Maite Ruiz Goikoetxea

Riesgo de lesiones no intencionadas y envenenamientos en niños y adolescentes con Trastorno por Déficit de Atención e Hiperactividad, y el efecto protector de la medicación

TESIS DOCTORAL

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Dr. D. César A. Soutullo Esperón

Dr. D. Samuele Cortese

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Los doctores Don César A. Soutullo Esperón y Don Samuele Cortese

CERTIFICAN QUE

El trabajo de investigación titulado "*Riesgo de lesiones no intencionadas y envenenamientos en niños y adolescentes con Trastorno por Déficit de Atención e Hiperactividad, y el efecto protector de la medicación*", del que es autora Dª Maite Ruiz Goikoetxea, ha sido realizado bajo su dirección y se encuentra en condiciones de ser presentado para su lectura y defensa ante el tribunal correspondiente, para que su autora obtenga el grado de Doctor.

Y para que conste a todos sus efectos, firma este documento en Pamplona a 16 de agosto de 2018.

Dr. D. César Soutullo Esperón

Dr. D. Samuele Cortese

Para Gonzalo, Juan y Martín

Para mi padre y mi madre

"*Decía Bernardo de Chartres que somos como enanos aupados a hombros de gigantes, de manera que podemos ver más cosas y más lejanas que ellos, no por la agudeza de nuestra vista o por nuestra elevada estatura, sino porque estamos alzados sobre ellos y nos elevamos sobre su altura gigantesca" (*Juan de Salisbury).

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Prólogo

La presente tesis ha sido estructurada según la normativa de compendio por publicaciones e incluye un total de 5 publicaciones, 4 de ellas indexadas (tres publicadas en revistas en el primer cuartil de la especialidad), así como el registro público de un protocolo. Todos los manuscritos han sido supervisados y aprobados por los Dres. César Soutullo Esperón, Director de la Unidad de Psiquiatría Infantil y del Adolescente de la Clínica Universidad de Navarra y Samuele Cortese, psiquiatría infantil en el NHS Solent Trust en Southampton (Reino Unido), profesor en la Universidad de Southampton y Nottingham (Reino Unido) y en la Universidad de Nueva York (Estados Unidos). Es el reflejo de un proyecto de 3 años de duración que se inició oficialmente en octubre de 2015, pero que empezó a perfilarse en Cambridge (Reino Unido) en Enero de 2014, con la dirección del trabajo de fin de máster por parte del Dr. Cortese, quien finalmente ha sido el codirector de esta tesis doctoral. A este trabajo le fue concedida una ayuda a la investigación del Departamento de Salud del Gobierno de Navarra en diciembre de 2016.

La realización de este trabajo ha permitido a la doctoranda la oportunidad de desarrollar sus capacidades como investigadora, enriquecer sus conocimientos y colaborar con profesionales de distintos campos de la investigación con los cuales emprender futuros proyectos.

- La primera publicación se titula "**Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: protocol for a systematic review and meta-analysis"** La doctoranda Maite Ruiz Goikoetxea, junto con los Dres. Soutullo, Cortese y Arrondo fueron los responsables de la hipótesis y del diseño metodológico del trabajo. Otros coautores de la Facultad de Educación y Psicología de la Universidad de Navarra y de la Unidad de Psiquiatría Infantil y del Adolescente de la Clínica Universidad de Navarra, contribuyeron con sus comentarios y sugerencias a enriquecer el manuscrito final. Siguiendo los consejos del revisor del proyecto de tesis en relación a las recomendaciones de las guías vigentes en la metodología de revisiones sistemáticas y metanálisis; el protocolo de este estudio fue registrado en PROSPERO, registro internacional prospectivo de protocolos de revisiones sistemáticas de la Universidad de York (Reino Unido). El trabajo fue presentado en el congreso anual de la Asociación Española de Psiquiatría del Niño y del Adolescente en junio de 2017 y publicado en la revista British Medical Journal Open (BMJ Open) en septiembre de 2017.
- La segunda publicación lleva por título **"Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: A systematic review and meta-analysis"**. La doctoranda Maite Ruiz Goikoetxea, junto con los Dres.

Soutullo, Cortese y Arrondo fueron los responsables de la hipótesis y del diseño del trabajo. Todo el proceso de selección, extracción de datos y análisis del riesgo de sesgos se realizó por duplicado siendo la doctoranda una de los dos investigadores que participaba en cada una de las fases. El análisis estadístico de los datos fue realizado gracias a la ayuda de los doctores Aznárez Sanado y Arrondo. Otros coautores de la Facultad de Psicología de la Universidad de Navarra y de la Unidad de Psiquiatría Infantil y del Adolescente de la Clínica Universidad de Navarra contribuyeron en la extracción duplicada de los datos además de con sus sugerencias en la redacción del manuscrito final. El artículo fue publicado en Neuroscience & Biobehavioral Reviews en enero de 2018, con un factor de impacto de 8.29, revista que se encuentra en primer decil de las revistas de Neurociencia. La comunicación oral de estos resultados recibió el premio a la mejor comunicación oral en la Reunión Científica de la Sociedad Vasco Navarra de Pediatría, celebrada en Pamplona el 2 de marzo de 2018.

- La tercera publicación presentada se titula ***"Risk of poisoning in children and adolescents with Attention Deficit Hyperactivity Disorder".*** Se trata del registro en PROSPERO del protocolo de la segunda parte de esta tesis doctoral. Si bien no es una publicación indexada hemos considerado oportuno incluirla porque el registro público del protocolo de una revisión sistemática es una medida de transparencia y reducción del riesgo de sesgo. Además, incluye una descripción detallada de la metodología que posteriormente se siguió. La doctoranda Maite Ruiz Goikoetxea, junto con los doctores Soutullo, Cortese y Arrondo fueron los responsables de la hipótesis del estudio y del diseño del manuscrito. El resto de autores contribuyeron con sus comentarios y aprobaron el protocolo final. El registro en PROSPERO (CRD42017079911) se efectuó el 23 de noviembre de 2017.
- La cuarta publicación lleva por título **"Risk of poisoning in children and adolescents with ADHD: a systematic review and meta-analysis"**. La doctoranda Maite Ruiz Goikoetxea, junto con los Dres. Soutullo, Cortese y Arrondo fueron los responsables de la hipótesis y del diseño del trabajo. El proceso de selección, extracción de datos, evaluación de calidad y sesgos de los estudios se realizó por dos investigadores de forma independiente, participando siempre la doctoranda en cada una de las fases. El análisis estadístico de los datos fue realizado gracias a la ayuda de los Dres. Aznárez Sanado y Arrondo. Otros coautores de la Facultad de Psicología de la Universidad de Navarra y de la Unidad de Psiquiatría Infantil y del Adolescente de la Clínica Universidad de Navarra, contribuyeron en la extracción de los datos y aportaron comentarios que aumentaron la solidez del manuscrito final. Los resultados del estudio se presentaron en el congreso anual de la Asociación Española de Psiquiatría

del Niño y del Adolescente en junio de 2018 y se publicó en la revista Scientific Reports en mayo de 2018. Esta revista tiene un factor de impacto de 4.257 y está en el primer cuartil de las revistas de su especialidad.

- La última publicación, titulada ***"Trastorno por déficit de atención e hiperactividad como factor de riesgo en intoxicaciones y lesiones no intencionadas",*** es una carta al editor publicada en la revista de la Asociación Española de Pediatría cuyo objetivo era llamar la atención de los pediatras españoles sobre los resultados de la investigación, dado el papel de los mismos en la detección precoz y manejo del TDAH. La idea inicial y diseño fue realizado por la doctoranda y los demás coautores, los Dres. Soutullo, Cortese y Arrondo, aportaron comentarios constructivos y aprobaron el manuscrito final. Fue publicado en Anales de Pediatría (factor de impacto de 1.14) en febrero de 2018.

1. Introducción

1.1. Trastorno por déficit de atención e hiperactividad

1.1.1. Historia

En la literatura científica se describieron los primeros esbozos del trastorno por déficit de atención e hiperactividad (TDAH) hace casi 2 siglos. En 1798, Alexander Crichton describía el estado de agitación e inquietud mental que ocurría en ciertos niños, y sus consecuencias en el rendimiento escolar (Palmer & Finger 2001; Crichton 1798). En una interesante revisión sobre la historia del TDAH en la literatura médica, se comparaban los criterios diagnósticos del TDAH en la cuarta edición del Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), con los comportamientos referidos por Crichton (Lange et al. 2010). Si bien Crichton no describió todas las características definitorias del TDAH, sus aportaciones son una evidencia de la existencia del trastorno desde finales del siglo XVIII.

Sin embargo, no encontramos la primera descripción clara de un niño con TDAH hasta 1845, cuando el escritor y psiquiatra alemán Heinrich Hoffman público su obra Der Struwwelpeter ("Pedro Melenas"); obra ilustrada en verso destinada al público infantil (Hoffman, 2015; Hoffmann, 1948). En uno de los capítulos se narraba la historia de Zappel Philip (Fidgety Phil en inglés o Felipe el enredador). Este es un niño con "mal comportamiento", en el que se aprecian claros síntomas de inatención e hiperactividad, que hoy día podría cumplir los criterios de TDAH hiperactivo-impulsivo.

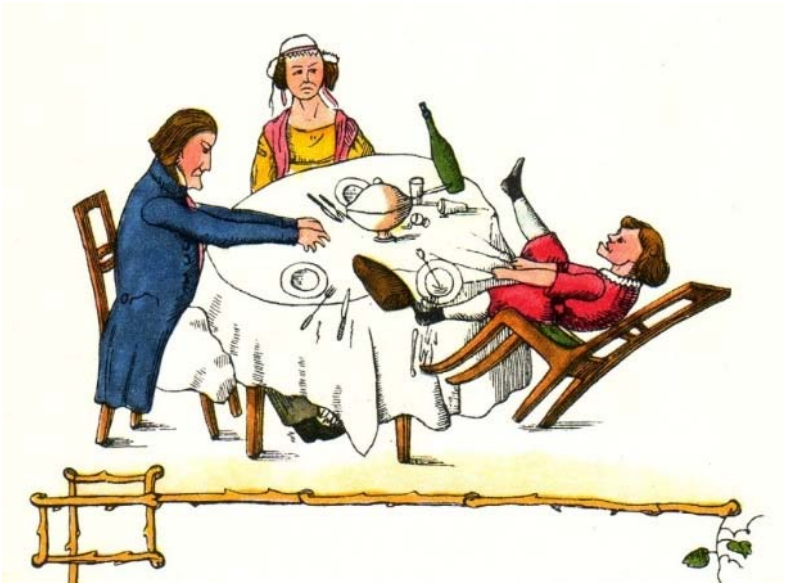

Figura 1. Ilustración en la que se muestra a Philip, que no está sentado en la mesa y a pesar de las advertencias de sus padres, él no escucha y finalmente cae de la silla arrastrando vajilla y mantel (Zappel-Philipp, ilustración de la edición de 1945, vía Wikimedia Commons: https://commons.wikimedia.org/wiki/File:Struwwelpeter_2.jpg)

En el año 1902 Sir George Still describía dificultades en la atención sostenida, conductas de oposición a la norma, así como problemas de desinhibición y comportamiento agresivo en una serie de pacientes (Still, 2006, 1902). En sus escritos relataba que ninguno de los pacientes que presentaba dificultades en el control de las acciones presentaba un retraso mental asociado que pudiese ser la casusa de los síntomas. Esta descripción es para muchos autores la primera descripción científica del TDAH.

En España la primera descripción clara del TDAH la encontramos en el año 1917, cuando Gonzalo Rodríguez-Lafora, neurólogo y psiquiatra español público su obra "Los niños mentalmente anormales". La descripción de los síntomas de los niños que aparece en su libro cumpliría los criterios de lo que hoy conocemos como TDAH. Además, fue el primer autor que relacionó el TDAH con un problema cerebral con una base genética (Rodríguez-Lafora, 1917).

Posteriormente, en 1932 Franz Kramer y Hans Pollnow diferenciaron por primera vez el trastorno hipercinético de la infancia (Kramer and Pollnow, 1932; Lange et al., 2010; Neumärker, 2005). Si bien los síntomas de este trastorno habían sido descritos anteriormente, hasta esa fecha no se habían agrupado y diferenciado de otras entidades que presentasen una clínica similar. Esta fue la primera vez que ser reconocía el trastorno hipercinético como un trastorno independiente. En sus escritos Kramer y Pollnow observaban que la sintomatología era únicamente diurna y que presentaba un pico de incidencia a los 6 años de edad.

1.1.2. Definición actual

La definición más reciente del TDAH (DSM-5) lo describe como un trastorno del neurodesarrollo, caracterizado por un patrón de inatención y/o hiperactividad o impulsividad que tiene un impacto en varias esferas de la vida del individuo (American Psychiatric Association, 2013). Estos síntomas deben producirse en mayor intensidad que en niños de la misma edad, estar presentes durante al menos 6 meses, con un inicio antes de los 12 años de edad, y deben producir alteraciones en el funcionamiento del individuo en al menos dos ambientes (por ejemplo escolar o laboral, social o familiar).

Hasta ahora en la Clasificación Estadística Internacional de Enfermedades (CIE-10) de la Organización Mundial de la Salud (OMS), los síntomas del TDAH se incluían dentro de los "trastornos hipercinéticos" (World Health Organization, 1992); sin embargo en la próxima de actualización de esta clasificación (CIE-11) que se espera que sea publicada en Mayo de 2019, el TDAH aparecerá dentro de la categoría general de "trastornos del neurodesarrollo".

1.1.3. Epidemiología

El TDAH, trastorno del neurodesarrollo más frecuente en niños y adolescentes, presenta una prevalencia mundial estimada entre 3-5% siendo entre 3-4 veces más común en varones (Biederman

and Faraone, 2005; Polanczyk et al., 2015). Entre el 25 y el 50% por ciento de los niños y adolescentes con TDAH presentan síntomas en la edad adulta; siendo la prevalencia total en este rango algo menor (en torno a 2.5%) a la encontrada en la infancia y adolescencia.(Cortese et al., 2016a; Kooij et al., 2010). Sin embargo, las manifestaciones de los síntomas varían entre los distintos grupos de edad. Tanto los niños como los adultos comparten los síntomas de la inatención, hiperactividad e impulsividad. No obstante, la hiperactividad es el síntoma que más disminuye con la edad, y tanto la inatención como la impulsividad tienden a conservarse (Ramos-Quiroga et al., 2006). Se ha encontrado que los adultos con TDAH presentan marcada impulsividad emocional y problemas en la autorregulación emocional (Faraone et al., 2018)

1.1.4. Etiología y neurobiología

El TDAH es un trastorno de origen multifactorial en el que intervienen factores genéticos y ambientales. Se sabe que es un trastorno de origen genético porque es más frecuente (3-4 veces más común) en los familiares de primer grado de los pacientes con TDAH (Neale et al., 2010). Es más concordante entre gemelos homocigóticos que heterocigóticos y en estudios de adopción (Langner et al., 2013; Willis et al., 2017) . Así, en estudios de pacientes adoptados, la prevalencia de TDAH es más alta en los que provienen de familias biológicas con TDAH, comparado con pacientes adoptados cuyas familias de adopción tienen más TDAH (Sprich et al., 2000). La mayoría de los genes identificados se relacionan con los neurotransmisores dopaminérgicos (Gizer et al., 2009; Middeldorp et al., 2016). Sin embargo, tal y como señalan Faraone y cols.; se han identificado genes que intervienen en la regulación de otros sistemas (noradrenérgicos, serotoninérgicos) que se asocian con impulsividad e hiperactividad (Faraone et al., 2015). Finalmente, Demontis y cols., informaron de la existencia de doce locis independientes en el genoma que se asociaban con el TDAH, uniéndose a otras evidencias que indican que el diagnóstico clínico de TDAH es el resultado de la expresión de uno o más rasgos hereditarios continuos (Demontis et al., 2017).

Por otro lado, existen determinados condicionantes ambientales tales como la exposición al alcohol durante la etapa prenatal y la prematuridad (Thapar et al., 2012), la exposición prolongada a paracetamol (Ystrom et al., 2017) o los traumatismos craneales (Adeyemo et al., 2014) que pueden aumentar la probabilidad de desarrollar TDAH. Aunque se ha planteado que la alimentación podría tener un papel en el desarrollo de TDAH, actualmente no se ha demostrado que la ingesta de determinados alimentos condicione la aparición del trastorno, excepto un pequeño efecto de los colorantes alimentarios (Sonuga-Barke et al., 2013).

Asimismo, se ha sugerido que las personas con TDAH presentan disfunciones en ciertos sistemas de neurotransmisores cerebrales, en concreto en los que implican a la dopamina y norepinefrina (Chandler et al., 2014). Estas alteraciones en los sistemas que modulan la función ejecutiva (control de atención, control inhibitorio y memoria de trabajo) podrían ser responsables de

los síntomas característicos de TDAH; mostrando áreas de baja actividad en estudios de resonancia magnética funcional en niños y adolescentes con TDAH (Cortese et al., 2012; Hart et al., 2013; Norman et al., 2016). Además se han encontrado otras diferencias neuroanatómicas en individuos con TDAH tales como una disminución del volumen de estructuras subcorticales y un retraso en la maduración cerebral (Hoogman et al., 2017). En adultos que fueron diagnosticados de TDAH en la infancia, se ha descrito una disminución en las conexiones de los tractos de materia blanca que conectan las áreas sensoriomotoras (Cortese et al., 2013b). Finalmente, existen diferencias en cuanto a la actividad neural. Así se describe una menor actividad de la vía fronto-parietal (implicada para la planificación de tareas) y de la red de atención ventral (importante en autoinstrucciones) (Hart et al., 2013) y una mayor actividad de la red de activación por defecto (Cortese et al., 2012).

1.1.5. Clínica y diagnóstico

En la última clasificación del DSM-5 los síntomas definitorios del trastorno deben estar presentes más de 6 meses en un mayor grado que en los niños y adolescentes de su misma edad, en más de un entorno (familiar, escolar y/o laboral) e influir de forma negativa en la el funcionamiento social y académico de los pacientes (American Psychiatric Association, 2013). Esta última versión retrasó hasta los 12 años el límite de edad antes del que debían manifestarse los síntomas porque, a veces, puede ser difícil detectar ciertos síntomas antes de los 7 años de edad. En ocasiones puede resultar complicado establecer el límite por encima de los cual los síntomas de hiperactividad, impulsividad e inatención indican un verdadero trastorno en el individuo, dejando de ser variaciones de la normalidad. La definición hace hincapié en que estos síntomas deben ser muchos (más de 6 ítems entre los subapartados), con intensidad elevada en al menos 2 ambientes y muy por encima de lo esperable para su edad de desarrollo. Existen diversas escalas tales como: ADHD-Rating Scale-IV (DuPaul et al., 1998), ADHD Symptom Rating Scale 10 (Holland et al., 1998), Conners Rating Scale (Conners, 2008), SNAP-IV Rating Scale y la reciente ADHD Rating Scale-5 (DuPaul et al., 2016) que permiten recabar información de padres y educadores sobre las manifestaciones del trastorno y servir de cribado; pero, en la actualidad, la entrevista clínica sigue siendo el “gold-standard” para el diagnóstico.

En el DSM-5, en función de las manifestaciones clínicas de los pacientes se describen 3 presentaciones del trastorno: predominantemente inatento, predominantemente hiperactivo-impulsivo, y tipo combinado.

Las siguientes tablas exponen los criterios diagnósticos del TDAH según la más reciente el DSM-5 (Tabla 1) y según el ICD-10 (Tabla 2).

Tabla 1. Criterios DSM 5 para el diagnóstico del TDAH (American Psychiatric Association, 2013)
A Patrón persistente de inatención y/o hiperactividad-impulsividad que interfiere con la función o el desarrollo, caracterizado por (1) y/o (2) **1.Inatención: 6 o más de los siguientes síntomas, o al menos 5 para mayores de 16 años, con persistencia durante al menos 6 meses hasta un grado inconsistente con el nivel de desarrollo y que impacta negativamente en las actividades sociales y académicas/ ocupacionales.** **A menudo no presta atención suficiente a los detalles o incurre en errores por descuido en las tareas escolares, en el trabajo o en otras actividades.** **A menudo tiene dificultades para mantener la atención en tareas o en actividades lúdicas.** **A menudo parece no escuchar cuando se le habla directamente.** **A menudo no sigue instrucciones y no finaliza tareas escolares, encargos, u obligaciones en el centro de trabajo** **A menudo tiene dificultades para organizar tareas y actividades.** **A menudo evita, le disgusta o es reticente en cuanto a dedicarse a tareas que requieren un esfuerzo mental sostenido.** **A menudo extravía objetos necesarios para tareas o actividades.** **A menudo se distrae fácilmente por estímulos irrelevantes.** **A menudo es descuidado en las actividades diarias.** **2.Hiperactividad e impulsividad: 6 o más de los siguientes síntomas, o al menos 5 para mayores de 16 años, con persistencia durante al menos 6 meses hasta un grado inconsistente con el nivel de desarrollo y que impacta negativamente en las actividades sociales y académicas/ocupacionales.** **A menudo mueve en exceso manos o pies, o se remueve en su asiento.** **A menudo abandona su asiento en la clase o en otras situaciones en que se espera que permanezca sentado.** **A menudo corre o salta excesivamente en situaciones en que es inapropiado hacerlo.** **A menudo tiene dificultades para jugar o dedicarse tranquilamente a actividades de ocio.** **A menudo "está en marcha" o suele actuar como si tuviera un motor.** **A menudo habla en exceso.** **A menudo precipita respuestas antes de haber sido completadas las preguntas.** **A menudo tiene dificultades para guardar tumo.**
A menudo interrumpe o se inmiscuye en las actividades de otros.
B Algunos síntomas de desatención o hiperactividad-impulsividad estaban presentes antes de los 12 años de edad.
C Algunos síntomas de desatención o hiperactividad-impulsividad se presentan en dos o más ambientes (por ejemplo, en casa, escuela o trabajo; con amigos o familiares; en otras actividades).
D Existen pruebas claras de que los síntomas interfieren o reducen la calidad de la actividad social, académica o laboral.
E Los síntomas no aparecen exclusivamente motivados por esquizofrenia u otro trastorno psicótico, y no se explican mejor por la presencia de otro trastorno mental (trastornos del estado de ánimo, ansiedad, trastorno disociativo, trastorno de la personalidad, abuso de sustancias o síndrome de abstinencia).

Tabla 2. Criterios diagnósticos para el trastorno hipercinético según la CIE - 10 (World Health Organization, 1992)

Déficit de atención

1. Frecuente incapacidad para prestar atención a los detalles junto a errores por descuido en las labores escolares y en otras actividades.
2. Frecuente incapacidad para mantener la atención en las tareas o en el juego.
3. A menudo aparenta no escuchar lo que se le dice.
4. Imposibilidad persistente para cumplimentar las tareas escolares asignadas u otras misiones.
5. Disminución de la capacidad para organizar tareas y actividades.
6. A menudo evita o se siente marcadamente incómodo ante tareas como los deberes escolares que requieren un esfuerzo mental mantenido.
7. A menudo pierde objetos necesarios para unas tareas o actividades, como material escolar, libros, etc.
8. Fácilmente se distrae ante estímulos externos.
9. Con frecuencia es olvidadizo en el curso de las actividades diarias.

Hiperactividad

1. Con frecuencia muestra inquietud con movimientos de manos o pies o removiéndose en su asiento.
2. Abandona el asiento en el aula o en otras situaciones en las que se espera que permanezca sentado.
3. A menudo corretea o trepa en exceso en situaciones inapropiadas.
4. Inadecuadamente ruidoso en el juego o tiene dificultades para entretenerse tranquilamente en actividades lúdicas.
5. Persistentemente exhibe un patrón de actividad excesiva que no es modificable sustancialmente por los requerimientos del entorno social.

Impulsividad

1. Con frecuencia hace exclamaciones o responde antes de que se le hagan las preguntas completas.
2. A menudo es incapaz de guardar turno en las colas o en otras situaciones en grupo.
3. A menudo interrumpe o se entromete en los asuntos de otros.
4. Con frecuencia habla en exceso sin contenerse ante las situaciones sociales.

Además se debe cumplir:

- ***El inicio del trastorno no es posterior a los siete años.***
- ***Los criterios deben cumplirse en más de una situación.***
- ***Los síntomas de hiperactividad, déficit de atención e impulsividad ocasionan malestar clínicamente significativo o una alteración en el rendimiento social, académico o laboral.***
- ***No cumple los criterios para trastorno generalizado del desarrollo, episodio depresivo o trastorno de ansiedad***

1.1.6. Comorbilidad

Los niños y adolescentes con TDAH muestran un mayor riesgo de enfermedades médicas tales como asma (Cortese et al., n.d.) u obesidad (Cortese et al., 2016b). Además, cerca de la mitad de los niños y adolescentes con TDAH presentan comorbilidad psiquiátrica (Artigas-Pallarés, 2003; Kadesjö and Gillberg, 2001); lo que supone una complicación añadida al manejo diagnóstico terapéutico y a la evolución del trastorno. Los trastornos más comúnmente identificados son: dificultades de aprendizaje, trastornos de conducta, trastorno obsesivo compulsivo trastorno de ansiedad, trastornos de sueño o abuso de sustancias (Díez-Suárez et al., 2006). Entre el 20-30% de estos niños asocian dificultades específicas para el aprendizaje de la lectura, escritura y/o cálculo (Artigas Pallarés and Narbona García, 2011; Miranda Casas et al., 2009; Schoemaker et al., 2005), así como trastornos del desarrollo de la coordinación/ trastorno aprendizaje procedimental (Crespo-Eguílaz et al., 2014). Estos trastornos son frecuentemente el motivo inicial de consulta de en la consulta de pediatría (Aguilera Albesa et al., 2014).

1.1.7. Tratamiento

El tratamiento del TDAH en niños y adolescentes se basa en tres pilares fundamentales: 1) la psicoeducación y el entrenamiento en manejo conductual, 2) el apoyo académico y 3) el tratamiento farmacológico. En la mayoría de los pacientes este tratamiento se realiza de forma combinada (Cortese and Rosello-Miranda, 2017), demostrando su eficacia el manejo sintomático, al menos a corto plazo (Cortese et al., 2017; Daley et al., 2014; Maia et al., 2014). Se estima que los costes medios del tratamiento de un niño con TDAH en nuestro país rondan los 5.800 euros por paciente, de los cuales el porcentaje más elevado deriva del apoyo psicológico/ psicoeducativo (45,2% de los costes directos y el 27,2% del coste total). El tratamiento farmacológico supone un 25,8% de los costes directos y un 15,5% de los costes totales (Quintero et al., 2018).

Psicoeducación y entrenamiento en manejo conductual

El tratamiento psicoeducativo consiste en explicar a padres y pacientes las características propias del trastorno (origen, manifestaciones…) así como pautas concretas de actuación que mejoren sus consecuencias. Así, se incluirían medidas tales como: proporcionar a los pacientes información clara, fraccionada y ordenada; establecer rutinas; limitar estímulos; clarificar las causas del trastorno y eximir de culpabilidad a padres y pacientes, etc. El tratamiento psicológico de elección en el caso del TDAH es la denominada terapia de modificación de conducta, ya que es el tratamiento no farmacológico de mayor eficacia en este grupo.

Las intervenciones conductuales que se recomiendan en niños y jóvenes con TDAH han encontrado resultados positivos en relación al funcionamiento emocional, social y académico de los

niños (Daley et al., 2017). El aumento del conocimiento de los padres respecto al trastorno, tiene un efecto positivo en el refuerzo de su capacidad de acción de los mismos (Daley et al., 2014).

Apoyo académico

Es prioritario coordinarse con el centro escolar de los pacientes con TDAH para establecer una serie de pautas de actuación del profesorado, así como definir las adaptaciones curriculares que se precisen (Grupo de trabajo de la Guía de Práctica Clínica sobre las Intervenciones Terapéuticas en el Trastorno por Déficit de Atención con Hiperactividad, 2017). También es fundamental el apoyo a áreas deficitarias (lectura, matemáticas) tanto en el colegio como en casa, y el entrenamiento en habilidades organizativas.

Tratamiento Farmacológico

En muchas ocasiones, es necesario establecer tratamiento farmacológico para alcanzar un control de los síntomas de los pacientes con TDAH. Actualmente no se recomienda el inicio del tratamiento farmacológico por debajo de los 6 años de edad excepto si los síntomas son graves y faltan los otros tratamientos (Grupo de trabajo de la Guía de Práctica Clínica sobre las Intervenciones Terapéuticas en el Trastorno por Déficit de Atención con Hiperactividad, 2017). Este tratamiento ha de ser individualizado para cada paciente y debe tener en cuenta los posibles efectos secundarios, que en general son leves y de fácil manejo (Cortese et al., 2013a) , y sus potenciales beneficios. Así mismo, la duración del tratamiento médico también ha de ajustarse a las circunstancias particulares de cada paciente (Diéz A; Soutullo C; Figueroa A; San Sebastián J., 2013; Soutullo and Álvarez-Gómez, 2013).

En líneas generales, las medicaciones eficaces y aprobadas para el tratamiento del TDAH se dividen en dos grandes bloques: los medicamentos estimulantes y no estimulantes (Cortese and Rosello-Miranda, 2017). En el caso de los primeros, los compuestos empleados son el metilfenidato (con diferentes formatos de presentación que varían fundamentalmente en su tasa de liberación) y la lisdexanfetamina; y en el caso de los segundos, la atomoxetina y la guanfacina de liberación prolongada.

Psicoestimulantes

Metilfenidato (MPH)

Es el tratamiento más frecuentemente empleado en nuestro medio (Courtabessis et al., 2018; Greenhill et al., 2002; Grupo de trabajo de la Guía de Práctica Clínica sobre las Intervenciones Terapéuticas en el Trastorno por Déficit de Atención con Hiperactividad, 2017). Su mecanismo de acción implica el bloqueo de la recaptación presináptica de dopamina y noradrenalina. Existen diferentes presentaciones del MPH según el porcentaje de fármaco de liberación retardada que presenten (Ramos-Quiroga et al., 2008). En función de la formulación de MPH elegida la duración del efecto del fármaco varía entre 4-12 horas, desapareciendo su acción fuera de este rango temporal. El

tratamiento se inicia con dosis bajas (0,3-0,5 mg/kg/día) y se aumenta progresivamente tras evaluar los posibles efectos secundarios y el beneficio terapéutico (dosis terapéutica máxima 1 -2,5 mg/kg/día). Los efectos secundarios más comúnmente descritos son insomnio de conciliación, pérdida de apetito, bajada de peso, cefalea y dolor abdominal, en general son leves y de fácil manejo (Cortese et al., 2013a).

Lisdexanfetamina

Es un fármaco que resulta de la combinación de la dexanfetamina o dextro-anfetamina (responsable de la actividad farmacológica) con el aminoácido lisina. La lisina se hidroliza tras su paso al torrente sanguíneo liberando gradualmente la dexanfetamina. El resultado final del proceso es un efecto de acción más prolongado (13 horas). Como en el caso del MPH actúa bloqueando la recaptación presináptica de dopamina y noradrenalina, pero además aumenta la liberación presináptica de dopamina y noradrenalina. A diferencia del MPH, en el que la dosis se ajustaba al peso de los pacientes, en este caso el tratamiento se inicia a dosis fijas de 30 mg/día y, en función de la respuesta y de sus efectos secundarios, la dosis se aumenta semanalmente hasta un máximo de 70 mg/día. Los efectos secundarios son similares a los observados con el MPH. La elección de este fármaco se realiza atendiendo a las características de cada paciente: se recomienda el uso de lisdexanfetamina en aquellos pacientes que no toleran o no responden al MPH o la atomoxetina, requieran periodos de acción más prolongados, requieran dosis muy elevadas de tratamiento farmacológico previo o presenten mayor intensidad de los síntomas (Alda et al., 2014).

No estimulantes

Atomoxetina

La atomoxetina actúa inhibiendo selectivamente la recaptación presináptica de noradrenalina. La diferencia con los estimulantes radica en el inicio de su efecto que no se objetiva hasta 3 o 4 semanas (a veces puede tardar hasta 12 semanas) del inicio del tratamiento y este efecto puede no ser pleno hasta 3 meses desde el inicio de los síntomas. Es especialmente importante explicar a padres y pacientes la necesidad de esperar más tiempo para evaluar el efecto positivo del fármaco (Savill et al., 2015). Al igual que el MPH la dosis se ajusta al peso del paciente, iniciándose a dosis bajas de 0,5 mg/kg/día la primera semana o 2 semanas y luego subiéndose a 1,2 mg/kg/día. Los efectos secundarios más comúnmente descritos son la pérdida de apetito, molestias gastrointestinales y somnolencia. La atomoxetina está especialmente indicada cuando hay comorbilidad con tics, ansiedad y abuso de sustancias (Cortese et al., 2013a; Grupo de trabajo de la Guía de Práctica Clínica sobre las Intervenciones Terapéuticas en el Trastorno por Déficit de Atención con Hiperactividad, 2017).

Guanfacina

La guanfacina es un agonista postsináptico alfa -2- adrenérgico que actúa inhibiendo de forma parcial la liberación presináptica de adrenalina. La dosis de inicio del tratamiento varía en función del peso de los niños (0,05-0.1 mg/kg/día) y se va incrementando de forma progresiva cada semana en dosis de 0,1 mg/día hasta los 7 mg/día (en adolescentes de 70 kg). Los efectos adversos más frecuentemente descritos son la somnolencia, cefalea, disminución de la tensión arterial y de la frecuencia cardíaca. Sus efectos hipotensores y cardiovasculares son los que más pueden limitar su uso, aunque en general son autolimitados y mejoran con la disminución de la dosis (Ruggiero et al., 2014).

1.2. Lesiones no intencionadas en la infancia y la adolescencia

1.2.1. Epidemiología e impacto de las lesiones no intencionadas en la población general

La Organización Mundial de la Salud (OMS) define el término lesión como: "el daño físico que se produce cuando un cuerpo humano se somete bruscamente a algún tipo de energía mecánica, térmica, química o radiada". Esta misma organización es la que ha acuñado el término "lesión no intencional" (LNI) en sustitución de "accidente", para resaltar el carácter prevenible del primer término. Dentro del término LNI se engloban los accidentes de tráfico, ahogamientos, quemaduras, caídas y envenenamientos/intoxicaciones.

Según la OMS, estas lesiones son responsables de alrededor de 830.000 muertes anuales en niños y adolescentes y sus, costes directos rondan los 4.000 millones de euros. Las lesiones no intencionadas (LNIs) son la primera causa de mortalidad en niños y adolescentes en el grupo de 1 a 19 años (Peden et al., 2008). Los envenenamientos e intoxicaciones suponen un subgrupo importante entre las LNIs. Llevan según la OMS a cerca de 45.000 muertes anuales. Los tóxicos más comúnmente identificados son: productos del hogar, fármacos y, en menor medida, pesticidas y mordeduras o picaduras de animales (Mintegi et al., 2017a). Las consecuencias de las lesiones son aún más dramáticas en los países en vías de desarrollo, donde las LNIs suponen el 95% de las muertes a partir de los 4 años de edad. En los países con rentas más altas esta proporción disminuye al 40% (Bartlett, 2002). Según datos del Instituto Nacional de Estadística (INE), en el año 2016 las causas externas (LNIs y suicidios) fueron la primera causa de mortalidad en España entre los 15-39 años, suponiendo el 39,4% de los fallecimientos. En este mismo periodo, las LNIs suponen la segunda causa de mortalidad, por delante de los accidentes de tráfico, en el total de la población española. Este informe del INE mostraba que había habido un incremento del 8,5% en la tasa de caídas y un incremento del 2,2% en la de ahogamientos y sumersiones accidentales respecto al año previo (Instituto Nacional de Estadistica, 2017). Con independencia del país de procedencia, las LNIs y sus consecuencias afectan más a los niños provenientes de ambientes menos favorecidos socioeconómicamente, aumentando aún más las

desigualdades sociales existentes. Características propias del desarrollo cognitivo y de la personalidad de la infancia, unido a las peculiaridades anatómicas de los niños provocan lesiones y secuelas más graves en este grupo etario (Bartlett, 2002).

Una circunstancia que hace más dramáticas si cabe las consecuencias de las LNIs, es el hecho de que en muchos casos son evitables o al menos es posible minimizar sus consecuencias siguiendo las estrategias educativas, legislativas o de modificación adecuada del entorno. En los países en que se ha estudiado las causas de las lesiones y puesto en marcha soluciones para problemas específicos, como en Suecia, se han reducido las muertes hasta en un 50% (Peden et al., 2008).

En resumen, el coste económico, social y para la vida del niño de las LNIs, es elevado tanto a corto como a largo plazo dado que muchas veces genera secuelas crónicas. Las LNIs en total suponen la inversión de aproximadamente 4.000 millones de euros para atenciones médicas inmediatas en EE.UU. (Guyer et al., 2009). El Servicio Nacional de Salud en el Reino Unido (NHS) gasta más de 45 millones de euros en el cuidado de la salud de los niños lesionados en comparación con los no lesionados en el mismo rango de edad (Ablewhite et al., 2015). En España en el periodo 2011-2012, el 15 % de los menores de 14 años refería haber presentado una LNI durante el año previo y el 80% de los menores de 4 años que había padecido alguna LNI había recibido asistencia médica en un servicio de urgencias (Ministerio de Sanidad Politica Social e Igualdad; and INE., 2013). En el servicio de urgencias de pediatría del Complejo Hospitalario de Navarra (centro de referencia de la Comunidad Foral) se atendieron 8.813 pacientes como resultado de lesiones no intencionadas durante el año 2013 (Ferraz-Torres et al., 2016).

Debido a todas estas razones, la prevención de LNIs en niños y adolescentes debe ser una prioridad para los profesionales sanitarios.

1.2.2. Epidemiología e impacto de las lesiones no intencionadas en pacientes con TDAH

El patrón continuo de hiperactividad, impulsividad y/o inatención que caracteriza y afecta negativamente en el funcionamiento global de los niños y adolescentes con TDAH desde la infancia y a lo largo de la vida (Barkley, 2006) hace que presenten un mayor riesgo de enfermedades crónicas como el asma (Cortese et al., n.d.) u obesidad (Cortese et al., 2016b), así como un incremento de problemas del sueño (Cortese et al., 2009; Vélez-Galarraga et al., 2016), que reducen sustancialmente la calidad de vida de los pacientes (Coghill et al., 2017; Escobar et al., 2005).

Además en el caso de los niños y adolescentes con TDAH, las consecuencias del trastorno se extienden más allá del ámbito familiar; con una mayor carga de estrés en las relaciones intrafamiliares y una disminución de la productividad laboral de los padres de los pacientes (Coghill et al., 2008). En último término el TDAH presenta consecuencias en el conjunto de la sociedad. Un ejemplo gráfico son

los altos costes sanitarios asociados al trastorno. Un estudio reciente en EE.UU. indicaba que el gasto sanitario en personas con TDAH era entre 600 dólares y 2.000 dólares superior a la de una persona sin TDAH (Doshi et al., 2012). Análogamente, en España se estima que el coste medio anual del TDAH por niño / adolescente fue de 5.733 euros (Quintero et al., 2018).

Esta disfunción académica, familiar y social del trastorno eleva el riesgo de accidentes y lesiones, por la impulsividad de estos pacientes, incluyendo la muerte por accidentes (Dalsgaard et al., 2015b; Faraone, 2015). Varios estudios habían señalado que algunas características clínicas como impulsividad, inatención, distracciones, disregulación emocional y agresividad, aumentan la probabilidad de sufrir una lesión infantil (Keyes et al., 2014). Estas características comúnmente descritas en el TDAH podrían ser factores de predicción de mayor vulnerabilidad a padecer LNIs. De hecho, algunos autores han señalado a esta probable mayor incidencia de lesiones en accidentes como responsable de una importante parte del incremento del gasto sanitario en los niños y adolescentes con TDAH (Swensen et al., 2004). Además, la comorbilidad con otros trastornos como el trastorno negativista desafiante ha mostrado un incremento del riesgo de LNIs en los niños con TDAH (Keyes et al., 2014), pero se desconoce si la comorbilidad con otros trastornos que comparten estas características (trastorno de conducta, trastorno específico del aprendizaje, trastorno del humor o ansiedad y trastornos del sueño) pudiera incrementar la frecuencia, intensidad o gravedad de estas LNIs en niños y adolescentes.

La asociación del TDAH con las LNIs como contusiones, lesiones superficiales, heridas abiertas, luxaciones, torceduras, esguinces y fracturas, o quemaduras y ahogamientos es elevada (Chou et al., 2014; Dalsgaard et al., 2014a; Mangus et al., 2004). Esta relación ha sido estudiada por muchos grupos de investigación, incluyendo grupos en España (Crujeiras Martinez et al., 2013).

En líneas generales, los estudios podrían dividirse en 2 grandes grupos:

1) Estudios de casos (sujetos con LNIs) y controles (sujetos sin LNIs) donde se estudia la prevalencia del TDAH en cada grupo.
2) Estudios de cohorte o longitudinales donde se estudia la incidencia de lesiones en un periodo de tiempo para niños con o sin TDAH.

Los estudios de casos y controles son los más frecuentes en la literatura. Estos estudios en muchas ocasiones se centran en un tipo de lesiones específico, tales como dentales (Altun et al., 2012), fracturas de estructuras anatómicas concretas (Ozer et al., 2010) o quemaduras (Mangus et al., 2004). La mayor limitación de estos estudios es el tamaño muestral, que suele ser reducido (los tres trabajos citados tenían menos de 250 sujetos por grupo), lo que dificulta el control estadístico de covariables que podrían estar mediando o en la relación entre TDAH y LNIs. Los resultados de estos estudios en general han indicado que la frecuencia de lesiones es mayor en los niños con TDAH.

Por otro lado, también existen grandes estudios longitudinales o de cohortes a partir de bases de datos existentes. Si bien el número de estos estudios es mucho menor, tienen tamaños muestrales muy grandes, y permiten un importante rigor metodológico. En 2014 se publicó un artículo utilizando una cohorte danesa en la que llevó a cabo un seguimiento de 7.000 niños con TDAH y 1.500 controles (Dalsgaard et al., 2014a), así como un artículo en Taiwán en el que se estudiaron las lesiones ocurridas en casi 4.000 pacientes y 14.000 controles (Chou et al., 2014). El trabajo de Dalsgaard, encontraba un ligero aumento del riesgo de sufrir lesiones en los sujetos con TDAH (odds ratio de 1,09; IC 95% 1,01-1,21), mientras que el trabajo de Chou, obtuvo una diferencia de riesgo de lesiones mayor (odds ratio de 1,35; IC 95% 1,19-1,52). Otros estudios similares han encontrado sin embargo odds ratios mucho mayores (3,01; IC 95% 1,67-5,42) (Constant et al., 2014).

Si bien algunos autores han propuesto distintas covariables que podrían mediar en la relación entre el TDAH y el riesgo de lesiones como la edad, el sexo de los participantes (Chou et al., 2014), el método de diagnóstico utilizado (Constant et al., 2014) y la comorbilidad con trastornos como el trastorno negativista desafiante, los trastornos de conducta (Bruce et al., 2007), o los trastornos de aprendizaje procedimental (Cairney, 2014); la interacción del TDAH con cada uno de estos factores no ha sido demostrada.

Por lo tanto, si bien parece comprobado que el riesgo de lesiones en niños con TDAH es mayor que en la población general, la magnitud de la relación está todavía por estudiar, así como el impacto de que otras variables como sexo, edad, o la presencia de comorbilidades pudieran influir en esta asociación. Es decir, no conocemos si el posible mayor riesgo de LNIs en pacientes con TDAH se debe intrínsecamente al TDAH o al hecho de que existan comorbilidades y factores asociados.

1.2.3. Lesiones no intencionadas y medicación para el TADH

La medicación para el TDAH es eficaz en el tratamiento de los síntomas y mejora el rendimiento escolar, al menos en el corto plazo (Prasad et al., 2013; Punja et al., 2016) y en el en el medio plazo (Maia et al., 2014). La evidencia obtenida de estudios observacionales nos indica que la medicación para el TDAH es eficaz a largo plazo ya que disminuye el número de desenlaces desfavorables. Así, existen indicios de que la medicación podría relacionarse en niños y jóvenes con un menor riesgo posterior de abuso de sustancias (Groenman et al., 2013; Purgato and Cortese, 2014) o criminalidad (Dalsgaard et al., 2014b; Lichtenstein et al., 2012). En los últimos 5 años se han desarrollado una serie de trabajos que se valían de la rapidez de acción de la medicación y estudiaban la frecuencia de los accidentes en los periodos con y sin tratamiento farmacológico. Estos estudios parecen indicar que la medicación para el tratamiento del TDAH podría reducir el número de LNIs, pero los resultados son contradictorios, probablemente debido al gran tamaño muestral necesario para que estos trabajos tengan la potencia estadística necesaria (Dalsgaard et al., 2015a; Man et al., 2015; Mikolajczyk et al., 2015; Raman et al., 2013).

El estudio del efecto de la medicación es intrínsecamente muy complejo ya que existen diferencias entre los grupos de sujetos que toman medicación y los que no la toman que impiden que la simple comparación entre ambas poblaciones sea informativa. Por ejemplo, los pacientes medicados podrían tener más síntomas o más gravedad de TDAH y por tanto podrían tener una mayor asociación con las LNIs (Dalsgaard et al., 2014a).

En este sentido, como se ha señalado anteriormente, existen estudios recientes metodológicamente muy interesantes que se aprovechan del hecho que el efecto de la medicación es en el corto plazo, para estudiar si las LNIs son más probables mientras el sujeto está tomando medicación o cuando no la está tomando. Esta técnica, conocida como "self controlled case-series" (SCCS), sin embargo, requiere que todos los sujetos a incluir hayan sufrido al menos una vez el evento de interés. Si unimos este hecho con la frecuencia de las LNIs (15% de LNIs en total de población infantil en el caso de España (Ministerio de Sanidad Politica Social e Igualdad; & INE. 2013)), necesariamente los mejores estudios deberán partir de muestras muy grandes para poder realmente estimar si la medicación reduce o no el riesgo de lesiones.

En un artículo pionero utilizando esta técnica (Raman et al., 2013) se encontró un efecto protector de la medicación solo en adolescentes varones, partiendo de una muestra de 328 casos. Un estudio de 2015 con 2.128 casos de lesiones encontró un efecto protector de la medicación solo para el riesgo de lesiones cerebrales (Mikolajczyk et al., 2015), mientras que en otro artículo reciente aun mayor (Man et al., 2015), en el que se incluyeron más de 4.934 pacientes que habían sufrido al menos una LNI, se encontró que la medicación sí reducía el riesgo de lesiones.

El uso clínico de la medicación para el TDAH debe tener en cuenta los efectos a corto y largo plazo, tanto los efectos adversos negativos como el efecto sobre el apetito y el peso (Díez-Suárez et al., 2017) como los positivos, como la mejora en el rendimiento académico, calidad de vida y reducción de riesgos y lesiones. Entre estos efectos, su influencia sobre las LNIs podría ser un factor importante por el alto coste de estas secuelas en los que las sufren y en la sociedad en su conjunto. A nivel poblacional, podrían ahorrarse millones de euros derivados de las LNIs tratando adecuadamente a los niños con TDAH que realmente lo necesitan si las medicaciones fuesen realmente eficaces en reducir este riesgo (Maia et al., 2015).

Vistas las inconsistencias y limitaciones metodológicas de los artículos publicados, así como la relevancia de la hipótesis de investigación, una revisión sistemática y metanálisis permitirán responder de la mejor manera posible a esa cuestión con los datos existentes y así guiar decisiones de planificación económico-sanitaria y, quizás más importante, clínicas.

Con todo lo anterior, y en términos estratégicos de prevención y reducción de costes, podemos concluir que es necesario invertir mayores recursos de investigación, para facilitar la toma de decisiones, valorando riesgos y beneficios de la toma y el cese de la medicación, y educar a los padres

en la prevención de riesgos mediante la explicación de los factores que interaccionan con el TDAH. Hallazgos en esta línea, podrían ser la clave para disminuir la cantidad de recursos que se invierten en el tratamiento de heridas físicas y secuelas graves de las LNIs. Esto es especialmente importante en los sistemas nacionales de salud donde los recursos económicos y humanos son limitados y cuyo uso debe optimizarse, primando la prevención primaria y secundaria sobre la atención especializada terciaria.

2. Objetivos generales e hipótesis

2.1. Objetivos generales

Los objetivos generales de nuestro trabajo son cuatro:

1) Determinar si los niños y adolescentes con TDAH presentan un riesgo significativamente más alto de sufrir LNIs y envenenamientos al compararlos con individuos sin dicho trastorno.
2) Evaluar si la edad, el sexo o la presencia de comorbilidad psiquiátrica modifican las posibles diferencias en el riesgo de LNIs entre los individuos con TDAH frente a individuos sin TDAH.
3) Evaluar si la medicación para el tratamiento del TDAH reduce el riesgo de sufrir LNIs en los pacientes que están tomando la medicación.
4) Determinar si los niños y adolescentes con TDAH sufren con más frecuencia envenenamientos que los controles sanos de su misma edad y sexo.

2.2. Hipótesis

2.2.1. Hipótesis 1

Los niños y adolescentes con TDAH tienen una mayor probabilidad de sufrir una LNI frente a individuos de su edad que no tienen TDAH. Cuando se combinen las razones de probabilidad, razones de productos cruzados u "Odds ratio" (OR) de sufrir una lesión en un metanálisis de efectos aleatorios, se espera que el riesgo de sufrir una LNI sea significativamente mayor para los sujetos con diagnóstico de TDAH.

