heritability informs us about the extent to which the differences in a trait are due to genetic factors and, indirectly, provides the same information about environmental ones. Therefore, it is a statistic that may vary from one population to another. These kinds of studies had been carried out previously but not in a Mediterranean country, such as Spain, with specific cultural characteristics related to sleep patterns. None of them had used a middle-aged sample of both sexes either. Therefore, the main objective of this study was to disentangle the role of genetic and environmental factors in a Spanish population and test for possible sex differences in the distribution of the variance. Our results showed that genetic factors explain a moderate proportion of the variance (34%), being the rest attributable to non-shared environmental factors. Furthermore, the Study found no sex differences. All PSQI components showed a substantial genetic influence (ranging from 30 to 45%) except sleep efficiency. Shared environment was only significant for sleep efficiency (20%). This Study adds novel information about the underpinnings of sleep quality, highlighting the consistency of the influence of genetic factors on sleep regardless of cultural conditions and sex.

Study 3 [Madrid-Valero, J. J., Martínez-Selva, J. M., & Ordoñana, J. R. (2017). Sleep quality and body mass index: a co-twin study. *J Sleep Res*, 26(4), 461-467. doi:10.1111/jsr.12493] addressed the analysis of the relationship between sleep and BMI.

This relationship had been previously studied but focusing on sleep duration rather than global sleep quality. Previous studies have shown that there is a strong relationship between sleep quality and BMI. However, the directionality of this relationship is not clear. In order to study this relationship, the Study conducted a co-twin control design which allowed for high levels of control (including genetic factors). The sample used was the same as in Study 1: 2150 participants in the MTR. When the influence of BMI on sleep quality was studied, a significant relationship in the whole sample was found. Nevertheless, when discordant twin pairs for sleep quality were selected this relationship appeared weaker and lost significance. On the contrary, when the influence of sleep quality on BMI was studied the relationship was significant in all conditions, including MZ twins discordant for BMI. These results confirm the strong relationship between sleep quality and BMI, suggesting a causal association and a possible directionality insofar sleep quality would strongly affect BMI, but not the other way around.

The last Study that conforms this doctoral thesis, Study 4 [Madrid-Valero, J. J., Ordoñana, J. R., Klump, K. L., & Burt, S. A. (2019). Children Sleep and Antisocial Behavior: Differential Association of Sleep with Aggression and Rule-Breaking. J Abnorm Child Psychol, 47(5), 791-799. doi:10.1007/s10802-018-0480-0] focused on studying the relationship between different characteristics of sleep and antisocial behaviour in children. Specifically, this study addressed the analysis of the genetic and environmental influences underlying the association between sleep characteristics and two dimensions of antisocial behaviour (aggression and rule-breaking). To do so, a sample of children twin pairs from the MSUTR, composed of 1030 twin pairs (range age 6-12y) was used. Sleep characteristics and the two dimensions of antisocial behaviour were measured trough the CBCL questionnaire. This study confirmed the strong association between sleep and antisocial behaviour in children. Higher values for

aggression and rule-breaking were found for those children with sleep problems (effect sizes between 0.25 and 0.77). All these phenotypes (i.e., six sleep variables and two dimensions of sleep) showed significant genetic influence (65% for aggression, 53% for rule-breaking and between 62% and 89% for sleep variables). However, the pattern of relationships between sleep and antisocial behaviour was different for each of those dimensions. A significant genetic overlap was found between aggression and sleep variables, whereas the genetic correlations between rule-breaking and sleep variables were mostly non-significant and of lower magnitude. On the contrary, the environmental correlations between sleep variables and the two dimensions of antisocial behaviour were non-significant in most of the cases. These results highlight the importance of sleep in order to explain antisocial behaviour, specifically aggression, in children. Furthermore, they showed that there is a significant genetic overlap between aggression and each sleep variable whereas this genetic overlap was lower for rule-breaking and most of the sleep variables.

On the whole, these four studies add novel information about sleep quality in the Spanish population and specifically deepen in the genetic and environmental influences on this phenotype. These results allow us to have a further knowledge about sleep quality, particularly in our country. The results obtained highlight the importance of sleep quality in different levels. Having a more precise knowledge about the aetiology of sleep quality will allow us to develop more effective and precise treatments and prevention programs that will help patients in both sleep quality and general health.

This doctoral thesis has been developed in the Faculty of Psychology of the University of Murcia with the collaboration of MTR and MSUTR. Short visits to other research centres both inside and outside Europe have been fundamental for a more

complete work and my training. These collaborations have been reflected in some of the articles that make up this thesis or related to. In addition, some studies derived from these short stays are currently in preparation or in review for publication.

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ANNEXES

Annex 1: Informed consents

Registro de Gemelos de Murcia

UNIVERSIDAD DE MURCIA

REGISTRO DE GEMELOS DE MURCIA

HOJA DE INFORMACIÓN Y CONSENTIMIENTO A PARTICIPAR

Registro de Gemelos de Murcia

El principal objetivo del Registro de Gemelos de Murcia es fomentar la investigación sobre la forma en que los factores genéticos y ambientales actúan conjuntamente sobre la salud y las conductas asociadas. En particular, la principal área de estudio se centra en los comportamientos relacionados con la prevención de enfermedades, por su importancia y por la relevancia que tienen en el bienestar de la persona.

¿Quién participa?

Este tipo de estudios compara las respuestas de hermanos gemelos según sean idénticos o mellizos. De esta forma se puede analizar la influencia de factores genéticos sobre el tema de interés. El hecho de que, casualmente, usted pertenezca a una pareja de gemelos hace que la información que pueda proporcionarnos sea muy valiosa para la ciencia.

Para esta investigación nos estamos poniendo en contacto con hermanos y hermanas gemelas nacidas o residentes en la Región de Murcia. Necesitamos recoger datos de muchas personas para que los resultados sean suficientemente fiables.

¿En qué consiste mi participación?