2.2.2. Hipótesis 2

Es posible que la edad y el sexo de los sujetos modifiquen la diferencia en el riesgo de sufrir LNIs entre pacientes y controles. Cuando se lleve a cabo un metanálisis en sub-muestras de estudios o de meta-regresión, incluyendo la edad media de cada estudio o el número de varones, la OR resultante se verá modificada. Otros factores como la comorbilidad, la definición de TDAH y controles o el lugar y tiempo del estudio podrían estar modificando también esta diferencia de riesgo.

2.2.3. Hipótesis 3.

La medicación empleada como tratamiento del TDAH es capaz de disminuir el número de LNIs. Las medicaciones empleadas en el tratamiento del TDAH mejoran el control de impulsos, disminuyendo las conductas de riesgo e hipotéticamente el número y/o gravedad de lesiones disminuirá. En este caso se seleccionarán estudios donde se compare el riesgo de sufrir una LNI cuando los sujetos con TDAH están siendo tratados con medicación respecto a cuándo no lo están. Cuando se combinen las Razones de Tasas de Incidencia o "Incident Rate Ratio" (IRR) de sufrir una lesión de los diversos estudios en un metanálisis, se espera que la probabilidad de ocurrencia resultante de sufrir una LNI sea significativamente menor para los sujetos con TDAH tratados con medicación.

2.2.4. Hipótesis 4

Los niños y adolescentes con TDAH presentan un riesgo aumentado de padecer un envenenamiento. Se espera que la medida de asociación obtenida de sufrir un envenenamiento (que resulte de combinar OR y las razones de tasas o "Hazard Ratio" (HR) en un metanálisis de efectos aleatorios) sea significativamente mayor para los sujetos con TDAH.

De forma análoga a las lesiones físicas se valorará si con los datos obtenidos, hay una influencia de la edad, sexo o comorbilidad en el riesgo de envenenamiento. Finalmente se espera que el riesgo relativo de sufrir envenenamientos sea superior al riesgo relativo de sufrir de LNIs.

3. Publicaciones

3.1. Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: protocol for a systematic review and meta-analysis

3.1.1. Antecedentes

Se ha postulado que los pacientes con TDAH presentan una mayor incidencia de LNIs. Sin embargo, no hay estudios concluyentes hasta la fecha sobre la magnitud del efecto y la posible relación con otras covariables como el sexo, la edad o la comorbilidad psiquiátrica. Más importante todavía, no se ha clarificado si la medicación para el tratamiento del TDAH podría disminuir el riesgo de padecer LNIs en este grupo de individuos. Se describe a continuación el protocolo de una revisión sistemática y metanálisis para dar respuesta a las dos cuestiones planteadas.

3.1.2. Metodología

La hipótesis del grupo de investigación era que el TDAH está asociado a un mayor riesgo de LNIs y que el tratamiento farmacológico del TDAH disminuye significativamente este riesgo de lesiones. Para realizar este protocolo se siguieron los estándares de calidad de las guías: "The Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA), "Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols" (PRISMA-P) y "The Meta-Analysis of Observational Studies in Epidemiology" (MOOSE). Atendiendo a dichas recomendaciones internacionales se planeó realizar una búsqueda bibliográfica en las principales bases de datos biomédicas y revisar las referencias de los artículos potencialmente incluibles en el metanálisis, para localizar posibles estudios de interés. Además, los procesos de selección de los estudios y extracción de los datos se llevarían a acabo simultáneamente por dos investigadores independientes. Posteriormente se evaluaría también por duplicado, la calidad de los estudios finalmente incluidos en el metanálisis; mediante la escala Newcastle-Otawa (escala diseñada para evaluar la calidad de los estudios no aleatorizados incluidos en una revisión sistemática o metanálisis).

La población a estudiar consistiría en individuos menores de 18 años con TDAH según diagnóstico médico, autoreferido o según su puntuación en cuestionarios validados. Para la realización del metanálisis del efecto de la medicación del TDAH en el riesgo de LNIs, sería necesario que los estudios originales comparasen el riesgo de lesiones cuando los pacientes con TDAH estuviesen tomando tratamiento farmacológico, frente a periodos en los que estos individuos no estuviesen tomando medicación. Se utilizaría la definición de la OMS de lesiones no intencionadas (códigos S00-T98 del capítulo 19 del ICIE-10), excluyéndose los traumatismos craneoencefálicos por la posible

bidireccionalidad de la relación con el TDAH. También se excluirían las intoxicaciones u envenenamientos porque los niños y adolescentes medicados para el TDAH tienen un mayor acceso a medicación que sus iguales sin el trastorno y este hecho podría ser una fuente de sesgo y de sobreestimación del riesgo de LNI por envenenamiento/intoxicación en niños y adolescentes con TDAH.

En el análisis de los datos obtenidos se emplearía el paquete estadístico STATA versión 12. Se combinarían los datos de artículos que aportasen: OR, HR, o datos suficientes para calcularlas. Para la combinación de estas medidas de riesgo/asociación se usaría la estimación robusta de la varianza o "Robust Variance Estimation" en inglés (RVE a partir de ahora), un método que permite incluir múltiples desenlaces no independientes en el análisis (Ver Anexo 1: Abreviaturas). Está técnica en lugar de calcular valores medios, modula la estructura anidada de los desenlaces del mismo estudio.

La principal ventaja de RVE respecto a otras técnicas estadísticas es que no precisa información sobre la estructura de la covarianza de los tamaños del efecto, una información que en general es difícil de adquirir. Se utilizaría un modelo de efectos aleatorios ya que se estimaba que la variabilidad entre estudios iba a ser grande. La heterogeneidad se estudiaría sistemáticamente utilizando la Q de Cochran y el índice I^2. La posibilidad de un sesgo de publicación por muestra pequeña se estudiaría mediante "funnel plots" (gráficos de embudo) y la correlación de Begg. Posteriormente se realizaría un análisis de subgrupos y metaregresión del sexo, edad y la comorbilidad con trastornos de conducta para evaluar su papel como posibles variables confusoras. En los análisis de sensibilidad se excluirían los artículos con periodos de seguimiento corto, aquellos con definiciones no estrictas de TDAH o controles y desenlaces no controlados estadísticamente por otras posibles variables confusoras.

Como hemos comentado previamente, en la segunda parte de este estudio, se realizaría un metanálisis que evaluaría si la medicación empleada para el tratamiento del TDAH influye en el riesgo de LNIs. En este caso, se requerirían estudios que empleasen una metodología que controlase por los factores fijos individuales, principalmente estudios con diseño de series de casos auto-controlados o "self-controlled case series" (SCCS) (estudios en los que se aportasen datos sobre la incidencia de lesiones en un mismo individuo con TDAH en periodos con y sin tratamiento farmacológico) y se combinarían según el modelo lineal generalizado mixto, basado en la distribución de Poisson. En este caso la variable de desenlace principal sería el IRR, medida relativa que se emplea para comparar la incidencia de eventos en un periodo de tiempo concreto en diferentes condiciones. En el modelo anteriormente descrito, la variable dependiente es el logaritmo del número de lesiones, y el logaritmo de la variable persona-tiempo se incluirá como constante. La medicación se incluiría como una variable explicativa del modelo.

Dado que el empleo de metodología auto-controlada es relativamente reciente se espera encontrar pocos estudios para incluir en metanálisis por lo que se emplearía un modelo simplificado

de efectos fijos. Finalmente, se realizaría un análisis de sensibilidad incluyendo solo los estudios que incluyesen series de casos auto-controlados o SCCS por ser los de mayor calidad

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Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: protocol for a systematic review and meta-analysis

Maite Ruiz-Goikoetxea,[1] Samuele Cortese,[2,3,4] Maite Aznarez-Sanado,[5] Sara Magallon,[5] Elkin O Luis,[5] Noelia Alvarez Zallo,[1] Pilar de Castro-Manglano,[6] Cesar Soutullo,[6] Gonzalo Arrondo[7]

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For numbered affiliations see end of article.

Correspondence to
Dr Gonzalo Arrondo;
garrondo@yahoo.es

ABSTRACT

Introduction Attention-deficit hyperactivity disorder (ADHD) has been related to increased rates of unintentional injuries. However, the magnitude of the effect and to which extent variables such as sex, age or comorbidity can influence this relationship is unknown. Additionally, and importantly, it is unclear if, and to which degree, ADHD medications can decrease the number of unintentional injuries. Due to the amount of economic and social resources invested in the treatment of injuries, filling these gaps in the literature is highly relevant from a public health standpoint. Here, we present a protocol for a systematic review and meta-analysis to estimate the relationship between ADHD and unintentional injuries and assess the impact of pharmacological treatment for ADHD

Methods and analysis We will combine results from 114 bibliographic databases for studies relating ADHD and risk of injuries. Bibliographic searches and data extraction will be carried out independently by two researchers. The studies' risk of bias will be assessed using the Newcastle-Ottawa Scale. Articles reporting ORs or HRs of suffering an injury in ADHD compared with controls (or enough data to calculate them) will be combined using Robust Variance Estimation, a method that permits to include multiple non-independent outcomes in the analysis. All analyses will be carried out in Stata. Age, sex and comorbid conduct disorders will be considered as potential causes of variance and their effect analysed through meta-regression and subgroup analysis. Sensitivity analyses will exclude articles with longer follow-ups, non-stringent definitions of ADHD or controls and statistically uncontrolled/controlled outcomes. Studies implementing a self-controlled case series methodology to investigate if ADHD drugs reduce the risk of injuries will be combined with a generalised linear mixed model using the Poisson distribution and a log link function.

Registration details PROSPERO—Prospective Register of Systematic Reviews (CRD42017064967)

Strengths and limitations of this study

- Search and data extraction conducted independently by two authors in three major databases (PubMed, Scopus, Web of Science) and a results aggregator searching simultaneously in 113 databases, without time or language limitations.
- Analytical plan including two different meta-analyses aimed at answering two different but related questions: risk of injuries in attention-deficit hyperactivity disorder (ADHD) and possible protective role of ADHD drugs for this risk.
- Clinical importance of answering whether ADHD medications have a significant influence on the risk of injuries.
- Usage of Robust Variance Estimation: a recent statistical methodology that permits the combination of non-independent outcomes.
- It is expected that the scope of this review will be limited by the number of studies reporting the relationship between medication for ADHD and risk of injuries.

INTRODUCTION

Unintentional injuries in childhood

According to WHO, injury can be defined as, 'The physical damage that results when a human body is suddenly subjected to energy in amounts that exceed the threshold of physiological tolerance or else the result of a lack of one or more vital elements, such as oxygen'.[1] Therefore, unintentional injuries in children and young people (CYP) include traffic injuries, drowning, poisoning, falls or any other traumatic injury and burns.

Childhood unintentional injury is a major cause of death and disability among children and adolescents: over 500 000 children die worldwide every year from unintentional injuries and many more are left with permanent

disabilities.[1] Injuries are especially relevant in childhood compared with adulthood. Developmental factors make CYP more prone to unintentional injuries compared with adults. Additionally, their anatomical fragility, smaller size and brain immaturity lead to more serious injuries and sequelae.[2] Injury risk varies by sex, with a higher risk in males. It also varies with age. According to the WHO 2008 report on child injury prevention,[1] in high-income countries children under 1 year and over 15 years have greater risks of death from unintentional injuries (28 and 23.9 death rates per 100 000, respectively). Socioeconomic deprivation is an additional factor associated with the probability of unintentional injury. Rates (per 100 000) of estimated mortality due to unintentional injuries in CYP in high-income countries were 12.2 as opposed to 41.7 in low-income and middle-income countries in this same report by WHO.[1]

Moreover, CYP from families from low socioeconomic areas have a higher incidence of unintentional injuries compared with those less deprived,[1] for example, a study found that across England rates of serious injury in children as pedestrians were higher in the most deprived areas than in the least deprived (rate ratio (RR) 4.1; 95% CI 2.8 to 6.0 domestic product).[3] As a result of the higher incidence of unintentional injuries in more economically deprived CYP, there is a contribution to ongoing inequalities between children within nations and comparing children from different nations.

There is little evidence on the evidence of the economic costs of injuries as a proportion of gross domestic product globally. However, acute treatment costs of unintentional injuries sum €4000 million worldwide every year,[4] whereas the National Health Service in the UK calculated that the extra cost of healthcare of injured children compared with non-injured children was €45 million.[5] The injuries that occurred in the year 2000 in CYP under the age of 14 years from the USA will have an estimated lifetime cost from medical treatments of US$11 899 million and US$38 664 million from lost productivity.[6]

Importantly, an issue that makes unintentional injuries an even bigger healthcare priority is the fact that most of the times their consequences could be prevented or minimised with the proper educational, legal or environmental measures. In fact, injuries are the first preventable cause of death and disability.[5]

Attention-deficit hyperactivity disorder

Attention-deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder, with an estimated worldwide prevalence between 3% and 5% among children and adolescents, being three to four times more prevalent in males than females.[7–9] The most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), defines ADHD as a disorder characterised by a persistent pattern of hyperactivity/impulsivity and/or inattention, affecting both development and functioning. The symptoms need to be present in at least two settings and influence negatively academic, occupational or social activities from childhood to adult life.[10]

The economic burden of ADHD is very high. Healthcare spending in patients with ADHD has been estimated to be between US$600 and US$2000 greater than for an individual without ADHD.[11 12] Importantly, a significant part of such increase in healthcare expenditure is a direct consequence of the higher likelihood of injuries in individuals with ADHD.[13] The relationship between ADHD and the risk of unintentional injuries has been widely studied.[14 15] However, available studies present with caveats and sample sizes and study methods have differed significantly across studies. Case-control studies are the most frequent in the literature, but, quite often, they assessed only one type of injuries such as dental,[16] fractures of specific body bones[17] or burns.[18] An important limitation of this type of studies is that they have typically relied on a small sample size, which hinders the statistical control of confounding factors that could be leading to a spurious correlation between ADHD and unintentional injuries. Nevertheless, studies tend to show a higher incidence of injuries in ADHD CYP. Longitudinal cohort studies have also been conducted on the relationship between ADHD and physical injuries. Although few in number, they included large sample sizes, hence permitting an increased statistical rigour. Estimates of the differences have varied greatly between studies. In a large sample, Rowe *et al* found an OR of 1.6 (95% CI 1.6 to 2.3) for a statistically significant increased risk of fractures in ADHD compared with controls, while others have found ORs over 3.[19–21]

Furthermore, comorbidity with oppositional defiant disorder (ODD) and conduct disorder (CD) has been related to an increased risk of unintentional injuries in some studies, so that it could be argued that both disorders, highly comorbid with ADHD, could play a major role in the relationship between ADHD and unintentional injuries. However, while a recent European study with a total sample of 4517 individuals found no differences between children with ADHD and controls (OR 0.91, 95% CI 0.56 to 1.48) when comorbidity and other variables were controlled for,[22] another study found a similar risk of injuries when ADHD with conduct problems were compared with controls than when ADHD without conduct problems were compared with controls (OR close to 1.5).[23] Another factor that could contribute to the differences in the risk estimation between studies could be an interaction between diagnosis and variables that influence the risk of injuries in the general population, namely age and sex.

Summarising, while there is evidence supporting a higher risk of injuries in ADHD CYP, the magnitude of the difference remains unclear. Additionally, to which extent variables such age and sex which could influence the possible association deserve further investigation.[24] Finally, the suggestion that comorbidity with ODD and CD[25] could lead to a higher risk of unintentional injuries needs to be more rigorously tested.

Unintentional injuries and ADHD medication

ADHD medications are effective for treating symptoms and improving academic achievement, at least in the short term.[26 27] There is evidence to suggest that the use of ADHD medication in children and adolescents could be associated with a reduced risk of drug abuse and criminality.[28–30] ADHD medication may also reduce the risk of unintentional injuries, but results are inconsistent across studies.[31–34]

Estimating and interpreting the effect of medication is not straightforward. For example, patients who receive medication could have more severe ADHD symptoms and, hence, they could have an increased risk of unintentional injuries.[35] Recent methodologically sound studies have taken advantage of the short half-life of stimulants and used it to compare the risk of accidents of individuals when taking the medication compared with themselves when not taking it. This statistical method is known as self-controlled case series and allows the control for all time time-invariant individual confounders (including sex, socioeconomic background and more importantly, severity of symptoms).[36] Importantly, the self-controlled case series methodology (SCCS from now on) requires that all study subjects have suffered at least one outcome (injury in our case) of interest. This, combined with the fact that unintentional injuries are not highly frequent, leads to the need of very large sample sizes to confidently estimate whether medication influences the risk of injuries. The first study using the self-controlled case series design in ADHD had a sample size of 328 individuals with ADHD who had suffered an injury and found a protective effect of medication only for male adolescents.[31] Similarly, Mikolajczyk *et al* found a protective effect only for the risk of traumatic brain injuries in a sample of 2128 injury cases among individuals with ADHD, whereas a more recent study with over 4000 patients concluded that medication decreases the risk of unintentional injuries.[37] Whereas the effect of medication on the risk of injury could theoretically only be rigorously assessed in randomised controlled trials, practical constraints associated with this design make them unsuitable to test the effect of a possible protective effect of medication on risk of injuries in the long term.

The short-term and long-term effects of medication should be taken into account when weighting the clinical decision of prescribing drugs for ADHD. A possible protective effect of ADHD medications on unintentional injuries could be an additional key factor to be considered when assessing the possible benefits and harms of the pharmacological treatment for ADHD. Gaining insight into the effects of ADHD drugs on injuries may have important implications for the day-to-day clinical practice. For instance, a sizeable number of practitioners recommend stopping medication during school holiday periods. Assuming that ADHD drugs do have a protective effect on the occurrence of injuries, such practice should be discouraged, at least in individuals with ADHD at higher risk (eg, adolescents).

Due to the high prevalence of ADHD, and the fact that unintentional injuries represent a source of major impairment for society as a whole, decreasing the risk of injuries in ADHD should be a public health priority.

In view of the inconsistencies in the literature and the significance of this research, a systematic review and meta-analysis on the differential risk between individuals with and without ADHD and on the effect of medications will allow to provide meta-analytic support to address these important gaps in the literature. Results will directly inform clinical practice and healthcare planning.

We note that during the final stages of the preparation of this manuscript (and after our protocol had been registered in Prospective Register of Systematic Reviews (PROSPERO)), a systematic review and meta-analysis on the risk of injuries in ADHD was published by Amiri *et al*,[38] showing a significant association between ADHD and risk of injuries (pooled OR 2.04 (95% CI 1,59 to 2,63)). We deem that the present systematic review/meta-analysis expands and complements the work by Amiri *et al* in a number of ways. First, the bibliographic searches in Amiri *et al* were conducted for articles published between 2000 and 2014. Of note, in the last 3 years there has been a surge of high-quality articles relevant for our meta-analysis. Second, we aimed to control for gender effects, an important confounder. Third, and perhaps more importantly, we address a very relevant clinical and public health question, namely the effect of ADHD drugs on the risk of injuries. Finally, the fact that the current project is registered and follows reporting guidelines (including the publication of the protocol) should give further confidence in the precision of its results. For all these reasons, we believe that the current meta-analysis will help to advance our current understanding of ADHD and contribute to build the evidence for programmes aiming to prevent unintentional injuries in CYP.

HYPOTHESIS AND OBJECTIVES

The overarching aim of the study will be to assess the degree of association between ADHD and unintentional physical injuries and to estimate the impact of the pharmacological treatment of ADHD on the association.

Main review questions and hypothesis

1. Is the risk of unintentional physical injuries significantly higher in children and adolescents compared with those without ADHD?
   We hypothesise that children and adolescents with ADHD will have a significantly higher probability of suffering an unintentional injury compared with individuals without ADHD.
2. Do ADHD medications affect the risk of unintentional injuries in ADHD individuals?
   Our research hypothesis is that the pharmacological treatment of ADHD symptomatology significantly decreases the risk of unintentional injuries.

Additional review questions

Do age, gender and psychiatric comorbidities (ODD or CD) moderate differences in the risk of unintentional physical injuries in individuals with versus individuals without ADHD?

Our hypothesis is that comorbid behavioural disorders (ODD or CD) will increase the risk of unintentional injuries. However, we predict that the increased risk of injuries will still be significant after controlling for these comorbidities. Additionally, it has not been previously tested if there is an interaction between age or sex and diagnosis in relation to the risk of injuries and we do not have a priori hypotheses on the effect of this interaction.

METHODS

We will follow healthcare and epidemiology meta-analytic research guidelines, namely: 1) the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA,[39 40]), a 27-item checklist and associated information that includes aspects deemed essential for transparent reporting of a systematic review, and its counterpart for the reporting of protocols (PRISMA-P[41 42]) and 2) the Meta-Analysis of Observational Studies in Epidemiology,[43] a framework highlighting the specificities of meta-analysing population-based studies.

Eligibility criteria

Participants/population

The population to be studied will consist of children and adolescents with ADHD aged <18 years. The presence of ADHD will be defined operationally as one of the following:

1. A categorical diagnosis according to standardised criteria, either the DSM (III, III-R, IV, IV-TR or 5) or the diagnosis of hyperkinetic disorder as per International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) or previous versions.
2. A positive answer to the question: 'Have you ever been told that you have ADHD by a doctor?'
3. Being prescribed ADHD medication(s).
4. Being above a pre-established threshold in a validated psychometric scale for the screening of ADHD symptoms. This threshold can also be a percentile of the sample. Studies in which the severity of ADHD symptoms is related to injuries, but no explicit diagnostic threshold is used, will not be included.
5. ADHD-related codes in medical, healthcare or administrative registries.

Operational definitions #1–3 have been designed to include articles identifying children with clinically known or recorded ADHD diagnoses. Operational definitions #4–5 have been chosen to include articles that evaluate ADHD in community studies or healthcare systems.

Studies will be included regardless of medication status (specific medications for ADHD or any other medication) or sex ratio. Comorbidities (psychiatric or other) in all or part of the study participants will not be exclusionary. Studies including only preschool children will not be eligible as diagnosis at this age range is controversial. Studies based on the diagnosis of deficits in attention, motor control and perception,[44] or equivalent constructs,[45] will not be included as the motor control problems required for their diagnosis and not needed in the case of ADHD diagnosis could be related to specific kinds of injuries or a different incidence of them, hence adding an extra source of variability.[46]

Intervention(s), exposure(s)

As the first part of this meta-analysis evaluates the risk of unintentional injuries in patients with ADHD compared with controls, no intervention will be assessed.

Regarding our second research question, we aim to evaluate the impact of any ADHD medication (ie, intervention) on the incidence of injuries and hence, we will be comparing only patient samples. ADHD medication intake will be defined as the medical advice for taking a drug containing dextroamphetamine, methylphenidate or atomoxetine as included in a medical registry, or the purchase of these compounds. To be included in this analysis, studies will have to compare the risk of injuries during periods with and without medication. Studies comparing the incidence of injuries in groups of medicated and unmedicated patients will be excluded since medication usage is related to confounding variables for our research question, such as symptoms severity.[35]

Unintentional injuries

The WHO definition of unintentional injuries will be followed to decide inclusion of articles. Hence, articles reporting injuries covered with the codes S00-T98 of the 19th chapter of the ICD-10[47] will be deemed eligible. An exception will be studies specifically on traumatic brain injury (TBI) or concussions. These will not be included in the systematic review as they may introduce bias, since traumatic brain injury can increase attentional and impulsivity problems, as well as the risk of an ADHD diagnosis.[48] Studies on intoxications will not be included either, as results would probably be influenced by the greater access of individuals with ADHD to medications and not the intrinsic characteristics of ADHD.[49]

We will include studies where injuries were documented in a medical setting, reported through medical registries, recorded in medical histories or self-reported. Articles in which the injuries were self-induced will be excluded. Examples of the latter type of injury include self-mutilation and fight-related injuries.

Studies in which individuals suffered an unintentional injury before being diagnosed will be included. Indeed, there is no reason to suspect a temporal relationship between injuries and diagnosis once TBI studies are omitted. Finally, studies reporting risk of injuries in general, that is, without discriminating between intentional or unintentional injury, will be included in the meta-analysis, as the majority of injuries in children or adolescents are expected to be unintentional in nature.

Controls

We will define controls as children and adolescents under the age of 18 without ADHD. Specifically, we will include as controls: 1) individuals recruited from samples thought to represent the general population that do not have any psychiatric or neurological disorder, 2) individuals thought to represent the general population that do not have ADHD but could have other psychiatric or neurological disorders or 3) individuals who were recruited specifically from other clinical populations other than ADHD that a priori were not judged by the study authors to be related to an increased risk unintentional injuries.

Types of studies to be included

We will pool the results from any published or unpublished study that contrasts unintentional injuries in children or adolescents with ADHD and in typically developing individuals (meta-analysis of risk), or alternatively in patients with ADHD while taking and not taking medication (meta-analysis on the effect of medications, which will compare time points with or without medication). Empirical papers that include statistical analyses (ie, typically not reviews, letters, commentaries and editorials) with any kind of design will be accepted (mainly cohort studies, case and controls and cross-sectional studies but also clinical trials). Any temporality of the design (ie, prospective, retrospective or cross-sectional) or setting (clinical or general population) will also be accepted.

It is well known that the risk of unintentional injuries is highly related to male gender. Similarly, ADHD diagnosis is fourfold more prevalent in males. Any outcome derived from a control and ADHD sample with a different proportion of sexes between them that is not statistically controlled will be doomed to show an spuriously high risk of injuries in the ADHD group due to this co-correlation. Therefore, we will only include studies that control for sex differences between individuals with ADHD and controls either by sample selection or statistically. It must be noted that the meta-analysis by Amiri *et al* did not take into account this confounder when selecting their outcomes and this could be yielding higher estimates of risk.[38]

When evaluating medication effects, only studies using a SCCS methodology will be included a priori.[31] Studies that controlled for individual differences between the medicated and unmedicated groups with different techniques than the SCCS will be judged on a case-by-case basis for inclusion in a secondary comparison aimed at evaluating the robustness of the main comparison in addition to SCCS studies. This could include randomised controlled trials, studies comparing a short period before and after starting medication usage or other designs not foreseen.

We will not limit the inclusion for papers to any specific language.

Information sources

Electronic searches will be performed separately in the following databases:

- PubMed (Medline Plus)
- Scopus
- Web of Science Core Collection

A similar search will be carried out in UNIKA (http://www.unav.edu/en/web/biblioteca), an institutional reference aggregator that uses the EBSCO discovery service (http://support.ebsco.com/help/index.php?lang=en&int=eds) to provide a combined list of references from both internal (library) and external (database vendors) sources. For a list with the 113 most important databases for medical research scoped through this service see the online supplementary file. We will perform searches in these databases from their inception to date without limiting the type of study, language or year. Additionally, the International Clinical Trials Registry Platform Search Portal and ClinicalTrial.gov will be checked to find ongoing or recently ended trials and, conversely, PROSPERO will be searched for ongoing or recently completed systematic reviews. Once the electronic search is completed, references from each pertinent paper will be checked in order to find out if there are any relevant studies which had been missed during the database searches.

Search strategy

The following search syntax will be used to find relevant terms in reference titles, abstracts or keywords (any field in the case of Medline-PubMed). Search terms and syntax will be adapted for each specific database: all the different searches can be found in the online supplementary file.

(ADHD OR adhd OR attention deficit disorder with hyperactivity OR syndrome hyperkinetic OR hyperkinetic syndrome OR hyperactivity disorder OR hyperactive child syndrome OR childhood hyperkinetic syndrome OR attention deficit hyperactivity disorders OR attention deficit hyperactivity disorder OR adhd attention deficit hyperactivity disorder OR adhd OR overactive child syndrome OR attention deficit hyperkinetic disorder OR hyperkinetic disorder OR attention deficit disorder hyperactivity OR attention deficit disorders hyperactivity OR child attention deficit disorder OR hyperkinetic syndromes OR syndromes hyperkinetic OR hyperkinetic syndrome childhood) AND ((fracture OR fractures OR traumatism OR traumatisms OR traumatology OR wound OR wounds OR drowning OR poisoning OR burning) OR ((trauma OR traumat* OR harm OR lesion OR lesions OR injury OR injuries) AND (emergency OR emergency visit OR emergency room OR hospital OR hospitaliz* OR er OR inpatient))).

The whole process of article selection will be presented in a diagram following the PRISMA guidelines.

OUTCOMES

Primary outcomes

Our primary outcome measure will be the OR of ADHD individuals suffering unintentional injuries that are evaluated at a medical setting (primary care doctor or any

other type of medical professional, emergency room or specialist care) compared with individuals without ADHD. The OR is the most common reported measure and the only one that can be obtained when comparing the number of individuals with ADHD in an injured sample to a non-injured group. The variable 'injuries' will have to be described dichotomously, that is, whether an individual has suffered an injury or not. If OR is not directly reported in the paper, but data to calculate it are, we will determine the OR for that particular study.

Since more than one injury can occur in one individual, the use of Cox Proportional Hazards Models is desirable since HR estimate the rate to injuries and are independent of the time of follow-up. Whereas this kind of studies is rare, we will additionally evaluate the average effect size of studies reporting HR outcomes.

In the case of the meta-analysis evaluating the efficacy of ADHD medication, the primary outcome will be the incident rate ratio (IRR) obtained from SCCS studies. The incident rate is a measure of event frequency during a period of time. It is defined as the count of events divided by the observed person-time. The IRR is a relative measure which consists of dividing the incident rates of two different conditions. We will specifically compare injury occurrence among subjects with ADHD when medicated to the periods without medication, taking into account the fact that the time on medication varies between subjects. The number of events (injuries) and the person-time at risk during the periods with and without medication will be needed for its calculation.

If effect measures other than OR, HR (from Cox models) or IRR are reported, and OR (or IRR for the medication case) cannot be calculated from the data in the studies, the authors will be contacted to gather relevant data.

Identification and selection of studies

Studies identified with electronic and manual searches will be listed with citation, titles and abstracts in Mendeley (Elsevier, New York) and duplicates will be excluded both using the function 'delete duplicates' of Mendeley and manually removing duplicates not discarded automatically. Members of the review team will be trained in software utilisation before starting the review.

Article screening against inclusion criteria will be carried out independently by two of the authors (MR and GA), who will try to reach consensus in case of discrepancies between them. A third author (SC) will arbitrate in the final decision whenever consensus is not reached.

There will be two stages in the articles selection process:

- The title and abstracts of all non-duplicated papers will be screened, and studies that clearly do not fulfil the inclusion criteria will be excluded from further analysis. If the two evaluators disagree in their ratings, articles will be moved forward to the next phase.
- All text of articles remaining from the previous screening will be downloaded. Eligibility will be judged following the same scheme than during the previous phase: the same two authors will independently evaluate the studies for eligibility and seek comments from a third author in case of discrepancy.

As studies may sometimes be published as several reports, we will actively search for duplicate reporting of studies, taking into account as main indicators location of the study, authors and year. Whenever a study includes data from multiple reports, they will be linked in the data extraction sheet and data from the largest sample, when possible, will be used. In the case of prospective studies, only baseline data will be analysed. Corresponding authors of the original studies will be contacted to clarify article eligibility if necessary.

A list of excluded studies will be provided with reasons for exclusion. This list will include all articles that were preliminarily retained after stage 1 (selection from title and abstract) but finally excluded in stage 2.

Data extraction

All articles considered appropriate in the previous stage will be read and analysed by at least two independent authors (one will always be MR or GA), who will extract the key information and include it in a Microsoft Excel document, with a third author acting as an arbitrator when consensus on discrepancies is not reached (SC). This phase will be first piloted with a small number of articles. The Excel file will have as many drop-down lists as possible to maximise inter-rater reliability, and also space for notes. Moreover, it will also include in-cell messages with help texts. A training session will be provided for all researchers involved in data coding.

Data on publication and data extraction details will be inserted in an excel sheet as follows: first author, journal, year of publication, country(ies) where the study was conducted and a more specific location such as region or hospital when applicable, final checking of fulfilment of inclusion and exclusion criteria and date and author of data extraction.

The description of the study design will include type of study (cross-sectional, case-control, cohort or clinical trial); temporal sequence (prospective, retrospective or cross-sectional, duration of follow-up, participants enrolment (consecutive, non-consecutive); setting (clinical vs epidemiological population study) and year in which data acquisition for the study was carried out.

Regarding participant details, we will code sample size, age, gender distribution, ethnicity and sociodemographic status, characteristics of participants without ADHD (no ADHD, no ADHD or other conditions or comparisons with other diagnostic categories other than ADHD); psychiatric comorbidities of individuals with and without ADHD (type and prevalence); method to establish the diagnosis of ADHD (self-reported diagnosis, diagnosis recorded in medical files/registry, structured or semi-structured interview according to DSM or ICD, questionnaires, per medication usage or positive answer to the question: "Have you ever been told you have ADHD?"); medication status of individuals with and

without ADHD (type of medication and percentage of treated participants).

The primary outcome will be the OR (or HR) of suffering an unintentional injury in individuals with ADHD versus children and adolescents without ADHD. In relation to outcomes, data that will be coded include treatment setting (acute care hospitals, emergency facilities, general practice, medical specialist or other, including extended care facilities such as nursing homes, offices, schools and communities), method to document injuries (registry, acute treatment, through expert retrospective analysis or self-report), type of injury (traumatology, traffic injuries, drowning, poisoning, burns and chemical, other unintentional, self-induced, any kind of accidental injury or any kind of injury) and body location of the injuries.

To obtain ORs, any numeric data (raw number of accidents in each of the samples or ORs and their CIs) will be coded including both unadjusted analyses and analyses adjusted for covariates. In the latter case, covariates will also be included in the data extraction sheet. Finally, the reporting of any subgroup analysis or comparison of interest, the presence of other intervention groups and the main conclusions of the reports will also be annotated.

Whether the incidence of unintentional injuries differs between individuals with ADHD with medication and patients with ADHD without it will be assessed in a second meta-analysis. The data extraction sheet used for this second analysis will have the same variables and coding, but IRR instead of OR will be used.

We will extract information on multiple outcomes per article. Specifically, outcomes from different age or gender groups, multiple control groups, varying diagnosis techniques or statistical models will be valid. We will not include outcomes differentiating by injured body part. Each outcome or comparison will all be included in the spread sheet using a different line. A different comparison ID will be used in such case in combination with a report and study ID to link all related data.

Assessment of study quality and bias in included studies

The evaluation of study quality and possible bias will be individually performed by two researchers for each article. As there is no agreement about the best method to evaluate study quality in meta-analyses of observational studies, we will use an adapted version (included in the online supplementary file) of the Newcastle-Ottawa Scale,[50] which has been used in several previous meta-analyses[51 52] and is reviewed in the Cochrane Handbook. This scale evaluates the sample selection methods, the comparability among studied groups and the ascertainment of either the exposure (in case-control studies) or outcome of interest (for cohort studies) of non-randomised studies.

ANALYSIS PLAN

All analyses will be carried out in Stata, R and Matlab.

Meta-analysis of differences in risk between ADHD and controls

ORs will be calculated from the reported data if they cannot be directly extracted. OR and HR above 1 will indicate a higher risk of unintentional injuries in the ADHD population compared with the non-ADHD groups. All valid outcomes from articles will be included in a single database. These will include any unadjusted or adjusted OR or HR which would fulfil independently the inclusion criteria of our meta-analysis. Multiple valid outcomes within the same report are expected, often due to studies using different diagnosis strategies, reporting results in subgroups or including different valid treatment settings. This database will also encode other continuous or dichotomous (dummies) variables of interest for the meta-regression and subgroup analyses.

If an article reports two separates studies they will be considered independent, and conversely, if two articles report results on the same data or database they will be considered as multiple outcomes from the same study.

Heterogeneity and small sample bias

Q-Cochran's[53] and the I^2 index[54] will be used to evaluate heterogeneity between studies. Cochran's Q is calculated as the weighted sum of squared differences between individual study effects and the meta-analytic estimate. Weights are the same as in the meta-analysis (basically sample sizes), and hence, this measure is known to have low power when there are few and small studies. Conversely, the test has excessive power with many or big studies. The I^2 index is a newer, complementary measure that describes the percentage of total variation across studies that is due to heterogeneity, and it does not depend on the number of studies considered. The higher the I^2 value the higher the heterogeneity in the results, with values >50% indicating substantial heterogeneity.

Begg's adjusted rank correlation test[55] will be used to formally assess the presence of 'small-sample' bias (which encompasses publication bias); an approach that will be combined with the use of funnel plots for a qualitative visual analysis, and statistical testing of asymmetry.[56]

A single effect size will be used per study to calculate the degree of between-study heterogeneity and the risk of small-sample bias. The most general and statistically controlled outcome per study will be used. If there is more than one possible outcome fulfilling these criteria, it will be chosen at random from the available outcomes.

Dependency among outcomes

Effect sizes are assumed independent in standard meta-analytical procedures. A common way to deal with the non-independence of outcomes has been to compute a mean outcome and use the study-level combined measure in the meta-analysis,[57] but this approach leaves out potentially relevant information. A recent alternative is Robust Variance Estimation (RVE), a statistical technique that models the nested structure between outcomes of the same study.[58] RVE empirically estimates

the sampling variance in a way that is robust to misspecification of the weights and regarding the assumptions on distributions of the effect. Estimation of the meta-analytic parameters through RVE is adequate for dichotomous outcomes when enough studies are included.[59 60] Moreover, RVE has been shown to produce similarly unbiased results to other, more complex, methods of dealing with multiple outcomes and it is more efficient than averaging effects within studies.[61] A main advantage compared with other methods is that it does not require to have information on the covariance structure of the effect sizes, an information that is typically hard to acquire.

Whereas this method yields valid results regardless of the weights used, a strategy using approximate inverse-variance weights has been proposed for efficiency purposes: a random-effects model with variation of effect sizes between studies (τ^2) and equicorrelation (p) between same-study effect sizes (I^2) is assumed.[58] This strategy is efficient to estimate a mean model from outcomes which are typically correlated at the study level, but are usually independent between studies. We will use p=0.8, similarly to previous studies,[62] but these same studies and simulations by the RVE authors have shown little change with different values of p.[63] Moreover, a sensitivity analysis with varying levels of p can be carried out to check the influence of such decision.[58] RVE has been implemented in Stata and R and there are published guidelines for it.[64 65] This implementation includes an improved estimation for small samples.[66] We will use RVE for the inference of a mean effect size and meta-regression analyses. Regarding meta-regression, as df are obtained from the number of studies (instead of outcomes) and variables are likely to be correlated, it will be performed separately for each variable (bivariate regressions). RVE distinguishes between interstudy effects (variability due to factors that change at the study level but are maintained for different outcomes) and intrastudy effects (variability due to factors that change at the outcome level). An example of the former would be publication date, and an example of the latter would be sex in the case of those studies that report ORs separately for boys and girls. It must be noted however, that factor can vary both interstudies and intrastudies, for example, mean age also changes between studies.

Mean effect sizes

We will first calculate a population-average effect size (ORs and HRs separately) through the combination of the most general and better statistically controlled outcome per study. If there is more than one possible outcome fulfilling these criteria they will all be included in the analysis.

Initial sensitivity analyses for this average effect size will be: 1) to vary in 0.1 steps the p correlation parameter, 2) to compare articles with a follow-up of a year or less to articles with a longer follow-up (including variable follow-ups). Since an individual can have more than one injury along their life, but only dichotomous outcomes are considered, different observation periods could modify differences between groups.

Additional sensitivity analyses will derive from the variety of designs accepted and the definitions of patients and controls. Data will be reanalysed excluding case-control studies (comparing injured vs non-injured individuals). Similarly, an analysis only using the most stringent definitions of ADHD (DSM, ICD, registry or clinical history) and controls (excluding studies with clinical control groups) will be carried out. Studies in which injuries are self-reported will be eliminated in another analysis. Risk of bias (number of stars in the Newcastle-Ottawa Scale) will be considered a continuous variable and its effect evaluated. A final analysis will compare the effect size of studies in which data were acquired before and after the year 2000.

Two other population average models will be obtained by 1) computing a mean effect size only including unadjusted OR and 2) computing a mean effect size only including adjusted OR.

Effect sizes whose 95% CIs do not cover zero will be considered significant. All the effects described in this section are interstudy.

Subgroup analyses and meta-regression

We will also assess, if feasible, the moderating role of clinical and design variables at the intrastudy and interstudy levels. The former include gender, age, comorbidity (mainly ODD and CD), medication status and prevalence of ADHD, whereas the latter includes the setting of treatment. The data to be used in these analyses will include any outcome which would independently fulfil the inclusion criteria as long as they differ in something else than the statistical model used to obtain them: If there is more than one statistical model for the same data, the outcome derived from the model controlling for more covariates will be used. Percentage of medicated patients, age (ideally the mean or median of the whole group, otherwise midpoint in the interval of ages) and prevalence of ADHD (percentage of ADHD that a given diagnostic strategy yields in a cohort) will be included as continuous variables and their effect estimated through meta-regression. We will also explore the feasibility of conducting the following subgroup analyses: 1) male vs female participants, 2) three age groups (4–8, 9–13 and 14–17 years), 3) clinical setting (physician office visits, emergency department visit and hospitalisation). In all these cases, differences between groups will be statistically tested ($p<0.05$ will be considered significant). In the case of sex, intrastudy outcomes reported only in males will be compared with outcomes of studies in which ORs are reported for both boys and girls, and the same will be done for outcomes in females.

The evaluation of the effect of comorbidity is important in our meta-analysis, but such an effect is difficult to meta-analyse since studies handle it very differently. We are especially interested in disentangling the effect ODD and CD from that of ADHD. We will compare outcomes from studies in which the rate of ODD/CD is not controlled to

those in which the presence of ODD or CD is controlled in the patient sample by design (excluding subjects with ODD or CD) or statistically, and to those in which all patients have comorbidity with these disorders. If feasible, a similar analysis including any other comorbidities will be executed.

Sensitivity and meta-regression analyses will be carried out only for the combination of ORs, as we do not expect enough studies to carry out this kind of analyses for the combination of HRs.

Meta-analysis on the effect of medication

The second objective of the present project will be to assess the medication effect in the probability of non-intentional injuries occurrence. For this purpose, the chosen measure of association will be the IRR. Heterogeneity and presence of 'small-sample' bias will be evaluated as in the first meta-analysis.

A generalised linear mixed model using the Poisson distribution with the log link function will be implemented.[67] Specifically, since it is expected that a small number of studies will be included in this meta-analysis, a fixed effects Poisson regression model will be carried out. In this model, the dependent variable is set as the logarithm of the total number of counts, the logarithm of the person-time is included as an offset and the medication is included as an explanatory variable. Additionally, the model incorporates dummy variables as study-specific fixed effects, in order to preserve the within studies comparison of medicated versus non-medicated groups.

Sensitivity analyses will be performed based on the exclusion of studies which do not implement a self-controlled case series design.

PLANNED CONTRIBUTIONS TO THE META-ANALYSIS

The tasks regarding the systematic review and the meta-analysis will be as follows: MRG and GA will conduct searches, screen papers and retain those that fulfil inclusion criteria. SC will arbitrate discrepancies between these researchers regarding article inclusion. MRG GA, NA, SM, EL and PdCM will read the included papers and extract the data. MAS, GA, MRG and SC will carry out the statistical analysis. PdCM, SC and CS will provide expertise on issues related to child and adolescent psychiatry and results interpretation/implications. GA and MR will draft the article discussing the results and SC and CS will further edit it. All collaborators will approve the final article.

ETHICAL CONSIDERATIONS AND DISSEMINATION PLANS

No ethical issues are predicted. All the authors will declare if they have any competing conflict of interest. The results will be published in a peer-reviewed journal and presented at national and international conferences of psychiatry, psychology, paediatrics and traumatology.

REGISTRATION AND STATUS

Before data extraction completion, the protocol of this meta-analysis was registered in PROSPERO, an international register of protocols for health-related systematic reviews supported by the National Institute of Health Research (NIHR) and maintained by the University of York (UK). Registration date: 8 May 2017, protocol number CRD42017064967. Writing of the protocol and preliminary searches started by June 2016. Data piloting commenced in September 2016. Data extraction started in December 2016 an ended in August 2017. Data analysis is estimated to end by August 2017.

Author affiliations
[1]Servicio Navarro de Salud-Osasunbidea, Servicio de Urgencias Extrahospitalarias, Pamplona, Spain
[2]Center for Innovation in Mental Health, University of Southampton, Academic Unit of Psychology, Southampton, UK
[3]Faculty of Medicine, Clinical and Experimental Sciences (CNS and Psychiatry), University of Southampton, Southampton, UK
[4]Department of Child and Adolescent Psychiatry, NYU Langone Medical Center, New York, NY, USA
[5]Facultad de Educación y Psicología, Universidad de Navarra, Pamplona, Spain
[6]Departamento de Psiquiatría y Psicología Médica, Unidad de Psiquiatría Infantil y Adolescente, Clínica Universidad de Navarra, Pamplona, Spain
[7]Instituto Cultura y Sociedad (ICS), Grupo Mente-Cerebro, Universidad de Navarra, Pamplona, Spain

Contributors GA is the guarantor of the project, MRG had the idea for the project, GA and MRG drafted the protocol, MAS provided statistical expertise and revised the analysis section, CS and SC provided feedback on ADHD, SC edited the first drafts and gave feedback on protocol and meta-analysis design. MRG, SC, MAS, SM, NAZ, EL, PdCM, CS and GA helped on the overall design of the meta-analysis and approved the final version of the protocol.

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3.1.4. Material suplementario

Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: protocol for a systematic review and meta-analysis

Supplementary Information

Maite Ruiz-Goikoetxea, Samuele Cortese, Maite Aznarez-Sanado, Sara Magallon Elkin Luis, Noelia Alvarez, Pilar de Castro-Manglano, Cesar Soutullo, Gonzalo Arrondo*

* Universidad de Navarra, Instituto Cultura y Sociedad (ICS), Grupo Mente Cerebro. Pamplona, Navarra, Spain. Email: garrondo@yahoo.es

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Pilar de Castro-Manglano , M.D., Ph.D.

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He has served as Consultant / Advisory Board for:

- Alicia Koplowitz Foundation,
- Editorial Médica Panamericana,
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He has served in the Speaker's Bureau / has given talks on Continuous Medical Education (not about a product) for:

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Databases included in the Unika Service

The databases included in the biomedical sciences profile of the Unika Service from the University of Navarra are named here in alphabetical order:

1. Academic Search Index (asx)
2. AccessAnesthesiology
3. AccessMedicine
4. AccessPediatrics
5. AccessScience
6. AccessSurgery
7. Ambrose Digital Library
8. ASM Handbooks Online (edsaho)
9. ASM Medical Materials Database
10. ASM Micrograph Database
11. BioOne Online Journals
12. Books at JSTOR
13. British Library Document Supply Centre Inside Serials & Conference Proceedings (edsbl)
14. British Standards Online
15. Business Source Complete
16. Canadian Electronic Library
17. Catálogo de la Biblioteca de la Universidad de Navarra (cat00378a)
18. Center for Research Libraries
19. ChemSpider
20. China/Asia On Demand
21. CINAHL (cin20)
22. CogPrints
23. Credo Reference Collections (edscrc)
24. DADUN (ir00048a)
25. DASH
26. Data-Planet Statistical Datasets & Statistical Ready Reference
27. Dialnet
28. Directory of Open Access Journals (edsdoj)
29. eArticle
30. eBook Academic Collection (EBSCOhost) (e000xww)
31. eBook Collection (EBSCOhost) (nlebk)
32. EconLit (ecn)
33. EDS Foundation Index (eda)
34. eLibro Premium
35. ERIC (eric)
36. eScholarship (edssch)
37. EThOS
38. EU Bookshop (edseub)
39. European Union Open Data Portal
40. Europeana
41. Expanded Academic ASAP
42. Films on Demand
43. Fuente Académica Premier (fua)
44. Gale Cengage Learning, Health & Wellness Resource Center
45. Gale Virtual Reference Library
46. Gallica Bibliothèque Numérique
47. Google Book Search (fe334f7c)
48. GreenFILE (8gh)
49. Harvard Library Bibliographic Dataset (edshlc)
50. HathiTrust (edshtl)
51. Henry Stewart Talks
52. HighWire Press (fa0f9666)
53. Idunn.no
54. IndianJournals.com
55. Informit Health Collection (edsihc)
56. Iprbooks
57. JSTOR (fd43b2a1)
58. JSTOR Life Sciences (edsjls)
59. KERIS Theses & Dissertations (edsker)
60. Knigafund.ru (edskig)
61. Korean Studies Information Service System (KISS) (edskis)
62. LexisNexis Academic: Law Reviews (edslex)
63. Maruzen eBook Library
64. McGraw-Hill
65. Medical Online
66. Medical Online E-books
67. Medical Online-E
68. MEDLINE (cmedm)
69. Minority Health Archive (edsuph)
70. NARCIS
71. Networked Digital Library of Theses & Dissertations (edsndl)
72. NORA (Norwegian Open Research Archive)
73. OAIster (edsoai)
74. OJS vid Lunds Universitet (edsojs)
75. Ovid Journals Full Text Medical Research Database (fb0698e8)
76. Oxford Bibliographies Online
77. Oxford Clinical Psychology
78. Oxford Handbooks Online (edsoho)
79. Oxford Medicine Online
80. Oxford Reference (edsoro)
81. Oxford Scholarship Online (edsoso)

82. ProQuest Dissertations and Theses (fb458d87)
83. PsycARTICLES (edspdh)
84. PsycBOOKS (edspzh)
85. PsycCRITIQUES (edspvh)
86. PsycheVisual
87. Psychology and Behavioral Sciences Collection (pbh)
88. PsycINFO (psyh)
89. Publisher Provided Full Text Searching File (edb)
90. PubMed Central (fd5a6824)
91. R2 Digital Library
92. RACO
93. RECERCAT
94. ReferenceSearch (edsref)
95. RÖMPP Online
96. SA ePublications Service
97. SAGE Research Methods Datasets
98. SAGE Video
99. Scielo
100. Scielo Books
101. Science Citation Index (edswsc)
102. ScienceDirect (edselp)
103. Scopus
104. Social Sciences Citation Index (edswss)
105. Springer Science+Business Media, SpringerProtocols
106. STAT!Ref
107. Supplemental Index (edo)
108. SveMed+ (edssmd)
109. Torrossa
110. TOXNET: GENETOX
111. TOXNET: TOXLINE
112. University Library Online - Университетская библиотека онлайн
113. World Bank eLibrary (edswbe)

Search syntax

The following search syntax will be used to find relevant terms in reference titles, abstracts or key words (any field in the case of PubMed-Medline Plus).