Consiste en responder a un cuestionario de salud periódicamente. Cada dos años, aproximadamente, nos pondremos en contacto con usted para hacerle una entrevista y recoger datos de salud (cuestionarios y/o medidas). En cada ocasión le explicaremos inicialmente en qué consistirá dicha entrevista y qué datos vamos a recoger. Así podrá usted decidir si sigue participando o no.

Sus datos de identificación (nombre, teléfono y dirección) serán incluidos en un Registro, con objeto de poder comunicar con usted y enviarle información por correo cuando sea necesario. Este Registro está notificado en la Agencia Española de Protección de Datos y, para la protección de esta información, cumple la normativa señalada por la *Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal*.

¿Es voluntario?

En el Registro de Gemelos participan solamente las personas que por libre voluntad desean hacerlo. Por otra parte, cualquier participante es libre de abandonar el Registro en cualquier momento sin necesidad de dar ninguna explicación y sin recibir ningún tipo de penalización. De la misma forma, puede negarse a responder a cualquiera de las preguntas por cualquier motivo sin necesidad de dar ninguna explicación.

Registro de Gemelos de Murcia

UNIVERSIDAD DE MURCIA

¿Qué se hará con la información que yo proporciono?

Toda la información que nos ofrezca, por cualquier vía (entrevista, cuestionario, carta,…) será tratada de forma estrictamente confidencial, y con el único objetivo de responder a preguntas de investigación científica. Sólo podrán usarse para este fin. Sus respuestas a los cuestionarios serán incluidas en una base de datos diferente. Su nombre no será incluido en esta base de datos y los técnicos que trabajen con estos datos no podrán relacionar las respuestas con las personas en ningún momento.

De acuerdo con la Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal le informamos que tiene usted derecho de acceso al fichero, rectificación y cancelación de sus datos, pudiendo ejercitar tales derechos mediante petición o solicitud dirigida a la Secretaría General de la Universidad de Murcia, como responsable del fichero, en la siguiente dirección: Avda. Teniente Flomesta 5 -30003 Murcia - España

¿Y si tengo alguna duda?

Puede usted ponerse en contacto con nosotros a través de los teléfonos 968-364262 o 968-367791 donde responderemos a cualquier duda relacionada con el Registro.

MUCHAS GRACIAS POR SU INTERES

Yo, D/Dña ……..

- Confirmo que se me ha dado una hoja informativa acerca del Registro de Gemelos de Murcia
- Confirmo que he recibido respuestas satisfactorias a todas mis preguntas sobre el Registro
- Muestro mi conformidad a participar en el Registro de Gemelos de Murcia en los términos mencionados
- Entiendo que toda la información concerniente a mi persona será tratada de forma estrictamente confidencial
- Entiendo que puedo abandonar el Registro en cualquier momento y por cualquier razón
- Entiendo que puedo negarme a responder cualquier pregunta por cualquier motivo.

Fecha: ……

Firma: ……..

DNI: ……..

Annex 2: Report from the ethic commission of the University of Murcia

INFORME DE LA COMISIÓN DE ÉTICA DE INVESTIGACIÓN DE LA UNIVERSIDAD DE MURCIA

Jaime Peris Riera, Catedrático de Universidad y Secretario de la Comisión de Ética de Investigación de la Universidad de Murcia,

CERTIFICA:

Que D. Juan José Madrid Valero ha presentado la Tesis Doctoral titulada *"Factores genéticos y ambientales implicados en la calidad del sueño"*, dirigida por D. Juan Ramón Ordoñana Martín a la Comisión de Ética de Investigación de la Universidad de Murcia.

Que dicha Comisión analizó toda la documentación presentada, y de conformidad con lo acordado el día cuatro de junio de dos mil dieciocho[1], por unanimidad, se emite INFORME FAVORABLE, desde el punto de vista ético de la investigación.

Y para que conste y tenga los efectos que correspondan firmo esta certificación con el visto bueno del Presidente de la Comisión.

Vº Bº
EL PRESIDENTE DE LA COMISIÓN
DE ÉTICA DE INVESTIGACIÓN DE LA
UNIVERSIDAD DE MURCIA

Fdo.: Francisco Esquembre Martínez

ID: 1974/2018

[1] A los efectos de lo establecido en el art. 19.5 de la Ley 40/2015 de 1 de octubre de Régimen Jurídico del Sector Público (B.O.E. 02-10), se advierte que el acta de la sesión citada está pendiente de aprobación

Annex 3: Murcia Twin Registry Questionnaire

VERSIÓN PRIMERA CITACIÓN

FACTORES GENÉTICOS Y AMBIENTALES EN EL DESARROLLO DE CARACTERES CONDUCTUALES COMPLEJOS

Cuestionario - 2009

A. DATOS DE REGISTRO

NIP |__|__|__|__| - |__|
Código del entrevistador |__|__|
Fecha de cumplimentación: Día |__|__| Mes |__|__| Año |__|__|__|__|
Hora de inicio de la entrevista: Hora |__|__| Minutos |__|__|

B. DATOS DEMOGRÁFICOS Y FAMILIARES

B.1. Sexo: **1.- Varón** **2.- Mujer** **B.2. Año de nacimiento: _____**

B.3. ¿Dónde ha residido usted desde su nacimiento? (Por periodos superiores a un año)

Municipio/Provincia/País	Duración (Años)

B.4. ¿Tiene algún hermano/a (con el que comparta al menos un padre o madre biológico)? (Sin contar a su hermana gemela)

1.- Si Nº de hermanos: _____ Nº de Hermanas: _____
2.- No
3.- No sabe

B.5. ¿Cuál es su orden de nacimiento dentro de la familia? (El del par de gemelas): _____

B.6. ¿Tiene algún familiar de primer grado con alguna discapacidad intelectual?

1.- Si Parentesco: _____ Grado de discapacidad (>33%, <60%, >65%): _____
2.- No

B.6. ¿De dónde procede su familia?

	Municipio/Provincia/País
Padre	
Madre	
Abuelo paterno	
Abuela paterna	
Abuelo materno	
Abuela materna	

BB.1. ¿Usted y su hermano/a se consideran?