PubMed (Medline Plus) and Unika

In the case of PubMed-Medline Plus, the search was not limited to any field. In the case of Unika, the search was limited to titles, keywords, and abstracts through the website options

(ADHD OR adhd OR attention deficit disorder with hyperactivity OR syndrome hyperkinetic OR hyperkinetic syndrome OR hyperactivity disorder OR hyperactive child syndrome OR childhood hyperkinetic syndrome OR attention deficit hyperactivity disorders OR attention deficit hyperactivity disorder OR adhd attention deficit hyperactivity disorder OR adhd OR overactive child syndrome OR attention deficit hyperkinetic disorder OR hyperkinetic disorder OR attention deficit disorder hyperactivity OR attention deficit disorders hyperactivity OR child attention deficit disorder OR hyperkinetic syndromes OR syndromes hyperkinetic OR hyperkinetic syndrome childhood) AND ((fracture OR fractures OR traumatism OR traumatisms OR traumatology OR wound OR wounds OR drowning OR poisoning OR burning) OR ((trauma OR traumat* OR harm OR lesion OR lesions OR injury OR injuries) AND (emergency OR emergency visit OR emergency room OR hospital OR hospitaliz* OR er OR inpatient)))

Scopus

TITLE-ABS-KEY ((ADHD OR adhd OR "attention deficit disorder with hyperactivity" OR "syndrome hyperkinetic" OR "hyperkinetic syndrome" OR "hyperactivity disorder" OR "hyperactive child syndrome" OR "childhood hyperkinetic syndrome" OR "attention deficit hyperactivity disorders" OR "attention deficit hyperactivity disorder" OR "adhd attention deficit hyperactivity disorder" OR adhd OR "overactive child syndrome" OR "attention deficit hyperkinetic disorder" OR "hyperkinetic disorder" OR "attention deficit disorder hyperactivity" OR "attention deficit disorders hyperactivity" OR "child attention deficit disorder" OR "hyperkinetic syndromes" OR "syndromes hyperkinetic" OR "hyperkinetic syndrome childhood") AND ((fracture OR fractures OR traumatism OR traumatisms OR traumatology OR wound OR wounds OR drowning OR poisoning OR burning) OR ((trauma OR traumat* OR harm OR lesion OR lesions OR injury OR injuries) AND (emergency OR "emergency visit" OR "emergency room" OR hospital OR hospitaliz* OR er OR inpatient))))

Web of Science (Core Collection)

TS= ((ADHD OR adhd OR "attention deficit disorder with hyperactivity" OR "syndrome hyperkinetic" OR "hyperkinetic syndrome" OR "hyperactivity disorder" OR "hyperactive child syndrome" OR "childhood hyperkinetic syndrome" OR "attention deficit hyperactivity

disorders" OR "attention deficit hyperactivity disorder" OR "adhd attention deficit hyperactivity disorder" OR adhd OR "overactive child syndrome" OR "attention deficit hyperkinetic disorder" OR "hyperkinetic disorder" OR "attention deficit disorder hyperactivity" OR "attention deficit disorders hyperactivity" OR "child attention deficit disorder" OR "hyperkinetic syndromes" OR "syndromes hyperkinetic" OR "hyperkinetic syndrome childhood") AND ((fracture OR fractures OR traumatism OR traumatisms OR traumatology OR wound OR wounds OR drowning OR poisoning OR burning) OR ((trauma OR traumat* OR harm OR lesion OR lesions OR injury OR injuries) AND (emergency OR "emergency visit" OR "emergency room" OR hospital OR hospitaliz* OR er OR inpatient)))

Modified Newcastle-Ottawa Scale

Studies comparing injured-non injured (case-control studies)

Selection

1) Is the case definition adequate?
a) yes, with independent validation * (acute injury or record linkage+interview or other validation)
b) yes, eg record linkage or based on self-reports
c) no description

2) Representativeness of the cases
a) consecutive or obviously representative series of cases*
b) potential for selection biases or not stated

3) Selection of Controls
a) community controls *
b) hospital controls
c) no description

4) Definition of Controls
a) no history of disease (endpoint) *
b) no description of source

Comparability (up to 2 stars)

1) Comparability of injured and non-injured individuals on the basis of the design or analysis (Note: all articles should control sex for inclusion).
a) study controls for AGE and COMORBIDITY **
b) study controls for AGE *
c) study controls for COMORBIDITY *

Exposure (ADHD)

1) Ascertainment of ADHD
a) secure record (eg surgical records) or data linkage *
b) structured interview *
c) written self-report, (not codified) medical history or clinical questionnaire
d) no description

2) Same method of ascertainment for cases and controls
a) yes *
b) no

3) Non-Response rate
a) same rate for both groups *
b) non respondents described
c) rate different and no designation

Cohort studies

Selection

1) Representativeness of the exposed cohort. Individuals with ADHD are
a) truly representative of the average child with ADHD in the community *
b) somewhat representative of the average child with ADHD in the community (individuals may differ slightly from the typical ADHD child)*
c) selected group of users eg only medicated ADHD, all ADHD+Comorbidity, only one sex, only hospitally-treated ADHD...
d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort (individuals without ADHD)
a) drawn from the same community as the exposed cohort *
b) drawn from a different source
c) no description of the derivation of the non-exposed cohort

3) Ascertainment of ADHD
a) secure record (eg surgical records) or data linkage *
b) structured interview *
c) written self-report, (not codified) medical history or clinical questionnaire
d) no description

4) Demonstration that outcome of interest was not present at start of study: IRRELEVANT IN OUR CASE THAT ADHD IS PRESENT BEFORE STUDY STARTS
a) yes *
b) no

Comparability (up to 2 stars)

1) Comparability of individuals with ADHD and no ADHD on the basis of the design or analysis (NOTE: all studies should control for gender)
a) study controls for AGE and comorbidity **
b) study controls for AGE *
c) study controls for comorbidity *

Outcome

1) Assessment of the lesions
a) independent blind assessment * (NOT RELEVANT IN OUR CASE)
b) record linkage *
c) self-report
d) no description

2) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for *
b) subjects lost to follow up unlikely to introduce bias - small number lost - >80 % follow up, or description provided of those lost) *
c) follow up rate < 80% and no description of those lost
d) no statement

Cross-sectional studies

Selection

1) Representativeness of the exposed cohort. Individuals with ADHD are
a) truly representative of the average child with ADHD in the community *
b) somewhat representative of the average child with ADHD in the community (individuals may differ slightly from the typical ADHD child)*
c) selected group of users eg only medicated ADHD, all ADHD+Comorbidity, only one sex, only hospitally-treated ADHD...
d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort (individuals without ADHD)
a) drawn from the same community as the exposed cohort *
b) drawn from a different source
c) no description of the derivation of the non-exposed cohort

3) Ascertainment of ADHD
a) secure record (eg surgical records) or data linkage *
b) structured interview *
c) written self-report, (not codified) medical history or clinical questionnaire
d) no description

4) Demonstration that outcome of interest was not present at start of study: IRRELEVANT IN OUR CASE THAT ADHD IS PRESENT BEFORE STUDY STARTS
a) yes *
b) no

Comparability (up to 2 stars)

1) Comparability of individuals with ADHD and no ADHD on the basis of the design or analysis (NOTE: all studies should control for gender)
a) study controls for AGE and comorbidity **
b) study controls for AGE *
c) study controls for comorbidity *

Outcome

1) Assessment of the lesions
a) independent blind assessment * (NOT RELEVANT IN OUR CASE)
b) record linkage *
c) self report
d) no description

2) Non-respondents:
a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. *
b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
c) No description of the response rate or the characteristics of the responders and the non-responders.

3.2. Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: A systematic review and meta-analysis

3.2.1. Antecedentes

Se describen a continuación los resultados de la revisión sistemática y metanálisis para evaluar la asociación entre el TDAH y el riesgo de padecer LNIs; y el efecto de la medicación sobre este riesgo.

3.2.2. Metodología

Estos resultados derivan de la metodología descrita en el artículo: "*Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: protocol for a systematic review and meta-analysis"*, resumida en la sección 3.1.

3.2.3. Resultados

Se combinaron los resultados de 114 bases de datos que incluyesen artículos publicados y fuentes de literatura gris ("La Literatura Gris," 2011) (tesis doctorales, actas de congresos, estudios no publicados, etc.) hasta junio de 2017. De un conjunto de 2.801 referencias potencialmente relevantes, que fueron evaluadas de forma independiente por dos investigadores 30 estudios se incluyeron finalmente en el metanálisis de riesgo y 5 estudios en el metanálisis sobre el efecto de medicación. Para el análisis del riesgo se combinaron estudios que evaluaban la asociación entre el TADH y el riesgo de lesiones y que aportaban OR o HR contralados por sexo en el diseño o en el análisis. Tras combinar 28 estudios que aportaban OR, se alcanzó un tamaño muestral de 350.938 individuos con TDAH y 4.055.620 individuos sin el trastorno. La OR combinada era de 1,53 (I.C. 95% =1,40-1,67). En el caso de HR se analizaron 4 estudios (20.363 individuos con TDAH y 901.891 individuos sin el trastorno), con una HR resultante de 1,39 (I.C. 95%: 1,06-1,86).

No se encontraron resultados estadísticamente significativos al realizar análisis de metaregresión, en los que se investigaba el posible efecto modificador de distintas variables clínicas de interés como la edad (B = −0,001; IC 95% = −0,069- 0,068; p = 0,984) o el sexo (B = 0,071; IC 95% = −0,061-0,204; p = 0,205). Asimismo, se evaluó la posible relación de la comorbilidad psiquiátrica (presencia de trastorno negativista desafiante o trastorno de conducta) en el riesgo de lesiones. Al comparar, en el modelo de efectos fijos, los estudios que controlaban por la presencia de trastorno negativista desafiante frente a estudios en los que no se controlaba, tampoco se encontró una relación estadísticamente significativa (B = 0,32; IC 95% = −0,152 – 0,794; p = 0,119).

En la segunda parte del estudio se evaluó el efecto de la medicación en el riesgo de LNIs. Fue especialmente importante evitar estudios que pudiesen presentar confusión por sesgo de indicación, es decir aquellos artículos en los que se comparase a un grupo de pacientes no tratados con medicación frente a otro grupo de pacientes en tratamiento; ya que en este caso la medicación puede ser un

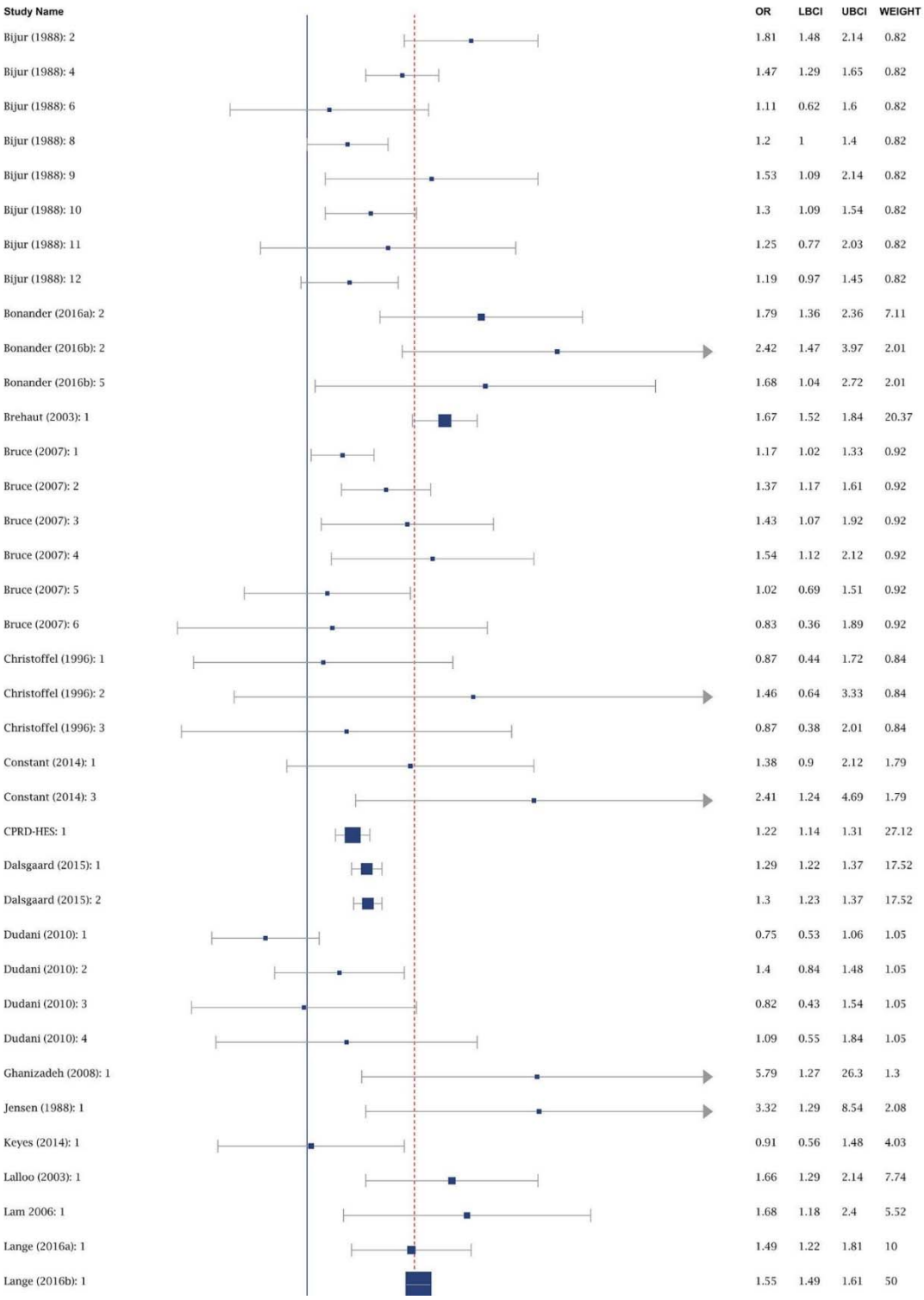
marcador de la gravedad del trastorno. Así se combinaron cuatro artículos que empleaban una metodología en la que cada individuo era su propio control y otro que evaluaba el riesgo a lo largo del tiempo y grupos (metodología "diferencia de las diferencias"). El medicamento más comúnmente prescrito en estos estudios era el MPH (en 4 de los 5 estudios incluidos, el quinto estudio no reportaba porcentajes de cada uno de los tratamientos farmacológicos). La combinación de estos cinco estudios llevó a un tamaño de efecto medio de 0,879 (I.C.95% = 0,838-0,922), resultante de combinar 13.524 individuos con TDAH. Este efecto protector se mantenía y no difería sustancialmente del obtenido al metanalizar únicamente los cuatro estudios con metodología auto-controlada (IRR= 0,898; I.C 95%: 0,851-0,948).

3.2.4. Conclusiones

Este estudio concluye que el TDAH está asociado significativamente a un aumento del riesgo de LNIs (OR 1,53; I.C. 95% =1,40-1,67) y que la medicación empleada como tratamiento para el TDAH tiene un efecto protector, reduciendo el riesgo relativo de sufrir una LNIs en un 12% en los periodos que los pacientes con TDAH reciben medicación frente a los no medicados. Por su diseño, el IRR obtenido a partir de los cuatro estudios que empleaban metodología auto-controlada indica una protección en el corto plazo. Por el contrario, los resultados encontrados en el único estudio que empleaba la metodología de "diferencia en las diferencias", combinados conjuntamente con los primeros (Dalsgaard et al., 2015a), indican que la medicación también podría resultar en una protección en el largo plazo, pero se requieren más estudios para evaluar si el efecto protector de la medicación se mantiene en el tiempo.

Ruiz-Goikoetxea M, Cortese S, Aznarez-Sanado M, Magallón S, Alvarez N, Luis EO, Castro-Manglano P, Soutullo C, Arrondo G. Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: A systematic review and meta-analysis. Neuroscience and Biobehavioral Reviews, 2018, 84: 63-71. https://doi.org/10.1016/j.neubiorev.2017.11.007

3.2.6. Imágenes suplementarias



Study Name	OR	LBCI	UBCI	WEIGHT
Bijur (1988): 2	1.81	1.48	2.14	0.82
Bijur (1988): 4	1.47	1.29	1.65	0.82
Bijur (1988): 6	1.11	0.62	1.6	0.82
Bijur (1988): 8	1.2	1	1.4	0.82
Bijur (1988): 9	1.53	1.09	2.14	0.82
Bijur (1988): 10	1.3	1.09	1.54	0.82
Bijur (1988): 11	1.25	0.77	2.03	0.82
Bijur (1988): 12	1.19	0.97	1.45	0.82
Bonander (2016a): 2	1.79	1.36	2.36	7.11
Bonander (2016b): 2	2.42	1.47	3.97	2.01
Bonander (2016b): 5	1.68	1.04	2.72	2.01
Brehaut (2003): 1	1.67	1.52	1.84	20.37
Bruce (2007): 1	1.17	1.02	1.33	0.92
Bruce (2007): 2	1.37	1.17	1.61	0.92
Bruce (2007): 3	1.43	1.07	1.92	0.92
Bruce (2007): 4	1.54	1.12	2.12	0.92
Bruce (2007): 5	1.02	0.69	1.51	0.92
Bruce (2007): 6	0.83	0.36	1.89	0.92
Christoffel (1996): 1	0.87	0.44	1.72	0.84
Christoffel (1996): 2	1.46	0.64	3.33	0.84
Christoffel (1996): 3	0.87	0.38	2.01	0.84
Constant (2014): 1	1.38	0.9	2.12	1.79
Constant (2014): 3	2.41	1.24	4.69	1.79
CPRD-HES: 1	1.22	1.14	1.31	27.12
Dalsgaard (2015): 1	1.29	1.22	1.37	17.52
Dalsgaard (2015): 2	1.3	1.23	1.37	17.52
Dudani (2010): 1	0.75	0.53	1.06	1.05
Dudani (2010): 2	1.4	0.84	1.48	1.05
Dudani (2010): 3	0.82	0.43	1.54	1.05
Dudani (2010): 4	1.09	0.55	1.84	1.05
Ghanizadeh (2008): 1	5.79	1.27	26.3	1.3
Jensen (1988): 1	3.32	1.29	8.54	2.08
Keyes (2014): 1	0.91	0.56	1.48	4.03
Lalloo (2003): 1	1.66	1.29	2.14	7.74
Lam 2006: 1	1.68	1.18	2.4	5.52
Lange (2016a): 1	1.49	1.22	1.81	10
Lange (2016b): 1	1.55	1.49	1.61	50

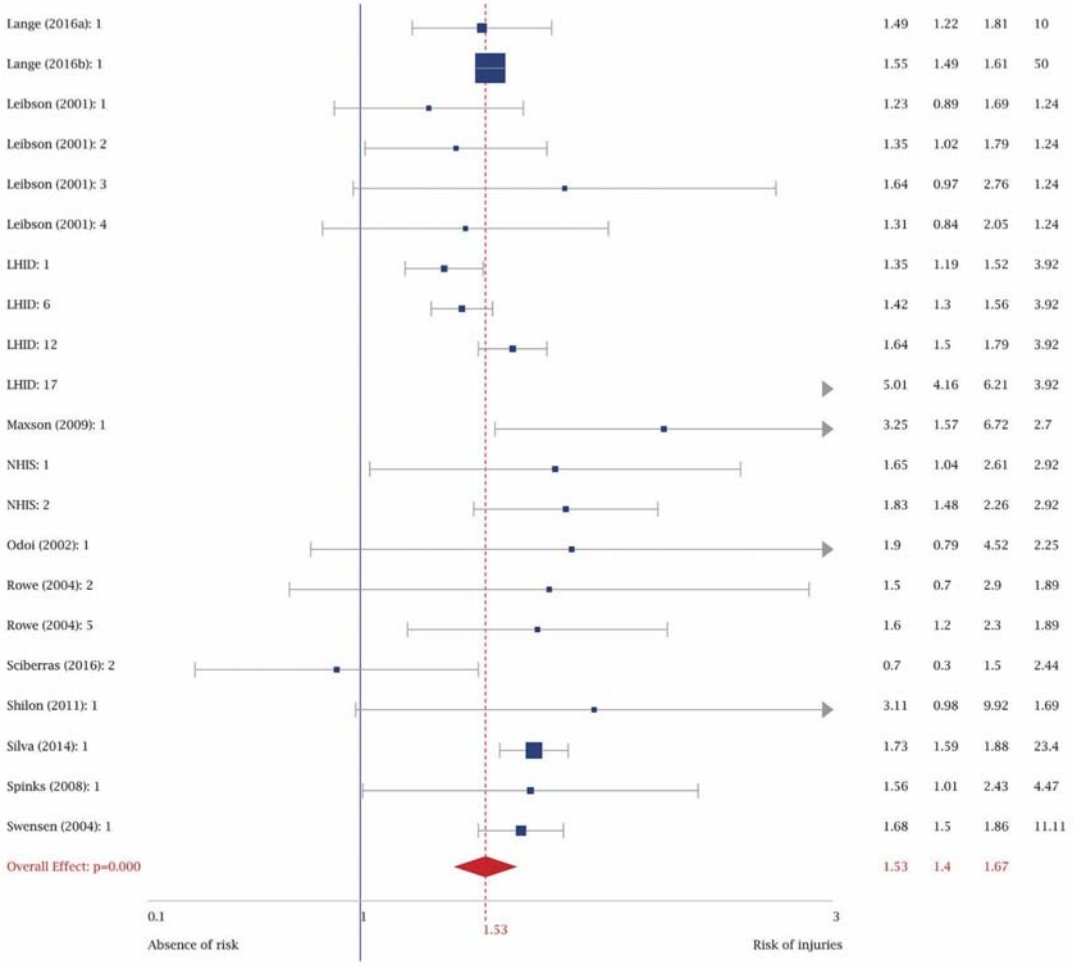


Figure S4 (Legend): Odds Ratios estimating the association between Unintentional Injury and ADHD.
Legend: a number identifying the study outcome follows study names. The area of each square is proportional to the weight that the individual study contributed to the meta-analysis. Weights are from a RVE random-effects model. The diamond indicates the overall weighted mean effect across all studies.

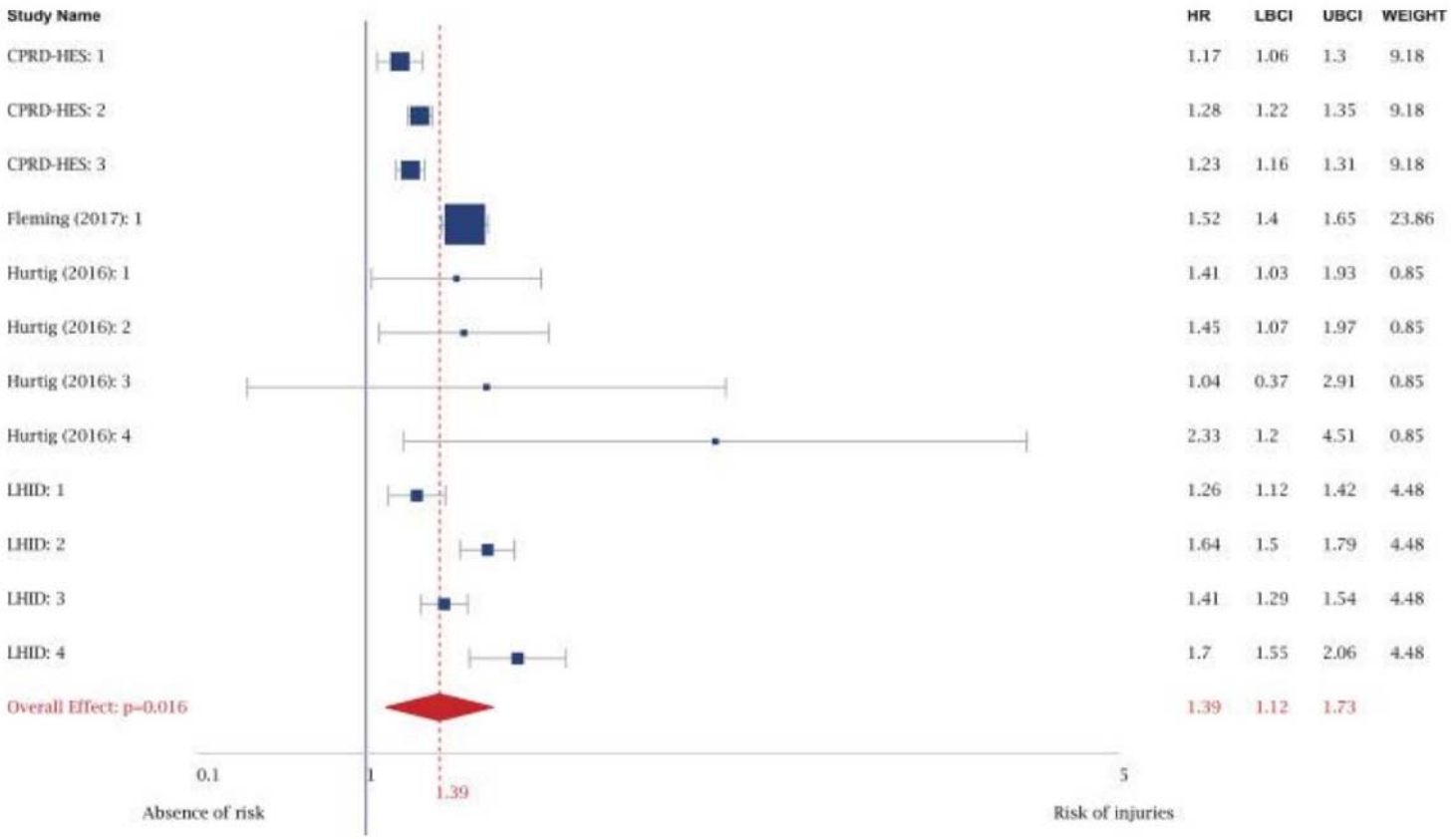


Figure S5 (Legend): Hazard Ratios estimating the association between Unintentional Injury and ADHD.
Legend: a number identifying the study outcome follows study names. The area of each square is proportional to the weight that the individual study contributed to the meta-analysis. Weights are from a RVE random-effects model. The diamond indicates the overall weighted mean effect across all studies.

3.2.7. Material suplementario

Supplementary Information. Neuroscience and Biobehavioral Reviews 84 (2018) 63–71

Doi: https://doi.org/10.1016/j.neubiorev.2017.11.007

Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: a systematic review and meta-analysis. Supplementary Information

Maite Ruiz-Goikoetxea, Samuele Cortese, Maite Aznarez-Sanado, Sara Magallon, Noelia Alvarez, Elkin Luis, Pilar de Castro-Manglano, Cesar Soutullo, Gonzalo Arrondo*

* Universidad de Navarra, Instituto Cultura y Sociedad (ICS), Grupo Mente Cerebro. Pamplona, Navarra, Spain. Email: garrondo@yahoo.es

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Methods S1: Search in databases and syntax

We searched

- PubMed (Medline Plus)
- Scopus
- Web of Science Core Collection,
- the International Clinical Trials Registry Platform Search Portal
- ClinicalTrial.gov
- UNIKA (An institutional reference aggregator that searches in 114 databases listed in the following section)

The following search syntax was used:

PubMed (Medline Plus) and Unika

(In relation to PubMed-Medline Plus, the search was not limited to any field. For Unika, the search was limited to titles, keywords, and abstracts through the website options)

(ADHD OR adhd OR attention deficit disorder with hyperactivity OR syndrome hyperkinetic OR hyperkinetic syndrome OR hyperactivity disorder OR hyperactive child syndrome OR childhood hyperkinetic syndrome OR attention deficit hyperactivity disorders OR attention deficit hyperactivity disorder OR adhd attention deficit hyperactivity disorder OR adhd OR overactive child syndrome OR attention deficit hyperkinetic disorder OR hyperkinetic disorder OR attention deficit disorder hyperactivity OR attention deficit disorders hyperactivity OR child attention deficit disorder OR hyperkinetic syndromes OR syndromes hyperkinetic OR hyperkinetic syndrome childhood) AND ((fracture OR fractures OR traumatism OR traumatisms OR traumatology OR wound OR wounds OR drowning OR poisoning OR burning) OR ((trauma OR traumat* OR harm OR lesion OR lesions OR injury OR injuries) AND (emergency OR emergency visit OR emergency room OR hospital OR hospitaliz* OR er OR inpatient)))

Scopus

TITLE-ABS-KEY ((ADHD OR adhd OR "attention deficit disorder with hyperactivity" OR "syndrome hyperkinetic" OR "hyperkinetic syndrome" OR "hyperactivity disorder" OR "hyperactive child syndrome" OR "childhood hyperkinetic syndrome" OR "attention deficit hyperactivity disorders" OR "attention deficit hyperactivity disorder" OR "adhd attention deficit hyperactivity disorder" OR adhd OR "overactive child syndrome" OR "attention deficit hyperkinetic disorder" OR "hyperkinetic disorder" OR "attention deficit disorder hyperactivity" OR "attention deficit disorders hyperactivity" OR "child attention deficit disorder" OR "hyperkinetic syndromes" OR "syndromes hyperkinetic" OR "hyperkinetic syndrome childhood") AND ((fracture OR fractures OR traumatism OR traumatisms OR traumatology OR wound OR wounds OR drowning OR poisoning OR burning) OR ((trauma OR traumat* OR harm OR lesion OR lesions OR injury OR injuries) AND (emergency OR "emergency visit" OR "emergency room" OR hospital OR hospitaliz* OR er OR inpatient))))

Web of Science (Core Collection)

TS= ((ADHD OR adhd OR "attention deficit disorder with hyperactivity" OR "syndrome hyperkinetic" OR "hyperkinetic syndrome" OR "hyperactivity disorder" OR "hyperactive child syndrome" OR "childhood hyperkinetic syndrome" OR "attention deficit hyperactivity disorders" OR "attention deficit hyperactivity disorder" OR "adhd attention deficit hyperactivity disorder" OR adhd OR "overactive child syndrome" OR "attention deficit hyperkinetic disorder" OR "hyperkinetic disorder" OR "attention deficit disorder hyperactivity" OR "attention deficit disorders hyperactivity" OR "child attention deficit disorder" OR "hyperkinetic syndromes" OR "syndromes hyperkinetic" OR "hyperkinetic syndrome childhood") AND ((fracture OR fractures OR traumatism OR traumatisms OR traumatology OR wound OR wounds OR drowning OR poisoning OR burning) OR ((trauma OR traumat* OR harm OR lesion OR lesions OR injury OR injuries) AND (emergency OR "emergency visit" OR "emergency room" OR hospital OR hospitaliz* OR er OR inpatient)))) OR TI=((ADHD OR adhd OR "attention deficit disorder with hyperactivity" OR "syndrome hyperkinetic" OR "hyperkinetic syndrome" OR "hyperactivity disorder" OR "hyperactive child syndrome" OR "childhood hyperkinetic syndrome" OR "attention deficit hyperactivity disorders" OR "attention deficit hyperactivity disorder" OR "adhd attention deficit hyperactivity disorder" OR adhd OR "overactive child syndrome" OR "attention deficit hyperkinetic disorder" OR "hyperkinetic disorder" OR "attention deficit disorder hyperactivity" OR "attention deficit disorders hyperactivity" OR "child attention deficit disorder" OR "hyperkinetic

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syndromes" OR "syndromes hyperkinetic" OR "hyperkinetic syndrome childhood") AND ((fracture OR fractures OR traumatism OR traumatisms OR traumatology OR wound OR wounds OR drowning OR poisoning OR burning) OR ((trauma OR traumat* OR harm OR lesion OR lesions OR injury OR injuries) AND (emergency OR "emergency visit" OR "emergency room" OR hospital OR hospitaliz* OR er OR inpatient)))

Methods S2: Databases included in the Unika Service

A search was carried out in UNIKA (http://www.unav.edu/en/web/biblioteca), an institutional reference aggregator that uses the EBSCO discovery service (http://support.ebsco.com/help/index.php?lang=en&int=eds) to provide a combined list of references from both internal (library) and external (database vendors) sources. The databases included in the biomedical sciences profile of the Unika Service from the University of Navarra are listed here in alphabetical order:

1. Academic Search Index (asx)
2. AccessAnesthesiology
3. AccessMedicine
4. AccessPediatrics
5. AccessScience
6. AccessSurgery
7. Ambrose Digital Library
8. ASM Handbooks Online (edsaho)
9. ASM Medical Materials Database
10. ASM Micrograph Database
11. BioOne Online Journals
12. Books at JSTOR
13. British Library Document Supply Centre Inside Serials & Conference Proceedings (edsbl)
14. British Standards Online
15. Business Source Complete
16. Canadian Electronic Library
17. Catálogo de la Biblioteca de la Universidad de Navarra (cat00378a)
18. Center for Research Libraries
19. ChemSpider
20. China/Asia On Demand
21. CINAHL (cin20)
22. CogPrints
23. Credo Reference Collections (edscrc)
24. DADUN (ir00048a)
25. DASH
26. Data-Planet Statistical Datasets & Statistical Ready Reference
27. Dialnet
28. Directory of Open Access Journals (edsdoj)
29. eArticle
30. eBook Academic Collection (EBSCOhost) (e000xww)
31. eBook Collection (EBSCOhost) (nlebk)
32. EconLit (ecn)
33. EDS Foundation Index (eda)
34. eLibro Premium
35. ERIC (eric)
36. eScholarship (edssch)
37. EThOS
38. EU Bookshop (edseub)
39. European Union Open Data Portal
40. Europeana
41. Expanded Academic ASAP
42. Films on Demand
43. Fuente Académica Premier (fua)
44. Gale Cengage Learning, Health & Wellness Resource Center
45. Gale Virtual Reference Library
46. Gallica Bibliothèque Numérique
47. Google Book Search (fe334f7c)
48. GreenFILE (8gh)
49. Harvard Library Bibliographic Dataset (edshlc)
50. HathiTrust (edshtl)
51. Henry Stewart Talks
52. HighWire Press (fa0f9666)
53. Idunn.no
54. IndianJournals.com
55. Informit Health Collection (edsihc)
56. Iprbooks
57. JSTOR (fd43b2a1)
58. JSTOR Life Sciences (edsjls)
59. KERIS Theses & Dissertations (edsker)
60. Knigafund.ru (edskig)
61. Korean Studies Information Service System (KISS) (edskis)
62. LexisNexis Academic: Law Reviews (edslex)
63. Maruzen eBook Library
64. McGraw-Hill
65. Medical Online
66. Medical Online E-books
67. Medical Online-E
68. MEDLINE (cmedm)
69. Minority Health Archive (edsuph)
70. NARCIS
71. Networked Digital Library of Theses & Dissertations (edsndl)
72. NORA (Norwegian Open Research Archive)

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73. OAIster (edsoai)
74. OJS vid Lunds Universitet (edsojs)
75. Ovid Journals Full Text Medical Research Database (fb0698e8)
76. Oxford Bibliographies Online
77. Oxford Clinical Psychology
78. Oxford Handbooks Online (edsoho)
79. Oxford Medicine Online
80. Oxford Reference (edsoro)
81. Oxford Scholarship Online (edsoso)
82. ProQuest Dissertations and Theses (fb458d87)
83. PsycARTICLES (edspdh)
84. PsycBOOKS (edspzh)
85. PsycCRITIQUES (edspvh)
86. PsycheVisual
87. Psychology and Behavioral Sciences Collection (pbh)
88. PsycINFO (psyh)
89. Publisher Provided Full Text Searching File (edb)
90. PubMed Central (fd5a6824)
91. R2 Digital Library
92. RACO
93. RECERCAT
94. ReferenceSearch (edsref)
95. RÖMPP Online
96. SA ePublications Service
97. SAGE Research Methods Datasets
98. SAGE Video
99. Scielo
100. Scielo Books
101. Science Citation Index (edswsc)
102. ScienceDirect (edselp)
103. Scopus
104. Social Sciences Citation Index (edswss)
105. Springer Science+Business Media, SpringerProtocols
106. STAT!Ref
107. Supplemental Index (edo)
108. SveMed+ (edssmd)
109. Torrossa
110. TOXNET: GENETOX
111. TOXNET: TOXLINE
112. University Library Online - Университетская библиотека онлайн
113. World Bank eLibrary (edswb

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Methods S3: Risk of bias (Items from the Newcastle-Ottawa Scale)

Studies comparing injured-non injured (case-control studies)
Selection

1) Is the case definition adequate?
a) yes, with independent validation * (acute injury or record linkage+interview or other validation)
b) yes, eg record linkage or based on self-reports
c) no description

2) Representativeness of the cases
a) consecutive or obviously representative series of cases*
b) potential for selection biases or not stated

3) Selection of Controls
a) community controls *
b) hospital controls
c) no description

4) Definition of Controls
a) no history of disease (endpoint) *
b) no description of source

Comparability (up to 2 stars)

1) Comparability of injured and non-injured individuals on the basis of the design or analysis (Note: all articles should control sex for inclusion).
a) study controls for AGE and COMORBIDITY **
b) study controls for AGE *
c) study controls for COMORBIDITY *

Exposure (ADHD)

1) Ascertainment of ADHD
a) secure record (eg surgical records) or data linkage *
b) structured interview *
c) written self-report, (not codified) medical history or clinical questionnaire
d) no description

2) Same method of ascertainment for cases and controls
a) yes *
b) no

3) Non-Response rate
a) same rate for both groups *
b) non respondents described
c) rate different and no designation

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Cohort studies

Selection

1) Representativeness of the exposed cohort. Individuals with ADHD are
a) truly representative of the average child with ADHD in the community *
b) somewhat representative of the average child with ADHD in the community (individuals may differ slightly from the typical ADHD child)*
c) selected group of users eg only medicated ADHD, all ADHD+Comorbidity, only one sex, only hospitally-treated ADHD...
d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort (individuals without ADHD)
a) drawn from the same community as the exposed cohort *
b) drawn from a different source
c) no description of the derivation of the non-exposed cohort

3) Ascertainment of ADHD
a) secure record (eg surgical records) or data linkage *
b) structured interview *
c) written self-report, (not codified) medical history or clinical questionnaire
d) no description

4) Demonstration that outcome of interest was not present at start of study: IRRELEVANT IN OUR CASE THAT ADHD IS PRESENT BEFORE STUDY STARTS
a) yes *
b) no

Comparability (up to 2 stars)

1) Comparability of individuals with ADHD and no ADHD on the basis of the design or analysis (NOTE: all studies should control for sex)
a) study controls for AGE and comorbidity **
b) study controls for AGE *
c) study controls for comorbidity *

Outcome

1) Assessment of the injuries
a) independent blind assessment * (NOT RELEVANT IN OUR CASE)
b) record linkage *
c) self-report
d) no description

2) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for *
b) subjects lost to follow up unlikely to introduce bias - small number lost - >80 % follow up, or description provided of those lost) *
c) follow up rate < 80% and no description of those lost
d) no statement

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Cross-sectional studies

Selection

1) Representativeness of the exposed cohort. Individuals with ADHD are
a) truly representative of the average child with ADHD in the community *
b) somewhat representative of the average child with ADHD in the community (individuals may differ slightly from the typical ADHD child)*
c) selected group of users eg only medicated ADHD, all ADHD+Comorbidity, only one sex, only hospitally-treated ADHD...
d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort (individuals without ADHD)
a) drawn from the same community as the exposed cohort *
b) drawn from a different source
c) no description of the derivation of the non-exposed cohort

3) Ascertainment of ADHD
a) secure record (eg surgical records) or data linkage *
b) structured interview *
c) written self-report, (not codified) medical history or clinical questionnaire
d) no description

4) Demonstration that outcome of interest was not present at start of study: IRRELEVANT IN OUR CASE THAT ADHD IS PRESENT BEFORE STUDY STARTS
a) yes *
b) no

Comparability (up to 2 stars)

1) Comparability of individuals with ADHD and no ADHD on the basis of the design or analysis (NOTE: all studies should control for sex)
a) study controls for AGE and comorbidity **
b) study controls for AGE *
c) study controls for comorbidity *

Outcome

1) Assessment of the injuries
a) independent blind assessment * (NOT RELEVANT IN OUR CASE)
b) record linkage *
c) self report
d) no description

2) Non-respondents:
a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. *
b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
c) No description of the response rate or the characteristics of the responders and the non-responders.

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Methods S4: Outcome selection and data extraction

The primary outcome was the odds ratios (ORs) of suffering one or more unintentional injuries in individuals with compared to those without ADHD. Unintentional injuries had to be evaluated at a medical setting. When ORs were not directly reported in the paper, we calculated them if the paper reported data to compute them. Hazard ratios (HRs) obtained from Cox Proportional Hazards Models were an additional outcome measure of interest. While our scoping of the literature indicated that studies with this outcome were unusual, arguably HRs have the advantage to be independent from the time of follow-up.

For our second meta-analysis (effect of medication), the primary outcome was the incident rate ratio (IRR) derived from self-controlled methodology during intervals of medication intake compared to periods without medication.

If effect measures other than OR, HR or IRR were reported, and ORs (or IRRs for the medication case) could not be calculated from the data in the studies, authors were contacted at least twice (one month apart) to try to gather relevant data. Authors of studies that used ADHD questionnaires without a dichotomous threshold were also contacted to gather data in a usable format for the present meta-analysis.

All articles considered appropriate were read independently by at least two authors who extracted the key information and included it in a Microsoft Excel document, with a third senior author acting as an arbitrator when consensus on discrepancies was not reached. A training session was provided for all researchers involved in data coding.

Extracted information included:

- author
- journal
- year of publication
- country(ies) where the study was conducted
- specific study location such as region or hospital when applicable
- type of study (cross-sectional, case-control, cohort, or clinical trial)
- temporal sequence (prospective, retrospective or cross sectional)
- duration of follow-up
- participants enrolment (consecutive, non-consecutive)
- setting (clinical *vs.* epidemiological population study)
- year of data acquisition
- sample size (ADHD and non-ADHD separately)
- age (ADHD and non-ADHD separately)
- sex distribution (ADHD and non-ADHD separately)
- ethnicity (ADHD and non-ADHD separately)
- socio-demographic status (ADHD and non-ADHD separately)
- characteristics of participants without ADHD (No ADHD, no ADHD nor other conditions, or comparisons with diagnostic categories other than ADHD)
- psychiatric comorbidities (ADHD and non-ADHD separately)
- method to establish the diagnosis of ADHD (self-reported diagnosis, diagnosis recorded in medical files/registry, structured or semi-structured interview according to DSM or ICD, questionnaires, questionnaire of symptoms, per medication usage, or positive answer to the question: "Have you ever been told you have ADHD?")
- medication status of individuals with and without ADHD (type of medication and percentage of treated participants)
- treatment setting (acute care hospitals, emergency facilities, general practice, medical specialist, or other, including extended care facilities such as nursing homes, offices, schools and communities)
- method to document injuries (registry, acute treatment, through expert retrospective analysis or self-report)
- type of injury (traumatology, traffic injuries, drowning, poisoning, burns and chemical, other unintentional, self-induced, any kind of accidental injury or any kind of injury)
- raw number of accidents (ADHD and non-ADHD separately)

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- OR (or HR) of suffering an unintentional injury in ADHD individuals *vs.* children and adolescents without ADHD
- confidence intervals for the outcome measure
- covariates controlled by design in each study
- covariates controlled statistically in each study

We extracted information on multiple outcomes per article. We coded outcomes from different age or sex groups, multiple control groups, varying diagnosis techniques or statistical models.

If the confidence interval was not reported for an outcome, we used, when available, the variance estimates for other outcomes reported in the same study; otherwise, the mean variance was used.

Methods S5: Additional details on statistical analysis

Definition of the most general and controlled outcome(s) for a study

Multiple outcomes fulfilling our inclusion criteria were expected for many of the studies. Any outcome usable in any analysis was extracted. However, the main comparisons in our study were carried out using the most general and controlled outcome(s) from each study. With "most general", we refer to the outcomes that better reflect the average population from all outcomes present in the study. For example, if there was an outcome that included both boys and girls and then, outcomes that separately reported risk ratios between sexes, we considered the former the most general. If, however, for a given study we could only find an outcome in boys or girls, this was considered the most general. It must be noted that there could be more than one "most general outcome": this was the case for example when outcomes for ADHD defined according to two valid diagnostic strategies (according to our inclusion criteria) were reported. With "most controlled" outcome, we refer to the outcome that statistically controlled for more confounders when there were several most general outcomes that only differed in the statistical model used to obtain them. However, it must be noted that if an article only reported uncontrolled outcomes, they were considered the most controlled ones.

Heterogeneity and small sample bias

A single effect size per study was used to calculate the degree of between-study heterogeneity and the risk of small-sample bias. The most general and statistically controlled outcome per study was used. If there was more than one possible outcome fulfilling these criteria, the outcome to be analysed was chosen at random from the available outcomes.

Dependency among outcomes (Robust Variance Estimation)

In standard meta-analytical procedures, effect sizes are assumed independent. Whereas a common way to deal with non-independence is to compute a mean outcome and use it in the meta-analysis,(Borenstein et al., 2009) this approach leaves out potentially relevant information. A way to address this issue is to use Robust Variance Estimation (RVE), a relatively novel statistical technique that models the nested structure between outcomes (including dichotomous ones, such as OR or HR) of the same study.(Hedges et al., 2010; Tipton, 2015, 2013) Whereas this method yields valid results regardless of the weights used, a strategy using approximate inverse-variance weights has been proposed for efficiency purposes. In this approach, a random-effects model with variation of effect sizes between studies (τ^2) and equicorrelation (*Rho*) between same-study effect sizes (i^2) is assumed.(Hedges et al., 2010) We used *Rho*=0.8, similarly to previous studies,(deVibe et al., 2012) although these same studies and simulations by the RVE authors have shown little change with different values of p.(Linck et al., 2014) Moreover, we carried out a sensitivity analysis with varying levels of p to check the influence of such decision.(Hedges et al., 2010) RVE has been implemented in Stata and R and there are published guidelines for its use.(Tanner-Smith et al., 2016; Tanner-Smith and Tipton, 2014) These implementations include an improved estimation for small samples.(Tipton, 2015) We used RVE for the inference of a mean effect size and meta-regression analyses. Regarding meta-regression, as degrees of freedom are obtained from the number of studies (instead of outcomes) and variables are likely to be correlated, it was performed separately for each variable (bivariate regressions).

Subgroup analyses and meta-regression for the meta-analysis of risk

We describe here analyses carried out in greater detail than in main article. All analyses were pre-specified in protocol.

Sensitivity analyses:

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- Including only controlled outcomes from the most general and controlled outcomes
- Including only uncontrolled outcomes from the most general and controlled outcomes
- Including all most general outcomes (independently of whether they were the most controlled ones)
- Excluding case-control studies (comparing injured vs. Non-injured individuals)
- Excluding studies in which injuries were self-reported.
- Included only studies using the most rigorous definitions of adhd (dsm, icd, registry or clinical history) and non-ADHD (excluding studies with clinical control groups).
- Including only articles with data originating before the year 2000.
- Including only articles with data originating after the year 2000.
- Including only corrected or uncorrected outcomes.
- Limiting outcomes to those included in studies with a follow-up of less than a year
- Limiting outcomes to those included in studies with a follow-up of more than a year
- Limiting outcomes to those in which the effect of comorbid of ODD and CD has been controlled

Meta-regression analyses:

- Considering as dependent variable the NOS number of stars
- Considering as dependent variable age (ideally the mean or median of the whole group, otherwise mid-point in the interval of ages; whenever the age at data acquisition was 1 year apart or less from the injury it was accepted as the age at injury)
- Considering as dependent variable percentage of medicated ADHD individuals
- Considering as dependent variable prevalence of ADHD (percentage of ADHD that a given diagnostic strategy yields in a cohort)
- Comparing effect sizes between sexes.
- Comparing the effect sizes of outcomes in which the effect of comorbidity with ODD and CD had been controlled to those in which it had not been controlled.

Meta-analysis on the effect of medication

For the "medication meta-analsysis", a generalized linear mixed model using the Poisson distribution with the log link function would have been desirable.(Bagos and Nikolopoulos, 2009) However, this analysis requires the total time of observation. Despite contacting authors of the studies, we were not able to get such data for two articles and hence a classical fixed effects model(DerSimonian and Laird, 1986) (due to the small number of studies and the similarity of designs) was carried out. Sensitivity analysis was limited to testing a random effects model with the same study.

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Table S1: Articles excluded with main reason for exclusion

Reference	Reason
Acar E, Dursun OB, Esin İS, Öğütlü H, Özcan H, Mutlu M. Unintentional Injuries in Preschool Age Children. Medicine (Baltimore). 2015;94(32):e1378.	It does not relate ADHD to injuries
Adeel S, Cryan E. Prevalence of the symptoms of attention deficit hyperactivity disorder in adults attending fracture and general out-patient clinics. J Neural Transm. 2007;114(7):LXIII-LXIV.	No control group
Adeyemo BO, Biederman J, Zafonte R, et al. Mild Traumatic Brain Injury and ADHD: A Systematic Review of the Literature and Meta-Analysis. *J Atten Disord*. 2014;18(7):576-584.	A Meta-analysis
Aduen PA, Kofler MJ, Cox DJ, Sarver DE, Lunsford E. Motor vehicle driving in high incidence psychiatric disability: Comparison of drivers with ADHD, depression, and no known psychopathology. J Psychiatr Res. 2015;64:59-66.	Adults
Alden NE, Rabbitts A, Rolls JA, et al. Burn injury in patients with early-onset neurological impairments: 2002 ABA paper. J Burn Care Rehabil. 2004;25(1):107-111.	It does not relate ADHD to injuries
Altun C, Guven G, Akgun OM, Acikel C. Dental injuries and attention-deficit/hyperactivity disorder in children. Spec Care Dentist. 2012;32(5):184-189.	Diagnosis is made by sequels of trauma
Amanullah S, Mello M, Aronson S, King C, Tai M, Becker BM. 404 The Prevalence of Injury Vs. Illness in Children With and Without ADD/ADHD Presenting for Treatment to Pediatric Emergency Departments. Abstracts of the 25th SAEM (Society for Academic Emergency Medicine) Annual Meeting. May 14-18, 2013. Atlanta, Geor. Acad Emerg Med. 2013;20 Suppl 1:S164.	Sex was not controlled for
Amiri S, Sadeghi-Bazargani H, Nazari S, Ranjbar F, Abdi S. Attention deficit/hyperactivity disorder and risk of injuries: a systematic review and meta-analysis. *J Inj Violence Res*. 2017;9(2).	A Meta-analysis
Anderson L, Monhollen L, Warden G, Kagan R. Attention Defecit Hyperactivity Disorder in the Pediatric Burn Patient. In: Journal Of Burn Care And Research. Vol 19. ; 1998:268.	No control group
Anderson M, Stea JB, Weston CG. ADHD and Injury. Psychiatric News.	Not empirical study
Avsar A, Akbaş S, Ataibiş T. Traumatic dental injuries in children with attention deficit/hyperactivity disorder. Dent Traumatol. 2009;25(5):484-489.	No control group
Ayaz M, Ayaz AB, Soylu N. Socio-demographic and behavioral factors related to unintentional injuries in preschool children diagnosed with attention-deficit/hyperactivity disorder. Bull Clin Psychopharmacol. 2015;25(2):1.	No control group
Badger K, Anderson L, Kagan RJ. Attention deficit-hyperactivity disorder in children with burn injuries. J Burn care Res. 2008;29(5):724-729.	No control group
Bakhshaee M, Hebrani P, Shams M, Salehi M, Ghaffari A, Rajati M. Psychological status in children with ear and nose foreign body insertion. Int J Pediatr Otorhinolaryngol. 2017;92:103-107.	Sex was not controlled for
Bani M, Bodur H, Kapci EG. Are behaviour risk factors for traumatic dental injuries in childhood different between males and females? Eur J Paediatr Dent. 2015;16(1):29-32.	Diagnosis is made by sequels of trauma
Barkley RA, Guevremont DC, Anastopoulos AD, DuPaul GJ, Shelton TL. Driving-related risks and outcomes of attention deficit hyperactivity disorder in adolescents and young adults: a 3- to 5-year follow-up survey. Pediatrics. 1993;92(2):212-218.	Adults
Barkley RA. Accidents and attention-deficit/hyperactivity disorder. Econ Neurosci. 2001;3(4):64-68.	Not empirical study

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Reference	Reason
Barkley RA. ADHD and Accident Proneness. (Cover story). ADHD Rep. 2002;10(2):2-6.	Not empirical study
Barkley RA. Major life activity and health outcomes associated with attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2002;63 Suppl 1:10-15.	Not empirical study
Bayar H, Coskun E, Öner V, et al. Association between penetrating eye injuries and attention deficit hyperactivity disorder in children. Br J Ophthalmol. 2015;99(8):1109-1111.	Scales without threshold
Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. Lancet 2005; 366:237-248.	Not empirical study
Bijur PE, Stewart-Brown S, Butler N. Child behavior and accidental injury in 11,966 preschool children. Am J Dis Child. 1986;140(5):487-492.	Pre-schoolers
Bimstein E, Wilson J, Guelmann M, Primosch R. Oral characteristics of children with attention-deficit hyperactivity disorder. Spec Care Dent. 2008;28(3):107-110.	Diagnosis is made by sequels of trauma
Blomqvist M, Holmberg K, Fernell E, Dahllöf G. A retrospective study of dental behavior management problems in children with attention and learning problems. Eur J Oral Sci. 2004;112(5):406-411.	It does not relate ADHD to injuries
Blomqvist M, Holmberg K, Fernell E, Ek U, Dahllöf G. Oral health, dental anxiety, and behavior management problems in children with attention deficit hyperactivity disorder. Eur J Oral Sci. 2006;114(5):385-390.	It does not relate ADHD to injuries
Bloom B, Jones LI, Freeman G. Summary health statistics for U.S. children: National Health Interview Survey, 2012. Vital Health Stat 10. 2013;10(258):1-81.	It does not relate ADHD to injuries
Bonfield CM, Stoklosa JB. Attention deficit hyperactivity disorder and traumatic brain injury: Connections, predictors, and outcomes. In: López-Muñoz F, Álamo-Gónzález C, eds. *Attention Deficit Hyperactivity Disorder (ADHD): Epidemiology, Treatment and Prevention*. Nova Science Publishers, Inc.; 2015:283-292.	Outcome: traumatic brain injury
Bradbury K, Janicke DM, Riley AW, Finney JW. Predictors of unintentional injuries to school-age children seen in pediatric primary care. J Pediatr Psychol. 1999;24(5):423-433.	It does not relate ADHD to injuries
Brenner RA, Taneja GS, Schroeder TJ, Trumble AC, Moyer PM, Louis GMB. Unintentional injuries among youth with developmental disabilities in the United States, 2006-2007. Int J Inj Contr Saf Promot. 2013;20(3):259-265.	Data are not dichotomous
Breslin FC, Pole JD. Work injury risk among young people with learning disabilities and attention-deficit/hyperactivity disorder in Canada. Am J Public Health. 2009;99(8):1423-1430.	Adults
Brook U, Boaz M. Adolescents with attention deficit and hyperactivity disorder/learning disability and their proneness to accidents. Indian J Pediatr. 2006;73(4):299-303.	It does not relate ADHD to injuries
Bruce BS, Ungar M, Waschbusch D a. Perceptions of risk among children with and without attention deficit/hyperactivity disorder. Int J Inj Contr Saf Promot. 2009;16(4):189-196.	It does not relate ADHD to injuries
Bussing R, Menvielle E, Zima B. Relationship between behavioral problems and unintentional injuries in US children. Findings of the 1988 National Health Interview Survey. Arch Pediatr Adolesc Med. 1996;150(1):50-56.	Sex was not controlled for
Byrne JM, Bawden HN, Beattie T, DeWolfe NA. Risk for injury in preschoolers: Relationship to attention deficit hyperactivity disorder. CHILD Neuropsychol. 2003;9(2):142-151.	Pre-schoolers
Cairney J. Deficits in attention, motor control, and perception and increased risk of injury in children. Dev Med Child Neurol. 2014;56(11):1040-1041.	Not empirical study
Cakmak M, Gollu G, Boybeyi O, et al. Cognitive and behavioral	Scales without

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Reference	Reason
characteristics of children with caustic ingestion. J Pediatr Surg. 2015;50(4):540-542.	threshold
Celenk F, Gokcen C, Celenk N, Baysal E, Durucu C, Kanlikama M. Association between the self-insertion of nasal and aural foreign bodies and attention-deficit/hyperactivity disorder in children. Int J Pediatr Otorhinolaryngol. 2013;77(8):1291-1294.	It does not relate ADHD to injuries
Chang Z, Lichtenstein P, D'Onofrio BM, Sjölander A, Larsson H. Serious transport accidents in adults with attention-deficit/hyperactivity disorder and the effect of medication: a population-based study. JAMA psychiatry. 2014;71(3):319-325.	Adults
Chang Z, Quinn PD, Hur K, et al. Association Between Medication Use for Attention-Deficit/Hyperactivity Disorder and Risk of Motor Vehicle Crashes. JAMA Psychiatry. 2017;74(6):597.	Adults
Chasle V, Riffaud L, Longuet R, et al. Mild head injury and attention deficit hyperactivity disorder in children. Child's Nerv Syst. 2016;32(12):2357-2361.	Outcome: traumatic brain injury
Chau YCY, Lai KYC, McGrath CPJ, Yiu CKY. Oral health of children with attention deficit hyperactivity disorder. Eur J Oral Sci. 2017;125(1):49-54.	Diagnosis is made by sequels of trauma
Chen G, Smith GA, Deng S, Chen D, Kelleher K, Xiang H. Psychological symptoms and nonfatal unintentional injuries among Chinese adolescents: A prospective study. J Adolesc Heal. 2005;37(6):460-466.	It does not relate ADHD to injuries
Chen G, Smith GA, Ranbom L, Sinclair SA, Xiang H. Incidence and pattern of burn injuries among children with disabilities. J Trauma. 2007;62(3):682-687.	It does not relate ADHD to injuries
Chien W-C, Chung C-H, Lin F-H, et al. The risk of injury in adults with attention-deficit hyperactivity disorder: A nationwide, matched-cohort, population-based study in Taiwan. Res Dev Disabil. 2017;65:57-73.	Adults
Chiu H-J, Chan C-L, Hsu J-C, et al. Nationwide retrospective cohort survey of orthopedic injuries in members of the Taiwanese population with psychiatric disorders, 2000-2005. J Orthop Sci. 2013;18(3):456-464.	Adults
Chou I-CCI-C, Lin C-C(3) C-CC, Sung F-C(3) F-CCF-C, et al. Attention-deficit hyperactivity disorder increases the risk of deliberate self-poisoning: A population-based cohort. Eur Psychiatry. 2014;29(8):523-527.	Outcome: intoxications
Connolly A, Fielding J, Papadopoulos N, McGinley J, Murphy A, Rinehart NJ. Factors Associated With Accidental Injuries in Children With ADHD-Combined Type: More Than a Motor Problem? *J Atten Disord*. March 2016. doi:10.1177/1087054716633857.	Data are not dichotomous
Cook NE, Huang DS, Silverberg ND, et al. Baseline cognitive test performance and concussion-like symptoms among adolescent athletes with ADHD: examining differences based on medication use. Clin Neuropsychol. April 2017:1-12.	Outcome: traumatic brain injury
Cronin KJ, Butler PEM, McHugh M, Edwards G. A 1-year prospective study of burns in an Irish paediatric burns unit. Burns. 1996;22(3):221-224.	No control group
Cronin SD, Gottschlich MM, Gose LM, Kagan RJ. Zolpidem and Sleep in Pediatric Burn Patients with Attention Deficit/Hyperactivity Disorder. Pediatr Nurs. 2015;41(3):132-134,140.	It does not relate ADHD to injuries
Crujeiras Martinez V, Gonzalez Pineiro Y, Perez Gay L, et al. [Do we have to wait for a child to suffer a serious injury to suspect a hyperactivity/attention deficit disorder? A case-control study of patients admitted to PICU]. An Pediatr (Barc). 2013;78(1):67-68.	Sex was not controlled for
Cuffe SP, Moore CG, McKeown R. ADHD and health services utilization in the national health interview survey. J Atten Disord. 2009;12:330-340.	It does not relate ADHD to injuries

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Reference	Reason
Schwebel DC, Tavares CL, Lucas EK, Bowling EB, Hodgens JB. Unintentional Injury Risk in Children with Externalizing Behavior Disorders at Summer Camp. *J Clin Psychol Med Settings*. 2007;14(2):145-151.	No control group
Dalsgaard S, Nielsen HS, Simonsen M. Consequences of ADHD medication use for children's outcomes. J Health Econ. 2014;37:137-151.	It does not relate ADHD to injuries
Davidson LL, Hughes SJ, O'Connor PA. Preschool behavior problems and subsequent risk of injury. Pediatrics. 1988;82(4):644-651.	Outcome measure is different from OR or HR
Davidson LL, Taylor EA, Sandberg ST, Thorley G. Hyperactivity in school-age boys and subsequent risk of injury. Pediatrics. 1992;90(5):697-702.	Outcome measure is different from OR or HR
Davidson LL. Hyperactivity, antisocial behavior, and childhood injury: a critical analysis of the literature. J Dev Behav Pediatr. 1987;8(6):335-340.	Not empirical study
De Ridder A, De Graeve D. Healthcare use, social burden and costs of children with and without ADHD in Flanders, Belgium. Clin Drug Investig. 2006;26(2):75-90.	Data are not dichotomous
DeBar LL, Lynch FL, Boles M. Healthcare use by children with attention deficit/hyperactivity disorder with and without psychiatric comorbidities. J Behav Health Serv Res. 2004;31(3):312-323.	It does not relate ADHD to injuries
DiScala C, Lescohier I, Barthel M, et al. Injuries to children with attention deficit hyperactivity disorder. Pediatrics. 1998;102(6):1415-1421.	No control group
Doupnik SK, Lawlor J, Zima BT, et al. Mental Health Conditions and Medical and Surgical Hospital Utilization. *Pediatrics*. 2016;138(6). doi:10.1542/peds.2016-2416.	It does not relate ADHD to injuries
Downey LVA, Zun LS. Identifying Undiagnosed Pediatric Mental Illness in the Emergency Department. *Pediatr Emerg Care*. April 2017. doi:10.1097/PEC.0000000000001151.	It does not relate ADHD to injuries
du Rietz E, Kuja-Halkola R, Brikell I, et al. Predictive validity of parent- and self-rated ADHD symptoms in adolescence on adverse socioeconomic and health outcomes. *Eur Child Adolesc Psychiatry*. 2017:1-11. doi:10.1007/s00787-017-0957-3.	Adults
Dunne RG, Asher KN, Rivara FP. Injuries in young people with developmental disabilities: comparative investigation from the 1988 National Health Interview Survey. Ment Retard. 1993;31(2):83-88.	It does not relate ADHD to injuries
Erdogan M, Desteli EE, Imren Y, Yuce M, Buyukceran I, Karadeniz E. Is attention deficit and hyperactivity disorder a risk factor for sustaining fractures of proximal humerus? Acta Chir Orthop Traumatol Cech. 2014;81(3):221-226.	No control group
Ertan C, Ozcan OO, Pepele MS. Paediatric trauma patients and attention deficit hyperactivity disorder: correlation and significance. Emerg Med J. 2012;29(11):911-914.	Scales without threshold
Farmer JE, Peterson L. Injury risk factors in children with attention deficit hyperactivity disorder. Health Psychol. 1995;14(4):325-332.	It does not relate ADHD to injuries
Finlayson J, Morrison J, Jackson A, Mantry D, Cooper SA. Injuries, falls and accidents among adults with intellectual disabilities. Prospective cohort study. J Intellect Disabil Res. 2010;54(11):966-980.	It does not relate ADHD to injuries
Freid VM, Makuc DM, Rooks RN. Ambulatory health care visits by children: principal diagnosis and place of visit. Vital Health Stat 13. 1998;(137)(137):1-23.	No control group
Fritz KM, Butz C. Attention Deficit/Hyperactivity Disorder and pediatric burn injury: important considerations regarding premorbid risk. Curr Opin Pediatr. 2007;19(5):565-569.	Not empirical study
Fuller EM. Injury-prone children. Am J Orthopsychiatry. 1948;18(4):708-723.	It does not relate ADHD to injuries

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Reference	Reason
Gaines BA, Cassidy L, Ford HR. Abstract: Does preexisting mental illness influence outcome in pediatric trauma? J Surg Res. 2004;121:284-285.	No control group
Garg N, Silverberg JI. Association between childhood allergic disease, psychological comorbidity, and injury requiring medical attention. Ann Allergy, Asthma Immunol. 2014;112(6):525-532.	Pre-schoolers
Garzon DL, Huang H, Todd RD. Do Attention Deficit/Hyperactivity Disorder and Oppositional Defiant Disorder Influence Preschool Unintentional Injury Risk? Arch Psychiatr Nurs. 2008;22(5):288-296.	Pre-schoolers
Garzon DL. Author's response to letter regarding unintentional injury risk among preschoolers with behavior disorders. Arch Psychiatr Nurs. 2010;24(1):2.	Not empirical study
Garzon DL. Contributing factors to preschool unintentional injury. J Pediatr Nurs. 2005;20(6):441-447.	Not empirical study
Gayton WF, Bailey C, Wagner A, Hardesty VA. Relationship between childhood hyperactivity and accident proneness. Percept Mot Skills. 1986;63(2 Pt 2):801-802.	It does not relate ADHD to injuries
Glania T, Lialiaris T, Tripsianis G, Papadakis N, Constandinidis TC. Is psychopathology related to children's unintentional injury?. Int J Adolesc Med Health. 2010;22(4):567-573.	Sex was not controlled for
Glendor U. Aetiology and risk factors related to traumatic dental injuries - a review of the literature. Dent Traumatol. 2009;25(1):19-31.	Not empirical study
Golubchik P, Kodesh A, Weizman A. No Superiority of Treatment With Osmotic Controlled-Release Oral Delivery System-Methylphenidate Over Short/Medium-Acting Methylphenidate Preparations in the Rate and Timing of Injuries in Children With Attention-Deficit/Hyperactivity Disorder. Clin Neuropharmacol. 2017;40(1):11-15.	It does not relate ADHD to injuries
Guevara J, Lozano P, Wickizer T, Mell L, Gephart H. Utilization and cost of health care services for children with attention-deficit/hyperactivity disorder. Pediatrics. 2001;108(1):71-78.	It does not relate ADHD to injuries
Guy JA, Knight LM, Wang Y, Jerrell JM. Factors Associated With Musculoskeletal Injuries in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder. Prim care companion CNS Disord. 2016;18(3).	No control group
Hariharan S, Pomerantz W. Correlation between hospitalization for pharmaceutical ingestion and attention deficit disorder in children aged 5 to 9 years old. Clin Pediatr (Phila). 2008;47(1):15-20.	Outcome: intoxications
Hartsough CS, Lambert NM. Medical factors in hyperactive and normal children: prenatal, developmental, and health history findings. Am J Orthopsychiatry. 1985;55(2):190-201.	Data are not dichotomous
Herguner A, Erdur AE, Basciftci FA, et al. Attention-deficit/hyperactivity disorder symptoms in children with traumatic dental injuries. Dent Traumatol. 2015;31(2):140-143.	Scales without threshold
Hoare P, Beattie T. Children with attention deficit hyperactivity disorder and attendance at hospital. Eur J Emerg Med. 2003;10(2):98-100.	Scales without threshold
Iverson GL, Wojtowicz M, Brooks BL, et al. High School Athletes With ADHD and Learning Difficulties Have a Greater Lifetime Concussion History. *J Atten Disord*. July 2016. doi:10.1177/1087054716657410.	Outcome: traumatic brain injury
Jaquess DL, Finney JW. Previous injuries and behavior problems predict children's injuries. J Pediatr Psychol. 1994;19(1):79-89.	Scales without threshold
Jokela M, Power C, Kivimäki M. Childhood problem behaviors and injury risk over the life course. J Child Psychol Psychiatry. 2009;50(12):1541-1549.	It does not relate ADHD to injuries
Karazsia BT, Guilfoyle SM, Wildman BG. The mediating role of hyperactivity and inattention on sex differences in paediatric injury risk. Child Care Health Dev. 2012;38(3):358-365.	Scales without threshold
Karazsia BT, Van Dulmen MHM. Regression models for count data: illustrations using longitudinal predictors of childhood injury. J Pediatr	Scales without threshold

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Reference	Reason
Psychol. 2008;33(10):1076-1084.	
Katrivanou A, Lekka NP, Beratis S. Psychopathology and behavioural trends of children with accidental poisoning. J Psychosom Res. 2004;57(1):95-101.	Outcome: intoxications
Katz-Sagi H, Redlich M, Brinsky-Rapoport T, Matot I, Ram D. Increased dental trauma in children with attention deficit hyperactivity disorder treated with methylphenidate--a pilot study. *J Clin Pediatr Dent.* 2010;34(4):287-289.	Diagnosis is made by sequels of trauma
Kaya A, Taner Y, Guclu B, et al. Trauma and adult attention deficit hyperactivity disorder. J Int Med Res. 2008;36(1):9-16.	Adults
Keenan HT, Hall GC, Marshall SW. Early head injury and attention deficit hyperactivity disorder: retrospective cohort study. BMJ. 2008;337(2):a1984.	No control group
Kemner JE. Effect of methylphenidate formulation on treatment patterns and use of emergency room services. Am J Heal Pharm. 2006;63(4):317-322.	It does not relate ADHD to injuries
Kirsch R, Wirrell E. Do cognitively normal children with epilepsy have a higher rate of injury than their nonepileptic peers? J Child Neurol. 2001;16(2):100-104.	Data are not dichotomous
Klein M. Unfallgefährdung bei Kindern und Jugendlichen mit Aufmerksamkeitsdefizit/ Hyperaktivitätsstörung. Psychoneuro. 2006;32(07/08):386-391.	Not empirical study
Kohlboeck G, Heitmueller D, Neumann C, et al. Is there a relationship between hyperactivity/inattention symptoms and poor oral health? Results from the GINIplus and LISAplus study. Clin Oral Investig. 2013;17(5):1329-1338.	Diagnosis is made by sequels of trauma
Komurcu E, Bilgic A, Herguner S. Relationship between extremity fractures and attention-deficit/hyperactivity disorder symptomatology in adults. Int J Psychiatry Med. 2014;47(1):55-63.	Adults
Krall V. Personality characteristics of accident repeating children. J Abnorm Psychol. 1953;48(1):99-107.	It does not relate ADHD to injuries
Lachaine J, De G, Sikirica V, et al. Treatment patterns, resource use, and economic outcomes associated with atypical antipsychotic prescriptions in children and adolescents with attention-deficit hyperactivity disorder in Quebec. Can J Psychiatry. 2014;59(11):1.	No control group
Lage M, Hwang P. Effect of methylphenidate formulation for attention deficit hyperactivity disorder on patterns and outcomes of treatment. J Child Adolesc Psychopharmacol. 2004;14(4):575-581.	It does not relate ADHD to injuries
Lalloo R, Sheiham A, Nazroo JY. Behavioural characteristics and accidents: findings from the Health Survey for England, 1997. Accid Anal Prev. 2003;35(5):661-667.	It does not relate ADHD to injuries
Lam LT. Attention Deficit Disorder and hospitalization due to injury among older adolescents in New South Wales, Australia. J Atten Disord. 2002;6(2):77-82.	No control group
Langley J, Mcgee R, Silva P, Williams S. Child behavior and accidents. J Pediatr Psychol. 1983;8(2):181-189.	Scales without threshold
Langley J, Silva PA, Williams S. A study of the relationship of ninety background, developmental, behavioural and medical factors to child hood accidents. A report from the Dunedin Multidisciplinary Child Development Study. Aust Paediatr J. 1980;16(4):244-247.	It does not relate ADHD to injuries
Langley JD. "Accident proneness": statistical and practical significance. Injury Prevention. 1997;3(2):80-81.	It does not relate ADHD to injuries
Lee L-C, Harrington RA, Chang JJ, Connors SL. Increased risk of injury in children with developmental disabilities. Res Dev Disabil. 2008;29(3):247-255.	Pre-schoolers
Levine M, Froberg B, Ruha AM, et al. Assessing the toxicity and associated costs among pediatric patients admitted with unintentional poisonings of attention-deficit/hyperactivity disorder drugs in the United	No control group

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Reference	Reason
States. Clin Toxicol. 2013;51(3):147-150.	
Loder RT, Warschausky S, Schwartz EM, Hensinger RN, Greenfield ML. The psychosocial characteristics of children with fractures. J Pediatr Orthop. 1995;15(1):41-46.	No control group
Lu Y-Y, Wang M-Y, Wei I-H, Lin C-C, Huang C-C. Tourette syndrome increases risk of bone fractures: a population-based cohort study. Eur Child Adolesc Psychiatry. 2017;26(5):531-539.	Outcome measure is different from OR or HR
Mangus R. S, Bergman D, Zieger M, Coleman J. J. Burn injuries in children with attention-deficit/hyperactivity disorder. Burns. 2004;30(2):148-150.	No control group
Manheimer DI, Mellinger GD. Personality characteristics of the child accident repeater. Inj Prev. 1967;9:87-101.	It does not relate ADHD to injuries
Marin M, Ponce G, Martinez I, Rubio G. P.8.a.018 Impact of methylphenidate treatment on the rate of accidents in adults with Attention Deficit Hyperactivity Disorder (ADHD). Eur Neuropsychopharmacol. 2011;21:S620-S621.	Adults
Matheny AP. Psychological Characteristics of Childhood Accidents. J Soc Issues. 1987;43(2):45-60.	It does not relate ADHD to injuries
Max JE, Bowers WA, Baldus D, Gaylor EE. Pediatric traumatic brain injury and burn patients in the civil justice system: the prevalence and impact of psychiatric symptomatology. J Am Acad Psychiatry Law. 1998;26(2):247-258.	It does not relate ADHD to injuries
Max JE, Schachar RJ, Dennis M, et al. Predictors of attention-deficit/hyperactivity disorder within 6 months after pediatric traumatic brain injury. J Am Acad Child Adolesc Psychiatry. 2005;44(10):1032-1040.	Outcome: traumatic brain injury
McCarthy C. ADHD plays role in student-athletes' injuries, well-being. Coll Athl Law. 2016;13(4):4.	Not empirical study
McDonald AS, Davey GCL. Psychiatric disorders and accidental injury. Clin Psychol Rev. 1996;16(2):105-127.	It does not relate ADHD to injuries
Merrill R, Lyon J, Baker R, Gren L. Attention Deficit Hyperactivity Disorder and Increased Risk of Injury. Adv Med Sci. 2009;54(1):20-26.	Adults
Meyer RJ, Roelofs HA, Bluestone J, Redmond S. Accidental injury to the preschool child. J Pediatr. 1963;63(1):95-105.	It does not relate ADHD to injuries
Miller AR, Brehaut JC, Raina P, McGrail KM, Armstrong RW. Use of medical services by methylphenidate-treated children in the general population. Ambul Pediatr. 2004;4(2):174-180.	Data are not dichotomous
Mota-Veloso I, Soares MEC, Homem MA, Marques LS, Ramos-Jorge ML, Ramos-Jorge J. Signs of attention deficit/hyperactivity disorder as a risk factor for traumatic dental injury among schoolchildren: a case-control study. Int J Paediatr Dent. 2016;26(6):471-476.	Diagnosis is made by sequels of trauma
Murphy N, Yanchar NL, N. M, N.L. Y, Murphy N, Yanchar NL. Yet more pediatric injuries associated with all-terrain vehicles: Should kids be using them? J Trauma - Inj Infect Crit Care. 2004;56(6):1185-1190.	No control group
Newcorn JH. Medication for ADHD and accidental injury. Lancet Psychiatry. 2015;2(8):669-671.	Not empirical study
Nigg JT. Attention-deficit/hyperactivity disorder and adverse health outcomes. Clin Psychol Rev. 2013;33(2):215-228.	Not empirical study
Ozcan K, Ozcan O, Muluk NB, Cingi C, Durukan K. Self-inserted foreign body and attention-deficit/hyperactivity disorder: evaluated by the Conners' Parent Rating Scales-Revised. Int J Pediatr Otorhinolaryngol. 2013;77(12):1992-1997.	Scales without threshold
Ozer K, Gillani S, Williams A, Hak DJ. Psychiatric risk factors in pediatric hand fractures. J Pediatr Orthop. 2010;30(4):324-327.	No control group
Perera H, Fernando SM, Yasawardena a DKSN, Karunaratne I. Prevalence of attention deficit hyperactivity disorder (ADHD) in children presenting with self-inserted nasal and aural foreign bodies. Int J Pediatr Otorhinolaryngol. 2009;73(10):1362-1364.	No control group

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Reference	Reason
Perera H, Jeewandra KC, Jayasuriya N, Dias R. Prevalence of attention deficit hyperactivity disorder in children with unintentional injuries. Sri Lanka J Child Heal. 2012;41(1):20-23.	No control group
Petridou E, Trichopoulos D, Mera E, et al. Risk factors for childhood burn injuries: a case-control study from Greece. Burns. 1998;24(2):123-128.	Scales without threshold
Pittsenbarger ZE, Grupp-Phelan J, Phelan KJ. Comparing the frequency of unrecognized Attention Deficit Hyperactivity Disorder symptoms in injured versus noninjured patients presenting for care in the pediatric emergency department. Pediatr Emerg Care. 2008;24(7):438-441.	It does not relate ADHD to injuries
Pless IB, Taylor HG, Arsenault L. The relationship between vigilance deficits and traffic injuries involving children. Pediatrics. 1995;95(2):219-224.	It does not relate ADHD to injuries
Pless IB, Verreault R, Tenina S. A case-control study of pedestrian and bicyclist injuries in childhood. Am J Public Health. 1989;79(8):995-998.	It does not relate ADHD to injuries
Ramos Olazagasti MA, Klein RG, Mannuzza S, et al. Does childhood attention-deficit/hyperactivity disorder predict risk-taking and medical illnesses in adulthood? J Am Acad Child Adolesc Psychiatry. 2013;52(2):153-162.e4.	It does not relate ADHD to injuries
Redelmeier DA, Chan WK, Lu H. Road trauma in teenage male youth with childhood disruptive behavior disorders: a population based analysis. PLoS Med. 2010;7(11):e1000369.	Adults
Reinhardt MC, Reinhardt C a U. Attention deficit-hyperactivity disorder, comorbidities, and risk situations. J Pediatr (Rio J). 2013;89(2):124-130.	Not empirical study
Rowe R, Simonoff E, Silberg JL. Psychopathology, temperament and unintentional injury: Cross-sectional and longitudinal relationships. J Child Psychol Psychiatry Allied Discip. 2007;48(1):71-79.	Scales without threshold
Sabuncuoglu O, Irmak MY. The attention-deficit/hyperactivity disorder model for traumatic dental injuries: a critical review and update of the last 10 years. Dent Traumatol. 2017;33(2):71-76.	Not empirical study
Sabuncuoglu O, Taser H, Berkem M. Relationship between traumatic dental injuries and attention-deficit/hyperactivity disorder in children and adolescents: proposal of an explanatory model. Dent Traumatol. 2005;21(5):249-253.	Diagnosis is made by sequels of trauma
Sabuncuoglu O. Understanding the relationships between breastfeeding, malocclusion, ADHD, sleep-disordered breathing and traumatic dental injuries. Med Hypotheses. 2013;80(3):315-320.	Not empirical study
Sadeghi-Bazargani H, Mohammadi R, Amiri S, et al. Individual-level predictors of inpatient childhood burn injuries: a case-control study. BMC Public Health. 2016;16(1):209.	Scales without threshold
Sadeghi-Bazargani H, Mohammadi R, Ayubi E, et al. Caregiver-related predictors of thermal burn injuries among Iranian children: A casecontrol study. PLoS One. 2017;12(2).	Scales without threshold
Sadeghi-Bazargani O, Abedi L, Mahini M, Amiri S, Khorasani-Zavareh D. Adult attention-deficit hyperactivity disorder, risky behaviors, and motorcycle injuries: a case-control study. Neuropsychiatr Dis Treat. 2015;11:2049-2054.	Adults
Safiri S, Haghdoost AA, Hashemi F, Amiri S, Raza O, Sadeghi-Bazargani H. Association Between Adult Attention Deficit Hyperactivity Disorder and Helmet Use Among Motorcycle Riders. Trauma Mon. 2016;21(2):e21066.	Adults
Salinas CM, Dean P, LoGalbo A, Dougherty M, Field M, Webbe FM. Attention-Deficit Hyperactivity Disorder Status and Baseline Neurocognitive Performance in High School Athletes. Appl Neuropsychol Child. 2016;5(4):264-272.	Outcome: traumatic brain injury
Scharnetzky E, Schill W, Glaeske G, Janhsen K. Are children and	Outcome measure is

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Reference	Reason
youths with attention-deficit/ hyperactivity disorder (ADHD) accident prone? In: *Jahrestagung 2004 Der GAA*. Jena; 2004:http://www.egms.de/static/en/meetings/gaa2004/04ga.	different from OR or HR
Schwebel DC, Gaines J. Pediatric unintentional injury: behavioral risk factors and implications for prevention. J Dev Behav Pediatr. 2007;28(3):245-254.	Not empirical study
Schwebel DC, Hodgens JB, Sterling S. How mothers parent their children with behavior disorders: Implications for unintentional injury risk. J Safety Res. 2006;37(2):167-173.	No control group
Schwebel DC, Roth DL, Elliott MN, et al. Association of externalizing behavior disorder symptoms and injury among fifth graders. Acad Pediatr. 2011;11(5):427-431.	Scales without threshold
Schwebel DC, Speltz ML, Jones K, Bardina P. Unintentional injury in preschool boys with and without early onset of disruptive behavior. J Pediatr Psychol. 2002;27(8):727-737.	Pre-schoolers
Schwebel DC. Temperamental risk factors for children's unintentional injury: the role of impulsivity and inhibitory control. Pers Individ Dif. 2004;37(3):567-578.	It does not relate ADHD to injuries
Schwebel DC. Unintentional Injury Risk Among Preschoolers With Behavior Disorders: Response to Garzon et al. Arch Psychiatr Nurs. 2009;23(2):94.	Not empirical study
Sherrard J, Tonge BJ, Ozanne-Smith J. Injury in young people with intellectual disability: Descriptive epidemiology. Inj Prev J Int Soc Child Adolesc Inj Prev. 2001;7(1):56-61.	It does not relate ADHD to injuries
Shi H, Yang X, Wang J, et al. Type A personality, hostility, time urgency and unintentional injuries among Chinese undergraduates: a matched case-control study. BMC Public Health. 2013;13:1066.	It does not relate ADHD to injuries
Shire. Treatment of Traumatic Brain Injury (TBI)-Related Attention Deficits. 2015.	Outcome: traumatic brain injury
Sinclair SA, Xiang H. Injuries among US children with different types of disabilities. Am J Public Health. 2008;98(8):1510-1516.	Outcome measure is different from OR or HR
Siwani R, Tombers NM, Rieck KL, Cofer SA. Comparative analysis of fracture characteristics of the developing mandible: The Mayo Clinic experience. Int J Pediatr Otorhinolaryngol. 2014;78(7):1066-1070.	No control group
Stavrinos D, Biasini FJ, Fine PR, et al. Mediating factors associated with pedestrian injury in children with attention-deficit/hyperactivity disorder. Pediatrics. 2011;128(2):296-302.	It does not relate ADHD to injuries
Stewart MA, Thach BT, Freidin MR. Accidental poisoning and the hyperactive child syndrome. Dis Nerv Syst. 1970;31(6):403-407.	Sex was not controlled for
Thikkurissy S, McTigue DJ, Coury DL. Children presenting with dental trauma are more hyperactive than controls as measured by the ADHD rating scale IV. Pediatr Dent. 2012;34(1):28-31.	Sex was not controlled for
Thomas CR, Ayoub M, Rosenberg L, Robert RS, Meyer WJ. Attention deficit hyperactivity disorder & pediatric burn injury: a preliminary retrospective study. Burns. 2004;30(3):221-223.	No control group
Uslu M, Uslu R, Eksioglu F, Ozen NE. Children with fractures show higher levels of impulsive-hyperactive behavior. Clin Orthop Relat Res. 2007;460(460):192-195.	Scales without threshold
Uslu M, Uslu R. Extremity fracture characteristics in children with impulsive/ hyperactive behavior. Arch Orthop Trauma Surg. 2008;128(4):417-421.	No control group
van der Ban E. ADHD-medicatie, meer en langduriger gebruikt. Huisarts Wet. 2015;58(7):362-364.	Not empirical study
Wazana A. Are there injury-prone children? A critical review of the literature. Can J Psychiatry. 1997;42(6):602-610.	Not empirical study
Yang L-Y, Huang C-C, Chiu W-T, Huang L-T, Lo W-C, Wang J-Y. Association of traumatic brain injury in childhood and attention-	Outcome: traumatic brain injury

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Reference	Reason
deficit/hyperactivity disorder: A population-based study. Pediatr Res. 2016;80(3):356-362.	
Zhang H, Li Y, Cui Y, Song H, Xu Y, Lee S-Y. Unintentional childhood injury: a controlled comparison of behavioral characteristics. BMC Pediatr. 2016;16(1):21.	It does not relate ADHD to injuries
Zheng P, Ju L, Ma X, Lou Y. Psychological-behavioral characteristics and fractures in children are closely related. J Pediatr Orthop B. 2014;23(6):560-565.	It does not relate ADHD to injuries
Ziegler AM. Analysis of a Comprehensive Dental Trauma Database: An Epidemiologic Study of Traumatic Dental Injuries to the Permanent Dentition. 2014.	No control group
Zwi M, Clamp P. Injury and attention deficit hyperactivity disorder. BMJ. 2008;337:a2244.	Not empirical study

The reference of the article and a main reason for exclusion from the meta-analysis is provided. When reason for exclusion is non-dichotomous data or not OR or HR outcomes authors were contacted for data in a usable format.

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Results S1: Combination of records into studies

This section includes additional details on data sources for the studies finally included in our study if there was more than one source for a study. Studies are included alphabetically following the name given to each study in main article.

Bonander (2016)

The article by Bonander et al. (2016) included two different school-based surveys that did not share participants, and were separated into Bonander (2016a) and Bonander (2016b).

The main reference is:

- Bonander C, Beckman L, Janson S, Jernbro C. Injury risks in schoolchildren with attention-deficit/hyperactivity or autism spectrum disorder: Results from two school-based health surveys of 6- to 17-year-old children in Sweden. *J Safety Res*. 2016; 58:49-56.

Additionally, Bonander et al. (2016) provided subgroup data through personal correspondence (raw data divided by sex and age for both studies)

CPRD-HES

Two recent PhD theses, for which we have not been able to find a peer-reviewed version, used data from the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) databases from England. Both of them reported Hazard Ratios, but for one of them (Hire, 2016) there were enough data to calculate an odds ratio in which sex was controlled by design.

These theses were:

Hire (2016)

- Hire AJ. ADHD incidence, treatment and associated comorbidity in children and adolescents : an epidemiological study using electronic healthcare records. University of Manchester. 2016.

Prasad (2016)

- Prasad V. The epidemiology of injuries in epilepsy and attention deficit-hyperactivity disorder (ADHD) in children and young people using the Clinical Practice Research Datalink (CPRD) and linked data. University of Nottingham. 2016.

In relation to the the latter, we also found a poster that did not add new data to the study:

- Prasad V, Sayal K, West J, Kendrick D. 355 The risk of injuries in children with Attention deficit-hyperactivity disorder (ADHD) in England. *Inj Prev*. 2016;22(Suppl 2):A130.1-A130.

Dalsgaard (2015)

The main reference for the study is:

Dalsgaard S, Leckman JF, Mortensen PB, Nielsen HS, Simonsen M. Effect of drugs on the risk of injuries in children with attention deficit hyperactivity disorder: a prospective cohort study. *The Lancet Psychiatry*. 2015;366(15):1-8.

Additionally, Dalsgaard et al. (2015) provided subgroup data through personal correspondence (raw data divided by sex and age)

We also found three previous manuscripts that did not add new data to the study:

- Dalsgaard S, Nielsen HS, Simonsen M. The Effects of Pharmacological Treatment of ADHD on Children's Health. Institute for the Study of Labor; 2012.
- Dalsgaard S, Nielsen HS, Simonsen M. Consequences of ADHD Medication Use for Children's Outcomes. Institute for the Study of Labor; 2014.

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- Dalsgaard S, Leckman JF, Nielsen HS, Simonsen M. Gender and injuries predict stimulant medication use. *J Child Adolesc Psychopharmacol*. 2014;24(5):253-259.(commented in the qualitative medication review table)

Lalloo (2003)
The main reference for the study is:

- Lalloo R, Sheiham A, Nazroo JY. Behavioural characteristics and accidents: findings from the Health Survey for England, 1997. Accid Anal Prev. 2003;35(5):661-667.

Additionally, we found two other references that did not add new data to the study:

- Lalloo R. Risk factors for major injuries to the face and teeth. *Dent Traumatol*. 2003;19(1):12-14.
- Lalloo R, Sheiham A. Risk factors for childhood major and minor head and other injuries in a nationally representative sample. *Injury*. 2003;34(4):261-266.

Lange (2016)
The article by Lange et al. (2016) included two different German datasets that did not share participants, and were separated into Lange (2016a) and Lange (2016b).

The main reference is:

- Lange H, Buse J, Bender S, Siegert J, Knopf H, Roessner V. Accident Proneness in Children and Adolescents Affected by ADHD and the Impact of Medication. J Atten Disord. 2016;20(6):501-509.

Additionally, we received additional data from the study by Lange et al. sent by J. Buse through personal correspondence (raw data divided by sex and age for both studies)

LHID
Several articles used data from the Taiwan Longitudinal Health Insurance Database 2000 (LHID), and were combined into a single study with multiple outcomes. For more information on this database, see: https://nhird.nhri.org.tw/en/Data_Subsets.html

These articles are

Chou (2014)

- Chou I-CC, Lin C-CC, Sung F-CC, Kao C-HH. Attention-deficit hyperactivity disorder increases the risk of deliberate self-poisoning: A population-based cohort. *Eur Psychiatry*. 2014;29(8):523-527.

Guo (2015)

- Guo N-W, Lin C-WC-LC-J, Lin C-WC-LC-J, et al. Fracture risk and correlating factors of a pediatric population with attention deficit hyperactivity disorder: a nationwide matched study. *J Pediatr Orthop B*. October 2015.

Kang (2013)

- Kang J-H, Lin H-C, Chung S-D. Attention-deficit/hyperactivity disorder increased the risk of injury: a population-based follow-up study. *Acta Paediatr*. 2013;102(6):640-643.

Tai (2013)

- Tai Y-M, Gau SS-F, Gau C-S. Injury-proneness of youth with attention-deficit hyperactivity disorder: a national clinical data analysis in Taiwan. *Res Dev Disabil*. 2013;34(3):1100-1108.

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Man (2015)
The main reference for the study is:

- Man K, Chan E, Coghill D, Douglas I. Methylphenidate and the Risk of Trauma. Pediatrics. 2015;30(6):4.

Additionally, we found two other references (abstracts to congress) which did not add new data to the study:

- Man KKC, Chan EW, Douglas I, et al. Attention-Deficit/Hyperactivity Disorder (ADHD) Pharmacological Treatment and Its Effect on Accident and Emergency Admission Due to Injury: A Self-Controlled Case-Series Study. *Pharmacoepidemiol Drug Saf*. 2014;23(1, SI):317.
- Man KKC, Chan EW, Coghill DR, et al. Effects of Methylphenidate Treatment for Attention-Deficit/Hyperactivity Disorder on Trauma Related Accident and Emergency Admissions: Self-Controlled Case Series Study. *DRUG Saf*. 2014;37(10):834.

Mikolajczyk (2015)
The main reference for the study is:

- Mikolajczyk R, Horn J, Schmedt N, Langner I, Lindemann C, Garbe E. Injury Prevention by Medication Among Children With Attention-Deficit/Hyperactivity Disorder. *JAMA Pediatr*. 2015;169(4):391-395.

Additionally, we found another reference (abstract to congress) which did not add new data to the study:

- Schmedt N, Mikolajczyk RT, Horn J, Langner I, Lindemann C, Garbe E. Does Drug Treatment for Attention Deficit/Hyperactivity Disorder (ADHD) Prevent Injuries Among Children with ADHD?: 754. *Pharmacoepidemiol Drug Saf*. 2013;22(S1):379.

NHIS
Two articles used data from the United States National Health Interview Survey (with overlapping years), and were combined into a single study.

Pastor (2006) used data from the years 1997-2002:

- Pastor PN, Reuben CA. Identified Attention-Deficit/Hyperactivity Disorder and Medically Attended, Nonfatal Injuries: US School-Age Children, 1997–2002. *Ambul Pediatr*. 2006;6(1):38-44.

Xiang (2005) used data from the years 2000-2002:

- Xiang H, Stallones L, Chen G, Hostetler SG, Kelleher K. Nonfatal injuries among US children with disabling conditions. *Am J Public Health*. 2005;95(11):1970-1975.

Spinks
The main reference for the study is:

- Spinks AB, Nagle C, Macpherson AK, Bain C, McClure RJ. Host factors and childhood injury: the influence of hyperactivity and aggression. J Dev Behav Pediatr. 2008;29(2):117-123.

Additionally, Spinks et al. provided subgroup data through personal correspondence (raw data divided by sex and age for both studies)

Van den Ban (2014)
The main reference for the study is:

- Van Den Ban E, Souverein P, Meijer W, et al. Association between ADHD drug use and injuries among children and adolescents. *Eur Child Adolesc Psychiatry*. 2014;23(2):95-102.

Additionally, we found the PhD thesis that originated the work, which did not add new data to the study:

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- Van den Ban EF. ADHD medication use and long-term consequences. Utrecht University. 2014.