1.- Gemelos/as idénticos 2.- Mellizos/as 3.- No estoy seguro/a

BB.2. ¿Han confirmado esta impresión con la ayuda de una prueba de cigosidad (análisis de sangre o de ADN)?

1.- Si 2.- No

BB.4. ¿Cuál de los dos nació primero?

1.- Yo nací primero 2.- Mi hermano/a gemelo nació primero 3.- No lo se

BB.5. ¿Cuál de los dos pesó más al nacer?

1.- Yo pesé más 2.- Mi hermano/a gemelo pesó más 3.- No lo se 4.- Igual

BB.6.¿Hasta qué punto eran su hermano/a y usted parecidos/as cuando eran niños en cuanto a…?

	Nada en absoluto	Algo (como dos hermanos normales)	Mucho
BB.6.1. Aspecto facial			
BB.6.2. Color natural de pelo			
BB.6.3. Color de la piel			
BB.6.4. Color de ojos			

BB.7. Dificultades de identificación *(Referido siempre a la infancia)*

	NO	SI
BB.7.1. ¿Eran ustedes idénticos/as cuando eran niños/as?		
BB.7.2. ¿En alguna ocasión su madre y su padre les confundían?		
BB.7.3. ¿En alguna ocasión otros miembros de la familia les confundían?		
BB.7.4. Las personas ajenas a la familia ¿Encontraban difícil diferenciarles?		

BB.8. ¿Cuántos gemelos hay en su familia? _____ pares (Sin incluirles a ellas) Hasta segundo grado (Primos, tíos, abuelos,…)

Anotar detalles:

_____

_____

_____

C. DATOS ANTROPOMÉTRICOS

C.1. Altura: _____ cm **C.2. Cintura:** _____ cm **C.3. Cadera:** _____ cm

C.3 ¿Cómo se siente actualmente con respecto a su peso?

1	2	3	4	5
Demasiado delgada	Algo delgada	Estoy bien	Algo de sobrepeso	Demasiado sobrepeso

C.4. ¿Le gustaría cambiar esa situación? (Sólo si han respondido 1 o 5)

1.- Si, mucho. He intentado cambiar (ganar o perder peso) tres veces o más.
2.- Si, algo. He intentado cambiar (ganar o perder peso) una o dos veces.
3.- Si. Pero no estoy dispuesta a hacer ningún esfuerzo
4.- No. Me encuentro bien así

C.5. ¿De qué color son sus ojos? 1.- Azul/gris 2.- Verde/Marrón claro 3.- Marrón

C.6. ¿Cuál es su color natural de pelo?

1.- Rubio 2.- Rojo 3.- Castaño claro 4.- Castaño oscuro 5.- Negro

C.7. ¿Es usted zurda o diestra? 1.- Zurda 2.- Diestra 3.- Ambidiestra

C.8. ¿Sabe cuánto peso al nacer?
1.- No 2.- Si ¿Cuánto? _____ gr

D. PREOCUPACIÓN POR LA SALUD Y CONDUCTAS DE PREVENCIÓN

D.1. ¿Hasta qué punto cree usted que se ha preocupado en el ÚLTIMO AÑO por su salud?

1.- Excesivamente 2.- Bastante 3.- Lo normal 4.- Poco 5.- Nada

D.2. Prácticas preventivas durante los DOS ÚLTIMOS AÑOS

	NO	SI	¿Hace cuanto fue la última vez?
1. ¿Se ha vacunado de gripe en la última campaña?	1	2	
2. ¿Le han hecho en los dos últimos años una citología vaginal?	1	2	
3. ¿Ha acudido al dentista para una revisión bucal durante los dos últimos años?	1	2	

D.3.A. ¿Ha acudido ALGUNA VEZ a realizarse una mamografía? 1.- Si 2.- No

D.3. ¿Ha acudido en los ÚLTIMOS DOS AÑOS a realizarse una mamografía? 1.- Si 2.- No

D.3.1. ¿Quién le recomendó que se la realizara?

1.- Lo solicité yo misma
2.- Me citaron desde el Programa de la Consejería/Asociación contra el Cáncer
3.- Me la recomendó mi ginecólogo particular
4.- Me la recomendaron en otro servicio público (Centro de Salud,...)

D.4. ¿Se ha realizado usted auto-exploración mamaria en los DOS ÚLTIMOS AÑOS? (Sólo si lo hace ella, no su médico)

1.- Sí. Sistemáticamente 2.- Si. Ocasionalmente 3.- Una o dos veces 3.- Nunca

D.5. ¿Cuando le dicen que debería hacerse una prueba para la detección precoz de una enfermedad (mamografía, analítica,...)...?

1.- Voy a hacérmela siempre sin ningún tipo de preocupación.
2.- Voy a hacérmela siempre, pero con preocupación
3.- La mayoría de las veces me la hago, aunque lo paso mal mientras espero el resultado
4.- La mayoría de las veces no me la hago o la retraso, porque lo paso mal mientras espero
5.- Casi nunca, o nunca me la hago.

E. PERCEPCIÓN DEL ESTADO DE SALUD Y CALIDAD DE VIDA

E.1. En los últimos 12 MESES, es decir, durante este año ¿cómo diría usted que ha sido su estado de salud?

1.- Muy bueno 2, Bueno 3.- Regular 4.- Malo 5.- Muy malo

Ahora vamos a preguntarle acerca de cómo se siente usted respecto a su salud. Voy a hacerle algunas cuestiones sobre cómo se siente HOY. Cada una de ellas tiene tres respuestas. Por favor, dígame cuál de las respuestas describe mejor su estado de salud en el día de HOY.