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Table S2: Description of studies for the meta-analysis of risk

Name	Country	Sample	Type of study	N outcomes	N non-ADHD	N ADHD	ADHD diagnosis	Medicated %	Duration	Age	Objetivation of injuries	Type of injury	NOS
Bijur (1988)(Bijur et al., 1988)	UK		Prospective cohort	12(8)/0	9335[c]	1059[c]	Scales with threshold	NR	>1	NR	Self-report	Any	2
Bonander (2016[a])(Bonander et al., 2016)	Sweden	ELSA	Population-based survey	9(1)/0	17817	588	Self-report	NR	<1	11.37 (6-17)	Self-report	Any	4
Bonander (2016b)(Bonander et al., 2016)	Sweden		Population-based survey	7(2)/0	3097	101	Self-report;		>1	NR	Self-report	Any	5
Brehaut (2003)(Brehaut et al., 2003)	Canada	BCLHD	Registry	1(1)/0	1010067	16806	Administrative coding (medication)	100	>1	NR	Registry	Any	4
Bruce (2007)(Bruce et al., 2007)	Canada	PMSID	Registry	6(6)/0	21308	955	Adminisrative coding	100	>1	NR	Registry	Unintentional	5
Christoffel (1996)(Christoffel et al., 1996)	US		Clinical	3(3)/0	247[b]	9[b]	Scales with threshold	NR	NA	NR (5-12)	Acute treatment	Pedestrian	4
Constant (2014)(Constant et al., 2014)	France		Population-based survey	3(1)/0	1152[a]	93[a]	Scales with threshold	NR	<1	8.2 (6-11)	Self-report	Unintentional	3
CPRD-HES(Hire, 2016; Prasad,	UK	CPRD-HES	Registry	1(1)/3	120190[a]	8968[a]	Administrative coding	44	>1	NR	Registry	Traumatology	5[a]

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Name	Country	Sample	Type of study	N outcomes	N non-ADHD	N ADHD	ADHD diagnosis	Medicated %	Duration	Age	Objetivation of injuries	Type of injury	NOS
2016)													
Daalsgard (2015)(Dalsgaard et al., 2015)	Denmark	DCRS	Registry	6(2)/0	705563	4557		31,97	<1	11	Registry	Any	6
Dudani (2010)(Dudani et al., 2010)	Canada	NLSCY	Population-based survey	4(4)/0	1666254[c]	274026[c]	Scales with threshold	NR	<1	NR (4-11)	Self-report	Unintentional	4
Fleming (2017)(Fleming et al., 2017)	UK	8 Scotish databases	Registry	0(0)/1	758831	7413	Administrative coding	100	>1	NR (4-18)	Registry	Any	5
Ghanizadeh (2008)(Ghanizadeh, 2008)	Iran		Clinical	1(1)/0	100	123	DSM-IV	NR	<1	NR (<18)	Self-report	Burns	4
Hurtig (2016)(Hurtig et al., 2016)	Finland	NFBC	Prospective cohort	0(0)/4	5639	288[a]	Clinical/Scales with threshold	0	>1	NR (0-15)	Registry	Any	4.5[a]
Jensen (1988)(Jensen et al., 1988)	US		Clinical	1(1)/0	38	38	Administrative coding	100	>1	NR	Registry	Traumatology	5
Keyes (2014)(Keyes et al., 2014)	Europe	SCHME	Population-based survey	3(1)/0	4359[b]	158[b]	Scales with threshold	NR	<1	NR (6-11)	Self-report	Any	2
Lalloo (2003)(Lalloo et al.,	UK	HSE:1997	Population-based	1(1)/0	4470	736	Scales with threshold	NR	<1	9.29 (4-15)	Self-report	Unintentional	3

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Name	Country	Sample	Type of study	N outcomes	N non-ADHD	N ADHD	ADHD diagnosis	Medicated %	Duration	Age	Objetivation of injuries	Type of injury	NOS
2003)			survey										
Lam (2006)(Lam et al., 2006)	China		Population-based survey	1(1)/0	1314	115	Scales with threshold	NR	<1	15 (13-17)	Self-report	Any	2
Lange (2016a)(Lange et al., 2016)	Germany	NHIESCA	Population-based survey	9(1)/0	12784	653	Self-report	21,71	<1	10.4 (3-17)	Self-report	Any	4
Lange (2016b)(Lange et al., 2016)	Germany	AOK plus	Registry	9(1)/0	364551	18741	Administrative coding (ICD-10)	33	<1	14.27 (4-23)	Registry	Any	5
Leibson (2001)(Leibson et al., 2001)	US		Registry	4(4)/0	3810[c]	309[c]	Administrative coding	NR	>1	NR	Registry	Any	5
LHID(Chou et al., 2014; Guo et al., 2016; Kang et al., 2013; Tai et al., 2013a)	China	LHID	Registry	17(4)/4	17231[a]	3694[a]	Administrative coding	74,3[a]	>1	NR	Registry	Any	5[a] (5.75 for HR[a])
Maxson (2009)(Maxson et al., 2009)	US		Clinical	1(1)/0	232	58	Scales with threshold	20,7	NA	9.24 (6-12)	Acute treatment	Traumatology	4
NHIS(Pastor and Reuben, 2006; Xiang et al., 2005)	US	NHIS	Population-based survey	2(2)/0	51921[a]	1502[a]	Self-report	NR	<1	NR (5-17)	Self-report	Any	3
Odoi	UK		Clinical	1(1)/0	164[c]	6	Scales with	NR	NA	10.74 (7-	Acute	Dental	5

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Name	Country	Sample	Type of study	N outcomes	N non-ADHD	N ADHD	ADHD diagnosis	Medicated %	Duration	Age	Objetivation of injuries	Type of injury	NOS
(2002)(Odoi et al., 2002)							threshold			15)	treatment	traumatology	
Rowe (2004)(Rowe et al., 2004)	UK	BCAMHS:99	Population-based survey	5(2)/0	10073[b]	365[b]	DSM-IV	NR	>1	NR	Self-report	Burns/ Fractures	6
Sciberras (2016)(Sciberras et al., 2016)	Australia		Prospective cohort	8(1)/0	212	177	Scales with threshold	11,86	<1	7.3 (6-8)	Self-report	Any	4
Shilon (2011)(Shilon et al., 2012)	Israel		Clinical	1(1)/0	29	29	DSM-IV	87,5	NA	11.4 (6-17)	Self-report	Unintentional	3
Silva (2014)(Silva et al., 2014)	Australia	MNS	Registry	2(1)/0	27304	11902	Administrative coding (ICD-9 and ICD-10)	100	>1	NR (0-4)	Registry	Leading to hospitalisation	5
Spinks (2008)(Spinks et al., 2008)	Australia	CHIPS	Prospective cohort	7(1)/0	690	121	Scales with threshold	NR	<1	8.04 (5-12)	Self-report	Any	4
Swensen (2004)(Swensen et al., 2004)	US		Registry	4(1)/0	1308	1308	Administrative coding (Other ICD)	NR	<1	16 (Any age admitted. 17% adults)	Registry	Unintentional	6

Country: country where data were collected; Sample: abbreviated name of the sample originating the data; N outcomes: number of outcomes reported as: number of outcomes in the OR analysis (number of outcomes in the main OR analysis)/ number of outcomes in the OR analysis; % medicated: percentage of medicated ADHD individuals, duration is duration of follow-up time for occurrence of injuries and is reported as <1 (less or equal to a year) or >1 (more than a year); Age: age at injury and is reported as mean or median age at injury (range) and NOS is the number of stars obtained with the Newcastle-Ottawa Scale for risk of bias.
a= Averaged from outcomes

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b= Estimated from total (3.5% of total for ADHD individuals and 96.5 for individuals without ADHD)(Polanczyk et al., 2014)
c= Summed from outcomes

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Table S3: Description of all outcomes included (OR)

Study Name	Id	Description of outcome	N ADHD	Sex of ADHD individuals (% Males)	Medicated (%)	N non-ADHD	Sex of non-ADHD (% Males)	Number of non-ADHD injured	Number of ADHD injured	OR	CI LB	CI UB	Main Analysis
Bijur (1988)	1	Boys. Hospitalization. High vs. low overactivity. Unadjusted	597	100.0	NR	1112	100.0	51	43	2.02	NR	NR	No
Bijur (1988)	2	Boys. Hospitalization. High vs. low overactivity. Adjusted	597	100.0	NR	1112	100.0	51	43	1.81	NR	NR	Yes
Bijur (1988)	3	Boys. Ambulatory care. High vs. low overactivity. Unadjusted	597	100.0	NR	1112	100.0	441	296	1.61	NR	NR	No
Bijur (1988)	4	Boys. Ambulatory care.	597	100.0	NR	1112	100.0	441	296	1.47	NR	NR	Yes[a]

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Doi: https://doi.org/10.1016/j.neubiorev.2017.11.007

Study Name	Id	Description of outcome	N ADHD	Sex of ADHD individuals (% Males)	Medicated (%)	N non-ADHD	Sex of non-ADHD (% Males)	Number of non-ADHD injured	Number of ADHD injured	OR	CI LB	CI UB	Main Analysis
		High vs. low overactivity. Adjusted											
Bijur (1988)	5	Girls. Hospitalization. High vs. low overactivity. Unadjusted	462	0.0	NR	1290	0.0	40	19	1.47	NR	NR	No
Bijur (1988)	6	Girls. Hospitalization. High vs. low overactivity. Adjusted	462	0.0	NR	1290	0.0	40	19	1.11	NR	NR	Yes
Bijur (1988)	7	Girls. Ambulatory care. High vs. low overactivity. Unadjusted	462	0.0	NR	1290	0.0	377	161	1.32	NR	NR	No

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Study Name	Id	Description of outcome	N ADHD	Sex of ADHD individuals (% Males)	Medicated (%)	N non-ADHD	Sex of non-ADHD (% Males)	Number of non-ADHD injured	Number of ADHD injured	OR	CI LB	CI UB	Main Analysis
Bijur (1988)	8	Girls. Ambulatory care. High vs. low overactivity. Adjusted	462	0.0	NR	1290	0.0	377	161	1.20	NR	NR	Yes
Bijur (1988)	9	Boys. Hospitalization. High vs. mid+low overactivity. Unadjusted	597	100.0	NR	4757	100.0	230	43	1.53	1.09	2.14	Yes
Bijur (1988)	10	Boys. Ambulatory care. High vs. mid+low overactivity. Unadjusted	597	100.0	NR	4757	100.0	2052	296	1.30	1.09	1.54	Yes
Bijur (1988)	11	Girls. Hospitalization. High vs. mid+low	462	0.0	NR	4578	0.0	152	19	1.25	0.77	2.03	Yes

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Study Name	Id	Description of outcome	N ADHD	Sex of ADHD individuals (% Males)	Medicated (%)	N non-ADHD	Sex of non-ADHD (% Males)	Number of non-ADHD injured	Number of ADHD injured	OR	CI LB	CI UB	Main Analysis
		overactivity. Unadjusted											
Bijur (1988)	12	Girls. Ambulatory care. High vs. mid+low overactivity. Unadjusted	462	0.0	NR	4578	0.0	1422	161	1.19	0.97	1.45	Yes
Bonander (2016a)	1	Survey A. Main outcome. Adjusted simple	588	71.6	NR	17817	50.1	1028	77	1.98	1.51	2.59	No
Bonander (2016a)	2	Survey A. Main outcome. Adjusted complex	588	71.6	NR	17817	50.1	1028	77	1.79	1.36	2.36	Yes[a]
Bonander (2016a)	3	Survey A. Boys. Unadjusted. Personal communication	422	100.0	NR	8832	100.0	583	50	1.90	1.40	2.59	No

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Study Name	Id	Description of outcome	N ADHD	Sex of ADHD individuals (% Males)	Medicated (%)	N non-ADHD	Sex of non-ADHD (% Males)	Number of non-ADHD injured	Number of ADHD injured	OR	CI LB	CI UB	Main Analysis
Bonander (2016a)	4	Survey A. Girls. Unadjusted. Personal communication	166	0.0	NR	8884	0.0	445	27	3.68	2.41	5.62	No
Bonander (2016a)	5	Survey A. Boys (4-8 years old). Unadjusted. Personal communication	21	100.0	NR	2381	100.0	91	1	1.26	0.17	9.48	No
Bonander (2016a)	6	Survey A. Boys (9-13 years old). Unadjusted. Personal communication	252	100.0	NR	4320	100.0	149	13	1.52	0.85	2.72	No
Bonander (2016a)	7	Survey A. Boys (14-18 years old). Unadjusted.	149	100.0	NR	2131	100.0	343	36	1.66	1.12	2.46	No

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Study Name	Id	Description of outcome	N ADHD	Sex of ADHD individuals (% Males)	Medicated (%)	N non-ADHD	Sex of non-ADHD (% Males)	Number of non-ADHD injured	Number of ADHD injured	OR	CI LB	CI UB	Main Analysis
		Personal communication											
Bonander (2016a)	8	Survey A. Girls (9-13 years old). Unadjusted. Personal communication	79	0.0	NR	4539	0.0	165	4	1.41	0.51	3.91	No
Bonander (2016a)	9	Survey A. Girls (14-18 years old). Unadjusted. Personal communication	77	0.0	NR	2127	0.0	200	23	4.10	2.47	6.83	No
Bonander (2016b)	1	Survey B. Hospital attendance due to injury over life time. Adjusted simple	101	54.0	NR	3097	48.3	968	47	2.29	1.48	3.53	No

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Study Name	Id	Description of outcome	N ADHD	Sex of ADHD individuals (% Males)	Medicated (%)	N non-ADHD	Sex of non-ADHD (% Males)	Number of non-ADHD injured	Number of ADHD injured	OR	CI LB	CI UB	Main Analysis
Bonander (2016b)	2	Survey B. Hospital attendance due to injury over life time. Adjusted complex	101	54.0	NR	3097	48.3	968	47	2.42	1.47	3.97	Yes
Bonander (2016b)	3	Survey B. Hospital attendance due to injury over life time. Boys. Unadjusted. Personal communication.	48	100.0	NR	1385	100.0	517	24	1.68	0.94	2.99	No
Bonander (2016b)	4	Survey B. Hospital attendance due to injury over life time. Girls. Unadjuste	38	0.0	NR	1418	0.0	433	23	3.49	1.80	6.75	No

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		d. Personal communication.											
Bonander (2016b)	5	Survey B. Injury in past 12 months. Adjusted	101	54	NR	3097	48.3	NR	NR	1.68	1.04	2.72	Yes[a]
Bonander (2016b)	6	Survey B. Injury in past 12 months. Boys. Unadjusted	54	100.0	NR	1405	100.0	419	29	2.73	1.58	4.72	No
Bonander (2016b)	7	Survey B. Injury in past 12 months. Girls. Unadjusted	41	0.0	NR	1514	0.0	310	12	1.61	0.81	3.19	No
Brehaut (2003)	1	Main outcome. Adjusted	16806	81.6	100.0	1010067	50.9	32242	1257	1.67	1.52	1.84	Yes[a]
Bruce (2007)	1	ADHD only vs. Controls. Office visits.	955	79.0	100.0	21308	40.0	11114	488	1.17	1.02	1.33	Yes

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Study Name	Id	Description of outcome	N ADHD	Sex of ADHD individuals (% Males)	Medicated (%)	N non-ADHD	Sex of non-ADHD (% Males)	Number of non-ADHD injured	Number of ADHD injured	OR	CI LB	CI UB	Main Analysis
		Adjusted.											
Bruce (2007)	2	ADHD only vs. Controls. Emergency room. Adjusted	955	79.0	100.0	21308	40.0	9036	509	1.37	1.17	1.61	Yes[a]
Bruce (2007)	3	ADHD only vs. Controls. Hospitalisation. Adjusted	955	79.0	100.0	21308	40.0	845	55	1.43	1.07	1.92	Yes
Bruce (2007)	4	ADHD+CD vs. Controls. Office visits. Adjusted	160	84.0	100.0	21308	40.0	11114	95	1.54	1.12	2.12	Yes
Bruce (2007)	5	ADHD+CD vs. Controls. Emergency room. Adjusted	160	84.0	100.0	21308	40.0	9036	82	1.02	0.69	1.51	Yes

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Bruce (2007)	6	ADHD+CD vs. Controls. Hospitalisation. Adjusted	160	84.0	100.0	21308	40.0	845	6	0.83	0.36	1.89	Yes
Christoffel (1996)	1	Achenbach child hyperactive questionnaire. Unadjusted	NR	NR	NR	NR	69.5	NR	NR	0.87	0.44	1.72	Yes
Christoffel (1996)	2	Achenbach teacher inatentive questionnaire. Unadjusted	NR	NR	NR	NR	NR	NR	NR	1.46	0.64	3.33	Yes
Christoffel (1996)	3	Achenbach teacher overactive questionnaire. Unadjusted.	NR	NR	NR	NR	NR	NR	NR	0.87	0.38	2.01	Yes[a]
Constant (2014)	1	SDQ scale (parents).	153	NR	NR	1105	50.2	NR	NR	1.38	0.90	2.12	Yes

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		Adjusted											
Constant (2014)	2	Dominic interactive scale (children). Adjusted	57	NR	NR	1201	50.2	NR	NR	3.01	1.67	5.42	No
Constant (2014)	3	Dominic interactive scale (children). Adjusted complex.	153	NR	NR	1105	50.2	NR	NR	2.41	1.24	4.69	Yes[a]
CPRD-HES: Hire 2016	1	Whole Sample. Unadjusted	5111	81.7	44.0	49489	81.5	8461	1029	1.22	1.14	1.31	Yes[a]
Dalsgaard (2015)	1	10 years old. Adjusted	4557;	84.0	32.0	705563	51.5	NR	NR	1.29	1.22	1.37	Yes
Dalsgaard (2015)	2	12 years old. Adjusted	NR	NR	32.0	NR	NR	NR	NR	1.30	1.23	1.37	Yes[a]
Dalsgaard (2015)	3	Boys 4-8. Unadjusted. Personal communication	3829	100	NR	363036	100	164234	2324	1.87	1.75	2.00	No
Dalsgaard (2015)	4	Boys 9-13.	2613	100	NR	293147	100	142141	1385	1.20	1.11	1.29	No

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		Unadjusted. Personal communication											
Dalsgaard (2015)	5	Girls 4-8. Unadjusted. Personal communication	782	0	NR	347084	0	127692	370	1.78	1.54	2.05	No
Dalsgaard (2015)	6	Girls 9-13. Unadjusted. Personal communication	442	0	NR	279737	0	125356	250	1.60	1.33	1.94	No
Dudani (2010)	1	ADHD only. Adjusted	145853	NR	NR	1666254	NR	0.118	NR	0.75	0.53	1.06	Yes
Dudani (2010)	2	ADHD with comorbid aggression. Adjusted	53037	NR	NR	1666254	NR	NR	NR	1.40	0.84	1.48	Yes
Dudani (2010)	3	ADHD with comorbid anxiety.	46408	NR	NR	1666254	NR	NR	NR	0.82	0.43	1.54	Yes

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		Adjusted											
Dudani (2010)	4	ADHD with comorbid anxiety and agression. Adjusted	28728	NR	NR	1666254	NR	NR	NR	1.09	0.55	1.84	Yes[a]
Ghanizadeh (2008)	1	Main outcome. Unadjusted	123	37.5	NR	100	NR	2	13	5.79	1.27	26.30	Yes[a]
Jensen (1988)	1	Main outcome. Unadjusted	38	68.0	100.0	38	68.0	15	26	3.32	1.29	8.54	Yes[a]
Keyes (2014)	1	Dominic interactive scale. Whole sample. Adjusted	NR	NR	NR	NR	NR	NR	NR	0.91	0.56	1.48	Yes[a]
Keyes (2014)	2	Dominic interactive scale. Boys. Unadjusted	NR	100.0	NR	NR	NR	NR	NR	0.78	0.33	1.89	No
Keyes (2014)	3	Dominic interactive scale.	NR	0.0	NR	NR	NR	NR	NR	0.96	0.53	1.72	No

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		Girls. Unadjusted											
Lalloo (2003)	1	Main outcome. Adjusted	736	67.6	NR	4470	NR	NR	NR	1.66	1.29	2.14	Yes[a]
Lam (2006)	1	Whole Sample. Adjusted	115	NR	NR	1314	47.5	301	39	1.68	1.18	2.40	Yes[a]
Lange (2016a)	1	Study 1. Main outcome. Adjusted	653	79.8	21.7	12784	48.5	1956	150	1.49	1.22	1.81	Yes[a]
Lange (2016a)	2	Study 1, boys. Unadjusted. Personal communication	516	100.0	NR	5783	100.0	970	127	1.62	1.31	2.00	No
Lange (2016a)	3	Study 1, girls. Unadjusted. Personal communication	131	0.0	NR	6136	0.0	863	22	1.23	0.78	1.96	No
Lange (2016a)	4	Study 1, boys 4-8. Unadjusted.	109	100.0	NR	2172	100.0	306	21	1.46	0.89	2.38	No

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		Personal communication											
Lange (2016a)	5	Study 1, girls 4-8. Unadjusted. Personal communication	27	0.0	NR	2243	0.0	276	3	0.89	0.27	2.98	No
Lange (2016a)	6	Study 1, boys 9-13. Unadjusted. Personal communication	256	100.0	NR	2097	100.0	369	63	1.53	1.13	2.08	No
Lange (2016a)	7	Study 1, girls 9-13. Unadjusted. Personal communication	72	0.0	NR	2227	0.0	347	14	1.31	0.72	2.37	No
Lange (2016a)	8	Study 1, boys 14-18. Unadjusted. Personal	151	100.0	NR	1514	100.0	295	43	1.65	1.13	2.40	No

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		communication											
Lange (2016a)	9	Study 1, girls 14-18. Unadjusted. Personal communication	32	0.0	NR	1666	0.0	240	5	1.10	0.42	2.89	No
Lange (2016b)	1	Study 2. Main outcome. Adjusted	18741	73.3	33.0	364551	50.0	160038	11335	1.55	1.49	1.61	Yes[a]
Lange (2016b)	2	Study 2, boys. Unadjusted. Personal communication	13536	100.0	33.0	132601	100.0	65585	8351	1.65	1.59	1.71	No
Lange (2016b)	3	Study 2, girls. Unadjusted. Personal communication	4910	0.0	33.0	133206	0.0	58115	2802	1.72	1.62	1.82	No
Lange (2016b)	4	Study 2, boys 4-8. Unadjuste	6819	100.0	33.0	31897	100.0	15386	4119	1.64	1.55	1.73	No

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		d. Personal communication											
Lange (2016b)	5	Study 2, girls 4-8. Unadjusted. Personal communication	2996	0.0	33.0	33836	0.0	15469	1687	1.53	1.42	1.65	No
Lange (2016b)	6	Study 2, boys 9-13. Unadjusted. Personal communication	4427	100.0	33.0	30118	100.0	14648	2721	1.68	1.58	1.80	No
Lange (2016b)	7	Study 2, girls 9-13. Unadjusted. Personal communication	1381	0.0	33.0	31718	0.0	14272	806	1.71	1.54	1.91	No
Lange (2016b)	8	Study 2, boys 14-18. Unadjusted.	2290	100.0	33.0	70586	100.0	35551	1511	1.91	1.75	2.09	No

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		Personal communication											
Lange (2016b)	9	Study 2, girls 14-18. Unadjusted. Personal communication	533	0.0	33.0	67652	0.0	28374	309	1.91	1.61	2.27	No
Leibson (2001)	1	Boys. Minor injuries. Unadjusted	229	100.0	NR	1896	100.0	1385	176	1.23	0.89	1.69	Yes
Leibson (2001)	2	Boys. Major injuries. Unadjusted	229	100.0	NR	1896	100.0	1037	142	1.35	1.02	1.79	Yes[a]
Leibson (2001)	3	Girls.Minor injuries. Unadjusted	80	0.0	NR	1914	0.0	1268	61	1.64	0.97	2.76	Yes
Leibson (2001)	4	Girls. Major injuries. Unadjusted	80	0.0	NR	1914	0.0	829	40	1.31	0.84	2.05	Yes
LHID:	1	Whole	3640	79.0	76.0	14560	76.0	1188	389	1.35	1.19	1.52	Yes[a]

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Chou (2014)		Sample. Unadjusted											
LHID: Chou (2014)	2	Boys. Unadjusted	2874	100.0	NR;	11496	100.0	1037	337	1.34	1.18	1.53	No
LHID: Chou (2014)	3	Girls. Unadjusted	766	0.0	NR;	3064	0.0	151	52	1.40	1.01	1.95	No
LHID: Chou (2014)	4	Ritalin no vs. non-ADHD. Unadjusted	962	NR	0.0	14560	NR	1188	137	1.87	1.55	2.26	No
LHID: Chou (2014)	5	Ritalin yes vs. non-ADHD. Unadjusted	2678	NR	100.0	14560	NR	1188	252	1.17	1.01	1.35	No
LHID: Guo (2015)	6	Whole Sample. Unadjusted	7200	79.8	NR	36000	79.8	2333	645	1.42	1.30	1.56	Yes
LHID: Guo (2015)	7	Boys. Unadjusted	5742	100.0	NR	28710	100.0	2070	561	1.39	1.26	1.54	No
LHID: Guo (2015)	8	Girls. Unadjusted	1458	0.0	NR	7920	0.0	263	84	1.78	1.38	2.29	No

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LHID: Guo (2015)	9	4 to 6 years old. Unadjusted	2200	NR	NR	11000	NR	773	204	1.35	1.15	1.59	No
LHID: Guo (2015)	10	7 to 9 years old. Unadjusted	2905	NR	NR	14525	NR	873	233	1.36	1.17	1.58	No
LHID: Guo (2015)	11	10 to 17 years old. Unadjusted	2095	NR	NR	10475	NR	687	208	1.57	1.33	1.85	No
LHID: Kang (2013)	12	Whole Sample. Unadjusted	3616	78.3	100.0	18080	78.0	2908	864	1.64	1.50	1.79	Yes
LHID: Kang (2013)	13	Boys. Unadjusted	2830	100.0	100.0	14150	100.0	2323	688	1.63	1.49	1.79	No
LHID: Kang (2013)	14	Girls. Unadjusted	786	0.0	100.0	3930	0.0	585	176	1.65	1.37	1.99	No
LHID: Kang (2013)	15	4 to 6 years old. Unadjusted	1382	NR	100.0	6910	NR	978	341	1.99	1.73	2.28	No
LHID: Kang (2013)	16	7 to 12 years old. Unadjusted	786	NR	100.0	11170	NR	1930	523	1.46	1.31	1.63	No

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LHID: Tai 2013	17	Whole Sample. Unadjusted	1965	81.2	54.0	7860	81.2	6052	1856	5.01	4.16	6.21	Yes
Maxson (2009)	1	Main outcome. Adjusted	58	79.3	20.7	232	63.4	20	38	3.25	1.57	6.72	Yes[a]
NHIS: Xiang (2005)	1	Main outcome. Adjusted	603	77.2	NR	55880	49.9	1397	27	1.65	1.04	2.61	Yes[a]
NHIS: Pastor (2006)	2	Main outcome. Adjusted	3741	74.3	NR	48243	49.2	NR	NR	1.83	1.48	2.26	Yes
Odoi (2002)	1	Main outcome. Adjusted	NR	NR	NR	NR	NR	NR	NR	1.90	0.79	4.52	Yes[a]
Rowe (2004)	1	Burns. Adjusted: simple model	NR	NR	NR	NR	NR	NR	NR	2.30	1.20	4.60	No
Rowe (2004)	2	Burns. Adjusted: psychiatric model	NR	NR	NR	NR	NR	NR	NR	1.50	0.70	2.90	Yes[a]
Rowe (2004)	3	Fractures. Adjusted: simple model	NR	NR	NR	NR	NR	NR	NR	1.70	1.20	2.40	No
Rowe (2004)	4	Fractures. Adjusted: psyquiatri	NR	NR	NR	NR	NR	NR	NR	1.70	1.20	2.40	No

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Study Name	Id	Description of outcome	N ADHD	Sex of ADHD individuals (% Males)	Medicated (%)	N non-ADHD	Sex of non-ADHD (% Males)	Number of non-ADHD injured	Number of ADHD injured	OR	CI LB	CI UB	Main Analysis
		c model											
Rowe (2004)	5	Fractures. Adjusted: full model	NR	NR	NR	NR	NR	NR	NR	1.60	1.20	2.30	Yes
Sciberras (2016)	1	Injuries in general. Adjusted simple	177	68.9	11.9	212	63.7	31	29	1.00	0.50	1.80	No
Sciberras (2016)	2	Injuries in general. Adjusted complex	177	68.9	11.9	212	63.7	31	29	0.70	0.30	1.50	Yes[a]
Sciberras (2016)	3	Injuries requiring hospitalization. Unadjusted	177	68.9	11.9	212	63.7	4	4	1.20	0.30	4.90	No
Sciberras (2016)	4	Injuries in general. Unadjusted	177	68.9	11.9	212	63.7	31	29	1.20	0.70	2.20	No
Sciberras (2016)	5	Injuries in general. Boys. Unadjusted. Personal communication.	117	100.0	NR	129	100.0	20	20	1.12	0.57	2.21	No

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Study Name	Id	Description of outcome	N ADHD	Sex of ADHD individuals (% Males)	Medicated (%)	N non-ADHD	Sex of non-ADHD (% Males)	Number of non-ADHD injured	Number of ADHD injured	OR	CI LB	CI UB	Main Analysis
Sciberras (2016)	6	Injuries in general. Girls. Unadjusted. Personal communication.	50	0.0	NR	73	0.0	11	9	1.24	0.47	3.25	No
Sciberras (2016)	7	Injuries requiring hospitalization Boys. Unadjusted. Personal communication.	117	100.0	NR	129	100.0	1	1	1.10	0.07	17.84	No
Sciberras (2016)	8	Injuries requiring hospitalization Girls. Unadjusted. Personal communication.	50	0.0	NR	73	0.0	3	3	1.49	0.29	7.70	No
Shilon (2011)	1	Main outcome. Unadjuste	29	72.4	87.5	29	72.4	6	13	3.11	0.98	9.92	Yes[a]

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Study Name	Id	Description of outcome	N ADHD	Sex of ADHD individuals (% Males)	Medicated (%)	N non-ADHD	Sex of non-ADHD (% Males)	Number of non-ADHD injured	Number of ADHD injured	OR	CI LB	CI UB	Main Analysis
		d											
Silva (2014)	1	Main outcome. Adjusted	11902	78.3	100.0	27304	78.0	1479	1112	1.73	1.59	1.88	Yes[a]
Silva (2014)	2	Main outcome. Unadjusted	11902	78.4	100.0	27304	78.0	1479	1112	1.80	1.66	1.95	No
Spinks (2008)	1	Main outcome. Adjusted	121	67.0	NR	690	0.5	137	34	1.56	1.01	2.43	Yes[a]
Spinks (2008)	2	Major injuries. Boys.Unadjusted. Personal communication	87	100.0	NR	382	100.0	83	24	1.37	0.81	2.33	No
Spinks (2008)	3	Major injuries. Girls.Unadjusted. Personal communication	45	0.0	NR	357	0.0	56	10	1.54	0.72	3.28	No
Spinks (2008)	4	Major injuries. Boys. 4-8 y.Unadjusted. Personal	41	100.0	NR	218	100.0	45	9	1.08	0.48	2.43	No

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Study Name	Id	Description of outcome	N ADHD	Sex of ADHD individuals (% Males)	Medicated (%)	N non-ADHD	Sex of non-ADHD (% Males)	Number of non-ADHD injured	Number of ADHD injured	OR	CI LB	CI UB	Main Analysis
		communication											
Spinks (2008)	5	Major injuries. Girls. 4-8 y.Unadjusted. Personal communication	27	0.0	NR	211	0.0	33	6	1.54	0.58	4.11	No
Spinks (2008)	6	Major injuries. Boys 9-13 y.Unadjusted. Personal communication	46	100.0	NR	164	100.0	38	15	1.60	0.78	3.28	No
Spinks (2008)	7	Major injuries. Girls 9-13 y.Unadjusted. Personal communication	18	0.0	NR	146	0.0	23	4	1.53	0.46	5.06	No
Swensen (2004)	1	Whole sample. Adjusted	1308	73.2	NR	1308	73.2	264	415	1.68	NR	NR	Yes[a]
Swensen (2004)	2	Whole Sample.	1308	73.2	NR	1308	73.2	264	415	1.84	1.54	2.20	No

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Study Name	Id	Description of outcome	N ADHD	Sex of ADHD individuals (% Males)	Medicated (%)	N non-ADHD	Sex of non-ADHD (% Males)	Number of non-ADHD injured	Number of ADHD injured	OR	CI LB	CI UB	Main Analysis
		Unadjusted											
Swensen (2004)	3	Children. Adjusted	416	NR	NR	416	NR	73	118	2.10	NR	NR	No
Swensen (2004)	4	Teens. Adjusted	670	NR	NR	670	NR	151	213	1.45	NR	NR	No

Outcome-level details of all the outcomes extracted from the studies for the OR analyses; Id: the identification for an outcome (arbitrary); N: number of individuals in each group, sex: percentage of males in each group, medicated: percentage of medicated ADHD individuals; OR: odds ratio between ADHD and non-ADHD; LB CI: lower bound of the 95% confident interval; HB CI: upper bound of the 95% confident interval; Main analysis: it indicates if the outcome has been included in the main analysis (most controlled and general outcome) and in the main sensitivity analyses. a=outcome (from main analysis) selected at random for risk of bias and heterogeneity analyses.

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Table S4: Description of all outcomes included (HR)

Name	ID	Description of outcome	N ADHD	Sex of ADHD (% Males)	Medicated (%)	N non-ADHD	Sex of non-ADHD (% Males)	Number of non-ADHD injured	Number of ADHD injured	HR	CI LB	CI UB	Main Analysis
CPRD-HES: Hire (2016)	1	Main outcome. Adjusted	5111	81.67	44.0	49489	81.46	3932	470	1.17	1.06	1.30	Yes
CPRD-HES: Prasad (2016)	2	Injuries. Adjusted	15737	84.6	44.0	291894	50.7	18598	1878	1.28	1.22	1.35	Yes[a]
CPRD-HES: Prasad (2016)	3	Burns.Adjusted	15741	84.6	44.0	291909	50.7	11958	1189	1.23	1.16	1.31	Yes
Fleming (2017)	1	Model 2: sociodemographic+comorbidity.Adjusted	7413	84.8	100.0	758831	50.6	NR	NR	1.52	1.40	1.65	Yes[a]
Hurtig (2016)	1	Rating scale, injury 0-6ys. Adjusted	875.00	75.20	0.00	5236.00	45.70	221.00	62	1.41	1.03	1.93	Yes
Hurtig (2016)	2	Rating scale, injury 7-15 ys. Adjusted	472	66.1	0.0	5639	50.98	383	54	1.45	1.07	1.97	Yes
Hurtig (2016)	3	ADHD diagnosis, injury 0-6 ys. Adjusted	105	72.38	0.0	352	NR	18	5	1.04	0.37	2.91	Yes[a]
Hurtig (2016)	4	ADHD diagnosis, injury 7-15ys.Adjusted	105	72.8	0.0	352	NR	28	15	2.33	1.2	4.51	Yes

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Name	ID	Description of outcome	N ADHD	Sex of ADHD (% Males)	Medicated (%)	N non-ADHD	Sex of non-ADHD (% Males)	Number of non-ADHD injured	Number of ADHD injured	HR	CI LB	CI UB	Main Analysis
LHID: Chou (2014)	1	Main outcome. Adjusted.	3640.00	79.00	76.00	14560	79.00	1188.00	389.00	1.26	1.12	1.42	Yes[a]
LHID: Kang (2013)	2	Main outcome. Adjusted.	3616	78.3	100.0	18080	78.0	2908	864	1.64	1.50	1.79	Yes
LHID: Tai (2013)	3	Main outcome. Adjusted	1965	81.17	54.0	7860	81.17	6052	1856	1.7	1.55	2.06	Yes
LHID: Guo (2015)	4	Main outcome. Adjusted.	7200	79.8	NR	36000	79.8	2333	645	1.41	1.29	1.54	Yes

Outcome-level details of all the outcomes extracted from the studies for the HR analyses. Id: identification for an outcome (arbitrary); N: number of individuals in each group; Sex: percentage of males in each group, medicated: percentage of medicated ADHD individuals; HR: hazard ratio between ADHD and non-ADHD obtained from a Cox proportional hazards model; LB CI: lower bound of the 95% confident interval; HB CI: upper bound of the 95% confident interval; Main analysis :it indicates if the outcome has been included in the main analysis (most controlled and general outcome) and in the main sensitivity analyses. a=outcome (from main analysis) selected at random for risk of bias and heterogeneity analyses.

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Table S5: Variables controlled for in relation to the main outcomes (OR outcomes)

Study	Outcome details	Variables controlled by design	Variables controlled statistically
Bijur (1988)	Boys/ Girls. Hospitalization/ ambulatory care. High against low overactivity. (4 outcomes in total)	Exclusion (for sample selection): Foreign country to UK Child in residential care at some point Not singleton births Exclusion (for analysis): Sex	SES Quality of housing Number of household moves Number of children Mother's employment Maternal malaise Other hospitalizations.
	Boys/ Girls. Hospitalization/ ambulatory care. High against mid+low overactivity. (4 outcomes in total)	Exclusion (for sample selection): Foreign country to UK Child in residential care at some point Not singleton births Exclusion (for analysis): Sex	
Bonander (2016a)			Sex Proxies for SES Grade Family structure Influence of ASD Guardian occupation Ethnic background
Bonander (2016b)	Hospital attendance/ Injury in past 12 months. (2 outcomes in total)	Age (all participants same age)	Sex Family structure Guardian birth region SES (Perceived economic status)
Brehaut (2003)			Age Sex SES Region
Bruce (2007)	ADHD only/ ADHD+CD. Hospitalizations/ office visits/ emergency room. (6 outcomes in total)	Comorbidity through exclusion: In half of the outcome,s ADHD individuals havecomorbid conduct problems. In the other half, all ADHD individuals have comorbid conduct problems	Age (6-12.12-19) Sex Person-years-observation
Christoffel (1996)	Diagnosis through Achenbach child hyperactive/ Achenbach teacher inattentive/ Achenbach	Age Sex Mother educational level Neighborhood Exclusion: Non English or Spanish speaking	

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	teacher overactive. (3 outcomes in total)		
Constant (2014)	Diagnosis through SDQ		Male sex Parental unemployment Living in rural area SES (School located in a deprived area)
	Diagnosis through Dominic Interactive		Male sex Parental unemployment Living in rural area SES (School located in a deprived area) CD ODD GAD
CPRD-HES	Hire (2016)	Age Sex GP	
Dalsgaard (2015)	10/12 years (2 outcomes in total)	Age (all participants same age)	Sex Birth-weight Birth complications Comorbid intellectual disability Maternal and paternal level of education Employment status Psychiatric history
Dudani (2010)	An outcome is ADHD without aggression or anxiety. an outcome is ADHD participants who also have aggression as comorbidity. an outcome is ADHD participants who also have anxiety as comorbidity. an outcome is ADHD participants who have both aggression and anxiety as comorbidity. (4 outcomes in total)		Child-related: Age Sex Previous injury Presence of behavior problem(s) Parental: Single parent status Biological parent status Parental education Parental depression Social and environmental factors: SES (income) Family functioning Positive interaction
Ghanizadeh (2008)		Sex	
Jensen (1988)		Age Sex	
Keyes	Diagnosis		Age of child

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(2014)	through Dominic Interactive		Sex Mother's education Mother's age Number of children Marital status East/west Europe Maternal employment Maternal psychological distress All disorders other than the focal disorder (ODD. Phobias. Separation Anxiety. Generalized Anxiety disorder. and Depressive symptoms)
Lalloo (2003)	Diagnosis though SDQ. High vs. low ADHD		Age Sex SES (Social class) Benefits received Family type
Lam (2006)			Sex Paternal level of education
Lange (2016a)			Age Sex
Lange (2016b)			Age Sex Medication status
Leibson (2001)	Boys/ Girls. Major/ Minor injuries. (4 outcomes in total)	Exclusion (for analysis): Sex	
LHID	Chou (2014)	Age (per 5y) Sex Parental occupation Area of residence (urbanization level)	
	Guo (2015)	Sex Sex Urbanization level Year of index	
	Kang (2013)	Age Sex Urbanization level Geographic region	
	Tai (2013)	Age Sex Date of diagnosis as index day	
Maxson (2009)		Exclusion: Non English or Spanish speaking Patients with known developmental delay Uncorrectable hearing Visual impairments Musculoskeletal or neurologic disease	Age Sex Race/ethnicity Past ED visits Current use of ADHD medication Parental education

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NHIS	Xiang (2005)		Age Sex SES Race Parents education Health insurance Family size
	Pastor (2006)		Age Sex Ethnicity Health insurance Survey year
Odoi (2002)		Age Sex Exclusion: Children with psychiatric problems Mentally disabled With parents could not communicate in English	
Rowe (2004)	Burns: psychiatric model		Age Sex ODD Anxiety
	Fractures: full model		Age Sex Depression Ethnic minority
Sciberras (2016)	Injuries in general/ Injuries with hospitalization (2 outcomes in total)	Sex School Exclusion: Intellectual disability Serious medical condition Parents who had insufficient English	Child age Child sex Parent high school completion Single-parent status Parent age ASD diagnosis Internalizing comorbidity Externalizing comorbidity.
Shilon (2011)		Age Sex	
Silva (2014)		Age Sex SES	Age Sex SES (SEIFA) Year of birth Maternal age Single marital status Birth weight Gestational age
Spinks (2008)		SES	Age Sex SES
Swensen (2004)		Age Sex	Age Sex Employment Treatment Presence of at least one mental health comorbidity Interaction between ADHD and comorbidity

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For each outcome included in the main analyses of the article (most general and controlled outcomes for each study). we indicate here the variables that were controlled by study design (either through sample selection or through exclusion criteria) and the variables that were controlled statistically. Outcome details describe the characteristics of the main outcomes when there are more than one (Author and year when outcomes from the same study have been obtained from different articles). SES: Socioeconomic Status. GAD: Generalized Anxiety Disorder.CD: Conduct Disorder. ODD: Oppositional Defiant Disorder. ASD: Autism Spectrum Disorder.GP: General Practice.

Table S6: Variables controlled in main outcomes (HR outcomes)

Study	Outcome details	Variables controlled by design	Variables controlled statistically
CPRD-HES	Hire (2016)	Age Sex GP	SES
	Prasad (2016)	Age	Age Sex SHA region SES (Deprivation) Calendar year at study entry
Fleming (2017)			Sociodemographic: Sex SES (Deprivation) Ethnic group Medication for comorbid conditions Maternity: Maternal age Maternal smoking Parity Mode of delivery Gestational week Birth-weight centile Apgar
Hurtig (2016)	ADHD scale/ADHD diagnosis. injuries between 0 and 6 years/ 7 and 15 years. (4 outcomes in total)	Age Exclusion: Those with a genetic syndrome or mild mental retardation from the ADHD sample	Sex Number of children in the family Family structure SES (Social status of the family)
LHID	Chou (2014)	Age (per 5y) Sex Parental occupation Area of residence (urbanization level)	Age (<12. >12) Sex Urbanization Parental occupation Fracture history DCD
	Guo (2015)	Age Sex Urbanization level Year of index	Age Sex Urbanization level Geographic region
	Kang (2013)	Age Sex Urbanization level Geographic region	Geographic region
	Tai (2013)	Age Sex	Psychiatric medication use Psychiatric comorbidity

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Study	Outcome details	Variables controlled by design	Variables controlled statistically
		Date of diagnosis as index day	

For each outcome included in the main analyses of the article (most general and controlled outcomes for each study). we indicate the variables that were controlled by study design (either through sample selection or through exclusion criteria) and the variables that were controlled statistically. Outcome details describe the characteristics of the main outcomes when there is more than one (Author and year when outcomes from the same study have been obtained from different articles). DCD: developmental coordination disorder.GP: General Practice

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Table S7: Medication studies reviewed qualitatively

Study name	Design	Sample characteristics	Outcome	Risk measure and results	Comments
Chen (2017)(Chen et al., 2017) Country: Taiwan-China Sample name: LHID	Retrospective cohort	6201 ADHD cases (administrative coding, ICD-9) 1: Non medicated 2:≤180 days MPH 3:≥180 days MPH. Age 6-11 Males (approximately 80%) Conduct disorder (CD): 2.1-3.8%	Risk of fracture between non medicated and medicated groups	Hazard Ratio adjusted by sex, age, level of urbanism and comorbidity ≤180 days MPH: HR 1.18 (95% CI: 0.98-1.43) ≥180 days MPH: HR 0.77 (95% CI: 0.63-0.94)	Risk of fractures decreased in the >180 days medicated group Limitations: higher rate of males in the long-term medicated group
Chorniy (2016)(Chorniy and Kitashima, 2016) Country: US Sample name: South Carolina medicaid	Retrospective cohort	58685 ADHD cases (administrative coding ICD-9) Males: 66% Mean age: 7.98±3.46 years (3-18)	Injuries in medicated and non-medicated ADHD.	Complex mathematical model. Medication reduces the risk of injuries by 2.3 percentage points or 0.081 injuries in a given year.	Medicated vs. not medicated. Medications reduced the risk of injuries in ADHD treated individuals.
Dalsgaard (2014)(Dalsgaard et al., 2014) Country: Denmark Sample name: DCRS	Population-based study with prospective and complete follow up.	11553 ADHD cases (administrative coding, ICD-10) Age: 0-5 years Males: 79%	Likelihood of later stimulant treatment medication in ADHD children having sustained an injury before the age of 5.	Odds ratio adjusted for parents' age, income. length of education, employment status, and psychiatric and somatic diseases OR 1.09 (95%CI 1.01-1.29)	Medicated vs. non medicated. Medicated ADHD had a slightly significant higher risk of having suffered an injury compared to non-medicated participants. Injuries could be used as a proxy of more severe ADHD cases

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Study name	Design	Sample characteristics	Outcome	Risk measure and results	Comments
Jacob (2017)(Jacob and Kostev, 2017) Country: Germany Sample name: DAD (IMS Health)	ADHD nested case-control study	2894 ADHD cases (administrative coding, ICD-10) Mean age: 10.3± 2.7 (6-17) Males: 76.5%	Risk of fracture between medicated (atomoxetine . dexamfetamine. lisdexamfetamine. or methylphenidate) and non-medicated children	Odds Ratio Model 1 (Medicated vs. not medicated): OR 0.61(95% CI: 0.51-0.73) Model 2 [Length of therapy (0-12 months]: OR 0.71 per month (95% CI 0.64-0.79)	Medicated children were associated with a decrease in the risk of fractures. The more months on medication the larger the protective effect.
Lange (2016)(Lange et al., 2016) Country: Germany Data sample: KIGGS/ AOK plus	Cross-sectional	Survey1: 653 ADHD cases (Self-reported) Mean age all sample: 10.4±4.23 (3-17) Males:79.8% Survey 2: 18741 ADHD cases (ICD-10) Mean age total cohort: 14.27± 5.19 (4-23) Males: 73.3%	Risk of injuries in medicated ADHD individuals vs. non-medicated ADHD individuals	Odds Ratio Survey 1: OR for accidents 1.28 (95% CI 0.93-1.77) Survey 2: OR 0.97 (95% CI 0.93 1.01)	Medicated vs. non-medicated.
Marcus (2008)(Marcus et al., 2008) Country: US	Retrospective cohort	11770 ADHD cases (administrative coding, ICD-9) 6-17 years Male: 76.1%	Risk of injuries in ADHD individuals treated with	Hazard Ratio adjusted to background demographic characteristics. treatment with psychotropic medications selected comorbid	All medicated. They found “a non-significant trend toward a decrease in risk of injury”

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Study name	Design	Sample characteristics	Outcome	Risk measure and results	Comments
Sample name: Medi-Cal		3 groups regarding adherence to treatment [medication possession ratio (MPR)]: 1) Low 2) Medium 3) High	stimulants compared to MPR.	diagnoses. and stimulant MPR group. Stimulant MPR: Medium: HR 0.97. p=0.64 High: HR 0.89; p=0.07	between high stimulants vs. low MPR.
Merrill (2016)(Merrill et al., 2016) Country : USA Sample name: DMBA	Retrospective cohort study	ADHD (administrative coding ICD-9) 0-64 years. Mean age 24.6 (43.6% <18).	Risk of injuries in individuals with ADHD or ADHD and comorbid mental illness.	Rate Ratio ADHD 1.20 (95% CI 1.16-1.25) ADHD adjusted by medication: RR methylphenidate RR 1.03 (95% CI 0.99-1.07). Other psycho-stimulants 1.00 (0.96-1.04). RR atomoxetine 0.99 (0.95-1.03)	It included Adults. Patients with ADHD had an increased risk of injury (even higher in those with ADHD and comorbid mental illness). Psychostimulants ameliorated the risk of injury in individuals with ADHD.
Perry (2016)(Perry et al., 2016) Country: US Sample Name: Vanderbilt's EMRs	Retrospective cohort	10.066 ADHD cases (administrative coding, ICD-9) Mean age: 16.7(95% CI: 13.4. 23.5) (≤40 years) Males: 66%	Risk of fracture in ADHD medicated individuals (stimulant and non-stimulants) vs. non-medicated ADHD individuals.	Hazard Ratio Non medicated vs medicated: HR 3.9 (95 % CI 2.6 – 5.9). No medication vs non stimulant medication: HR 3.92 (95% CI: 2.59-5.93). Stimulant vs non stimulant medication HR 0.92 (95% CI 0.6-1.41).	It included Adults. ADHD individuals with ≥2 prescriptions had higher risk of fractures than individuals with no documented medication prescriptions. Limitations: Details of medication therapy, including duration of treatment, adherence, and history of medication crossover were not available

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Study name	Design	Sample characteristics	Outcome	Risk measure and results	Comments
Schmedt (2013)(Schmedt et al., 2013) Country: Germany Sample name: (GePaRD)	Case crossover (CCO) and self-controlled case series (SCCS)[a].	37650 ADHD (Administrative coding ICD-10) Age: 3-17 years.	Risk of experiencing an injury under MPH or ATX	Odds Ratio 0.98 (95% CI 0.76-1.28)	Medicated vs. not medicated. No preventive effect of ADHD medication was found.
Tai (2013)(Tai et al., 2013b) Country: Taiwan-China Sample name: LHID	Retrospective cohort	1965 ADHD cases (administrative coding, ICD-9) Age: 10.6± 2.95 years (6-18) Males: 81.17% ODD/CD: 5.14%	Risk of injuries in those individuals treated with MPH vs non-ADHD	Hazard ratio adjusted by ADHD diagnosis. other medications and other psychiatric comorbidities: HR 1.03 (CI 95% 0.9-1.18)	Medicated vs. not medicated.

Table summarizing the characteristics and results of studies comparing outcomes in medicated *vs.* unmedicated individuals but not controlling for fixed characteristics of the individuals.
[a]= SCCS is analysed and described in the main article

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Results S2: Results for each analysis carried out:

For each analysis, the mean effect size, 95% confidence interval (CI), number of studies included (*k*), number of outcomes (*q*), p-value of the comparison (p) and degrees of freedom (df). Assumed correlation between intra-study outcomes is 0.8 (Rho), but sensitivity analysis was carried out varying p and results are summarized.

In meta-regression models, odds ratios were included in logarithmic scale in. Degrees of freedom in meta-regression analyses were adjusted to account for small number of articles(Tipton, 2015). In such cases, when degrees of freedom fall below 4 confidence intervals are untrustworthy and likely wider. *B*: beta coefficient for the variable of interest. p: p-value of the beta coefficient.

We note that the evaluation of a within-study effect of ODD with RVE was not possible due to small number of studies that compared unintentional injuries in ADHD individuals with and without comorbid behavioral problems.

OR main average effect (meta-analysis of risk)
The analysis showed an increased risk of unintentional injuries in ADHD individuals. OR=1.53, CI=1.40, 1.67; *k*=28; *q*=56; df=27. Estimates and confidence intervals did not change at all with varying levels of Rho.

HR main average effect (meta-analysis of risk)
The analysis showed an increased risk in ADHD individuals. OR=1.39; CI=1.06, 1.83; *k*=4; *q*=12; df=3. Estimates and confidence intervals did not change at all with varying levels of Rho.

OR average effect of statistically uncontrolled outcomes (meta-analysis of risk)
OR=1.66; CI=1.35, 2.04; *k*=11; *q*=27; df=10. Estimates and confidence intervals only changed slightly with varying levels of Rho.

OR average effect of statistically controlled outcomes (meta-analysis of risk)
OR=1.54; CI=1.42, 1.67; *k*=21; *q*=44; df=20. Estimates and confidence intervals did not change at all with varying levels of Rho.

OR average effect of all most general outcomes (meta-analysis of risk)
OR=1.55; CI=1.42, 1.70; *k*=28; *q*=70; df=27. Estimates and confidence intervals did not change at all with varying levels of Rho.

OR average effect of studies with a follow-up of a year or less (meta-analysis of risk)
OR=1.50; CI=1.36, 1.67; *k*=15; *q*=23; df=14. Estimates and confidence intervals did not change at all with varying levels of Rho.

OR average effect of studies with a follow-up of more than a year l (meta-analysis of risk)
OR=1.54; CI=1.30, 1.84; *k*=10; *q*=31; df=9. Estimates and confidence intervals only changed slightly with varying levels of Rho.

OR average effect of studies with data before the year 2000 (meta-analysis of risk)
OR=1.61; CI=1.46, 1.77; *k*=11; *q*=30. Estimates and confidence intervals did not change at all with varying levels of Rho.

OR average effect of studies with data after the year 2000 (meta-analysis of risk)
OR=1.49; CI=1.32, 1.69; *k*=15; *q*=21; df=14. Estimates and confidence intervals only changed slightly with varying levels of Rho.

OR average effect after exclusion of case-control studies, (meta-analysis of risk)
OR=1.53; CI=1.40, 1.67; *k*=25; *q*=51; df=24. Estimates and confidence intervals did not change at all with varying levels of Rho.

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OR average effect with at stringent definition of ADHD (DSM, ICD, registry or clinical history) and non-ADHD (excluding studies with clinical control groups; meta-analysis of risk)
OR=1.57; CI=1.36, 1.82; *k*=13; *q*=26; df=12. Estimates and confidence intervals only changed slightly with varying levels of Rho.

OR average effect after exclusion of self-reported injuries studies (meta-analysis of risk)
OR=1.53; CI=1.36, 1.73; *k*=13; *q*=27; df=12. Estimates and confidence intervals only changed slightly with varying levels of Rho.

OR meta-regression of the effect of risk of bias (Newcastle-Ottawa Scale; meta-analysis of risk)
B=-0.018; CI=-0.114, 0.078; p=0.674; *k*=28; *q*=56; df=7.86. Estimates and confidence intervals did not change at all with varying levels of Rho.

OR meta-regression of the prevalence of ADHD (meta-analysis of risk)
B=0.016; CI=-0.012, 0.044; p=0.231 k=19; q=71; df=6.69. Estimates and confidence intervals did not change at all with varying levels of Rho.

OR meta-regression of studies that control for ODD and CD compared to those that do not (meta-analysis of risk)
B=0.32; CI=-0.152, 0.794; p=0.119 k=26; q=54; df=2.98. Estimates and confidence intervals did not change at all with varying levels of Rho.

OR average effect of studies that control for the presence of ODD and CD (meta-analysis of risk)
OR=1.32; CI=0.86, 2.05; *k*=7; *q*=10; df=6. Estimates and confidence intervals only changed slightly with varying levels of Rho.

OR meta-regression of outcomes in boys compared to girls (within-study model; meta-analysis of risk)
B=0.072; CI=-0.061, 0.204; p=0.205 k=11; q=40; df=3.89. Estimates and confidence intervals did not change at all with varying levels of Rho.

OR meta-regression of the effect of age (meta-analysis of risk)
B=-0.001; CI=-0.069, 0.068; p=0.984; *k*=18; *q*=26; df=2.09. Estimates and confidence intervals only changed slightly with varying levels of Rho

IRR average effect of the effect of medication with a fixed-effects model (meta-analysis of the effect of medication).
The analysis showed a protective effect of medication. OR=0.898; CI=0.851, 0.948; *k*=4; df=3.

IRR average effect of the effect of medication with a random-effects model (meta-analysis of the effect of medication).
The analysis showed a protective effect of medication. OR=0.868; CI=0.780, 0.965; *k*=4; df=3.

Average effect (IRR and OR) of the effect of medication with a fixed-effects model (meta-analysis of the effect of medication).
The analysis showed a protective effect of medication. OR=0.879; CI=0.838, 0.922; *k*=5; df=4.

Average effect (IRR and OR) of the effect of medication with a fixed-effects model (meta-analysis of the effect of medication).
The analysis showed a protective effect of medication. OR=0.854; CI=0.785, 0.929; *k*=5; df=4.

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Figure S1: funnel plot for the OR analysis (risk study)
Figure depicts the single most general and best controlled outcome from each study (selected at random when there was more than one).

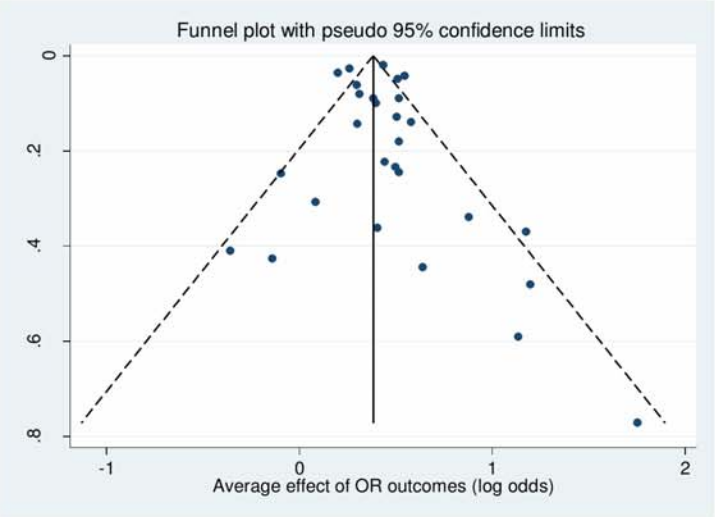

Figure S2: funnel plot for the HR analysis (risk study)
Figure depicts the single most general and best controlled outcome from each study (selected at random when there was more than one).

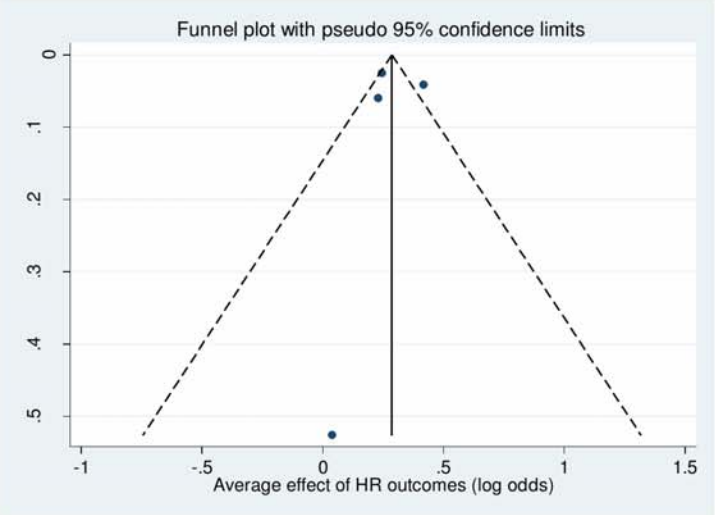

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Figure S3: funnel plot for the medication analysis

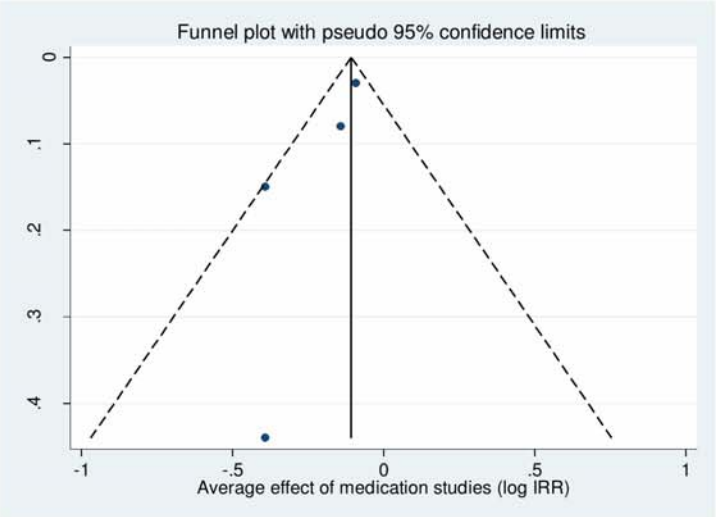

Figure S4 (Legend): Odds Ratios estimating the association between Unintentional Injury and ADHD.
Legend: a number identifying the study outcome follows study names. The area of each square is proportional to the weight that the individual study contributed to the meta-analysis. Weights are from a RVE random-effects model. The diamond indicates the overall weighted mean effect across all studies.

Figure S5 (Legend): Hazard Ratios estimating the association between Unintentional Injury and ADHD.
Legend: a number identifying the study outcome follows study names. The area of each square is proportional to the weight that the individual study contributed to the meta-analysis. Weights are from a RVE random-effects model. The diamond indicates the overall weighted mean effect across all studies.

Appendix S1: Conflict of Interest Disclosures

Samuele Cortese, M.D., Ph.D.
Dr. Cortese has received grant/research support from the Solent National Health Service (NHS) Trust, UK. He has received honorarium and travel expenses from the Association for Child and Adolescent Mental Health (ACAMH).

Pilar de Castro-Manglano, M.D., Ph.D.
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César Soutullo, M.D., Ph.D.
Dr. Cesar Soutullo has received research funds for his department (non-personal) from

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- Caja Navarra Foundation,
- Eli Lilly,
- Lundbeck,
- Shire
- TEVE (2017)
- Janssen (2017)

He has served as Consultant / Advisory Board for:

- Alicia Koplowitz Foundation,
- Editorial Médica Panamericana,
- Eli Lilly,
- EUNETHYDIS (European Network on Hyperkinetic Disorder),
- Medice Group
- NeuroTech Solutions Ltd,
- Spanish Health Ministry Quality Plan (Clinical Practice Guidelines on TDAH and Clinical Practice Guidelines on Depression),
- Rubió
- Shire

He has served in the Speaker's Bureau / has given talks on Continuous Medical Education (not about a product) for:

- Eli Lilly,
- Shire,
- Universidad Internacional Menéndez Pelayo
- Universidad Internacional de La Rioja (UNIR).

He has received Royalties from:

- DOYMA,
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3.3. Risk of poisoning in children and adolescents with Attention Deficit Hyperactivity Disorder. Protocol for a systematic review and meta-analysis

3.3.1. Antecedentes

A continuación, se resume el protocolo del segundo apartado de la presente tesis doctoral que tiene como principal objetivo evaluar el riesgo de envenenamiento en niños y adolescentes con TDAH. En concreto, se quiere cuantificar si el riesgo es significativamente mayor en este grupo frente a sus controles sanos, así como el efecto de la edad en el mismo. El último objetivo será conocer si el riesgo relativo de padecer un envenenamiento es significativamente más alto que el riesgo de padecer LNIs en la población con TDAH comparado con la población control.

3.3.2. Metodología

En la elaboración de este protocolo, se ha seguido una metodología similar a la descrita en el artículo *"Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: protocol for a systematic review and meta-analysis*". Los motivos por los que no se analizaron de forma conjunta los envenenamientos/intoxicaciones junto con el resto de lesiones físicas no intencionadas fueron los siguientes:

1) El mayor acceso de los niños y adolescentes con TDAH a fármacos (su propia medicación).
2) No es sencillo clarificar la intencionalidad de las lesiones (sobre todo en estudios retrospectivos de bases de datos administrativas).
3) Hay autores que han señalado que la proporción de auto-envenenamientos en niños y adolescentes con TDAH es mayor que sus homólogos sin TDAH.

El empleo de criterios de inclusión similares, y de un proceso de extracción y análisis de los datos parejos, permite que ambos estudios sean comparables. Sin embargo, el estudio del riesgo de envenenamientos presentaría algunas diferencias frente al metanálisis previo que se detallan a continuación. La definición de envenenamiento o intoxicación de la OMS sería la escogida como desenlace del estudio. Sin embargo, dado que el término intoxicación es también empleado para referirse al abuso de drogas y alcohol, se preferiría el empleo del término envenenamiento. De esta forma, el desenlace principal sería la HR de los niños y adolescentes que hubiesen sufrido un envenenamiento y que hubiesen requerido asistencia médica; puesto que esta medida de riesgo, mide la probabilidad de que ocurra un desenlace teniendo en cuenta la variable tiempo. Aun así, se aceptarían como desenlaces secundarios las ORs dado que son más prevalentes en la literatura y que son la única medida de asociación que podría calcularse en un estudio de casos y controles.

Por otro lado, en el análisis de los datos se combinarían de forma conjunta las HRs y ORs de padecer un envenenamiento en individuos con TDAH frente a individuos sin el trastorno y se obtendría

el efecto medio de tener TDAH en el riesgo de padecer un envenenamiento. Posteriormente se realizaría un análisis de sensibilidad combinando por separado las ORs y las HRs para evaluar la posible modificación del efecto.

Por último, se emplearía el método estadístico de RVE para comprobar si el riesgo relativo de envenenamientos es significativamente superior al riesgo relativo del resto de lesiones físicas no intencionadas en individuos con TDAH. Para ello se emplearían los datos sobre el riesgo de LNIs de aquellos estudios que incluyesen desenlaces de LNIs y envenenamientos en la misma población, ya que la comparación entre efectos del mismo estudio, es más robusta que cuando se comparan estudios con diferentes efectos. La hipótesis de este estudio sería que el riesgo de envenenamientos es significativamente más alto que el riesgo de otros tipos de LNIs. Dado que se prevé un número notablemente más bajo de estudios que en el metanálisis sobre el riesgo de LNIs en niños y adolescentes con TDAH se evaluaría la posibilidad de realizar un análisis de comorbilidades asociadas y de la influencia de la edad en el riesgo

Systematic review

This record is locked because it is being assessed by the editorial team

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Risk of poisoning in children and adolescents with Attention Deficit Hyperactivity Disorder

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

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5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	Yes	No
Risk of bias (quality) assessment	Yes	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

Review is an extension of a previous review by the authors on the risk of unintentional injuries. See section 37 of the present registration (other reviews by same authors on related topics) for further details.

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Gonzalo Arrondo

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:
Dr Arrondo

7. * Named contact email.

Give the electronic mail address of the named contact.

garrondo@yahoo.es

8. Named contact address

PLEASE NOTE this information will be published in the PROSPERO record so please do not enter private information

Give the full postal address for the named contact.

Mind-Brain Group, Institute for Culture and Society (ICS), Edificio Bibliotecas, University of Navarra, Pamplona, Spain

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

33-679133224

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Unversity of Navarra

Organisation web address:

11. Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Dr Maite Ruiz-Goikoetxea. Servicio Navarro de Salud-Osasunbidea, Servicio de Urgencias Extrahospitalarias, Pamplona, Spain.
Dr Samuele Cortese. Center for Innovation in Mental Health, University of Southampton, Academic Unit of Psychology, Southampton, UK. Faculty of Medicine, Clinical and Experimental Sciences (CNS and Psychiatry), University of Southampton, Southampton, UK. Department of Child and Adolescent Psychiatry, NYU Langone Medical Center, New York, NY, USA
Dr Maite Aznarez-Sanado. School of Education and Psychology, University of Navarra, Pamplona, Spain
Dr Sara Magallon. School of Education and Psychology, University of Navarra, Pamplona, Spain
Dr Noelia Álvarez Zallo. Servicio de Urgencias Extrahospitalarias, Servicio Navarro de Salud-Osasunbidea, Pamplona, Spain
Dr Elkin Luis. School of Education and Psychology, University of Navarra, Pamplona, Spain
Dr Pilar de Castro-Manglano. Child and Adolescent Psychiatry Unit, Department of Psychiatry and Medical Psychology, University of Navarra Clinic, Pamplona, Spain
Dr Dr Cesar Soutullo. Child and Adolescent Psychiatry Unit, Department of Psychiatry and Medical Psychology, University of Navarra Clinic, Pamplona, Spain.

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

This research is supported by the 2016 research program of the Health department of the Government of Navarre (grant number 89/2016), Spain. This program is 50% co-financed by the operational programme of the European Regional Development Fund (ERDF) 2014-2020 of Navarre. This systematic review is also supported by the University of Navarra, which will provide database and bibliographic access, and licenses for proprietary programs (Mendeley institutional and STATA).

The sponsor of this review is the Child and Adolescent Psychiatry Unit, Department of Psychiatry and Medical Psychology, University of Navarra Clinic, which has the final responsibility over the study.

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

Yes

Dr. Cortese has received grant/research support from the Solent National Health Service (NHS) Trust, UK. He has received honorarium and travel expenses from the Association for Child and Adolescent Mental Health (ACAMH). Dr de Castro has received research funds for his department from Caja Navarra Foundation and Shire and she has served as Consultant for the Alicia Koplowitz Foundation. Dr. Soutullo has received compensation for serving as consultant or speaker for, or him or his department has received research support or royalties from the following companies or organizations: Alicia Koplowitz Foundation, DOYMA, Editorial Médica Panamericana, Eli Lilly, EUNETHYDIS (European Network on Hyperkinetic Disorder), EUNSA, Janssen, Lundbeck, Mayo Ediciones, Medice Group, NeuroTech Solutions Ltd, Rubió, Shire, Spanish Health Ministry Quality Plan (Clinical Practice Guidelines on TDAH and Clinical Practice Guidelines on Depression), TEVE, Universidad Internacional de La Rioja (UNIR) and Universidad Internacional Menéndez Pelayo. All other authors do not have any conflicts of interest to disclose.

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

The main goal of the study will be to assess the degree of association between attention deficit hyperactivity disorder (ADHD) and poisoning.

Is the risk of poisoning significantly higher in children and adolescents with compared to those without ADHD?

Is this risk higher than the general risk of unintentional physical injuries? Are children with ADHD compared to those without ADHD more likely suffer from poisoning when they get older?

The present meta-analysis aims to fill-in the gap in the literature left by our previous meta-analysis on the risk of unintentional injuires in ADHD while using similar inclusion criteria, data extraction and analysis so results are comparable between the two studies.

16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

Electronic searches will be performed separately in the following databases (following previous meta-analysis):

• PubMed (MEDLINE Plus)

• Scopus

• Web of Science core database

A similar search will be carried out in UNIKA (http://www.unav.edu/en/web/biblioteca), an institutional reference aggregator that uses the EBSCO discovery service (http://support.ebsco.com/help/index.php?lang=en&int=eds) to provide a combined list of references from both internal (library) and external (database vendors) sources.

We will perform searches in these databases from their inception to date without limiting the type of study, language or year. Once the electronic search is completed, references from each pertinent paper will be checked in order to find out if there are any relevant studies that had been missed during the database searches. We will also review the references that were excluded with reasons and included in the previous meta-analysis.

The following search syntax (modified from previous meta-analysis) will be used to find relevant terms in reference titles, abstracts or key words (In any field in the case of PubMed-MEDLINE). Search terms and syntax will be adapted for each specific database:

(ADHD OR adhd OR attention deficit disorder with hyperactivity OR syndrome hyperkinetic OR hyperkinetic syndrome OR hyperactivity disorder OR hyperactive child syndrome OR childhood hyperkinetic syndrome OR attention deficit hyperactivity disorders OR attention deficit hyperactivity disorder OR adhd attention deficit hyperactivity disorder OR adhd OR overactive child syndrome OR attention deficit hyperkinetic disorder OR hyperkinetic disorder OR attention deficit disorder hyperactivity

OR attention deficit disorders hyperactivity OR child attention deficit disorder OR hyperkinetic syndromes OR syndromes hyperkinetic OR hyperkinetic syndrome childhood) AND (intox* OR overdos* OR poison*)

17. URL to search strategy.

Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Attention deficit hyperactivity disorder (ADHD).

Poisoning:

According to the World Health organisation, poisoning refers to an injury that results from being exposed to an exogenous substance that causes cellular injury or death. Conversely, intoxication is defined as “a condition that follows the administration of a psychoactive substance and results in disturbances in the level of consciousness, cognition, perception, judgement, affect, or behaviour, or other psychophysiological functions and response”. Since the term "intoxication" can be used in relation to alcohol or drug abuse, outcomes describing poisoining will be preferred to those reporting intoxications. However, if an article only reports intoxications it will also be included.

The WHO definition of poisoning or intoxication will be followed to decide inclusion of articles. Hence, articles reporting health problems related to the codes T36-T61 of the 19th chapter of the International Classification of Diseases (ICD-10)(World Health Organization, 2010) or similar problems will be deemed eligible.

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

The presence of ADHD will be defined operationally as one of the following (following the previous meta-analysis):

1) A categorical diagnosis according to standardized criteria, either the DSM (III, III-R, IV, IV-TR or 5) or the diagnosis of hyperkinetic disorder as per ICD-10 or previous versions;

2) Being above a pre-established threshold in a validated psychometric scale for the screening of ADHD. If there were studies, in which the severity of ADHD symptoms are related to intoxications, but no explicit diagnostic threshold is used, they will not be included. This threshold can also be a percentile of the sample;

3) The coding of the diagnosis in a medical registry;

4) A positive answer to the question: “Have you ever been told that you have ADHD by a doctor?” or similar questions;

5) Being prescribed ADHD medication(s).

Studies will be included regardless of medication status (specific medications for ADHD or any other medication) or sex ratio.

Comorbidities (psychiatric or other) in all or part of the study participants will not be exclusionary.

Studies including only pre-school children will not be eligible as diagnosis at this age range is controversial.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

As this meta-analysis evaluates the risk of poisoning in patients with ADHD compared to non ADHD individuals no intervention will be assessed.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Controls will be defined as children and adolescents under the age of 18 without ADHD. Specifically, and following our previous article, we will include:

1- individuals recruited from samples thought to represent the general population that do not have any psychiatric or neurological disorder,

2-individuals thought to represent the general population that do not have ADHD but could have other psychiatric or neurological disorders, or

3-individuals that were recruited specifically from other clinical populations other than ADHD that a priori were not judged by the study authors to be related to an increased risk of poisoning.

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

We will pool the results from any published or unpublished study that contrasts risk of poisoning in children or adolescents with ADHD and in typically developing individuals. Empirical papers that include statistical analyses (i.e. typically not reviews, letters, commentaries and editorials) with any kind of design will be accepted (mainly cohort studies, case and controls and cross sectional studies but also clinical trials). Any temporality of the design (i.e. prospective, retrospective or cross sectional) or setting (clinical or general population) will also be accepted.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

We will include studies where poisonings were treated in a clinical setting, reported through medical registries, recorded in medical histories, or self-reported. Studies reporting information requests to poison information centres or similar entities will not be included.

The sequence of events relating poisonings and diagnosis will not be considered important. Hence, articles in which poisoning occur before and after diagnosis will be included.

24. * Primary outcome(s).

Give the pre-specified primary (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Our primary outcome measure will be the hazard ratio obtained from Cox proportional hazards models (HR) of ADHD individuals suffering poisonings that are evaluated at a medical setting (primary care doctor or any other type of medical professional, emergency room or specialist care) compared to individuals without ADHD.

Timing and effect measures

25. * Secondary outcome(s).

List the pre-specified secondary (additional) outcomes of the review, with a similar level of detail to that required for primary outcomes. Where there are no secondary outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review

Since odds ratios (ORs) are the most commonly reported effect measure, and the only one that can be obtained when comparing the number of ADHD individuals in a poisonined sample and a non-poisoned group, they will be accepted as secondary valid measures.

The variable “poisonings” will have to be described as dichotomous one i.e. whether an individual has suffered a poisoning or not. If ORs are not directly reported in the paper, but data to calculate them are, we will determine the OR for that particular study

In the case of those studies that provide data on poisoning and other types of unintentional injuries, these outcomes will also be included in the database. They will be used to identify if the risk of poisoning is greater than the risk of other types of injuries.

Timing and effect measures

26. Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

Studies identified with electronic and manual searches will be listed with citation, titles and abstracts in Mendeley (Elsevier Inc., New York) and duplicates will be excluded both using the function “delete duplicates” of Mendeley and manually removing duplicates not discarded automatically. Members of the review team will be trained in software utilization before starting the review.

Article screening against inclusion criteria will be carried out independently by two of the authors (MR and GA), who will try to reach consensus in case of discrepancies between them. A third author (SC) will arbitrate in the final decision whenever consensus is not reached.

There will be two stages in the articles selection process:

• The title and abstracts of all non-duplicated papers will be screened, and studies that clearly do not fulfill the inclusion criteria will be excluded from further analysis. If the two evaluators disagree in their ratings, they will try to reach consensus through discussion. If this is not possible, a third author will give its opinion and act as an arbitrator. If there is still a disagreement between authors, articles will be moved forward to the next phase.

• All text of articles remaining from the previous screening will be downloaded. Eligibility will be judged following the same scheme than during the previous phase: the same two authors will independently evaluate the studies for eligibility and seek comments from a third author in case of discrepancy.

As studies may sometimes be published as several reports, we will actively search for duplicate reporting of studies, taking into account as main indicators location of the study, authors and year. Whenever a study includes data from multiple reports, they will be linked in the data extraction sheet and data from the largest sample, when possible, will be used. Corresponding authors of the original studies will be contacted to clarify article eligibility if necessary.

A list of excluded studies will be provided with reasons for exclusion. This list will include all articles that were preliminarily retained after stage one (selection from title and abstract) but finally excluded in stage 2.

2-DATA EXTRACTION

All articles considered appropriate in the previous stage will be read and analysed by at least two independent authors (one will always be MR or GA) who will extract the key information and include it in an Microsoft Excel document, with a third author acting as an arbitrator when consensus on discrepancies is not reached (SC).

The Excel file will have as many drop-down lists as possible to maximize inter-rater reliability, and also space for notes. Moreover, it will also include in-cell messages with help texts.

Data on publication and data extraction details will be inserted in an excel sheet as follows: first author, journal, year of publication, country(ies) where the study was conducted, and a more specific location such as region or hospital when applicable, final checking of fulfillment of inclusion and exclusion criteria and date and author of data extraction.

The description of the study design will include type of study (cross-sectional, case-control, cohort, or clinical trial.); temporal sequence (prospective, retrospective or cross sectional, duration of follow-up, participants enrollment (consecutive, non-consecutive); setting (clinical vs epidemiological population study) and year in which data acquisition for the study was carried out.

Regarding participant details, we will code sample size, age, gender distribution, ethnicity and socio-demographic status, characteristics of participants without ADHD (No ADHD, no ADHD or other conditions, or comparisons with other diagnostic categories other than ADHD); psychiatric comorbidities of individuals with and without ADHD (type and prevalence); method to establish the diagnosis of ADHD (self-reported diagnosis, diagnosis recorded in medical files/registry, structured or semi-structured interview according to DSM or ICD, questionnaires, per medication usage, or positive answer to the question: Have you ever been told you have ADHD?); medication status of individuals with and without ADHD (type of medication and percentage of treated participants).

In relation to outcomes, data that will be coded includes treatment setting (acute care hospitals, emergency facilities, general practice, medical specialist, or other, including extended care facilities such as nursing homes, offices, schools and communities) and method to document intoxications (registry, acute treatment, through expert retrospective analysis or self-report).

The primary outcome will be the Hazard Ratio of suffering a poisoning or intoxication in ADHD individuals vs. children and adolescents without ADHD. If HRs are not available odds ratios will be used. To obtain effect measures, any numeric data (raw number of poisonings in each of the samples or HR or OR and their confidence intervals) will be coded including both unadjusted analyses and analyses adjusted for covariates. In the latter case, covariates will also be included in the data extraction sheet.

Finally, the reporting of any subgroup analysis or comparison of interest, the presence of other intervention groups and the main conclusions of the reports will also be annotated.

We will extract information on multiple outcomes per article. Specifically outcomes from different age or gender groups, multiple control groups, varying diagnosis techniques or statistical models will be valid.

If a report includes more than one equally valid outcome or group comparison, they will all be included in the spread sheet, using a different line per outcome or comparison. A different comparison ID will be used in such case in combination with a report and study ID to link all related data.

27. * Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

The evaluation of study quality and possible bias will be individually performed by two researchers for each article. As there is no agreement about the best method to evaluate study quality in meta-analyses of observational studies, we will use the Newcastle-Ottawa Scale, which has been used in several previous meta-analyses and is mentioned in the Cochrane Handbook. This scale evaluates the sample selection methods, the comparability among studied groups and the ascertainment of either the exposure (in case-control studies) or outcome of interest (for cohort studies) of non-randomised studies.

If there is any disagreement in the rating of study quality and bias, a consensus between the two authors will be gained. If there is no consensus, another author will act as an arbitrator.

28. * Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

META-ANALYSIS OF DIFFERENCES IN RISK OF POISONINGS BETWEEN INDIVIDUALS WITH AND WITHOUT ADHD

Odds ratios will be calculated from the reported data if they cannot be directly extracted. All valid outcomes from articles will be included in a single database. These will include any unadjusted or adjusted HR or OR which would fulfil independently the inclusion criteria of our meta-analysis. This database will also encode other continuous or dichotomous (dummies) variables of interest for the metaregression and subgroup analyses.

A-HETEROGENEITY AND SMALL SAMPLE BIAS

Q-Cochran's (Cochran, 1950) and the I^2 test (Higgins, Thompson, Deeks, & Altman, 2003) will be used to evaluate heterogeneity between studies. Begg's adjusted rank correlation test (Begg & Mazumdar, 1994) will be used to formally assess the presence of "small-sample" bias (which encompasses publication bias); an approach that will be combined with the use of funnel plots for a qualitative visual analysis, and statistical testing of asymmetry (Egger, Davey Smith, Schneider, & Minder, 1997).

A single effect size will be used per study to calculate the degree of between-study heterogeneity and the risk of small-sample bias. The most general and statistically controlled outcome per study will be used. If there is more than one possible outcome fulfilling these criteria it will be chosen at random from the available outcomes.

B-DEPENDENCY AMONG OUTCOMES

We will use Robust Variance Estimation (RVE), a statistical technique that models the nested structure between outcomes of the same study (Hedges, Tipton, & Johnson, 2010), for the inference of a mean effect size and metaregression analyses. Whereas this method yields valid results regardless of the weights used, a strategy using approximate inverse-variance weights has been proposed for efficiency purposes: a random-effects model with variation of effect sizes between studies (τ^2) and equicorrelation (p) between same-study effect sizes (I^2) is assumed (Hedges et al., 2010). This strategy is efficient to estimate a mean model from outcomes which are typically correlated at the study level, but are usually independent between studies. We will use p=0.8, similarly to previous studies (deVibe, Bjørndal, Tipton, Hammerstrøm, & Kowalski, 2012), but these same studies and simulations by the RVE authors have shown little change with different values of p (Linck, Osthus, Koeth, & Bunting, 2014). Moreover, a sensitivity analysis with varying levels of p can be carried out to check the influence of such decision (Hedges et al., 2010).

C-MEAN EFFECT SIZES AND BETWEEN-STUDY EFFECTS

We will first calculate a population average effect size through the combination of the most general and statistically controlled outcome per study. If there is more than one possible outcome fulfilling these criteria they will all be included in the analysis.

Sensitivity analyses for this average effect size will be: 1-to vary in 0.1 steps the p correlation parameter, 2-to include ORs and HRs in separate analyses. Risk of bias (number of stars in the Newcastle-Ottawa Scale) will be considered a continuous variable and its effect evaluated. Two other population average models will be obtained by: 1-computing a mean effect size

only including unadjusted OR or HR, 2-computing a mean effect size only including adjusted OR or HR. Finally, we will test the influence of removing articles that report risk of intoxications (instead of poisoning).

Effect sizes whose 95% confidence intervals (CIs) do not cover 0 will be considered significant.

29. * Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

We will assess, if feasible, the effect of age. We predict that the age will increase the risk of poisonings. This will be done if possible 1-searching for a linear trend with age and 2-comparing the effect in those under and above the age of 10.

We will use RVE to investigate if there is evidence for a within or between study effect indicating that the risk of poisoning in ADHD is significantly greater than the risk for other types of unintentional injuries. We predict that there will be such an effect. For this analysis, data obtained in our previous meta-analysis on the risk of injuries will be combined with the outcomes obtained in the present work regarding the risk of poisonin.

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness	No
Diagnostic	No
Epidemiologic	Yes
Individual patient data (IPD) meta-analysis	No
Intervention	No
Meta-analysis	Yes
Methodology	No
Network meta-analysis	No
Pre-clinical	No
Prevention	No
Prognostic	No
Prospective meta-analysis (PMA)	No
Qualitative synthesis	No
Review of reviews	No
Service delivery	No
Systematic review	Yes
Other	No

Health area of the review

Alcohol/substance misuse/abuse	No
Blood and immune system	No
Cancer	No
Cardiovascular	No
Care of the elderly	No
Child health	Yes

Complementary therapies	No
Crime and justice	No
Dental	No
Digestive system	No
Ear, nose and throat	No
Education	No
Endocrine and metabolic disorders	No
Eye disorders	No
General interest	No
Genetics	No
Health inequalities/health equity	No
Infections and infestations	No
International development	No
Mental health and behavioural conditions	Yes
Musculoskeletal	No
Neurological	No
Nursing	No
Obstetrics and gynaecology	No
Oral health	No
Palliative care	No
Perioperative care	No
Physiotherapy	No
Pregnancy and childbirth	No
Public health (including social determinants of health)	No
Rehabilitation	No
Respiratory disorders	No
Service delivery	No
Skin disorders	No
Social care	No
Tropical Medicine	No
Urological	No
Wounds, injuries and accidents	Yes
Violence and abuse	No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

English

There is an English language summary.

32. Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

England
Spain

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

No I do not make this file publicly available until the review is complete

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

The results will be published in a peer-reviewed journal and presented at national and international conferences of psychiatry, psychology and paediatrics.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

systematic review

meta-analysis

ADHD

Attention deficit hyperactivity disorder

intoxication

poisoning

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

We recently carried out a systematic review and meta-analysis on the risk of unintentional physical injuries in ADHD children and adolescents compared to children and adolescents without the disorder (registration: CRD42017064967; in process of publication as of November 2017). Outcomes that reported solely the risk of intoxications or poisonings were excluded from the analysis. The reason for this decision was that we hypothesized that risk of poisoning would be much higher as 1-ADHD children have more access to medications (at least their own) and 2-it is very hard to distinguish between unintentional or intentional poisoning (specially when using institutional databases), and whereas in normally-developing children most poisonings would be accidental in nature, the proportion of intentional self-poisonings could be greater in ADHD children (Hurtig et al., 2012).

The present meta-analysis aims to fill-in the gap in the literature left by our previous meta-analysis on the risk of unintentional injuires in ADHD while using similar inclusion criteria, data extraction and analysis so results are comparable between the two studies.

Hence, this review, while an independent work, will be very related to the previous one.

38. * Current review status.

Review status should be updated when the review is completed and when it is published.

Ongoing

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

Regarding the present text, full sections have been copied and edited from the previous registration (CRD42017064967) and protocol (Ruiz-Goikoetxea et al., 2017) (the latter is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial license (CC BY-NC 4.0), which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See:http://creativecommons.org/licenses/by-nc/4.0/ and http://dx.doi.org/10.1136/bmjopen-2017-018027 for the protocol of the previous work).

Ruiz-Goikoetxea, M., Cortese, S., Aznarez-Sanado, M., Magallon, S., Luis, E.O., Alvarez Zallo, N., de Castro-Manglano, P., Soutullo, C., Arrondo, G., 2017. Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: protocol for a systematic review and meta-analysis. Br. Med. J. Open. doi:10.1136/bmjopen-2017-018027

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

3.4. Risk of poisoning in children and adolescents with ADHD: a systematic review and meta-analysis

3.4.1. Antecedentes

El envenenamiento, es un subtipo de lesión física que supone una importante causa de muerte y discapacidad en la infancia y adolescencia, siendo una de las principales causas de morbimortalidad prevenibles en pediatría. De la misma forma que se ha demostrado que el TDAH está asociado con un mayor riesgo de lesiones no intencionadas (Ruiz-Goikoetxea et al., 2018), podría ser que los niños y adolescentes con este trastorno presenten una mayor propensión a sufrir un envenenamiento.

3.4.2. Metodología

Se realizó una revisión sistemática y metanálisis para evaluar el riesgo de envenenamientos en niños y adolescentes con TDAH de acuerdo a la metodología descrita en el protocolo pre-registrado:"*Risk of poisoning in children and adolescents with Attention Deficit Hyperactivity Disorder".*

3.4.3. Resultados

Se realizó una búsqueda sistemática en 114 bases de datos de todos los estudios publicados hasta noviembre de 2017. De un conjunto de 826 referencias potencialmente relevantes, evaluadas de forma independiente por dos investigadores, nueve estudios se incluyeron finalmente en el metanálisis. La combinación de los diferentes estudios aportó un tamaño muestral de 84.756 individuos con TDAH y 1.398.946 sin el trastorno. Se ponderaron la HR y OR utilizando el RVE.

La combinación de los desenlaces permitió concluir que el TDAH se asocia con un riesgo relativo (RR) significativamente mayor de intoxicación (RR = 3,14; IC 95%= 2,23 - 4,4). Además, la asociación entre TDAH y riesgo de intoxicaciones era aún mayor cuando se analizaron conjuntamente los estudios que únicamente empleaban HR como medida de efecto (HR global= 4,00; IC 95% = 3,49 - 4,58). Igualmente, esta relación continuó siendo significativa cuando solo se combinaron los estudios que empleaban OR (OR global: 2,59, IC 95% = 1,81 – 3,71).

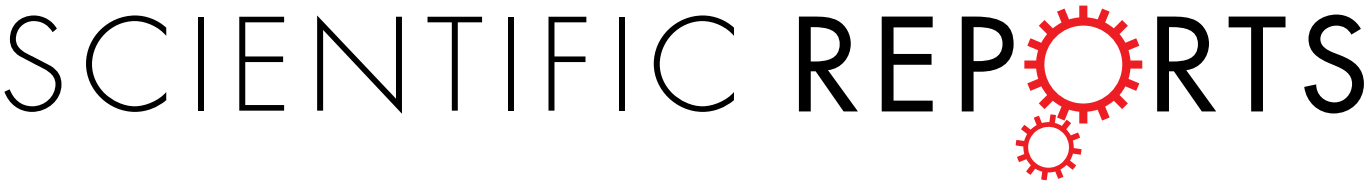
Los análisis de metarregresión realizados para evaluar la influencia de la edad de los individuos y del riesgo de sesgo de los estudios originales de acuerdo a sus puntuaciones en la escala Newcastle-Otawa no alcanzaron resultados estadísticamente significativos. No se pudo cuantificar el efecto de la comorbilidad en el riesgo de envenenamientos, ya que la mayoría de los estudios incluidos en el metanálisis no aportaban datos al respecto.

Para evaluar si los niños y adolescentes con TDAH presentaban mayor riesgo relativo de envenenamientos que de LNIs, se analizaron 8 estudios que recogían datos de ambos desenlaces en el mismo estudio. Así, se estimó un RR de LNIs en estos estudios (1.54; IC 95% 1,33-1,78) similar al obtenido en el metanálisis previo (1.53; IC 95% 1, 40-1,67) e inferior al RR de envenenamientos en este

mismo grupo de sujetos (3,14 IC 95%; 2,23-4,42). Esta diferencia se evaluó utilizando un efecto intra-estudio con RVE y fue estadísticamente significativa. Los resultados de comparar los desenlaces de lesiones y envenenamientos indicaron que el riesgo relativo de envenenamiento es mayor que el riesgo relativo de sufrir una LNIs cuando se comparan niños y adolescentes con y sin TDAH (Coeficiente beta = 0,686; IC 95% = 0,166-1,206, p=0.021).

3.4.4. Conclusiones

Los niños y adolescentes con TDAH presentan un riesgo casi tres veces mayor de padecer un envenenamiento que sus iguales sanos. Este riesgo es significativamente más elevado que el riesgo de padecer una LNIs. Estos hallazgos deberían ser tenidos en cuenta en la elaboración de guías clínicas y los programas de salud pública dirigida a reducir la morbimortalidad y mejorar la calidad de vida de los niños y adolescentes con TDAH.



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Risk of poisoning in children and adolescents with ADHD: a systematic review and meta-analysis

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Maite Ruiz-Goikoetxea[1], Samuele Cortese[2,3,4,5,6], Sara Magallón[7], Maite Aznárez-Sanado[7], Noelia Álvarez Zallo[1], Elkin O. Luis[7], Pilar de Castro-Manglano[8], Cesar Soutullo[8] & Gonzalo Arrondo[9]

Poisoning, a subtype of physical injury, is an important hazard in children and youth. Individuals with ADHD may be at higher risk of poisoning. Here, we conducted a systematic review and meta-analysis to quantify this risk. Furthermore, since physical injuries, likely share causal mechanisms with those of poisoning, we compared the relative risk of poisoning and injuries pooling studies reporting both. As per our pre-registered protocol (PROSPERO ID CRD42017079911), we searched 114 databases through November 2017. From a pool of 826 potentially relevant references, screened independently by two researchers, nine studies (84,756 individuals with and 1,398,946 without the disorder) were retained. We pooled hazard and odds ratios using Robust Variance Estimation, a meta-analytic method aimed to deal with non-independence of outcomes. We found that ADHD is associated with a significantly higher risk of poisoning (Relative Risk = 3.14, 95% Confidence Interval = 2.23 to 4.42). Results also indicated that the relative risk of poisoning is significantly higher than that of physical injuries when comparing individuals with and without ADHD (Beta coefficient = 0.686, 95% Confidence Interval = 0.166 to 1.206). These findings should inform clinical guidelines and public health programs aimed to reduce physical risks in children/adolescents with ADHD.

Poisoning is defined by the World Health Organization as "an injury that results from being exposed to an exogenous substance that causes cellular injury or death"[1]. Poisons can be inhaled, ingested, injected or absorbed. On a global scale, poisoning is estimated to cause 350,000 deaths every year, of which 45,000 refer to individuals under the age of twenty[1], and, more generally, it leads to higher mortality and morbidity rates in this age group[2–6].

Risk factors for poisonings include age and sex, among others. Being male is related to a higher poisoning risk across all age groups[1,5]. The relationship between age and risk of poisoning has a bimodal distribution with two peaks of highest risk between the ages of 1 and 4, as well as between 13 and 18 years of age[1,5]. Age is also associated with a change in the mechanism of poisoning: whereas most poisonings before the age of fourteen are unintentional, the proportion of intentional poisonings increases dramatically from that age onward[1,7]. The majority of suicide intents in adolescents consist of intentional intoxications[1,6], accounting for one third of total poisonings in that age range[5].

Attention-deficit/hyperactivity disorder (ADHD) has a world-wide estimated prevalence of around 5%[8], which makes it the most frequent neurodevelopmental disorder in children and adolescents. It is characterized

[1]Servicio de Urgencias Extrahospitalarias, Servicio Navarro de Salud-Osasunbidea, Pamplona, Spain. [2]Center for Innovation in Mental Health, University of Southampton, Academic Unit of Psychology, Southampton, UK. [3]Faculty of Medicine, Clinical and Experimental Sciences (CNS and Psychiatry), University of Southampton, Southampton, UK. [4]Department of Child and Adolescent Psychiatry, NYU Langone Medical Center, New York, NY, USA. [5]Solent NHS Trust, Southampton, UK. [6]Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, Nottingham, UK. [7]Facultad de Educación y Psicología, Universidad de Navarra, Pamplona, Spain. [8]Unidad de Psiquiatría Infantil y Adolescente, Departamento de Psiquiatría y Psicología Médica, Clínica Universidad de Navarra, Pamplona y Madrid, Spain. [9]Instituto Cultura y Sociedad (ICS), Grupo Mente-Cerebro, Universidad de Navarra, Pamplona, Spain. Correspondence and requests for materials should be addressed to G.A. (email: garrondo@yahoo.es)

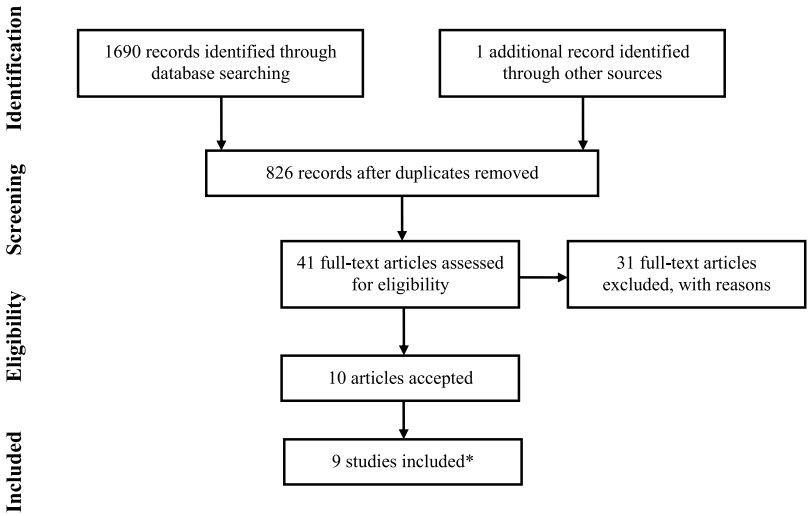

Figure 1. PRISMA flow diagram of record identification and study selection. *Four additional articles only reporting physical injuries for two of the included studies were also found.

by inattentive and/or hyperactive- impulsive symptoms that have a negative impact on social[9], academic[10], and health domains[11–13], and reduce the quality of life[14]. ADHD is approximately four times more common in boys than in girls. Pharmacological treatment, including psychostimulants (methylphenidate and amphetamines) and non-psychostimulants (e.g., atomoxetine, guanfacine), is an important component of the multimodal treatment of ADHD[15]. In addition, a high percentage of patients have comorbid disorders hence increasing the probability of patients being poly-medicated[16].

A recent meta-analysis by our group has demonstrated that the risk of physical injuries is significantly higher in children and adolescents with ADHD compared to the typically developing population. Additionally, this risk is significantly reduced by the use of ADHD medications[17]. Therefore, a plausible hypothesis is that ADHD symptoms (inattention, hyperactivity and impulsivity) could lead to a similar increase in the risk of poisoning. Impulsivity might be an important factor, especially considering that it is significantly associated with suicide attempts, as shown in a recent meta-analysis[18]. Indeed, a recent systematic review on the relationship between ADHD and suicide concluded that there is a positive association between ADHD and suicidality in both sexes and in all age groups that was likely mediated by the presence of comorbid disorders[19]. Furthermore, individuals with ADHD frequently have more access to potentially harmful medications that many of them take either for the disorder or for its comorbidities.

Whereas a higher rate of poisoning in children and adolescents with ADHD in comparison with their typically developing peers has been reported in individual studies, the magnitude of the association is unclear[20,21]. Therefore, a meta-analysis quantifying the risk of poisoning in children/adolescents with ADHD is timely. Of note, the previous meta-analysis on the risk of physical injuries excluded studies that specifically analyzed the risk of poisoning[17]. To fill this gap and complement the previous meta-analysis, we conducted the present meta-analysis aimed to quantifying the pooled risk of poisoning in children/adolescents with ADHD compared to non-ADHD controls. A secondary aim was to compare the magnitude of the risk of unintentional physical injuries and poisoning from studies that reported both. We hypothesized that children and adolescents meeting criteria of ADHD would have significantly higher rates of poisoning compared to those without ADHD, and this increased probability of poisoning would be greater than that of physical injuries.

Results

Searches carried out in 114 databases (including three major bibliographic databases plus 111 additional resources from a database aggregator) in November 2017 led to 826 articles, whereas nine studies were included in the final stage of the systematic review and meta-analysis[20–29]. Articles that were considered possible candidates for inclusion during the first screening stage but were later deemed ineligible when the full text was assessed are listed in Table S1, with reasons for exclusion (see Supplementary material). Multiple reports derived from the Taiwan Longitudinal Health Insurance Database (LHID) were treated as the same study[20,25,30–32], similarly to the Clinical Practice Research Datalink and Hospital Episode Statistics (CPRD-HES) from the United Kingdom[23,33]. The full process of article search and selection is shown in the PRISMA flow diagram in Fig. 1. Details from the included studies are reported in Table 1 (overall description) and Table 2 (identification of poisoning). Outcome-level data extracted from each article on the risk of poisoning can be found in Table 3 (16 outcomes in total).

The origin of the studies was varied, comprising North-America, Europe, Asia and Australia. All studies but one[21] were based on large epidemiological databases. More specifically, there were two regional[22,28] and three national databases[20,23,26], a nationally representative survey[27], a population-based prospective cohort[24], a study using administrative claims from a self-insured company[29], and a case-control study using a hospital-based registry[21]. Therefore, all studies but two[21,27] analyzed administrative databases not specifically designed for research purposes at their inception[34]. A strength of the included studies is that they tended to have large sample sizes (between 87 and 1,010,067; median 10,073; for the controls and between 16 and 37,650; median 3,685; for

Name	Country	Sample	Type of study	N non-ADHD	N ADHD	ADHD diagnosis	% Male ADHD	% Male Control	Medicated %	Duration	Age range	Risk Measure
Brehaut[22]	Canada	BCLHD	Registry	1010067	16806	Administrative coding (medication)	81,6	50,9	100	>1	0–19	OR
CPRD-HES[23,33]	UK	CPRD-HES	Registry	291909[c]	15742[c]	Administrative coding	84,6	50,7	44	>1	3–17	HR
Hariharan[21]	US		Registry (Case-control)	87	16	Administrative coding (medication and ICD-9)	NR	NR	45	NA	5–9	OR
Hurtig[24]	Finland	NFBC	Prospective cohort	5639[a]	288[d]	Clinical/Scales with threshold	66.1[a]	48.5[a]	0	>1	0–15	HR
LHID[20,25,30–32]	Taiwan	LHID	Registry	36850[ac]	3685[ac]	Administrative coding	79.0[ac]	79.0[ac]	74.3[ac]	>1	3–18	OR and HR
Lindemann[26]	Germany	GEPARD	Regystry	37650	37650	Administrative coding (medication and ICD-10)	NR	NR	NR	>1	3–17	HR
Rowe[27]	UK	BCAMHS:99	Population-based survey	10073[b]	365[b]	DSM-IV	NR	NR	NR	>1	5–15	OR
Silva[28]	Australia	MNS	Registry	5363	8896	Administrative coding (ICD-9 and ICD-10)	78.3	78	100	>1	0–4	OR
Swensen[29]	US		Registry	1308	1308	Administrative coding (Other ICD)	73.2	73.2	NR	<1	Any (17% over 18)	OR

Table 1. Description of studies included in the meta-analysis. Country: country where data were collected; Sample: abbreviated name of the sample originating the data; % medicated: percentage of medicated individuals with ADHD, duration is duration of follow-up time for occurrence of injuries and is reported as <1 (less or equal to a year) or >1 (more than a year); Age range at injury; NR: not reported; NA: not applicable. [a]Obtained from biggest outcome. [b]Estimated from total (3.5% of total for individuals with ADHD and 96.5 for individuals without ADHD)[69]. [c]Number obtained from article(s) reporting poisoning. [d]Averaged between outcomes.

Name	Method for diagnosis	Classification system(s): codes	Types of poisoning
Brehaut (2003)[22]	Registry	ICD-9: 960–989	Medicinal and non-medicinal
CPRD-HES: Prasad (2016)[23]	Registry	ICD-10 and OPCS4	Medicinal and non-medicinal
Hariharan (2008)[21]	Registry	ICD-9	Medicinal (self-taken, not inhaled or by contact).
Hurtig (2016)[24]	Registry	ICD-8, ICD-9 and ICD-10	Medicinal and non-medicinal
LHID: Tai (2013)[20]	Registry	ICD-9: 960–989	Medicinal and non-medicinal[70]
LHID: Chou (2014)[25]	Registry	ICD-9: 960–979 and E930–949	Medicinal (deliberate)
Lindemann (2017)[26]	Registry	ICD-10 T36–75, T96–97	System-wide injuries[71]
Rowe (2004)[27]	Self-report	NA	Medicinal and non-medicinal
Silva (2014)[28]	Registry	ICD-9 and ICD-10: T36-T65	Medicinal and non-medicinal
Swensen (2004)[29]	Registry	ICD-9: 960–989	Medicinal and non-medicinal

Table 2. Identification of poisoning cases. Registry indicates that a retrospective registry was used to identify poisoning cases. OPCS4: Office of Population Censuses and Surveys (OPCS-4) version 4. NA: not applicable.