Primero voy a preguntarle sobre movilidad
E.2.1. Diría usted que
1. ... no tengo problemas para caminar
2. ... tengo algunos problemas para caminar
3. ... tengo que estar en la cama

Ahora le preguntaré acerca del cuidado personal
E.2.2. Diría usted que
1. ... no tengo problemas con el cuidado personal
2. ... tengo algunos problemas para lavarme o vestirme
3. ... soy incapaz de lavarme o vestirme

Ahora acerca de actividades cotidianas, como trabajar, estudiar, hacer las tareas domésticas, actividades familiares o actividades durante el tiempo libre
E.2.3. Diría usted que
1. ... no tengo problemas para realizar mis actividades cotidianas
2. ... tengo algunos problemas para realizar mis actividades cotidianas
3. ... soy incapaz de realizar mis actividades cotidianas

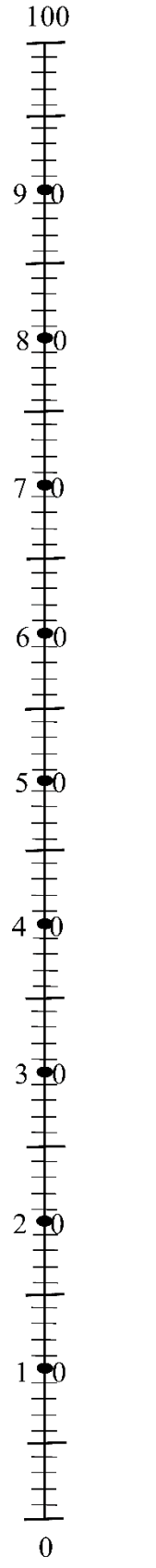
La siguiente pregunta se refiere al dolor o malestar
E.2.4. Diría usted que
1. ... no tengo dolor ni malestar
2. ... tengo moderado dolor o malestar
3. ... tengo mucho dolor o malestar

A continuación nos referimos a si se siente ansiosa o deprimida
E.2.5. Diría usted que
1. ... no estoy ansiosa ni deprimida
2. ... estoy moderadamente ansiosa o deprimida
3. ... estoy muy ansiosa o deprimida

E.2.6

Para ayudar a la gente a describir lo bueno o malo que es su estado de salud hemos dibujado una escala parecida a un termómetro en el cual se marca con un 100 el mejor estado de salud que pueda imaginarse y con un 0 el peor estado de salud que pueda imaginarse.

Nos gustaría que nos indicara en esta escala, en su opinión, lo bueno o malo que es su estado de salud en el día de HOY. Por favor, dibuje una línea desde el casillero donde dice "Su estado de salud hoy" hasta el punto del termómetro que en su opinión indique lo bueno o malo que es su estado de salud en el día de HOY.



Su estado de salud hoy

E.3. Comparado con su estado general de salud durante los últimos 12 meses, su estado de salud hoy es …

1 … mejor 2 … igual 3 … peor

F. EVENTOS Y ESTILOS DE VIDA

F.1. ¿Recuerda haber experimentado durante los ÚLTIMOS 5 AÑOS alguna experiencia vital que le haya resultado traumática? (Divorcio, accidentes, asaltos, fallecimiento de un ser querido, despidos,...) Recoger evento y tiempo aproximado cuando sucedió (Hace …. Años/meses)

A continuación vamos a iniciar el siguiente apartado de la encuesta, donde vamos a preguntarle sobre sus HÁBITOS DE VIDA. Para cada una de las preguntas, por favor diga la opción que mejor corresponda a su respuesta.

F.2. ¿Ha fumado usted alguna vez en su vida?

1.- No. Nunca 2.- En alguna ocasión, por probar 3.- Si

F21. ¿Durante cuantos años ha fumado/estuvo fumando usted?

_____ años

F22. ¿Fuma usted actualmente?

1.- Dejé de fumar y no he fumado desde _____
2.- Fumo una vez/semana o menos
3.- Fumo varias veces/semana pero no a diario
4.- Fumo diariamente

F23. ¿Cuántos cigarrillos fuma al día habitualmente?

_____ cigarrillos diarios

F.3.. ¿Ha tomado en alguna ocasión bebidas con alcohol (vino, cerveza o licores)?

1.- No. Nunca 2.- En alguna ocasión 3.- Si

F.3.2. ¿Toma usted bebidas con alcohol actualmente? (Incluye pequeñas cantidades)

1.- No bebo nada 3.- Algunas veces/año 5.- Algunas veces/mes 7.- Algunas veces/semana
2.- Una/año o menos 4.- Una/mes (aprox) 6.- Una/semana 8.- A diario

F.4. ¿Cuántas tazas de café o té toma habitualmente al día?

Café: _____ Café descafeinado: _____ Té: _____

F.5. ¿Cuál de estas posibilidades describe mejor su actividad principal en el centro de trabajo, centro de enseñanza, hogar (labores domésticas), etc.?

1.- Sentado la mayor parte del tiempo
2.- De pie la mayor parte de la jornada sin efectuar grandes desplazamientos o esfuerzos
3.- Caminando, llevando algún peso, efectuando desplazamientos frecuentes que no requieran gran esfuerzo físico
4.- Realizando tareas que requieren gran esfuerzo físico

F.6. ¿Qué tipo de ejercicio físico hace en su tiempo libre?

1.- No hago ejercicio. Mi tiempo libre lo ocupo casi completamente sedentario (leer, ver la TV, ir al cine, etc.)
2.- Alguna actividad física o deportiva ocasional (caminar o pasear en bicicleta, jardinería, gimnasia suave, actividades recreativas de ligero esfuerzo, etc.)
3.- Actividad física regular, varias veces al mes (tenis, correr, natación, ciclismo, juegos de equipo, etc.)
4.- Entrenamiento físico varias veces por semana

F.7. Por favor, responda a las siguientes preguntas en relación a sus hábitos de alimentación (TFEQ) (Clave: 4 - *Completamente cierto*; **3 –** *La mayoría de las veces cierto*; **2.-** *La mayoría de las veces falso*; **1 –** *Completamente falso*)

	Completamente cierto	La mayoría de las veces cierto	La mayoría de las veces falso	Completamente falso
1. Cuando huelo un buen filete o una jugosa pieza de carne, encuentro muy difícil abstenerme de comerlo, aún aunque haya comido ya.	4	3	2	1
2. Tomo deliberadamente pequeñas raciones como forma de controlar mi peso.	4	3	2	1
3. Cuando me siento ansioso/a como	4	3	2	1
4. A veces cuando empiezo a comer parece que no puedo parar	4	3	2	1
5. Estar con alguien que está comiendo a menudo me da hambre suficiente para comer yo también	4	3	2	1
6. Cuando me siento triste, a menudo como demasiado	4	3	2	1
7. Cuando veo una *delicatessen*, a menudo me da tanta hambre que tengo que comer	4	3	2	1
8. Me da tanta hambre que mi estómago a menudo parece un pozo sin fondo	4	3	2	1
9. Siempre tengo hambre, así que es difícil para mi dejar de comer hasta que termino toda la comida de mi plato	4	3	2	1
10. Cuando me siento solo/a, me consuelo comiendo	4	3	2	1
11. Conscientemente me contengo en las comidas para no ganar peso	4	3	2	1
12. No como algunos alimentos porque engordan	4	3	2	1
13. Siempre tengo hambre suficiente para comer a cualquier hora	4	3	2	1

14. ¿Con qué frecuencia siente hambre?

1.- Solo a la hora de las comidas 3.- A menudo entre comidas
2.- A veces entre comidas 4.- Casi siempre

15. ¿Con qué frecuencia evita tener alimentos apetecibles ("tentaciones") en casa?

1.- Casi nunca 3.- Habitualmente
2.- Pocas veces 4.- Casi siempre

16. ¿Qué probabilidad hay de que conscientemente coma menos de lo que quisiera?

1.- Improbable 3.- Moderadamente probable
2.- Poco probable 4.- Muy probable

17. ¿Se da atracones aunque no esté hambriento(a)?

1.- Nunca 3.- Alguna vez
2.- Raras veces 4.- Al menos una vez por semana

18. En una escala de 1 a 8 donde 1 significa no contenerse con la comida (comer lo que quiera, cuando quiera) y 8 significa una contención total (limitar constantemente la ingesta de alimentos y nunca rendirse), que número se daría a si mismo/a?: _____

G. HISTORIA REPRODUCTIVA

G.1. ¿A qué edad tuvo usted su primera menstruación? _____ años

G.2. ¿Quién tuvo primero su menstruación usted o su gemela?

1.- Yo 2.- Mi hermana 3.- No recuerdo 4.- Las dos a la vez

G.3. ¿Ha tenido usted hijos?

1.- No
2.- Si Nº de hijos biológicos _____ niños _____ niñas
Nº de hijos adoptivos _____ niños _____ niñas

G.3. ¿A qué edad tuvo el primer hijo? _____ años

G.4. ¿Dio usted el pecho a sus hijos?

1.- No
2.- Si

G.4.1. ¿Durante cuánto tiempo?

1º _____ meses	4º _____ meses	7º _____ meses
2º _____ meses	5º _____ meses	8º _____ meses
3º _____ meses	6º _____ meses	9º _____ meses

G.5. ¿Cuál fue el sexo de su primer hijo? 1.- Masculino 2.- Femenino

G.6. ¿Recuerda el motivo por el que dejo de dar el pecho al PRIMER hijo?

.....

.....

G.7. ¿Qué opinaba su pareja respecto a que le diera el pecho a su hijo/a? (El primer hijo/a)

1.- Le parecía bien 2.- Le daba igual 3.- No le gustaba

G.8. ¿Toma o ha tomado alguna vez píldoras anticonceptivas?

1.- Si lo estoy haciendo 2.- Si, las he tomado, pero ahora no 3.- No, nunca

G.9. ¿Ha comenzado/pasado ya la menopausia?

1.- No
2.- Si. De forma natural
3.- Si. Debido a tratamiento hormonal H.7.1. ¿A qué edad? _____ Años
4.- Si. Debido a cirugía/quimioterapia

G.10. ¿Quién tuvo los síntomas de menopausia primero, usted o su hermana?

1.- Yo 2.- Mi hermana 3.- No aplicable 4.- No se 5.- Las dos a la vez

(Si no ha comenzado la menopausia pasar a BLOQUE H)

MENCAV

G.7. A continuación le haré unas preguntas. Intente recordar con qué frecuencia ha presentado en los últimos 4 meses alguno de los síntomas que le mencionaré a continuación.
Podrá elegir entre 5 respuestas que serán: siempre, muy a menudo, a veces, casi nunca y nunca. No dude en preguntar si le surge alguna duda.

1	Dolores y calambres musculares	1 Siempre	2 Muy a menudo	3 A veces	4 Casi nunca	5 Nunca
2	Hormigueo en las manos	1 Siempre	2 Muy a menudo	3 A veces	4 Casi nunca	5 Nunca
3	Dolores de cabeza	1 Siempre	2 Muy a menudo	3 A veces	4 Casi nunca	5 Nunca
4	Dolores o molestias en la espalda	1 Siempre	2 Muy a menudo	3 A veces	4 Casi nunca	5 Nunca
5	Incapacidad para andar tanto como los demás	1 Siempre	2 Muy a menudo	3 A veces	4 Casi nunca	5 Nunca
6	Escozor al orinar	1 Siempre	2 Muy a menudo	3 A veces	4 Casi nunca	5 Nunca
7	Palpitaciones	1 Siempre	2 Muy a menudo	3 A veces	4 Casi nunca	5 Nunca
8	Sudores fríos	1 Siempre	2 Muy a menudo	3 A veces	4 Casi nunca	5 Nunca
9	Mareos	1 Siempre	2 Muy a menudo	3 A veces	4 Casi nunca	5 Nunca

G.8. En general cómo diría que es su salud en relación a antes de la menopausia …
1. Mucho mejor 2. Mejor 3. Más o menos igual 4. Peor 5. Mucho peor

G.9. Ahora le haré unas preguntas sobre cómo se siente usted consigo misma y sobre algunos aspectos de su vida *durante los últimos 4 meses*