ADHD). The systematic review and meta-analysis pooled data from a total sample of 84,756 and 1,398,946 children and adolescents with and without ADHD respectively.

Overall, poisoning cases were uncommon. The median number per study of poisoned individuals that suffered from ADHD was 14 (range 2–184), whereas the median number per study of poisoned individuals who did not suffer from ADHD was 29 (range 3–3,882). Prevalence (per 1000) ranged between 3.5 and 60 (median 16) in children and adolescents with ADHD and between 0.8 and 37.3 (median 4.8) in children and adolescents without ADHD.

The ranges of ages of poisoning were large in most cases. An exception was a study in which ADHD was diagnosed in school-age children but retrospectively considered the risk of poisoning during pre-school[28]. This is a probable cause for the much higher risk of poisoning in both the group with and without ADHD in this study. The retrospective nature of studies and the use of administrative databases were also related to the type of strategies used to identify cases with ADHD and to define poisoning. In the majority of studies, ADHD diagnosis was defined based on ICD codes at visit discharges[20,23,25,28,29], by taking medications for ADHD[22], or based on the combinations of the two. However, two studies[24,27] used scales of symptoms and DSM criteria. Similarly, diagnoses of poisoning were defined based on ICD codes. Whereas most studies included poisoning from medicinal and non-medicinal origins, two studies[21,25] only included poisoning from medicinal drugs. Specifically, one[25] analyzed poisoning cases that were intentional in nature, which led to a much smaller prevalence of poisoning in in adhd and controls.

The main analysis, showing the relative risk (RR) of poisoning between adolescents with and without ADHD, included eleven outcomes derived from nine studies. Variation among effect sizes was important as they ranged between 1.2 and 7.98 (median 3.47). The overlap between confidence intervals (CIs) was small. The lower bound of the CI ranged between 0.5 and 3.58 (median 1.91) and the upper bound between 2.6 and 49.35 (median 5.64). All analyses were carried out using Robust Variance Estimation (RVE) to take into account dependence between outcomes. Individuals with ADHD had a significantly increased risk of poisoning compared to individuals

First author (year)	Measure	Description of outcome	N non-ADHD	N ADHD	Number of non-ADHD poisoned	Number of ADHD poisoned	Prevalence (per 1000) of poisoning in non-ADHD	Prevalence (per 1000) of poisoning in ADHD	Relative Risk	LBCI	UBCI	Main Analysis
Brehaut (2003)[22]	OR	Adjusted	1010067	16806	3882	184	3.8	10.9	2.67	2.27	3.14	Yes
CPRD-HES: Prasad (2016)[23]	HR	Adjusted	291909	15742	2033	463	7.0	29.4	3.99	3.58	4.44	Yes
Hariharan (2018)[21]	OR	Unadjusted	87	16	20	11	NR	NR	7.98	2.64	24.13	Yes
Hurtig (2016)[24]	HR	Rating scale, injury between 0 and 6 years. Adjusted.	5236	875	44	14	8.4	16.0	1.51	0.76	3.01	Yes
Hurtig (2016)[24]	HR	Rating scale, injury between 7 and 15 years. Adjusted	5639	472	27	9	4.8	19.1	3.42	1.46	8.02	Yes
Hurtig (2016)[24]	HR	Clinical criteria, injury between 7 and 15 years. Adjusted	352	105	3	2	8.5	19.0	6.29	0.8	49.35	Yes
LHID: Tai (2013)[20]	OR	Unadjusted	7860	1965	98	30	12.5	15.3	1.23	0.81	1.85	No
LHID: Chou[2] (2014)[5]	HR	Unadjusted	36850	3685	29	13	0.8	3.5	4.51	2.35	8.68	No
LHID: Chou (2014)[25]	HR	Adjusted.	36850	3685	29	13	0.8	3.5	4.65	2.41	8.94	Yes
LHID: Chou (2014)[25]	OR	Unadjusted	36850	3685	29	13	0.8	3.5	4.50	2.33	8.65	No
LHID: Chou (2014)[25]	HR	0 to12 years. Adjusted.	NR	NR	29	13	NR	NR	2.42	0.99	5.89	No
LHID: Chou (2014)[25]	HR	12 to 18 years. Adjusted.	NR	NR	29	13	NR	NR	17.86	5.23	61.02	No
Lindemann (2017)[26]	HR	Adjusted	37650	37650	NR	NR	NR	NR	3.47	2.14	5.64	Yes
Rowe (2004)[27]	OR	Psychiatric model. Adjusted	NR	NR	NR	NR	NR	NR	1.2	0.5	2.6	Yes
Silva (2014)[28]	OR	Adjusted	8896	5363	332	322	37.3	60.0	2.24	1.91	2.65	Yes
Swensen (2004)[29]	OR	Unadjusted	1308	1308	5	22	3.8	16.8	4.46	1.68	11.81	Yes

Table 3. Outcome-level details of all the outcomes extracted from the studies included in the risk of poisoning analyses. N: number of individuals in each group; OR: odds ratio between children and adolescents with ADHD and without ADHD; HR: hazard ratio between children and adolescents with ADHD and without ADHD; LBCI: lower bound of the 95% confident interval; UBCI: upper bound of the 95% confident interval; Main analysis: it indicates if the outcome has been included in the main analysis (most controlled and general outcome) and in the main sensitivity analyses. NR: not reported.

without the disorder (RR = 3.14, 95% CI- = 2.23 to 4.42) as shown in the forest plot in Fig. 2. Heterogeneity of studies, as measured by Cochran's Q test and I^2 index[35], was high ($\chi^2 = 49.42$, df = 8, $p < 0.001$, $I^2 = 83.8\%$). Risk of small sample bias was not significant according to Begg's adjusted rank correlation and Egger's test (Egger t = −0.07, p = 0.949; Begg Z = 0.52, p = 0.602, see also the funnel plot in Fig. 3).

In general, results were relatively robust to sensitivity analyses. When only studies using hazard ratios as effect measure were included, the resulting average RR was 3.91 (95% CI = 3.41 to 4.5, $I^2 = 0\%$). The average RR was 2.59 (95% CI = 1.81 to 3.71, $I^2 = 64.4\%$) when only odds ratios were taken into account. Similarly, the pooled RR changed to 3.01 (95% CI = 2.01 to 4.50, $I^2 = 87\%$) when only statistically adjusted RRs were entered in the meta-analysis, and increased to 5.62 (95% CI = 2.51 to 12.61, $I^2 = 0\%$) when uncontrolled effect sizes were used. Since only two studies did not combine poisoning and intoxication cases (defined using the ICD codes), we could not carry out a sensitivity analysis including only studies that focused on a strict definition of poisoning. It must be noted that in the case of crude effect sizes and hazard ratios only three and four studies were respectively included in the analyses and, therefore, confidence intervals with RVE are unreliable[36]. Changing the p parameter within RVE, a value that accounts for the correlation between outcomes within studies, did not change the previously stated estimation of effects.

Regarding the risk of bias, ratings on the Newcastle-Ottawa Scale (NOS) tended to be high (range 3 to 6, median 5, out of 7 possible stars as 2 items were deemed inadequate for our study). The items of the scale used in the present meta-analysis, subscores and total score for each study can be found in Table 4. A meta-regression including the NOS[37] scores as a regressor showed no significant effects (Beta Coefficient-B- = −0.060, 95% CI = −1.087 to 0.967, p = 0.843).

Similarly, the sub-group analyses carried out in order to assess the effect of age were not statistically significant: results of the between-studies comparison of outcomes in children under ten years old against outcomes in which age was not specified were B = 0.299, 95% CI = −0.404 to 1.000 p = 0.279; when outcomes from participants with unspecified age were compared to outcomes obtained from participants over 10 years, results were not significant (B = −0.417, 95% CI = −0.737 to 1.571 p = 0.185); finally, when outcomes from individuals under and above 10 were compared, results were not significant either (B = −0.042, 95% CI = −2.080 to 1.996 p = 0.937).

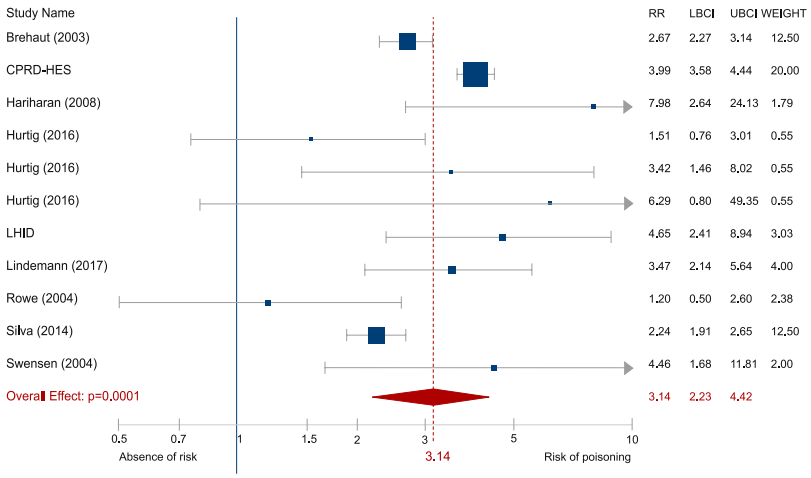

Figure 2. Pooled effect size estimating the association between ADHD and poisoning. Hazard and odds ratios were combined. The area of each square is proportional to the weight that the individual study contributed to the meta-analysis. Weights are from a ramdom-effects model using RVE. The diamond indicates the overall weighted mean effect across all studies. Study name is the first author and year except when several articles come from the same database. RR: relative risk, UBCI: upper bound of the 95% confidence interval, LBCI: lower bound of the 95% confidence interval

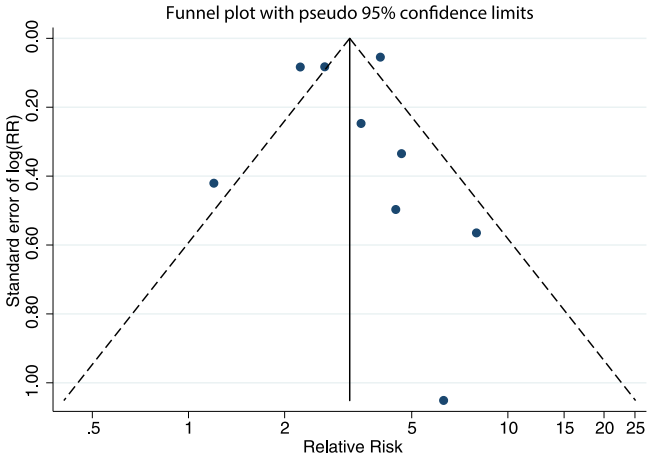

Figure 3. Funnel plot of the studies included in the risk of poisoning meta-analysis.

Name	NOS version	Selection (up to 3 stars)[a]	Comparability(up to 2 stars)	Outcome/Exposure (up to 2 stars)[a]	NOS total (up to 7 stars)
Brehaut[22]	Cohort	2	1	1	4
CPRD-HES: Prasad[23]	Cohort	3	1	1	5
Hariharan[21]	Case-control	1	1	1	3
Hurtig[24]	Cohort	2.5*	1	1	4.5
LHID[20,25]	Cohort	3	1	1	5
Lindemann[26]	Cohort	3	1	1	5
Rowe[27]	Cohort	3	2	0	5
Silva[28]	Cohort	3	1	1	5
Swensen[29]	Cohort	3	2	1	6

Table 4. Newcastle Ottawa Scale scores. Number of stars for each subsection of the Newcastle-Ottawa Scale (NOS) and the total score. [a]An item from the original scale was not relevant for our meta-analysis (see Supplementary Material, S3 Methods). *Averaged between outcomes.

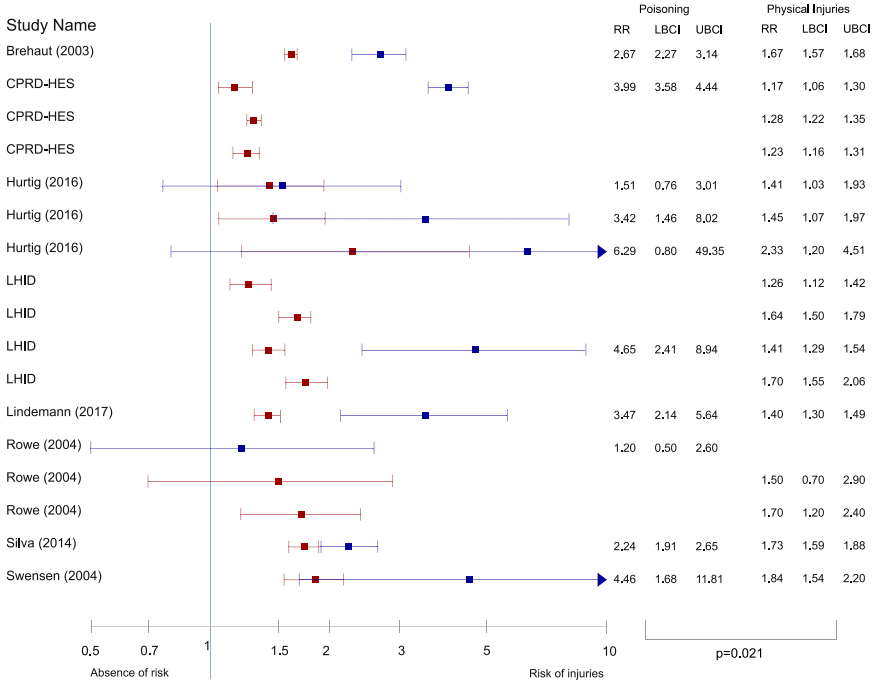

Figure 4. Comparison between the relative risk of poisoning and that of physical injuries in ADHD. Hazard and odds ratios from studies which reported both physical injuries and poisoning outcomes were combined. Poisoning relative risks are shown in blue and relative risks of physical injuries in red. Study name is the first author and year, except when several articles come from the same database. RR: relative risk, UBCI: upper bound of the 95% confidence interval, LBCI: lower bound of the 95% confidence interval. p value is obtained from a within-study analysis and indicates that the relative risk of poisoning is greater than that of physical injuries in children and adolescents with ADHD compared to their peers.

An important question of our systematic review and meta-analysis was whether the relative risk of poisoning was statistically different from the relative risk of suffering physical injuries in general. In order to answer this question, we extracted effect sizes reporting the relative risk of unintentional injuries from studies that reported both. Eight studies reported outcomes for both poisoning and physical injuries and one study[21] reported only poisoning outcomes. The outcomes related to physical injuries (10 in total) are summarized in Table S3 (see supplementary material). The pooled RR of physical injuries was 1.54 (95% CI = 1.33 to 1.78). Heterogeneity of studies was significant ($\chi^2 = 64.72$, df = 7, $p < 0.001$, $I^2 = 89.2\%$). Risk of small sample bias was not significant (Egger $t = -0.27$, $p = 0.798$; Begg $Z = 0.37$, $p = 0.711$). The relative risk of physical injuries was significantly smaller than the one in the case of poisoning ($B = 0.686$, 95% CI = 0.166 to 1.206, $p = 0.021$). A forest plot comparing the two combinations of outcomes, with effect measures from studies which reported both physical injuries and poisoning outcomes, is shown in Fig. 4.

The confidence intervals of the pooled estimates of physical injuries reported in the present meta-analysis (ES = 1.54, 95% CI = 1.33 to 1.78, derived from the combination of studies that also reported estimates of poisoning), and those in our previous article (ES = 1.53, 95% CI = 1.40 to 1.67, derived from any study reporting injuries), did not overlap with the confidence intervals for the overall effect of poisoning (ES = 3.14, 95% CI = 2.23 to 4.42)[17]. The same occurred when the analysis was limited to studies reporting hazard ratios, as the confidence intervals reported in our previous article for the pooled estimates of physical injuries (HR = 1.39, 95% CI = 1.06 to 1.83) did not overlap with the confidence intervals for the overall effect of poisoning (HR = 3.91, 95% CI = 3.41 to 4.40)[17]. This is further evidence to support that the relative risk of poisoning is significantly greater than the relative risk of suffering physical injuries in children and adolescents with ADHD.

Discussion

Poisoning is an important cause of morbidity among children and adolescents worldwide. Children with ADHD may represent a particularly vulnerable group, but so far, no pooled estimates of this risk were available. The present meta-analysis has concluded that there is a significantly higher risk of poisoning in children and adolescents with ADHD compared with their non-ADHD peers, with an estimated relative risk of 3.14 (95% CI = 2.23 to 4.42). Taking into account the prevalence of ADHD, the disorder could be a major factor contributing to the overall number of pediatric poisonings. Results derive from the combination of nine large population-based studies with a combined sample close to 1.4 million children and adolescents from the general population and 85k individuals with ADHD. The confidence interval of the estimate is quite narrow (95% CI = 2.23 to 4.42) because of the large sample size.

This increased risk is consistent with previous research, showing a significantly higher risk of physical injuries in individuals with ADHD[38]. Specific features of the disorder such as impulsivity and inattention are likely a

major risk factor for poisoning. Our work provides solid meta-analytic evidence further highlighting that ADHD is a disorder with consequences that are not limited to the behavioral or educational domains. It has an impact on different health aspects[39] and hence, leads to a reduction in the overall quality of life of the patients and their families[14].

Results were generally robust to different sensitivity analyses. Furthermore, there was no statistical indication of small-sample bias, including publication bias. However, these analyses were limited by the final number of outcomes and studies in our meta-analysis, so that our results could partly reflect a lack of statistical power. A possible qualitative interpretation of the funnel plot related to our analyses is that studies with greater standard errors (typically smaller studies) were more likely published if they showed an increased risk of poisoning in children/adolescents with ADHD. If real, hidden reporting bias could be leading to an overestimation of the overall effect. However, a line of evidence makes this overestimation unlikely. In most published studies, relative risk of poisoning was only a secondary outcome among several other subgroups of injuries, whereas the central finding of these studies was an overall increased risk of injuries. In such case, publication bias due to results of only one of many secondary outcomes is unlikely. Moreover, within study comparisons are robust to publication biases. If there was an overall publication bias towards a higher risk of injuries in ADHD (and not only of poisoning), our within-study analytic strategy demonstrating that the relative risk of poisoning is greater than the relative risk of physical injuries in general would not be affected.

As already mentioned, whereas the pooled sample in our meta-analysis was very big, the number of studies was limited. This can be explained by the fact that poisoning cases are a rare event and, therefore, very large databases are typically needed to be able to carry out epidemiological studies on this outcome. These large epidemiological studies are difficult to conduct: on the one hand, prospective cohorts are expensive and limited; on the other hand, administrative databases (that is, databases for which the main aim and design was not initially research)[34] are also limited in number and in many cases will not include measures of interest for the specific research question. Both issues, number of studies and measures reported in them, limited our analyses. We were not able to carry out possibly informative regression analyses, such as evaluating a relationship between the risk of poisoning and ADHD symptoms, or controlling for comorbidity. Similarly, the statistical power of our regression analyses was also very low. Indeed, as it is always the case in frequentist statistics, a lack of significance only indicates that there is not enough evidence for an effect, which does not necessary involve that there is not such an effect. Given that our statistical power was limited due to the characteristics of existing research, our results leave an open door for future studies evaluating such effects.

It is also noteworthy that despite our strict inclusion criteria, heterogeneity among studies was significant. Heterogeneity was dealt through the use of random-effects models that assume that the true effect size might differ from study to study, and that studies included in the analysis are a random sample of all possible studies that meet the inclusion criteria. Additionally, we investigated the origins of heterogeneity through meta-regression. The most influential factor driving heterogeneity was the type of outcome measure (Hazard or odds ratios), which influenced not only the pooled effect size (RR = 3.91, 95% CI = 3.41 to 4.5 for HR; RR = 2.59, 95% CI = 1.81 to 3.71 for OR) but also the I^2 statistic (64.4% when only OR were included and 0% when only HR were included). However, this difference between results cannot be explained by the different outcome measure per se but from other study characteristics that co-occur with the selection of the outcome measure. Taking into account the fact that studies reporting HR tended to be larger, more representative of the population, had better statistical control of possible confounders, and the heterogeneity of their results was smaller, the estimation obtained when only including HR studies might better reflect the true relative risk of poisoning in children and adolescents with ADHD. It must be noted, however, that only four studies were included in the case of HRs and hence the confidence intervals calculated through RVE could be wider than expected[36].

An additional major finding of the meta-analysis is that the relative risk of poisoning in individuals with ADHD compared to individuals without it was statistically higher than the overall relative risk of physical injuries. Eight studies reported both injuries in general and poisoning cases, hence permitting a within-study evaluation of the effect of type of injury. Of note, the risk of injuries from the combination of the eight studies was 1.54 (95% CI = 1.33 to1.78), closely matching the results from our previous meta-analysis on the risk of physical injuries, in which the mean RR was 1.53 (95% CI = 1.40 to 1.67). Several factors could be accounting for this increased relative risk. Accidental overdoses due to a difference between the taken and prescribed doses are common in pediatric populations[40], and they increase with an easier access to pharmacological drugs. Indeed, access to medications has been reported as a risk factor for unintentional poisoning[41,42]. Children and adolescents with ADHD have more access to medications than developmentally normal individuals do. Nearly 60% of ADHD diagnosed children receive pharmacological treatment with stimulants and other drugs[43,44], and in many cases a single individual will be prescribed several formulations of the same medication[45]. In addition, many individuals will receive additional medications for comorbid disorders[16], such as oppositional defiant disorder, conduct disorder, anxiety, coordination problems, depression, tic disorders and Tourette syndrome. Hence, the poly-pharmacy status in many ADHD patients could increase the likelihood of an accidental poisoning. Moreover, comorbid mental disorders might make children and adolescents with ADHD even more prone to an accidental poisoning. Data on comorbidity was not reported in most of the studies included in the present meta-analysis, so that the impact of comorbidity could not be elucidated. Further research should clarify whether medicated individuals are at a greater risk of poisoning, if comorbidities increase the risk of intoxications, and to which extent these effects can be disentangled. The role of ADHD medication is even more complex. ADHD pharmacological treatment has already been shown to reduce the risk of suffering an unintentional injury[17], and conversely, it reduces the risk of driving accidents in adults[46,47]. Drugs used to treat ADHD could have a similar effect on the risk of poising: as they improve attention and impulsivity, they could lead to a reduction in the risk of poisoning. However, our systematic review was not able to find any studies on the effect of medication on poisoning risk. Therefore, the relationship between medication effects and risk of poisoning in ADHD deserves further clarification.

In terms of age effects, poisoning incidence has two peaks across the child life span. The first peak occurs in the first years of life and the second is around the beginning of adolescence, changing also the causal factors of poisoning[1,5]. As the child grows, there is an increase of intentional poisonings, although the total percentage of intentional poisonings remains lower than the percentage of unintentional cases[1,5]. For the second age group, recreational drug usage and suicide attempts are important causes of poisoning. Regarding the specific case of individuals with ADHD, adolescents with the disorder use more frequently drugs recreationally[48], including their own medications[49]. For example, a study carried out among adolescents and young adults with the disorder reported that 14.3% of the participants in the study had once abused of their prescribed pharmacological treatment[50]. Furthermore, evidence tends to support the fact that individuals with ADHD have a higher risk of suicide and suicide attempts[19]. In summary, ADHD adolescents could be especially prone to intentional (suicide attempts) or semi-intentional (recreational drug use) cases of poisoning, compared to younger children with the disorder and also the general population, and this could be driving in part the higher risk of poisonings compared to physical injuries. However, a direct test of this hypothesis was not possible in our meta-analysis since included studies did not differentiate between intentional and unintentional poisonings. Whereas future studies should try to address this issue, it must be noted that this differentiation is likely impossible when using administrative databases. We sought for indirect support for the role of intentional poisoning through a meta-regression including age as a covariate, but the results of this meta-regression analysis were not significant. Therefore, the role of age as a mediator in this issue still remains unknown.

The results of our systematic review/meta-analysis should be considered in the light of its strengths and limitations. As for the strengths, we pre-registered the protocol in a publicly available repository (PROSPERO), reducing the risk of reporting bias. Furthermore, we endeavored to perform a comprehensive and systematic search in several databases, with no restrictions in terms of language, date, or document type. Additionally, we used a state-of-the-art tool, the Newcastle-Ottawa scale, to assess the quality of the retained studies. Furthermore, the included studies typically used big longitudinal or administrative cohorts or national surveys, which provide adequate statistical power to estimate the overall incidence of an infrequent type of event, such as is poisoning. There are also a number of limitations that should be taken into account, which are mostly related to the individual studies that we included rather than to methodological issues with our systematic review/meta-analysis. First, intentionality of poisoning was not controlled in the included studies. Second, we could not find sufficient data to evaluate the effects of age, medication status or comorbidities on the risk of poisoning in ADHD. Since these major confounders were not controlled for in our analyses, the increased relative risk cannot be directly ascribed to ADHD. Although our results support the conclusion that individuals with ADHD in the real world suffer more poisoning events than those without it, we cannot know what factor or factors are at the origin of this relationship and in this regard, any causative explanation derived from them should be taken with caution.

Our findings have important implication from a public health standpoint. Poisoning remains a leading cause of preventable injuries in childhood and adolescence[1], whose treatment involves a huge cost of economic and human resources[51,52]. The present meta-analysis has shown that children and adolescents with ADHD are a population with an increased risk of poisoning. Specific preventive measures in this population could help to minimize this risk or the detrimental consequences of poisoning. Health providers should ensure a correct understanding of treatment dosages and frequency intakes, as well as alarm signs regarding side effects or poisoning and how should parents and or patients act in a case of possible poisoning. They should also emphasize the hazard of having dangerous household products out of the reach of children. Further studies on the incidence of intentional injuries (recreational drug use and suicide intents) in this population, and the effect of medication on the risk of poisoning are needed.

Methods

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)[53,54], the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA)[55,56] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[57] guidelines were followed when planning and carrying out our work. The protocol for the study was registered in the international prospective register of systematic reviews held by the University of York (PROSPERO) prior to data analysis (registration number CRD42017079911). Methods reflected those of our previous meta-analysis on the risk of physical injuries in order to make results comparable[58].

Three major databases –PubMed (Medline Plus), Web of Science core database and Scopus- were searched. Furthermore, we searched over 110 additional databases from an institutional reference aggregator (*UNIKA*: http://www.unav.edu/en/web/biblioteca), that uses the EBSCO discovery service (http://support.ebsco.com/help/index.php?lang=en&int=eds) to provide a list of references combining both internal (library) and external (database vendors) sources. Searches were carried out on November 30th 2017, with no time or language restrictions. References of retrieved pertinent papers were scanned to find additional possibly relevant studies. References of interest from our previous meta-analysis on the risk of physical injuries were also evaluated for potential inclusion[17]. See additional details, including search syntax, in Supplementary Methods 1 and 2 (Supplementary material).

Study selection. *Study type.* Data from published or unpublished empirical studies that compared the risk of poisoning in children and/or adolescents with ADHD and in typically developing individuals were combined regardless of the design, the temporality (i.e., prospective, retrospective or cross-sectional) or setting (clinical or epidemiological).

ADHD diagnosis is more common in males[59] and, similarly, poisoning injuries occur more frequently in males than in females[1]. Therefore, we included only articles that took into account this bias either by sample selection (no differences in the number of male and females between the ADHD and no ADHD samples) or statistically (sex controlled as a confounding covariate).

Population. The majority of the sample of a study had to be children and/or adolescents (defined as less than 18 years-old). The accepted operational definitions of ADHD were the following: (1) A categorical diagnosis according to standardized criteria, either the DSM (III, III-R, IV, IV-TR or 5) or the diagnosis of hyperkinetic disorder as per ICD-10 or previous versions; (2) Being above a pre-established threshold in a validated psychometric scale for the screening of ADHD; (3) The coding of the diagnosis in a medical registry; (4) A positive answer to the question: "Have you ever been told by a doctor that you have ADHD?" or similar questions; and (5) Being prescribed ADHD medication(s). Studies on preschoolers and those using the diagnosis of "Deficits in attention, motor control, and perception" (DAMP)[60], or equivalent constructs[61], were excluded, since they are not equivalent to ADHD.

Outcomes. The World Health Organization (WHO) definition of poisoning or intoxication was used to define eligible outcomes. Intoxication is defined by WHO as "a condition that follows the administration of a psychoactive substance and results in disturbances in the level of consciousness, cognition, perception, judgment, affect, or behavior, or other psychophysiological functions and response"1. Since the term "intoxication" can be used in relation to alcohol or drug abuse, outcomes describing poisoning were preferred to those reporting intoxications. However, if an article only reported intoxications, it was also included. Hence, outcomes from articles reporting health problems related to the codes T36-T61 of the 19th chapter of the International Classification of Diseases (ICD-10) or similar problems were deemed eligible.

Poisoning cases had to be attended at medical settings and a registry created or self-reported. Studies reporting information requests to poison information centers or similar entities were not included. Poisoning could occur before or after the diagnosis of ADHD. Risk measures had to describe the ratio in the risk of poisoning between children and adolescents with and without ADHD. The primary outcome measure was defined as the hazard ratio (HR) obtained from Cox proportional hazards models, as it provides a time-independent estimation of the risk. However, odds ratios (ORs) are more frequently reported than HR, and they are the only risk measure that can be obtained from case-control studies that compare ADHD rates in a poisoned and a non-poisoned group. Therefore, ORs were accepted as secondary valid estimations of relative risk and combined with HRs.

In order to address the secondary aim of the present meta-analysis (i.e., assess if there is a significantly higher relative risk of poisoning compared to the relative risk of suffering other physical injuries), studies which reported outcomes on the relative risk of physical injuries in general and also provided similar data on the relative risk of poisoning were eligible.

Identification and selection of studies. Studies were identified and selected following a two-stage process: (1) Two investigators independently and blindly screened retrieved titles and abstracts of all non-duplicated papers to exclude non-pertinent ones. Discrepancies were resolved by consensus; (2) Articles carried to this stage were assessed after reading the full-text following a similar process of double evaluation similar to the one of the previous step. Multiple reports of the same study were linked together.

Data extraction. M.R.-G. and G.A. independently extracted data from articles that had been deemed eligible in the selection stage.

A modified version of the Newcastle-Ottawa Scale (NOS)37 was used to assess the risk of bias of each study and rated independently by the same authors. Any discrepancies at this stage were resolved by consensus between M.R.-G. and G.A. Two items, one in the selection and one in the exposure subsections, were eliminated as they were deemed inadequate for our study. Hence, the maximum score in the scale was seven instead of nine stars. Final items of the scale can be found in Supplementary Methods 3 in supplementary material.

Data synthesis. Summary effect measures (HRs or ORs) were combined in order to estimate a population-average relative risk between ADHD and poisoning in children and adolescents. Hazard Ratios and Odds Ratios were considered equivalent measures of relative risk as the baseline prevalence of poisoning was expected to be very low (less than 1%). In such cases the two measures yield very close results[62,63].

Robust Variance Estimation[64,65], a statistical technique that models the nested structure between outcomes of the same study and allows to account for the non-independence of outcomes, was used for the inference of a mean effect size and meta-regression analyses. We carried out a mixed-effect model with robust variance and random-effect estimates. A model with variation of RRs between studies and equicorrelation between same-study effect sizes (p; $p = 0.8$ in this case) was assumed. This strategy is highly efficient to estimate a mean model from outcomes which are typically correlated at the study level, but are usually independent between studies[64]. The influence of the equicorrelation value chosen here, the most commonly used in previous studies[65,66], was evaluated in a sensitivity analysis with varying levels of p (0.1 steps between 0 and 1).

Cochran's Q test and I^2 index[35] were used to evaluate heterogeneity among studies, whereas Begg's adjusted rank correlation and Egger's test were implemented to formally assess the presence of "small-sample" bias. These analyses were carried out using a single outcome per study. This outcome was selected at random whenever more than one existed. We planned to combine all outcomes fulfilling our inclusion criteria independently of the results of heterogeneity analyses and deal with heterogeneity through the use of a random-effects model and meta-regression, as the exclusion of studies prior to performing a meta-analysis affects the validity of the subsequent results[67]. Additional sensitivity/subgroup analyses consisted in: 1-Including ORs and HRs in separate analyses; 2-Calculating a mean effect size including only statistically unadjusted outcomes (from studies that, at least, controlled for sex by design); 3-Calculating a mean effect size including only adjusted outcomes (controlled covariates could include sex. If this was not the case, sex was controlled through sample selection); 4-Evaluating the influence of removing articles that report intoxication risk (instead of poisoning); 5-Investigating the influence of the risk of bias as evaluated by the rating in the Newcastle-Ottawa Scale by carrying out a meta-regression analysis with the number of stars on the scale for each article as a predictor. We also investigated the effect of age on the risk of poisoning by splitting outcomes into

3 groups according to the age distribution of the participants: outcomes in which participants were under the age of 10, outcomes that included individuals of any age and outcomes in which participants were between 11 and 18 years old. The three groups of outcomes were compared pair-wise using a between-study meta-regression model as we hypothesized that the risk of poisoning would be significantly greater in the older group when compared to younger individuals or to individuals of all ages.

Finally, we investigated whether, compared to those without, children/adolescents with ADHD had a significantly higher risk of poisoning than of suffering other kinds of physical injuries. To this end, in order to control for confounding variables which could affect this comparison (i.e. country of origin and socio-cultural background of participants), only studies that reported both outcomes (effect measure of poisoning and of suffering physical injuries) were evaluated. These two groups of outcomes were compared using a within-study meta-regression model[64,65]. This analysis is optimal in cases where there exists within-studies variability in the covariate (outcome type in our case). This variability is studied by including the distance value around the study regressor mean as a covariate in the regression model[68].

Effect sizes whose 95% confidence intervals (CIs) did not include 1 were considered significant. Analyses were carried out in STATA v13. Forest plots were created using the DistillerSR Forest Plot Generator from Evidence Partners (https://www.evidencepartners.com/resources/forest-plot-generator/).

Data statement. All data used in the preparation of the systematic review and meta-analysis is available upon request.

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Author Contributions

M.R.-G. and G.A. contributed equally to this work. M.R.-G. and G.A. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: M.R.-G., S.C. and G.A. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: M.R.-G., S.C., S.M, C.S.G.A. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: M.A.-S. and G.A. Obtained funding: All authors. Administrative, technical, or material support: C.S. and G.A. Study Supervision: S.C., C.S. and G.A.

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3.4.6. Material suplementario

Supplementary Material
Risk of Poisoning in children and adolescents with ADHD: a systematic Review and Meta-analysis.

Maite Ruiz-Goikoetxea[1]; Samuele Cortese[23456]; Sara Magallón[7]; Maite Aznarez-Sanado[7,] Noelia Alvarez-Zallo[1]; Elkin O. Luis[7]; Pilar de Castro-Manglano[8]; Cesar Soutullo[8]; Gonzalo Arrondo[9]*

*Corresponding author

Correspondence to: garrondo@yahoo.es

1: Servicio de Urgencias Extrahospitalarias Servicio Navarro de Salud-Osasunbidea, Pamplona, Spain.

2: Center for Innovation in Mental Health, University of Southampton, Academic Unit of Psychology, Southampton, UK

3: Faculty of Medicine, Clinical and Experimental Sciences (CNS and Psychiatry),

University of Southampton, Southampton, UK

4: Department of Child and Adolescent Psychiatry, NYU Langone Medical Center, New York, NY, USA

5: Solent NHS Trust, Southampton, UK

6: Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, Nottingham, UK

7: Facultad de Educación y Psicología, Universidad de Navarra, Pamplona, Spain

8: Departamento de Psiquiatría y Psicología Médica, Unidad de Psiquiatría Infantil y Adolescente, Clínica Universidad de Navarra, Pamplona and Madrid, Spain

9: Instituto Cultura y Sociedad (ICS), Grupo Mente-Cerebro, Universidad de Navarra, Pamplona, Spain

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Methods S1: Search and syntax for each database.

The following databases were searched

- PubMed (Medline Plus)
- Scopus
- Web of Science Core Collection,
- UNIKA (An institutional reference aggregator that searches in 114 databases listed in the following section)

The following search syntax was used:

PubMed (Medline Plus) and Unika
(In the case of PubMed-Medline Plus, the search was not limited to any field. In the case of Unika, the search was limited to titles, keywords, and abstracts through the website options. The medicine profiles was used for the Unika search)

(ADHD OR adhd OR attention deficit disorder with hyperactivity OR syndrome hyperkinetic OR hyperkinetic syndrome OR hyperactivity disorder OR hyperactive child syndrome OR childhood hyperkinetic syndrome OR attention deficit hyperactivity disorders OR attention deficit hyperactivity disorder OR adhd attention deficit hyperactivity disorder OR adhd OR overactive child syndrome OR attention deficit hyperkinetic disorder OR hyperkinetic disorder OR attention deficit disorder hyperactivity OR attention deficit disorders hyperactivity OR child attention deficit disorder OR hyperkinetic syndromes OR syndromes hyperkinetic OR hyperkinetic syndrome childhood) AND (intox* OR overdos* OR poison*)

Scopus
TITLE-ABS-KEY ((ADHD OR adhd OR "attention deficit disorder with hyperactivity" OR "syndrome hyperkinetic" OR "hyperkinetic syndrome" OR "hyperactivity disorder" OR "hyperactive child syndrome" OR "childhood hyperkinetic syndrome" OR "attention deficit hyperactivity disorders" OR "attention deficit hyperactivity disorder" OR "adhd attention deficit hyperactivity disorder" OR adhd OR "overactive child syndrome" OR "attention deficit hyperkinetic disorder" OR "hyperkinetic disorder" OR "attention deficit disorder hyperactivity" OR "attention deficit disorders hyperactivity" OR "child attention deficit disorder" OR "hyperkinetic syndromes" OR "syndromes hyperkinetic" OR "hyperkinetic syndrome childhood") AND (intox* OR overdos* OR poison*))

Web of Science:
(TS= ((ADHD OR adhd OR "attention deficit disorder with hyperactivity" OR "syndrome hyperkinetic" OR "hyperkinetic syndrome" OR "hyperactivity disorder" OR "hyperactive child syndrome" OR "childhood hyperkinetic syndrome" OR "attention deficit hyperactivity disorders" OR "attention deficit hyperactivity disorder" OR "adhd

attention deficit hyperactivity disorder" OR adhd OR "overactive child syndrome" OR "attention deficit hyperkinetic disorder" OR "hyperkinetic disorder" OR "attention deficit disorder hyperactivity" OR "attention deficit disorders hyperactivity" OR "child attention deficit disorder" OR "hyperkinetic syndromes" OR "syndromes hyperkinetic" OR "hyperkinetic syndrome childhood") AND (intox* OR overdos* OR poison*)) OR TI= ((ADHD OR adhd OR "attention deficit disorder with hyperactivity" OR "syndrome hyperkinetic" OR "hyperkinetic syndrome" OR "hyperactivity disorder" OR "hyperactive child syndrome" OR "childhood hyperkinetic syndrome" OR "attention deficit hyperactivity disorders" OR "attention deficit hyperactivity disorder" OR "adhd attention deficit hyperactivity disorder" OR adhd OR "overactive child syndrome" OR "attention deficit hyperkinetic disorder" OR "hyperkinetic disorder" OR "attention deficit disorder hyperactivity" OR "attention deficit disorders hyperactivity" OR "child attention deficit disorder" OR "hyperkinetic syndromes" OR "syndromes hyperkinetic" OR "hyperkinetic syndrome childhood") AND (intox* OR overdos* OR poison*)))

Methods S2: Databases included in the UNIKA Service.

A search was carried out in UNIKA (http://www.unav.edu/en/web/biblioteca), an institutional reference aggregator that uses the EBSCO discovery service (http://support.ebsco.com/help/index.php?lang=en&int=eds) to provide a combined list of references from both internal (library) and external (database vendors) sources. The databases included in the biomedical sciences profile of the UNIKA Service from the University of Navarra are listed here in alphabetical order:

1. Academic Search Index (asx)
2. AccessAnesthesiology
3. AccessMedicine
4. AccessPediatrics
5. AccessScience
6. AccessSurgery
7. Ambrose Digital Library
8. ASM Handbooks Online (edsaho)
9. ASM Medical Materials Database
10. ASM Micrograph Database
11. BioOne Online Journals
12. Books at JSTOR
13. British Library Document Supply Centre Inside Serials & Conference Proceedings (edsbl)
14. British Standards Online
15. Business Source Complete
16. Canadian Electronic Library
17. Catálogo de la Biblioteca de la Universidad de Navarra (cat00378a)
18. Center for Research Libraries
19. ChemSpider
20. China/Asia On Demand
21. CINAHL (cin20)
22. CogPrints
23. Credo Reference Collections (edscrc)
24. DADUN (ir00048a)
25. DASH
26. Data-Planet Statistical Datasets & Statistical Ready Reference
27. Dialnet
28. Directory of Open Access Journals (edsdoj)
29. eArticle
30. eBook Academic Collection (EBSCOhost) (e000xww)
31. eBook Collection (EBSCOhost) (nlebk)
32. EconLit (ecn)
33. EDS Foundation Index (eda)
34. eLibro Premium
35. ERIC (eric)
36. eScholarship (edssch)
37. EThOS
38. EU Bookshop (edseub)
39. European Union Open Data Portal
40. Europeana
41. Expanded Academic ASAP
42. Films on Demand
43. Fuente Académica Premier (fua)
44. Gale Cengage Learning, Health & Wellness Resource Center
45. Gale Virtual Reference Library
46. Gallica Bibliothèque Numérique

47. Google Book Search (fe334f7c)
48. GreenFILE (8gh)
49. Harvard Library Bibliographic Dataset (edshlc)
50. HathiTrust (edshtl)
51. Henry Stewart Talks
52. HighWire Press (fa0f9666)
53. Idunn.no
54. IndianJournals.com
55. Informit Health Collection (edsihc)
56. Iprbooks
57. JSTOR (fd43b2a1)
58. JSTOR Life Sciences (edsjls)
59. KERIS Theses & Dissertations (edsker)
60. Knigafund.ru (edskig)
61. Korean Studies Information Service System (KISS) (edskis)
62. LexisNexis Academic: Law Reviews (edslex)
63. Maruzen eBook Library
64. McGraw-Hill
65. Medical Online
66. Medical Online E-books
67. Medical Online-E
68. MEDLINE (cmedm)
69. Minority Health Archive (edsuph)
70. NARCIS
71. Networked Digital Library of Theses & Dissertations (edsndl)
72. NORA (Norwegian Open Research Archive)
73. OAIster (edsoai)
74. OJS vid Lunds Universitet (edsojs)
75. Ovid Journals Full Text Medical Research Database (fb0698e8)
76. Oxford Bibliographies Online
77. Oxford Clinical Psychology
78. Oxford Handbooks Online (edsoho)
79. Oxford Medicine Online
80. Oxford Reference (edsoro)
81. Oxford Scholarship Online (edsoso)
82. ProQuest Dissertations and Theses (fb458d87)
83. PsycARTICLES (edspdh)
84. PsycBOOKS (edspzh)
85. PsycCRITIQUES (edspvh)
86. PsycheVisual
87. Psychology and Behavioral Sciences Collection (pbh)
88. PsycINFO (psyh)
89. Publisher Provided Full Text Searching File (edb)
90. PubMed Central (fd5a6824)
91. R2 Digital Library
92. RACO
93. RECERCAT
94. ReferenceSearch (edsref)
95. RÖMPP Online
96. SA ePublications Service
97. SAGE Research Methods Datasets
98. SAGE Video
99. Scielo
100. Scielo Books
101. Science Citation Index (edswsc)
102. ScienceDirect (edselp)
103. Scopus
104. Social Sciences Citation Index (edswss)
105. Springer Science+Business Media, SpringerProtocols
106. STAT!Ref
107. Supplemental Index (edo)
108. SveMed+ (edssmd)
109. Torrossa
110. TOXNET: GENETOX
111. TOXNET: TOXLINE
112. University Library Online - Университетская библиотека онлайн
113. World Bank eLibrary (edswb

Methods S3: Risk of bias (Items from the Newcastle-Ottawa Scale).

Studies comparing poisoned vs non-poisoned (case-control studies)

Selection

1) Is the case definition adequate?
a) yes, with independent validation * (acute poisoning or record linkage+interview or other validation)
b) yes, eg. record linkage or based on self-reports
c) no description

2) Representativeness of the cases
a) consecutive or obviously representative series of cases*
b) potential for selection biases or not stated

3) Selection of Controls

a) community controls *
b) hospital controls
c) no description

4) Definition of Controls : IRRELEVANT IN OUR CASE
a) no history of disease (endpoint) *
b) no description of source

Comparability (up to 2 stars)

1) Comparability of poisoned and non-poisoned individuals on the basis of the design or analysis (Note: all articles should control sex for inclusion).
a) study controls for AGE and COMORBIDITY **
b) study controls for AGE *
c) study controls for COMORBIDITY *

Exposure (ADHD)

1) Ascertainment of ADHD
a) secure record (eg surgical records) or data linkage *
b) structured interview *
c) written self-report, (not codified) medical history or clinical questionnaire
d) no description

2) Same method of ascertainment for cases and controls
a) yes *
b) no

3) Non-Response rate: IRRELEVANT IN OUR CASE
a) same rate for both groups *
b) non respondents described
c) rate different and no designation

Cohort studies

Selection

1) Representativeness of the exposed cohort. Individuals with ADHD are
a) truly representative of the average child with ADHD in the community *
b) somewhat representative of the average child with ADHD in the community (individuals may differ slightly from the typical ADHD child)*
c) selected group of users eg only medicated ADHD, all ADHD+Comorbidity, only one sex, only hospitally-treated ADHD.
d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort (individuals without ADHD)
a) drawn from the same community as the exposed cohort *
b) drawn from a different source
c) no description of the derivation of the non-exposed cohort

3) Ascertainment of ADHD
a) secure record (eg surgical records) or data linkage *

b) structured interview *
c) written self-report, (not codified) medical history or clinical questionnaire
d) no description

4) Demonstration that outcome of interest was not present at start of study: IRRELEVANT IN OUR CASE THAT ADHD IS PRESENT BEFORE STUDY STARTS
a) yes *
b) no

Comparability (up to 2 stars)

1) Comparability of individuals with ADHD and no ADHD on the basis of the design or analysis (NOTE: all studies should control for sex)
a) study controls for AGE and comorbidity **
b) study controls for AGE *
c) study controls for comorbidity *

Outcome

1) Assessment of the poisonings
a) independent blind assessment *
b) record linkage *
c) self-report
d) no description

2) Was follow-up long enough for outcomes to occur : IRRELEVANT IN OUR CASE: ANY FOLLOW-UP WAS CONSIDERED ADEQUATE.
a) yes (select an adequate follow up period for outcome of interest) *
b) no

3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for *
b) subjects lost to follow up unlikely to introduce bias - small number lost - >80 % follow up, or description provided of those lost) *
c) follow up rate < 80% and no description of those lost
d) no statement

Table S1: Articles excluded with main reason for exclusion.