1. Le resulta difícil concentrarse en sus tareas habituales	1 Muy frecuentem.	2 A menudo	3 A veces	4 Casi nunca	5 Nunca
2. Tiene la sensación de que todo se le viene encima	1 Constantemente	2 A menudo	3 A veces	4 Casi nunca	5 Nunca
3. Se nota nerviosa y a punto de explotar	1 Constantemente	2 A menudo	3 A veces	4 Casi nunca	5 Nunca
4. Ha notado que no puede hacer nada porque tiene los nervios desquiciados	1 Muy frecuentem.	2 A menudo	3 A veces	4 Casi nunca	5 Nunca
5. Se siente satisfecha de sí misma	1 Siempre	2 Muy a menudo	3 A veces	4 Casi nunca	5 Nunca
6. Piensa que haga lo que haga todo le sale mal	1 Siempre	2 A menudo	3 A veces	4 Casi nunca	5 Nunca
7. Se encuentra tan desanimada que no le apetece hacer nada	1 Muy frecuentem.	2 A menudo	3 A veces	4 Casi nunca	5 Nunca
8. Piensa que la vida no vale la pena vivirla	1 Muy frecuentem.	2 A menudo	3 A veces	4 Casi nunca	5 Nunca
9. Se siente triste y deprimida	1 Muy frecuentem.	2 A menudo	3 A veces	4 Casi nunca	5 Nunca

G.10. Las siguientes preguntas tratan acerca de su vida sexual *durante los últimos 4 meses* *(Estas preguntas se incluyen por la importancia de los cambios hormonales que ocurren a partir de cierto momento en la vida sexual. Le recordamos que puede dejarlas en blanco sin ningún problema si no se siente cómoda respondiendo)*

G.10.1. La frecuencia de sus relaciones sexuales:

1	2	3	4	5
Ha aumentado mucho	Ha aumentado algo	No se ha modificado	Ha disminuido algo	Ha disminuido mucho

G.10.2. Sus relaciones sexuales son:

1	2	3	4	5
Muy satisfactorias	Bastante satisfactorias	Satisfactorias	Poco satisfactorias	Nada satisfactorias

G.10.3. Se encuentra tan cansada que las relaciones sexuales no le apetecen:

1	2	3	4	5
Muy frecuentemente	A menudo	A veces	Casi nunca	Nunca

G.10.4. Ha perdido interés por sus relaciones sexuales:

1	2	3	4	5
Mucho	Bastante	Algo	Poco	Nada

G.11. Ahora le preguntaré sobre sus relaciones de pareja *durante los últimos 4 meses*

G.11.1. En relación con su pareja se encuentra:

1	2	3	4	5
Muy satisfecha	Bastante satisfecha	Algo satisfecha	Poco satisfecha	Nada satisfecha

G.11.2. Se considera necesaria como esposa:

1	2	3	4	5
Mucho	Bastante	Algo	Poco	Nada

G.11.3. En su marido confía:

1	2	3	4	5
Mucho	Bastante	Algo	Poco	Nada

G.11.4. Su marido le da oportunidades para opinar:

1	2	3	4	5
Muy frecuentemente	Con frecuencia	En algunas ocasiones	Me da pocas oportunidades	Nunca

G.12. En cuanto a sus relaciones sociales *durante los últimos 4 meses,* conteste a las siguientes preguntas

	1	2	3	4	5
1. ¿Visita a sus amistades habitualmente?	A diario.	Bastantes veces	Normalmente	Pocas veces	Nunca
2. ¿Encuentra con quién pasar sus ratos libres?	Siempre	Muy a menudo	A veces	Casi nunca	Nunca
3. ¿Suele ir a las actividades, charlas, etc. que se organizan en su localidad?	A todas	A bastantes	A algunas	A muy pocas	A ninguna
4. ¿Cómo considera su vida social?	Muy satisfactoria	Bastante satisfactoria	Satisfactoria	Poco satisfactoria	Nada satisfactoria
5. Sale a entretenerse	Siempre	Bastantes veces	Algunas veces	Pocas veces	Nunca
6. Sus relaciones sociales son	Muy buenas	Bastante buenas	Normales	Malas	Muy malas
7. ¿Le gusta estar rodeada de amigos?	Muy frecuentemente	A menudo	A veces	Casi nunca	Nunca
8. ¿Llama por teléfono a familiares y amigos?	Muy frecuentemente	A menudo	A veces	Casi nunca	Nunca

H. PITTSBURGH

Las siguientes preguntas hacen referencia a cómo ha dormido Vd. **normalmente durante el último mes**. Intente ajustarse en sus respuestas de la manera más exacta posible a lo ocurrido durante la **mayor parte** de los días y noches del **último mes**.

H.7. Durante el **último mes**, ¿Cuál ha sido, normalmente, su hora de acostarse?: _____

H.8. ¿Cuánto tiempo habrá tardado en dormirse, **normalmente**, las noches del **último mes**?: _____ minutos

H.9. Durante el **último mes**, ¿a qué hora se ha levantado **habitualmente** por la mañana?: _____

H.10. ¿Cuántas horas calcula que habrá dormido **verdaderamente** cada noche durante el **último mes**? (El tiempo puede ser diferente al que Vd. permanezca en la cama): _____ horas

H.11. Durante el **último mes**, cuántas veces ha tenido Vd. Problemas para dormir a causa de :

	Ninguna vez en el último mes	Menos de 1 vez a la semana	1 ó 2 veces a la semana	3 o más veces a la semana
1. No poder conciliar el sueño en la primera media hora				
2. Despertarse durante la noche o de madrugada				
3. Tener que levantarse para ir al servicio				
4. No poder respirar bien				
5. Toser o roncar ruidosamente				
6. Sentir frío				
7. Sentir demasiado calor				
8. Tener pesadillas o "malos sueños"				
9. Sufrir dolores				
10. Otras (especificar)_____				

H.12. Durante el **último mes**, ¿cómo valoraría, en conjunto, la calidad de su sueño?

1.- Bastante buena 2.- Buena 3.- Mala 4.- Bastante mala

H.13. Durante el **último mes**, ¿cuántas veces habrá tomado medicinas (por su cuenta o recetadas por el médico) para dormir?

1.- Ninguna vez en el último mes
2.- Menos de una vez a la semana
3.- Una o dos veces a la semana
4.- Tres o más veces a la semana

H.14. Durante el **último mes**, ¿cuántas veces ha sentido somnolencia mientras conducía, comía, o desarrollaba alguna otra actividad?

1.- Ninguna vez en el último mes
2.- Menos de una vez a la semana
3.- Una o dos veces a la semana
4.- Tres o más veces a la semana

H.15. Durante el **último mes**, ¿ha representado para Vd. mucho problema el "tener ánimos" para realizar alguna de las actividades detalladas en la pregunta anterior?

1.- Ningún problema
2.- Solo un leve problema
3.- Un problema
4.- Un grave problema

I. ANTECEDENTES MÉDICOS

I.1. ¿Ha padecido alguna enfermedad importante A LO LARGO DE SU VIDA? ¿En los últimos dos años? ¿Se lo ha dicho un médico?

_____

_____

(Tabla de codificación)

Enfermedad/es	I.A. ¿Ha padecido alguna vez alguna de ellas?		*En caso de respuesta afirmativa en la pregunta 16.A preguntar y anotar lo que proceda*			
			I.B. ¿La ha padecido en los últimos 2 años?		I.C. ¿Le ha dicho un médico que la padece?	
	Sí	No	Sí	No	Sí	No
I1.1.Dolor de espalda crónico (cervical)	1	2	1	2	1	2
I1.2. Dolor de espalda crónico (lumbar)	1	2	1	2	1	2
I1.3. Bronquitis crónica.	1	2	1	2	1	2
I1.4. Asma.	1	2	1	2	1	2
I1.5. Migraña o dolor de cabeza frecuente.	1	2	1	2	1	2
I1.6. Depresión, ansiedad u otros trastornos mentales	1	2	1	2	1	2
I1.7. Úlcera de estómago o duodeno.	1	2	1	2	1	2
I1.8. Alergia crónica.	1	2	1	2	1	2
I1.9. Problemas crónicos de piel.	1	2	1	2	1	2
I1.10. Anemia.	1	2	1	2	1	2
I1.11. Diabetes.	1	2	1	2	1	2
I1.12. Estreñimiento crónico.	1	2	1	2	1	2
I1.13. Problemas de tiroides.	1	2	1	2	1	2
I1.14. Colesterol alto.	1	2	1	2	1	2
I1.15. Tensión alta.	1	2	1	2	1	2
I1.H1. Infarto de miocardio.	1	2	1	2	1	2
I1.17. Otras enfermedades del corazón.	1	2	1	2	1	2
I1.18. Varices en las piernas.	1	2	1	2	1	2
I1.19. Artrosis, artritis o reumatismo.	1	2	1	2	1	2
I1.20. Hemorroides.	1	2	1	2	1	2
I1.21. Tumores malignos.	1	2	1	2	1	2
I1.22. Embolia.	1	2	1	2	1	2
I1.23. Cataratas.	1	2	1	2	1	2
I1.24. Incontinencia urinaria	1	2	1	2	1	2
I1.25. Osteoporosis	1	2	1	2	1	2
I1.26. Problemas de próstata (sólo hombres)	1	2	1	2	1	2
I1.27. Problemas del periodo menopáusico (sólo mujeres)	1	2	1	2	1	2
Otra (especificar) _____	1	2	1	2	1	2

I.2. Durante las DOS ÚLTIMAS SEMANAS ¿Ha tenido que reducir o limitar sus actividades habituales por algún dolor o síntomas

1.- No 2.- Si

Anotar comentarios:

_____

_____

J. USO DE SERVICIOS SANITARIOS

J.1. ¿Cuánto tiempo hace que consultó a un médico por última vez, por algún problema, molestia o enfermedad suya?

1.- Nunca he ido al médico
2.- Hace un año o más
3.- Hace > 4 semanas y < 1 año
4.- Hace 4 semanas o menos
J.1.1. Médico de familia/Último mes _____ veces
J.1.2. Especialista/Último mes _____ veces

J.2. Durante los últimos DOCE MESES ¿ha tenido que ingresar en un hospital como paciente al menos durante una noche?

1.- No 2.- Si ¿Cuántas veces? _____- veces

Anotar comentarios:

_____

_____

K. CONSUMO DE MEDICAMENTOS

K.1. En el ÚLTIMO MES ¿ha utilizado algún tipo de medicamento (gotas, pastillas, inyecciones, supositorios, etc…? ¿Se los había recetado un médico?

_____

_____

Medicamentos	Medicamentos consumidos		Medicamentos recetados	
	Sí	No	Sí	No
1. Medicinas para el catarro, gripe, garganta, bronquios.	1	2	1	2
2. Medicinas para el dolor.	1	2	1	2
3. Medicinas para la fiebre.	1	2	1	2
4. Reconstituyentes como vitaminas, minerales, tónicos.	1	2	1	2
5. Laxantes.	1	2	1	2
6. Antibióticos.	1	2	1	2
7. Tranquilizantes, relajantes, pastillas para dormir.	1	2	1	2
8. Medicamentos para la alergia.	1	2	1	2
9. Medicamentos para la diarrea.	1	2	1	2
10. Medicinas para el reuma.	1	2	1	2
11. Medicinas para el corazón	1	2	1	2
12. Medicinas para la tensión arterial.	1	2	1	2
13. Medicinas para el estómago y/o las alteraciones digestivas.	1	2	1	2
14. Antidepresivos, estimulantes.	1	2	1	2
15. Píldoras para no quedar embarazadas (sólo para mujeres)	1	2	1	2
16. Hormonas para la menopausia.	1	2	1	2
17. Medicamentos para adelgazar.	1	2	1	2
18. Medicamentos para bajar el colesterol	1	2	1	2
19. Medicamentos para la diabetes.	1	2	1	2
20. Otros medicamentos	1	2	1	2
21. Productos homeopáticos.	1	2		
22. Productos naturistas.	1	2		

K.2. Cuestionario Adherencia SMAQ. Sólo si ha tomado medicación durante el último mes recetada por un médico

	Sí	No
K.2.1. ¿Alguna vez ha olvidado tomar la medicación?	1	2
K.2.2. ¿Toma siempre los fármacos a la hora indicada?	1	2
K.2.3. ¿Alguna vez ha dejado de tomar los fármacos si se siente mal (por el fármaco)?	1	2
K.2.4. ¿Ha olvidado tomar la medicación durante el fin de semana?	1	2

K.2.5. En la última semana de tratamiento, ¿Cuántas veces no tomo alguna dosis?
A.- Ninguna B.- 1-2 C.- 3–5 D: 6–10 E: Más de 10

K.2.6. Durante la última semana de tratamiento, ¿Cuántos días completos no tomo la medicación? Días: ____

L. IDER

A continuación se presentan unas frases que la gente usa para describirse a sí misma. Por favor rodee con un círculo el número que más se aproxime a cómo se siente EN ESTE MOMENTO y GENERALMENTE. No hay respuestas correctas e incorrectas. No emplee demasiado tiempo en cada frase.