Reference	Reason
Ayaz AB, Ayaz M, Şentürk E, Soylu N, Yüksel S, Yulaf Y. Factors related with unintentional injuries in children with newly diagnosed attention-deficit/ hyperactivity disorder. *Int J Inj Contr Saf Promot*. 2016;23(1):93-98.	No control group
Ballinger L. Rave On. CounterPunch. 2013;20(4):14.	Not empirical
Barkla XM, Mcardle PA, Newbury-birch D. Are there any potentially dangerous pharmacological effects of combining ADHD medication with alcohol and drugs of abuse ? A systematic review of the literature. *BMC Psychiatry*. 2015;15(1):15-19.	Not empirical
Barkley RA. Accidents and attention-deficit/hyperactivity disorder. Econ Neurosci. 2001;3(4):64-68.	Not empirical
Barkley RA. ADHD and Accident Proneness. (Cover story). ADHD Rep. 2002;10(2):2-6.	Not empirical
Basavaraj DS, Forster DP. Accidental poisoning in young children. J Epidemiol Community Health. 1982;36(1):31-34.	Pre-school
Bekdas M, Goksugur SB, Balaban A DF. Methylphenidate Poisoning: Carpopedal Spasm in a Child. J Med Cases VO - 5. 2014;(1):31-33.	Not empirical
Cakmak M, Gollu G, Boybeyi O, et al. Cognitive and behavioral characteristics of children with caustic ingestion. J Pediatr Surg. 2015;50(4):540-542.	Scales without threshold
De Alwis D, Agrawal A, Reiersen AM, et al. ADHD symptoms, autistic traits, and substance use and misuse in adult Australian twins. J Stud Alcohol Drugs. 2014;75(2):211-221.	Adults
Gordon S. Abuse of ADHD Drugs on the Rise; Jump in poison control center calls mirrors increasing prescriptions, study shows. Consumer Health News (English).	Not empirical
Harris M. Self-Induced Overdose of Adhd Medication. J Paediatr Child Health. 1997;33(2):176-176.	Not empirical
Hartsough CS, Lambert NM. Pattern and progression of drug use among hyperactives and controls: a prospective short-term longitudinal study. J Child Psychol Psychiatry. 1987;28(4):543-553.	It does not relate ADHD to poisoning
Hawton K, Saunders K, Topiwala A, Haw C. Psychiatric disorders in patients presenting to hospital following self-harm: A systematic review. J Affect Disord. 2013;151(3):821-830.	Systematic Review. No control group
Huang Y-S, Tsai M-H. Long-term outcomes with medications for attention-deficit hyperactivity disorder: current status of knowledge. CNS Drugs. 2011;25(7):539-554..	Not empirical
Katrivanou A, Lekka NP, Beratis S. Psychopathology and behavioural trends of children with accidental poisoning. J Psychosom Res. 2004;57(1):95-101.	Pre-school
Knouse L. Cost of Accidents. ADHD Rep. 2005;13(3):12.	Not empirical
Levine M, Froberg B, Ruha AM, et al. Assessing the toxicity and associated costs among pediatric patients admitted with unintentional poisonings of attention-deficit/hyperactivity disorder drugs in the United States. Clin Toxicol. 2013;51(3):147-150.	No control group
LoVecchio F, Ozimek J, Sawyers B, Thole D. Outcomes after accidental pediatric ingestions of (dextro)amphetamine and methylphenidate. Am J Emerg Med. 2009;27(8):933-934.	It does not relate ADHD to poisoning
McCarthy S, Cranswick N, Potts L, Taylor E, Wong ICK. Mortality associated with attention-deficit hyperactivity disorder (ADHD) drug treatment: A retrospective cohort study of children, adolescents and young adults using the general practice research database. Drug Saf. 2009;32(11):1089-1096.	It does not relate ADHD to poisoning
Minde K. The use of psychotropic medication in preschoolers: some recent	Not empirical

Reference	Reason
developments. Can J Psychiatry. 1998;43(6):571-575.	
Nelson J. Reduce unintentional poisoning. Breckenridge Am. June 2008:5A.	It does not relate ADHD to poisoning
Niemelä S, Sourander A, Poikolainen K, et al. Childhood predictors of drunkenness in late adolescence among males: A 10-year population-based follow-up study. Addiction. 2006;101(4):512-521.	It does not relate ADHD to poisoning
Ramon F, Ballesteros S. Exposures to drugs used to treat attention deficit hyperactivity disorder (ADHD): A Poison Control Center experience. Clin Toxicol. 2016;Conference:36th International Congress of the European Associ.	No control group
Rey JM, Walter G, Hazell PL. Psychotropic drugs and preschoolers. Med J Aust. 2000;173(4):172-173.	Not empirical
Setlik J, Bond GR, Ho M. Adolescent Prescription ADHD Medication Abuse Is Rising Along With Prescriptions for These Medications. Pediatrics. 2009;124(3):875-880.	No control group
Sheikh S, Hendry P, Lynch S, Kalynych CJ, Aldridge P, Kraemer D. Poisonings with Suicidal Intent Aged 0-21 Years Reported to Poison Centers 2003-12. West J Emerg Med. 2015;16(4):497-502.	No control group
Sibert JR, Newcombe RG. Accidental ingestion of poisons and child personality. Postgrad Med J. 1977;53(619):254-256.	It does not relate ADHD to poisoning
Stewart MA, Thach BT, Freidin MR. Accidental poisoning and the hyperactive child syndrome. Dis Nerv Syst. 1970;31(6):403-407.	Sex is uncontrolled
Stoltzfoos L. Abuse of Stimulant Medications By Youths Increases Along With Access. Prim Psychiatry. 2009;16(10):12-13	Not empirical
van den Ban E, Souverein P, Meijer W, et al. Association between ADHD drug use and injuries among children and adolescents. Eur Child Adolesc Psychiatry. 2014;23(2):95-102.	It does not relate ADHD to poisoning
Yule A, Wilens T, Carrellas N. Attention Deficit Hyperactivity Disorder (ADHD) and Overdose (OD) Risk in Transitional Age Youth (TAY) with Substance Use Disorders (SUD). Am J Addict. 2016;25(4):341.	Sex is uncontrolled. It assessed drug overdose on a population with substance use disorder

The reference of the article and a main reason for exclusion from the meta-analysis are provided

Table S2: Outcomes included in each analysis.

	Relative Risk	Main RR of poisoning	HR outcomes	OR outcomes	Adjusted outcomes	Unadjusted outcomes	NOS meta-regression	Under 10 vs. Age unspecified	Over 10 vs. Age unspecified	Under 10 vs. Over 10	Poisoning vs physical injuries
Brehaut (2003)	2.67	1	x	1	1	x	1	1	1	x	1
CPRD-HES: Prasad (2016)	3.99	1	1	x	1	x	1	1	1	x	1
Hariharan (2008)	7.98	1	x	1	x	1	1	0	x	0	x
Hurtig (2016)	1.51	1	1	x	1	x	1	0	x	0	1
Hurtig (2016)	3.42	1	1	x	1	x	1	x	0	1	1
Hurtig (2016)	6.29	1	1	x	1	x	1	x	0	1	1
LHID: Tai (2013)	1.23	x	x	1	x	x	x	x	0	1	x
LHID: Chou (2014)	4.51	x	1	x	x	1	x	x	x	x	x
LHID: Chou (2014)	4.65	1	1	x	1	x	1	x	x	x	1
LHID: Chou (2014)	4.50	x	x	x	x	1	x	x	x	x	x
LHID: Chou (2014)	2.42	x	x	x	x	1	x	0	x	0	x
LHID: Chou (2014)	17.86	x	x	x	x	1	x	x	0	1	x
Lindemann (2017)	3.47	1	1	x	1	x	1	1	1	x	1
Rowe (2004)	1.2	1	x	1	1	x	1	1	1	x	1
Silva (2014)	2.24	1	x	1	1	x	1	0	x	0	1
Swensen (2004)	4.46	1	x	1	x	1	1	1	1	x	1

Table indicates which poisoning outcomes were included in each analysis. X indicates that the outcome was not included in each analysis. 1 indicates that the outcome was included in a meta-analysis or meta-regression analysis and compared to outcomes marked with 0 when appropriate.

Table S3: Description of all outcomes included in the risk of physical injuries *vs.* risk of poisoning analysis.

First author (year)	Measure	Type of injury	Description of outcome	N ADHD	N non-ADHD	Number of non-ADHD injured	Number of ADHD injured	Effect measure	LBCI	UBCI
Brehaut (2003)[1]	OR	Any injury	Adjusted	16806	1010067	32242	1257	1.67	1.57	1.68
CPRD-HES: Hire (2016)[11a]	HR	Fractures	Adjusted	5111	49489	8461	470	1.17	1.06	1.3
CPRD-HES: Prasad (2016)[2]	HR	Fractures	Adjusted	15737	291894	18598	1878	1.28	1.22	1.35
CPRD-HES : Prasad (2016)[3]	HR	Burns	Adjusted	15741	291909	11958	1189	1.23	1.16	1.31
Hurtig (2016)[4]	HR	Any Injury	Rating Scale, injury between 0 and 6 years. Adjusted	875	5236	221	62	1.41	1.03	1.93
Hurtig (2016)[4]	HR	Any Injury	Rating scale, injury between 7 and 15 years. Adjusted	472	5639	383	54	1.45	1.07	1.97
Hurtig (2016)[4]	HR	Any Injury	ADHD diagnosis, injury between 7 and 15 years. Adjusted	105	352	28	15	2.33	1.2	4.51
LHID: Chou (2014)[12a]	HR	Fractures	Adjusted	3640	14560	1188	389	1.26	1.12	1.42
LHID: Kang (2013)[13a]	HR	Any Injury	Adjusted	3616	18080	2908	864	1.64	1.5	1.79
LHID: Guo (2015)[14]	HR	Fractures	Adjusted	7200	36000	2333	645	1.41	1.29	1.54
LHID: Tai (2013)[5]	HR	Any injury	Adjusted	1965	7860	6052	1856	1.7	1.55	2.06
Lindemann (2017)[7]	HR	Any injury	Adjusted	37650	37650	NR	NR	1.4	1.3	1.49

First author (year)	Measure	Type of injury	Description of outcome	N ADHD	N non-ADHD	Number of non-ADHD injured	Number of ADHD injured	Effect measure	LBCI	UBCI
Rowe (2004)[8]	OR	Burns	Psychiatric model. Adjusted	NR	NR	NR	NR	1.5	0.7	2.9
Rowe (2004)[8]	OR	Fractures	Psychiatric model. Adjusted	NR	NR	NR	NR	1.7	1.2	2.4
Silva (2014)[9]	OR	Any Injury	Adjusted	11902	27304	1479	1112	1.73	1.59	1.88
Swensen (2004) [10]	OR	Any Injury	Unadjusted	1308	1308	264	415	1.84	1.54	2.20

Outcome-level details of all the outcomes reporting risk of unintentional physical injuries included in the risk of poisoning vs. risk of UPI; N: number of individuals in each group; OR: odds ratio between ADHD and non-ADHD; HR: hazard ratio between ADHD and non-ADHD; LBCI: lower bound of the 95% confident interval; UBCI: upper bound of the 95% confident interval.. NR: not reported.

a= Articles that do not report poisoning but report unintentional injuries from the same samples (and hence have been considered the same study).

Table S4: PRISMA checklist

Section/topic	*#*	*Checklist item*	*Reported on page #*
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	17
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	18-19
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	17. S4-S5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S3-S4

Section/topic	*#*	*Checklist item*	*Reported on page #*
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	18-19
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	20-21
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	In protocol
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	22
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	19
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	21-22
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	21-22
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	21-22
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-8, tables 2 and 4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	8, table 3

Section/topic	*#*	*Checklist item*	*Reported on page #*
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2 and 4, table 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-10, Figures 2 and 4, Table S2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7, Figure 3.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	10-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	10-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	30

PRISMA checklist indicating the location within the article of the recommended content. Pages correspond to the unformatted manuscript for reviewers. The original publication is: Liberati, A. *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 339, b2700 (2009).

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3.5. Trastorno por déficit de atención e hiperactividad como factor de riesgo en intoxicaciones y lesiones no intencionadas

Esta publicación tenía como objetivo llamar la atención de los pediatras hispano-hablantes sobre la importancia del TDAH y de sus consecuencias en la población infantil y adolescente. Este trastorno es bien conocido dentro de este grupo de facultativos por sus consecuencias en el ámbito académico y profesional pero sus consecuencias en otros ámbitos como el del riesgo de LNIs e intoxicaciones, no es del todo conocido. Se pretende difundir mediante esta carta los resultados de los dos estudios realizados al respecto.

Recientemente se habían publicado dos artículos en la revista "Anales de Pediatría" en relación al manejo que se hace en los servicios de urgencias pediátricas de las lesiones accidentales e intoxicaciones. El primero de los artículos publicado por Rubio-García y cols., versaba sobre la actitud diagnóstico-terapéutica en menores de 12 meses que acudían a un centro hospitalario tras padecer una caída. Resaltaban los autores que el traumatismo craneal leve constituyó el principal diagnóstico (85,6%), seguido de las fracturas (9,3%), especialmente fracturas craneales (7%)(Rubio García et al., 2017). Los autores señalaban que, si bien no existía mucha demora desde el accidente hasta la consulta en urgencias, el conocimiento y establecimiento de medidas de prevención de lesiones en los cuidadores continuaba siendo deficitario.

El segundo artículo, publicado por García-González y cols., llamaba la atención sobre el hecho de que en un porcentaje no desdeñable de los niños y adolescentes atendidos por un episodio de intoxicación (9%), existía el antecedente de una intoxicación previa (episodios recurrentes)(García González et al., 2017). Señalaban que la puesta en marcha de la historia clínica informatizada, con la inclusión de un ítem específico para detectar episodios previos, ayuda a detectar pacientes de riesgo más fácilmente. Además, referían que, si bien el mecanismo de las intoxicaciones es principalmente accidental, el mayor porcentaje de intoxicaciones voluntarias ocurre en la adolescencia periodo en el que debutan múltiples trastornos psiquiátricos y momento de mayor acceso a drogas de abuso. Concluían que es necesario ahondar en medidas de prevención en el episodio agudo de intoxicación, puesto que es el periodo de mayor sensibilización de las familias y los pacientes, así como asegurar un seguimiento estrecho por parte de trabajadores sociales, psiquiatría y pediatra de atención primaria del paciente tras el alta hospitalaria.

Así pues, es vital que los profesionales que trabajan en los servicios de urgencias conozcan la relación de las LNIs y envenenamientos con el TDAH, de manera que este trastorno este en la mente de los facultativos y pueda diagnosticarse de forma más precoz. Además, el mayor acceso a la medicación por parte de los niños y adolescente con TDAH, para su propio tratamiento o para comorbilidades asociadas, les pone en una situación de mayor riesgo de envenenamiento (ya sea intencional o accidental) que a individuos sin el trastorno.

Finalmente, el conocimiento de esta relación puede ayudar a establecer pautas de prevención específicas en este grupo de pacientes. Instruir a padres y educadores en posología adecuada de los tratamientos, almacenaje seguro y adecuado de medicación, así como también reforzar medidas para la adquisición hábitos seguros (educación vial, etc.) y prevención de conductas de riesgo en ámbitos deportivos, de ocio, etc. puede disminuir considerablemente la morbimortalidad en este grupo de pacientes de riesgo.

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Título: Trastorno por déficit de atención e hiperactividad como factor de riesgo en intoxicaciones y lesiones no intencionales.

Título corto: TDAH, intoxicaciones y lesiones no intencionales

Title: Attention deficit hyperactivity disorder as a risk factor for intoxications and unintentional injuries

Short title: ADHD, intoxications and unintentional injuries

Maite Ruiz-Goikoetxea[a]; Samuele Cortese[bcd]; Cesar Soutullo[e]; Gonzalo Arrondo[f]*.

a: Servicio de Urgencias Extrahospitalarias Servicio Navarro de Salud-Osasunbidea, Pamplona, España.

b: Center for Innovation in Mental Health, University of Southampton, Academic Unit

of Psychology, Southampton, UK

c: Faculty of Medicine, Clinical and Experimental Sciences (CNS and Psychiatry),

University of Southampton, Southampton, UK

d: Department of Child and Adolescent Psychiatry, NYU Langone Medical Center, New

York, NY, USA

e: Departamento de Psiquiatría y Psicología Médica, Unidad de Psiquiatría Infantil y Adolescente, Clínica Universidad de Navarra, Pamplona, España

f: Instituto Cultura y Sociedad (ICS), Grupo Mente-Cerebro, Universidad de Navarra, Pamplona, España

Autor para correspondencia:

Gonzalo Arrondo (garrondo@yahoo.es).

Grupo Mente-Cerebro, Instituto Cultura y Sociedad (ICS), Universidad de Navarra, Pamplona.

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Sra Editora:

Hemos leído con gran interés los estudios de Rubio-García et al [1]. y García-González et al [,2], cuyo tema común son las lesiones no intencionales.

Según la Organización Mundial de la Salud las lesiones no intencionales son responsables de alrededor 830.000 muertes anuales en niños y adolescentes, cuyos costes directos rondan los 4.000 millones de euros. Las causas más frecuentes son accidentes de tráfico, ahogamientos, quemaduras, caídas y envenenamientos/intoxicaciones. Los envenenamientos e intoxicaciones suponen un subgrupo importante entre las lesiones no intencionales siendo los tóxicos más comúnmente identificados los productos del hogar, los fármacos, y en menor medida pesticidas y mordeduras de animales[3]. Si bien en la infancia el mecanismo es casi exclusivamente accidental; en la adolescencia el patrón se va asemejando más al del adulto, ya que los casos de intoxicación no accidental aumentan como resultado del uso recreacional de sustancias psicoactivas pero también de eventos autolíticos. Así pues, como señalan Rubio García et al. y García González et al, la prevención de lesiones no intencionales es una prioridad de salud pública y un deber para los pediatras[1,2].

El trastorno por déficit de atención e hiperactividad (TDAH) es el trastorno del neurodesarrollo más frecuente con una prevalencia mundial del 3-5%. Un reciente meta-análisis [4], en el que se combinaron datos de aproximadamente 350.000 niños y adolescentes con TDAH y 4.000.000 sin TDAH, ha destacado su papel como factor de riesgo para sufrir una lesión no intencional (OR=1,53; IC 95%=1,47-1,67), así como el efecto protector que ofrece la medicación estimulante frente a este riesgo (Riesgo relativo 0.879 IC 95%=0,838-0,922).

Así mismo, el haber padecido un episodio de intoxicación supone un riesgo añadido de padecer un nuevo episodio. Señalan García González et al. que el 60.9% de las intoxicaciones en su estudio eran no intencionadas, si bien en el grupo de episodios repetidos aumentaba el porcentaje de intención suicida/maltrato hasta un 59,1% frente al 14,9% del grupo con sólo una intoxicación [2]. Consideramos muy interesante valorar la comorbilidad médica y psiquiátrica como factor de riesgo de intoxicación en este tipo de estudios. Por un lado la existencia de patologías médicas) puede suponer un mayor acceso a la medicación, pero por otro lado va a asociarse a una mayor carga psicológica de enfermedad que puede hacer más proclive al individuo a una intoxicación intencionada o accidental. Por tanto, la presencia de TDAH es un factor de riesgo para lesiones no intencionadas y posiblemente también para intoxicaciones accidentales o intencionales, que es pocas veces tenida en cuenta en pediatría En este sentido, nuestro grupo también está llevando a cabo un meta-análisis para estudiar la relación entre el TDAH y riesgo de envenenamientos/intoxicaciones (registro en PROSPERO CRD42017079911; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=79911) En resumen, un mayor conocimiento de la relación entre TDAH y lesiones no intencionales, incluyendo intoxicaciones, puede ayudar a tomar decisiones clínico-terapéuticas más acertadas, así como para establecer las medidas de prevención más adecuadas en este tipo de pacientes.

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4. Discusión

4.1. El TDAH como factor de riesgo de lesiones no intencionadas y envenenamientos

La presente tesis doctoral ha encontrado que los niños y adolescentes con TDAH presentan un riesgo 1,53 veces más elevado de padecer una LNI (OR: 1,53; I.C. 95% =1,40-1,67) y 3 veces superior de padecer un envenenamiento o intoxicación frente a niños y adolescentes sin este trastorno (RR = 3,14; I.C. 95%= 2,23 -4,4).

4.1.1. Riesgo de Lesiones no intencionadas

Algunos autores (Dudani et al., 2010) habían apuntado previamente la posibilidad de que los niños y adolescentes con TDAH presentasen una mayor probabilidad de padecer LNIs. Sin embargo existían grandes diferencias en los hallazgos, ya que en ocasiones los resultados no habían alcanzado la significación estadística para probar la asociación (OR: 0,75; IC 95%=0,53-1,06) (Dudani et al., 2010); y en otras casos las asociaciones eran dispares. Algunos estudios concluían que el riesgo era menor en el grupo de pacientes que en el de controles sanos (OR ajustada: 0,91; IC 95%= 0,56-1,48) (Keyes et al., 2014), otros no encuentran diferencias (OR ajustada: 0,7; IC 95% =0,3-1,5) (Sciberras et al., 2016) o por el contrario se señalaba que el riesgo era más elevado en el grupo de pacientes con TDAH (OR ajustada: 5,01; IC 95%=4,16-6,21) (Dalsgaard et al., 2015a; Tai et al., 2013). Además, existía gran variabilidad en las medidas de asociación encontradas, con cifras de OR que oscilaban entre 1,29; IC 95% =1,22-1,37 (Dalsgaard et al., 2015a) y 5,01; IC 95% =4,16-6,21 (Tai et al., 2013).

Durante la realización de este proyecto se publicó un metanálisis (Amiri et al., 2017) en el que los autores trataban de evaluar la posible relación entre el TDAH y el riesgo de LNIs. Este trabajo obtuvo una medida de asociación superior a la encontrada por nosotros (OR ponderada: 1,96; IC 95%: 1,6-2,4). No obstante, el estudio de Amiri y cols. presentaba algunas limitaciones que tendían a sobreestimar la medida del riesgo en el grupo de niños y adolescentes con TDAH, como por el ejemplo el hecho de que no ajustase por la variable sexo o no incluya fuentes de literatura gris en la busqueda sistemática. Creemos que nuestro trabajo ha superado las limitaciones más importantes de este metanálisis.

En primer lugar, nuestro estudio ha incluido una búsqueda bibliográfica más amplia tanto en el tiempo como en bases de datos, incluyendo no solo artículos publicados sino también tesis doctorales y otras fuentes de literatura gris. De esta manera, se ha conseguido ampliar el tamaño muestral del estudio de Amiri y cols. en 3.700.000 controles y 329.000 individuos con TDAH.

En segundo lugar, el pre-registro del presente metanálisis asi como el empleo de unos criterios de inclusión más exigentes (la exclusión de estudios en prescolares y estudios en los que los resultados

no estuviesen controlados por sexo), otorgan mayor rigor a los resultados. Es especialmente relevante el hecho de que el estudio de Amiri y cols. no controlase por la variable sexo, dado que como señalan diferentes autores, el sexo masculino está asociado con mayor incidencia de lesiones por las características del desarrollo de los niños versus la niñas (Gaub and Carlson, 1997; Peden et al., 2008).

Nuestros resultados se han mantenido robustos tras realizar diferentes análisis de sensibilidad: el tipo de OR ajustada o no ajustada, el método utilizado para llevar a cabo el diagnóstico, la definición de lesión, y la duración del seguimiento en los estudios originales. Posteriormente, en el análisis de metarregresión no se ha visto que la puntuación del estudio según la escala NOS influya significativamente en los resultados. Por último, en este mismo análisis, tampoco encontramos un efecto significativo del sexo, edad o presencia de comorbilidad en la medida de asociación. No obstante, estos resultados deben ser tomados con cautela, puesto que el número de estudios analizados era pequeño. Estudios futuros podrían continuar esta línea de investigación para cuantificar el efecto de estas variables en la asociación del TDAH y el riesgo de LNIs.

Cuando se analizaron por separado los artículos que empleaban HR como medida de asociación, es decir cuando se tenía en cuenta el tiempo que pasaba desde que un individuo era diagnosticado de TDAH hasta que se producía el desenlace (LNI); sigue existiendo un riesgo significativamente más elevado entre tener TDAH y el riesgo de LNIs (HR combinada: 1,39; I.C. 95%: 1,06-1,86). Estos resultados son similares a los obtenidos por otro gran estudio longitudinal (Lindemann et al., 2017) realizado tras la publicación de nuestro metanálisis, en el que se seguía a una cohorte de 75.300 niños y adolescentes y se analizaba el riesgo de LNIs en sujetos con TDAH (HR ajustada: 1,40; IC 95%: 1,30–1,49). Creemos que la HR es la mejor medida de asociación para poder evaluar la relación entre el TDAH y el riesgo de LNIs, ya que se tiene en cuenta la influencia del tiempo en esta asociación. Al ser las LNIs un desenlace relativamente común en la infancia y adolescencia, si seguimos durante un periodo de tiempo lo suficientemente largo a una población, todos sus componentes (pacientes y controles) presentarán el desenlace. Por esta razón consideramos que la HR, que tiene en cuenta no solo el que ocurra una lesión, sino el tiempo que tarda en producirse la misma, es la medida de asociación más correcta (Martínez-González et al., 2008). Sin embargo, tal y como se ha explicado previamente, se escogió la OR como desenlace principal ya que es la más comúnmente usada en la literatura científica y la única que podía calcularse en estudios de casos y controles.

4.1.2. Riesgo de intoxicaciones y envenenamientos

Como ya hemos comentado, muchos de los estudios que incluían desenlaces de intoxicaciones lo hacían en el marco de las lesiones accidentales, incluyendo también este riesgo general. RVE es una técnica estadística ideal para analizar esta situación, ya que permite estimar el efecto intra-estudio, teniendo en cuenta que los desenlaces procedentes de intoxicaciones y de lesiones accidentales no

son independientes entre sí, ya que provienen de la misma (o similar) muestra de sujetos en cada estudio. Por tanto, con esta técnica se puede estimar de manera más precisa hasta qué punto el riesgo de intoxicaciones es distinto que el de lesiones accidentales a partir de medidas relacionadas por provenir de los mismos estudios. En este caso, el coeficiente beta mide el cambio que se produce en el riesgo de sufrir una lesión en función del tipo de lesión (intoxicación o lesión accidental). En resumen, un resultado significativo en este análisis indica que el riesgo de sufrir una intoxicación es distinto que el riesgo de sufrir una lesión accidental, teniendo en cuenta que la población de la que se obtienen las estimaciones para un tipo y otro de lesiones es la misma o similar.

Los niños y adolescentes con TDAH presentan un riesgo más elevado de envenenamientos que sus iguales y este riesgo relativo es mayor que el resto LNIs en su conjunto. Los resultados de esta investigación demuestran que los niños y adolescentes con TDAH presentan una probabilidad 3 veces mayor de ser víctimas de un envenenamiento frente a niños y adolescentes sin TDAH y además esta probabilidad es más elevada que la probabilidad de padecer cualquier otro tipo de LNI. Pensamos que existen varias razones que hacen que este riesgo sea significativamente más elevado.

La primera razón sería el mayor acceso a la medicación en niños con TDAH. Las intoxicaciones farmacológicas son una causa frecuente de envenenamiento en pediatría (Mintegi et al., 2017a; Peden et al., 2008), tanto por el mayor acceso a los fármacos para el TDAH, como por la presencia de para comorbilidad asociada, la cual supone un factor de riesgo adicional.

En segundo lugar, el resultado puede estar sobrestimado ya que en algunas ocasiones no ha podido clarificarse la intencionalidad de los envenenamientos, ya que los estudios originales no separaban ambos mecanismos. Si bien el mecanismo accidental es el más frecuente en la infancia (Peden et al., 2008), a medida que se avanza en edad, aumenta el número de episodios intencionados (gestos o intentos de suicidio o uso recreativo de tóxicos), pero siempre en número inferior a los episodios no intencionados (Mintegi et al., 2017a). Es posible que esta circunstancia ocurra también en el grupo de niños con TDAH. Sin embargo, nuestros resultados no variaban significativamente al realizar un análisis de sensibilidad en niños con 10 años de edad o menos frente a niños por encima de esa edad. Este hecho puede deberse a no haber alcanzado el tamaño muestral suficiente para valorar el efecto de la edad en el riesgo. Podría resultar útil analizar la prevalencia de intentos autolíticos (Ljung et al., 2014) o abuso de sustancias en pacientes con TDAH (Biederman et al., 1999; Chang et al., 2014b) y tratar de estimar la prevalencia de intoxicaciones no intencionadas a partir de la misma.

4.2. Efecto protector de la medicación para el TDAH en la disminución de LNIs

Los niños y adolescentes con TDAH presentan un riesgo inferior de padecer LNIs en los periódos en los que estan tomando el tratamiento farmacológico para el trastorno frente a los periódos en los que no reciben medicación (Efecto combinado: 0,879 ; I.C. 95% = 0,838-0,922). Es decir

la presencia de TDAH aumenta el riesgo de LNI en 1,53 veces y el tratamiento con medicación del TDAH reduce el riesgo relativo de padecer una LNI en este grupo de pacientes en un 12%.

En los últimos años se han publicado una serie de estudios muy eficientes desde el punto de vista epidemiológico. Son los llamados “self controlled case series” o estudios autocontrolados. En este tipo de estudio cada individuo actúa como su propio control, evitando otros posibles confusores. El objetivo es evaluar si se presenta un determinado desenlace en los periódos en los que los niños y adolescentes son reciben tratamiento con medicación frente a periodos sin medicación. La combinación de estos estudios ha permitido alcanzar un tamaño muestral suficiente (13.254 pacientes) para encontrar una evidencia significativa que demuestre que el tratamiento farmacológico para el TDAH (MPH en el 98% de los casos) disminuye la probabilidad de padecer una LNI en niños y adolescentes tratados con medicación para el TDAH. Estos resultados han sido replicados en un metanálisis realizado a posteriori que obtiene un tamaño de efecto similar (0,88; IC 95%: 0,85–0,92) (Man et al., 2017b).

Debido a que solamente uno de los 5 estudios incluidos en el metanálisis evaluaba la presencia de lesiones a largo plazo (Dalsgaard et al., 2015a), solo podemos afirmar con los datos de nuestro metanálisis que existe un efecto protector de la medicación a corto plazo. El estudio de Dalsgaard y cols., consideraba a los individuos “medicados” si el tratamiento con MPH se había iniciado como mínimo seis meses antes y empleaba una técnica estadística diferente, “diferencia de la diferencia”, con la que evaluaba la presencia de LNIs en un periodo de tiempo más amplio. Cuando se analizan por separado los otros cuatro estudios que empleaban la metodología “autocontrolada”, el tamaño del efecto de la medicación sobre la incidencia de lesiones era similar (Efecto medio combinado: (0,898; I.C. 95% = 0,851- 0,948). Así pues, se abre una interesante línea de investigación para estudiar si tal y como apuntaban Dalsgaard y cols.; este efecto protector se mantiene a largo plazo o no. Para ello serían necesarios estudios de cohortes de tamaño considerable en el que los individuos pudiesen ser seguidos durante un periodo suficiente de tiempo para que se produjese el desenlace. Por lo tanto, podrían pasar años para recopilar nuevas cohortes. Otra opción para evaluar este efecto sería examinar retrospectivamente en estudios de adultos con TDAH, cuantos padecieron lesiones en la infancia y si estaban tomando medicación en esos periodos. No obstante, este segundo estudio tendría más limitaciones y probabilidad de sesgos; ya que pueden existir variables de interés o de confusión que no estén recogidas en los estudios originales, como por ejemplo comorbilidades asociadas.

4.3. Limitaciones y puntos fuertes

4.3.1. Limitaciones

Este trabajo presenta algunas limitaciones importantes que deben considerarse para interpretar los resultados y su aplicabilidad clínica.

Carácter retrospectivo

La primera es que se trata de un estudio retrospectivo utilizando la técnica de metanálisis. Este hecho hace que nuestro trabajo se vea influenciado por las características de los estudios originales incluidos. En muchos de los casos los estudios originales se han realizado a partir de grandes bases de datos administrativas (registros hospitalarios, compañías de seguros, etc.) cuya finalidad inicial no era la investigación, presentando limitaciones en cuanto al método diagnóstico o a la recogida de variables de interés para nuestro estudio. Así pues, no se han podido analizar algunas variables relevantes para la práctica clínica, puesto que no se describían en los estudios originales. Por ejemplo, no podemos saber la influencia de la presentación del TDAH (combinada, hiperactiva-impulsiva o inatenta) en la frecuencia de LNIs. Sería interesante conocer si las lesiones que padecen estos pacientes son fruto de una mayor impulsividad, que les lleva a tomar conductas más arriesgadas, o si por el contrario el componente de inatención les hace más vulnerables (no ver obstáculos, olvido del casco, no leer etiquetas...) a padecer la lesión, o si resultan de una combinación de ambas.

Por esta misma razón, no se ha podido valorar si la comorbilidad psiquiátrica modifica la asociación entre el riesgo de lesiones o envenenamientos y si aumenta aún más el riesgo de lesiones o intoxicaciones (mayor acceso a la medicación). En el caso de las lesiones, los resultados hallados en relación a la comorbilidad no alcanzan la significación estadística, hecho que puede ser debido al escaso tamaño muestral; y en el segundo caso, en el metanálisis sobre intoxicaciones, ya que los estudios originales no aportaban datos al respecto y este efecto no ha podido ser evaluado.

Otro problema de estos estudios es que el diagnóstico del TDAH incluye diagnósticos clínicos, autoreferido o por cuestionarios, ya que las tasas de prevalencia del TDAH pueden variar en función del método para realizar el diagnóstico. Sin embargo nuestros resultados del mayor riesgo de LNIs en individuos con TDAH se mantienen robustos tras realizar un análisis de metarregresión según el método de diagnóstico de TDAH (Polanczyk et al., 2014).

Medidas de asociación empleadas

En segundo lugar, como se ha comentado en la discusión, consideramos que la HR es la mejor medida de asociación para evaluar la relación entre el TDAH y el riesgo de lesiones. Sin embargo, nos encontramos con que no es la medida de asociación más empleada. Por tanto, si bien hemos encontrado una relación estadísticamente significativa entre el TDAH y el riesgo de lesiones, desconocemos si el tamaño del efecto podría ser aún mayor. Si bien el tamaño muestral obtenido es suficiente para obtener un efecto medio fiable, el número limitado de estudios que reportaban esta medida de asociación ha limitado los análisis de metarregresión, que solo se pudieron llevar a cabo en el caso del metanálisis de ORs.

Efecto de la medicación para el tratamiento del TDAH

La tercera limitación hace referencia al efecto de la medicación. El efecto protector que se ha encontrado en la disminución de las lesiones no intencionadas ocurre en el corto plazo, pero aún no está demostrado si este se mantiene en el largo plazo, puesto que solo uno de los estudios analizados en el metanálisis sobre el efecto de las lesiones aportaba datos a largo plazo. A pesar de ello, se trataba de grandes estudios poblacionales, que en conjunto reúnen un tamaño muestral suficiente para demostrar el efecto de la medicación en la disminución del riesgo. Por otro lado, los estudios originales sobre intoxicaciones en pacientes en TDAH no aportaban datos sobre el porcentaje de pacientes medicados y no medicados y el número de intoxicados en cada caso. Dada la utilidad de los estudios "self controlled case series" para estudiar el cambio en el desenlace en función de la modificación de las variables de estudio en un individuo, esta metodología podría ser la clave en un futuro próximo para confirmar si, al igual que en el caso de las lesiones no intencionadas, el tratamiento farmacológico para el TDAH disminuye el riesgo de envenenamientos en este grupo.

En este segundo estudio (riesgo de envenenamientos en TDAH) existe otra posible limitación: la no distinción del mecanismo de intoxicaciones y envenenamientos en la mayor parte de los artículos. A pesar de que el riesgo global de envenenamientos/intoxicaciones es más elevado, el conocimiento de la intencionalidad del episodio nos ayudaría a prevenirlo de manera más eficaz. Es decir, en un caso accidental, quizás los clínicos deberemos hacer un mayor énfasis en el almacenaje seguro de productos o en la posología de los fármacos. Sin embargo, en casos intencionados, deberemos ahondar en la prevención de conductas de riesgo, (reducción de impulsividad, consumo de tóxicos, etc.) o en la detección de primeros síntomas de trastornos de ansiedad o depresión.

Por último, si bien existe una gran variabilidad en el tipo de estudios incluidos en cada uno de los dos metanálisis sobre el riesgo de LNIs y envenenamientos, hemos intentado limitarla; mediante el uso de unos criterios de inclusión muy exigentes (en la selección de los estudios), así como el análisis por separado del riesgo de LNIs y envenenamientos, para no sobrestimar la medida de asociación entre el TDAH y el desenlace. Además, se han realizado distintos análisis de sensibilidad que han mostrado que los resultados se mantienen robustos tras la modificación de distintas variables de interés. Finalmente, en la medida que la heterogeneidad existente entre los estudios tendía a disminuir en los análisis de metarregresión, que sin embargo tendían a incluir pocos artículos, estos hallazgos abren nuevos caminos a investigaciones futuras en relación a factores que estén posiblemente mediando la relación entre el trastorno y las lesiones.

4.3.2. Puntos fuertes

A pesar de las posibles limitaciones este trabajo destacan las siguientes fortalezas que le confieren valor en sí mismo.

La primera de ellas es el gran tamaño muestral que se ha conseguido reunir: cerca de 350.000 niños y adolescentes con TDAH y 4.000.000 de individuos sin el trastorno en el caso de las LNIs; y alrededor de 88.000 individuos con TDAH y más de 1.000.000 de controles en el caso de envenenamientos. Como se ha comentado en la introducción, se habían realizado distintos intentos para tratar de evaluar la relación del TDAH con estos dos desenlaces (LNIs y envenenamientos) con resultados diversos. La combinación de los diferentes estudios ha permitido alcanzar un tamaño muestral, que difícilmente podría alcanzarse en un estudio de cohortes longitudinal y que ha permitido demostrar sin lugar a dudas que el TDAH asocia un mayor riesgo de lesiones y envenenamientos.

En segundo lugar, existe una corriente en el ámbito científico que promueve la transparencia en la investigación, para evitar la posibilidad de "alterar" los análisis de los datos obtenidos en los diferentes estudios en aras de encontrar la significación estadística, y aumentar la reproducibilidad de los estudios (Munafò et al., 2017). En este sentido se insiste mucho en la necesidad del preregistro de los protocolos de investigación. Esto es especialmente importante en el caso de las revisiones sistemáticas y metanálisis que precisamente se definen por su transparencia y reproducibilidad. Nuestro proyecto se ha llevado a cabo siguiendo las recomendaciones internacionales de calidad para la elaboración de revisiones sistemáticas y metanánalisis; publicándose en un registro público los protocolos de ambos estudios (PROSPERO antes de la extracción y análisis de los datos. Además, nuestros resultados en relación con la disminución del riesgo de LNIs en niños y adolescentes con TDAH se han visto respaldados por un metanálisis realizado con posterioridad al nuestro, en el que se obtiene una disminución relativa del riesgo en individuos con TDAH, similar, aunque algo mayor, a la obtenida en nuestro estudio.

En último término queremos destacar la aplicabilidad a de este estudio en la práctica clínica diaria. La elevada prevalencia de morbimortalidad de las LNIs y los envenenamientos en los niños y adolescentes en pediatría (Arribas Sánchez et al., 2018; Mintegi et al., 2017b), unido a que entre el 3%-5% de los niños de nuestra población según las series (Catalá-López et al., 2012; Lasa Aranzasti et al., 2017; Polanczyk et al., 2014) tienen TDAH, nos da una idea del coste económico y humano derivado de las LNIs y envenenamientos. La OMS acuñó el término lesión no intencional en lugar de accidente, para reflejar el carácter prevenible de las mismas. Es aquí dónde radica la importancia de nuestro estudio. Por un lado, el aumento del riesgo de estos desenlaces en el grupo de niños y adolescentes con TDAH, nos obliga a aplicar medidas preventivas especiales y a reforzar las medidas preventivas de seguridad en este grupo y sus padres o educadores. Por otro lado, ha encontrado un elemento clave en la prevención del riesgo en estos niños: el tratamiento correcto del TDAH con medicación. Si bien los costes económicos del tratamiento son importantes, son inferiores a los costes económicos y humanos derivados del tratamiento de las lesiones no intencionadas (Quintero et al., 2018).

4.4. Importancia clínica. Dimensión global de las consecuencias del TDAH

Las características definitorias del TDAH (hiperactividad, inatención e impulsividad) harían a estas personas más afines al "riesgo" en su totalidad. Por un lado, la impulsividad les puede hacer más proclives a determinadas conductas y aficiones consideradas "arriesgadas" por la población general; y por otro lado la inatención les conduce a olvidos o descuidos en medidas de prevención necesarias para evitar determinados desenlaces. Por lo tanto, hemos de tener en cuenta la dimensión del TDAH en todos los ámbitos de la vida del individuo. Nuestro trabajo ha puesto en evidencia el riesgo aumentado de LNIs y envenenamientos en niños con TDAH, lo cual se suma a otras evidencias de las consecuencias negativas del trastorno en la calidad de vida del individuo (Coghill et al., 2008, 2017; Escobar et al., 2005), como trastornos de la conducta alimentaria, conductas sexuales de riesgo, adicciones o aumento de accidentes de tráfico.

En el caso de los trastornos de la conducta alimentaria, la literatura científica ha aportado evidencias de una mayor prevalencia de obesidad y sobrepeso en los niños y adolescentes con TDAH (Cortese et al., 2016b). Este aumento de peso es consecuencia de un patrón inadecuado de alimentación (mayor frecuencia de picoteos, elección de alimentos más "atractivos" y calóricos…) y por otro lado de una mayor índice de sedentarismo (Cortese and Tessari, 2017). De esta forma, la mayor impulsividad de estos chicos, inhibe su mecanismo de control y les puede llevar a comer mayor cantidad de alimentos con poco nivel nutricional. En lo que respecta al ejercicio físico, los problemas de relación derivados del TDAH les hacen menos proclives a la participación en deportes de equipo y a la elección de videojuegos o televisión como alternativas de ocio (Cook et al., 2015; Ebenegger et al., 2012; Khalife et al., 2014; Lingineni et al., 2012; McWilliams et al., 2013). Además, en el caso de adultos con TDAH; el trastorno se ha relacionado también con un mayor riesgo de accidentes de tráfico (Barkley et al., 1993; Curry et al., 2017) y con otras conductas de riesgo en materia de salud sexual (Ramos Olazagasti et al., 2013) y abuso de sustancias (Chorniy and Kitashima, 2016).

Todos estos "aumentos de riesgo" hacen de los pacientes con TDAH una población especialmente vulnerable, aumentando de manera considerable su morbilidad y su mortalidad de forma prematura (Dalsgaard et al., 2015b; Faraone, 2015).

4.4.1. Medidas de prevención: tratamiento farmacológico y actuaciones específicas

Una vez conocidas las consecuencias negativas del TDAH en el individuo, son necesarias actuaciones que eviten estos desenlaces. La medicación empleada como tratamiento farmacológico para el TDAH ha demostrado ser una ayuda en la disminución de estos problemas, disminuyendo la probabilidad de LNIs, intentos autolíticos (Man et al., 2017a), accidentes de tráfico (Chang et al., 2014a) y en definitiva en la mejora de la calidad de vida de los pacientes con este trastorno (Coghill et al., 2017). Quizás este efecto podría ser aún mayor, puesto que uno de los problemas del tratamiento

farmacológico es que quienes más lo necesitan menos se adhieren al mismo, subestimando el posible papel protector de la medicación (Gau et al., 2008).

A pesar del efecto de los fármacos, hay que reseñar que, en la prevención de estas conductas, es necesario una modificación en los estilos de vida de los individuos. Sin embargo, esta labor no es fácil puesto que la propia impulsividad inherente al TDAH dificulta aún más la adquisición de estos hábitos saludables. Por esta razón, es imprescindible que estas modificaciones comiencen en edades tempranas. En nuestro caso particular, prevención de lesiones no intencionadas y envenenamientos, es crucial que padres y educadores sean conscientes del riesgo incrementado de lesiones en sus hijos para poner en marcha medidas preventivas específicas.

En el caso del refuerzo y apoyo de padres de los pacientes con TDAH cabrían dos actuaciones. La primera correspondería a los pediatras de atención primaria y debería llevarse a cabo en los controles rutinarios del niño. Es necesario, ahondar más profundamente en las revisiones de salud en medidas de prevención de accidentes tales como casco de protección en bicicletas y patines, cinturones de seguridad, chaleco salvavidas en actividades deportivas acuáticas, correcto almacenaje de tóxicos y fármacos en domicilio, etc. La segunda medida, debería realizarse durante el seguimiento clínico de los pacientes con TDAH. Tanto en el diagnóstico como en el seguimiento, se debe remarcar la importancia de la adhesión al tratamiento no solo para la mejoría en rendimiento académico-laboral; sino como protector frente a otras posibles conductas de riesgo. Además, consideramos muy útil instruir a los padres sobre los efectos secundarios de la medicación y los primeros síntomas de una eventual intoxicación por este fármaco. Dada la posibilidad de que los padres de estos niños tengan una prevalencia más alta de padecer o haber padecido TDAH (Starck et al., 2016), y por ende de tener unas conductas hacia el riesgo más permisivas que otros progenitores, es necesario insistir en estas actuaciones.

En el ámbito escolar el conocimiento por parte del profesorado de otras consecuencias del trastorno podría ayudar por un lado a identificar niños “con riesgo” de TDAH más precozmente y por otro lado a desarrollar estrategias de prevención de lesiones más eficaces en este ámbito, dentro del currículo del centro escolar, de la misma forma que se realiza por ejemplo en otros aspectos como la promoción de dieta saludable y la práctica ejercicio físico (Cohen et al., 2014; Dudley et al., 2015). En un reciente estudio (Schaeffer et al., 2017), se planteaba el empleo de un juego de mesa en grupo de niños de 5 a 11 años como estrategia preventiva de lesiones. Se trataba de valorar la mejora de conocimientos de los niños tras sesiones de 45 minutos jugando a “Safety land” un informal “juego de la oca”, en el que las casillas versaban sobre seguridad vial, fármacos… Este tipo de estrategias integradoras de los ámbitos escolar y sanitario pueden ser de gran ayuda en la educación para la salud e integración de estilos de vida saludables.

Finalmente, nuestro trabajo quiere ser una ayuda en la toma de decisiones de los facultativos en su práctica diaria, dadas las variaciones en el manejo del TDAH según la procedencia geográfica de los pacientes (Cardo et al., 2017). Por un lado, el incremento de riesgo de LNIs y envenenamientos; y el papel protector del tratamiento farmacológico es un punto más a tener en cuenta a la hora de iniciar, suspender o mantener la medicación en niños y adolescentes con TDAH. Por otro lado, este riesgo alertará de la sospecha de TDAH en niños y adolescentes que acudan de forma reiterativa a los servicios de urgencias por LNIs e intoxicaciones, y presenten además otros factores de riesgo de este para el desarrollo del trastorno como por ejemplo prematuridad al nacimiento, dificultades académicas, etc. (Sucksdorff et al., 2015), adelantando así el diagnóstico de TDAH.

4.5. Futuras líneas de investigación

Los hallazgos de este proyecto han dejado distintas preguntas sin respuesta abriendo posibles líneas de investigación futuras.

La primera de ellas es clarificar la relación de posibles variables de interés que puedan estar relacionadas con un mayor aumento de riesgo de LNIs y envenenamientos como son la comorbilidad y las diferentes presentaciones de TDAH. Sería muy interesante evaluar mediante la puesta en marcha de estudios cohortes prospectivas que siguiesen a niños desde la etapa preescolar hasta la edad adulta; valorar si la presentación del trastorno (antes llamada subtipo) influye en el tipo y frecuencia de lesión. Análogamente este tipo de estudios podría evaluarse la influencia de la comorbilidad en el riesgo. Por otro lado, y como se ha comentado previamente se podría crear un sub-estudio dentro de estas cohortes, un “self-controlled case series” en el grupo de niños con TDAH con el objetivo de evaluar si el efecto protector de la medicación en el riesgo de lesiones se mantiene a largo plazo y si disminuye además el riesgo de un posible envenenamiento. Otro punto interesante sería evaluar las medidas de prevención en los hogares de los niños con TDAH y compararlas con las de los hogares de niños sin TDAH. En la medida que los niños son más impulsivos y esto es percibido por el entorno, es posible que haya mayores medidas preventivas que estén reduciendo las consecuencias negativas del trastorno. Además, en la medida que el diagnóstico de TDAH es frecuente en los padres de los pacientes con TDAH (Starck et al., 2016), podría ocurrir que estos padres tuviesen conductas más permisivas, tomasen menos medidas preventivas o su inatención derive en mayores situaciones de riesgo en sus hijos, aumentando el riesgo de lesiones o envenenamientos.

Finalmente, dado que la mayoría de los accidentes en niños y adolescentes se producen en el domicilio (Esparza and Mintegi, 2016), sería interesante evaluar la influencia del entorno de los niños y adolescentes con TDAH en el riesgo de lesiones. En un primer lugar se podría realizar un estudio transversal sobre los conocimientos de los padres sobre “entornos seguros” (bien en un estudio de cohortes como el anteriormente mencionado) o bien en una muestra representativa, como podría ser el cupo de un pediatra de un centro de salud (cada pediatra cuenta con un cupo asignado de unos

1.000 niños entre los 0-14 años). De esta forma podríamos detectar las carencias y fortalezas de los cuidadores habituales de los niños con TDAH, de cara a plantear un segundo estudio de intervención en este grupo de pacientes y sus familiares (talleres formativos, role playing, refuerzo por escrito de medidas de prevención en todas sus visitas al centro de salud, etc.

5. Conclusiones

I. Los niños y adolescentes con TDAH presentan un riesgo 1,5 veces más elevado de padecer lesiones no intencionadas (LNIs) que niños y adolescentes sin dicho trastorno. Por cada 10 niños sin TDAH que presenten una lesión no intencional, habrá 15 niños con TDAH que las padezcan.

II. Los niños y adolescentes con TDAH presentan un 39% más de riesgo de sufrir una lesión que los controles sanos cuando se evalúan durante el mismo periodo de tiempo. Es decir, el aumento de riesgo de LNI en niños y adolescentes con TDAH se mantiene cuando se evalúa no sólo el desenlace (LNI) sino el tiempo que transcurre hasta que se produce.

III. La medicación empleada como tratamiento para el TDAH (fundamentalmente MPH en los estudios incluidos) disminuye en un 12% el riesgo relativo de padecer en el corto plazo una LNI en individuos con TDAH tratados farmacológicamente. Debido al limitado número de estudios que evalúan el efecto del tratamiento sobre las lesiones, son necesarias más investigaciones y en concreto, a largo plazo.

IV. Los niños y adolescentes con TDAH presentan un riesgo 3 veces más elevado que sus iguales sin este trastorno de sufrir un envenenamiento. Además, el riesgo relativo de envenenamientos e intoxicaciones es aún más elevado que el riesgo relativo general de padecer lesiones no intencionadas.

V. Los datos obtenidos sugieren que no existe asociación entre sexo, edad y comorbilidad en el riesgo de envenenamiento y LNIs. Sin embargo, son necesarios más estudios para esclarecer si realmente estas variables influyen en el riesgo de LNIs y envenenamientos en individuos con TDAH.

6. Anexo 1: Glosario de Abreviaturas y definiciones

6.1. Glosario de Abreviaturas

TDAH: Trastorno por déficit de Atención e Hiperactividad

OMS: Organización Mundial de la Salud

LNIs: Lesiones no intencionadas

DSM: Diagnostic and Statistical Manual of Mental Disorders

CIE: Clasificación Internacional de Enfermedades

INE: Instituto Nacional de Estadística

ICD: International Classification of Diseases

MPH: metilfenidato

NOS: Newcastle Otawa Scale

OR: Odds Ratio

HR: Hazard Ratio

IC: Intervalo de Confianza

RVE: Robust Variance Estimation, estimación robusta de la varianz

IRR: Incident Risk Ratio

RR: Riesgo Relativo

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis

PRISMA P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

MOOSE: Meta-analysis of Observational Studies in Epidemiology

PROSPERO: International prospective register of systematic reviews, University of York (U.K.)

SCCS: self-controlled case series

6.2. Definiciones

Literatura gris: se define como los documentos que no se difunden por los métodos de comunicación ordinarios y que puede conllevar problemas de acceso. Tal es el caso de tesis doctorales, trabajos de grado, actas de congresos, informes de investigación, memorias, proyectos, patentes, normas, traducciones científicas, documentos de sociedades científicas, boletines, cuadernos de trabajo, informes técnicos, programas de computación, autobiografías, etc. Recibe también el nombre de literatura no convencional, invisible, menor o informal.

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