EN ESTE MOMENTO…	Nada	Algo	Bastante	Mucho		GENERALMENTE…	Casi nunca	A veces	A menudo	Casi siempre
1. Me siento bien	1	2	3	4		11. Disfruto de la vida	1	2	3	4
2. Estoy apenada	1	2	3	4		12. Me siento desgraciada	1	2	3	4
3. Estoy decaída	1	2	3	4		13. Me siento plena	1	2	3	4
4. Estoy animada	1	2	3	4		14. Me siento dichosa	1	2	3	4
5. Me siento desdichada	1	2	3	4		15. Tengo esperanzas sobre el futuro	1	2	3	4
6. Estoy hundida	1	2	3	4		16. Estoy decaída	1	2	3	4
7. Estoy contenta	1	2	3	4		17. No tengo ganas de nada	1	2	3	4
8. Estoy triste	1	2	3	4		18. Estoy hundida	1	2	3	4
9. Estoy entusiasmada	1	2	3	4		19. Me siento triste	1	2	3	4
10. Me siento enérgica	1	2	3	4		20. Me siento enérgica	1	2	3	4

M. DATOS DE CARACTERIZACIÓN

M.1.- ¿Está usted casada o tiene una pareja estable actualmente?

1.- No
2.- Si. Vivimos juntos ¿Cuánto tiempo? _____ años _____ meses
3.- Si. No vivimos juntos

M.1.B.- ¿Ha estado casada o ha tenido pareja estable anteriormente?

1.- No
2.- Sí. La relación terminó (se rompió) → Duración de la última relación: _____ años
3.- Si. La relación terminó por fallecimiento de la pareja → Año de finalización de la relación: _____

Anotar comentarios: _____

M.2. ¿Cuál es su situación laboral actual?

1.- En paro
2.- Estudiante/opositor
3.- Ama de casa
4.- Trabajador autónomo
5.- Empresario (Hasta 10 empleados)
6.- Empresario (Más de 10 empleados)
7.- Trabajo por cuenta ajena
8.- Funcionario
9.- Jubilado

M.3.- ¿Cuál es el mayor nivel de estudios que ha alcanzado?

_____

M.4.- ¿Cuál es su ocupación, profesión u oficio actual o el último que ha tenido?

_____

MUCHAS GRACIAS POR SU PARTICIPACIÓN

Annex 4: Authors contribution to each study

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Juan José Madrid Valero, doctorando de la Facultad de Psicología con el propósito de presentar la Tesis Doctoral, titulada "Genetic and environmental factors involved in sleep quality" en la modalidad de compendio de publicaciones

INFORMA

De su aportación en los siguientes artículos que la componen:

- Madrid-Valero, J. J., Martínez-Selva, J. M., Ribeiro do Couto, B., Sánchez-Romera, J. F., & Ordoñana, J. R. (2017). Age and gender effects on the prevalence of poor sleep quality in the adult population. *Gac Sanit*, *31*(1), 18-22. doi:10.1016/j.gaceta.2016.05.013

  La contribución en este estudio consistió en la participación en el diseño del estudio, búsqueda bibliográfica, análisis de datos, descripción e interpretación de los resultados y elaboración del manuscrito, siendo todos estos pasos supervisados.

- Madrid-Valero, J. J., Martínez-Selva, J. M., & Ordoñana, J. R. (2017). Sleep quality and body mass index: a co-twin study. *J Sleep Res, 26*(4), 461-467. doi:10.1111/jsr.12493

  La contribución en este estudio consistió en la participación en el diseño del estudio, búsqueda bibliográfica, análisis de datos, descripción e interpretación de los resultados y elaboración del manuscrito, siendo todos estos pasos supervisados.

- Madrid-Valero, J. J., Sanchez-Romera, J. F., Gregory, A. M., Martinez-Selva, J. M., & Ordonana, J. R. (2018). Heritability of sleep quality in a middle-aged twin sample from Spain. *Sleep, 41*(9). doi:10.1093/sleep/zsy110

  La contribución en este estudio consistió en la participación en el diseño del estudio, búsqueda bibliográfica, análisis de datos, descripción e interpretación de los resultados y elaboración del manuscrito, siendo todos estos pasos supervisados.

- Madrid-Valero, J. J., Ordoñana, J. R., Klump, K. L., & Burt, S. A. (2018). Children Sleep and Antisocial Behavior: Differential Association of Sleep with Aggression and Rule-Breaking. *J Abnorm Child Psychol.* doi:10.1007/s10802-018-0480-0

  La contribución en este estudio consistió en la participación en el diseño del estudio, búsqueda bibliográfica, análisis de datos, descripción e interpretación de los resultados y elaboración del manuscrito, siendo todos estos pasos supervisados.

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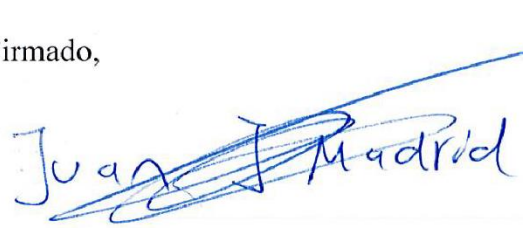

D. Juan José Madrid Valero

V°B°. Director de la tesis

Dr. Juan Ramón Ordoñana Martín