UNIVERSITAT AUTÒNOMA DE BARCELONA

FACULTAD DE MEDICINA

DEPARTAMENTO DE PEDIATRÍA, DE OBSTETRICIA Y GINECOLOGÍA, Y DE MEDICINA PREVENTIVA

Evidencias en nutrición infantil: Revisiones sistemáticas y Evaluación de Guías de práctica clínica

Mario Delgado Noguera

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Memoria presentada por Mario Delgado Noguera para aspirar al grado de Doctor en Medicina por la Universitat Autònoma de Barcelona y realizada bajo la dirección del Dr. Xavier Bonfill Cosp.

Certificación

El doctor Xavier Bonfill Cosp, profesor asociado de Medicina Preventiva y Salud Pública en la Facultad de Medicina de la Universitat Autònoma de Barcelona,

CERTIFICA

Que la tesis doctoral presentada por Mario Delgado Noguera, con el título "Evidencias en nutrición infantil: revisiones sistemáticas y evaluación de Guías de Práctica Clínica" ha sido realizada bajo mi dirección.

Y para que conste a los efectos oportunos firma el presente certificado el 12 de diciembre de 2010.

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Resumen

Antecedentes: La nutrición materna e infantil se ha descrito como uno de los principales factores que influyen en el crecimiento y desarrollo infantiles. Tanto los países desarrollados como los que están en desarrollo presentan cambios en el estilo de vida que comprometen la nutrición y están en la llamada transición nutricional. Esta transición se asocia con mayor morbi-mortalidad por causas cardiovasculares, diabetes tipo II y ciertos tipos de cáncer. Por consiguiente, existe una necesidad global de prevención de estas enfermedades crónicas desde la infancia por medio de una nutrición adecuada y, así mismo, se requiere tener evidencias sólidas para las decisiones informadas de los clínicos y del personal que toma las decisiones en el área de la nutrición infantil. Desde esta perspectiva, el presente trabajo tiene como objetivo revisar tres temas de la nutrición materna e infantil con la metodología de la Medicina Basada en la Evidencia

Metodología: Se llevaron a cabo dos revisiones sistemáticas que se publicaron en revistas internacionales indexadas: la primera, sobre la efectividad de la suplementación de la madre lactante con LCPUFA (*Long Chain Polyunsaturated Fatty Acids*) en el crecimiento y neurodesarrollo de sus hijos; la segunda, una evaluación de la calidad de las guías sobre prevención y tratamiento de la obesidad infantil por medio del instrumento AGREE (*Appraisal of Guidelines Research and Evaluation*). En la misma línea de investigación, se ha realizado una revisión sistemática que actualmente está en proceso editorial sobre la efectividad de las intervenciones en el ámbito escolar para incrementar el consumo de frutas y verduras. Tanto la primera como la tercera revisiones sistemáticas realizaron un análisis cuantitativo o metanálisis.

Resultados: En la primera revisión sobre la eficacia de la suplementación con LCPUFA a las madres lactantes en el crecimiento y neurodesarrollo de sus hijos se identificaron seis estudios de calidad moderada, pero no se encontró un efecto consistente de la suplementación en los distintos estudios. Respecto

a la evaluación de las guías sobre prevención y tratamiento de la obesidad infantil, se identificaron 23 guías que cumplían con los estándares metodológicos, recomendándose sólo la utilización de seis de mayor calidad. En relación a la revisión de las intervenciones a nivel escolar para promocionar el consumo de frutas y verduras, se observó que las intervenciones realizadas con ordenador fueron efectivas, si bien las intervenciones multicomponente estuvieron cerca del nivel de significancia.

Conclusión: La evidencia de un efecto beneficioso de la suplementación con LCPUFA a madres lactantes en el crecimiento y desarrollo de sus hijos es escasa y por lo tanto, no se recomienda. Futuros estudios deben contar con mediciones más uniformes, con plazos más largos y que evalúen los efectos secundarios de esta suplementación. La calidad de las GPC sobre la prevención y tratamiento de la obesidad infantiles no es suficientemente adecuada y por ello es necesario mejorar su calidad y elaborarse en base al instrumento AGREE. La revisión sobre la eficacia en el consumo de frutas y verduras mostró la efectividad de las intervenciones llevadas a cabo con ordenadores. También se encontraron limitaciones en algunos aspectos metodológicos que deben mejorarse en futuros estudios.

Abstract

Background: Maternal and infant nutrition has been reported as one of the main factors influencing children's growth and development. Both developed and developing countries show changes in lifestyle that jeopardise nutrition. This situation is called nutrition transition and it is associated with increased morbidity and mortality from cardiovascular causes, type II diabetes and certain types of cancer. Consequently, there is a global need to prevent these chronic diseases since childhood by means of an appropriate nutrition. In addition, solid evidence-based research is now required to provide a sound basis for informed decisions of doctors and policymakers working on child nutrition area. In this perspective, the aim of this work is to review three maternal and child nutrition issues with evidence-based methodology.

Methodology: We conducted two systematic reviews that were published in international journals. The first one was on the effectiveness of supplementation with Long Chain Polyunsaturated Fatty Acids (LCPUFA) to breastfeeding mothers for improving child growth and development. The second review was a quality assessment of clinical practice guidelines (CPGs) on the prevention and treatment of childhood obesity using the AGREE (Appraisal of Guidelines Research and Evaluation) instrument. In the same line of research, we conducted another systematic review (currently in editorial process) on the effectiveness of school-based interventions to increase consumption of fruits and vegetables. Both the first and the third systematic reviews provided a meta-analysis.

Results: In the first review of the effectiveness of LCPUFA supplementation to breastfeeding mothers for the growth and neurodevelopment of children, we identified six studies of moderate quality but no consistent effect of supplementation among the studies was observed. Regarding the evaluation of CPGs on the prevention and treatment of childhood obesity, we identified 23 CPGs that met the methodological standards but we only recommended the use of six of higher quality ones. In relation with the review of school-based interventions to promote consumption of fruits and vegetables, we found that

computer-based interventions were effective and multicomponent interventions were near the level of significance.

Conclusion: The evidence of a beneficial effect of LCPUFA supplementation to breastfeeding mothers for the growth and development of their children is limited and therefore, not recommended. Future studies should have more uniform measurements, should be of longer duration and should also assess adverse effects of supplementation. The quality of CPGs on the prevention and treatment of obesity in children is not adequate enough and it is necessary to improve it and to develop CPGs in accordance with the AGREE instrument. The review on the effectiveness of school-based interventions in consumption of fruits and vegetables showed the effectiveness of computer-based interventions. We also found some methodological limitations that need to be improved in future studies.

INTRODUCCIÓN

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Es creciente la evidencia de que las condiciones nutricionales en las primeras etapas vitales de los humanos influencian la salud en la etapa del adulto (Barker 2004). Entre las enfermedades crónicas no trasmisibles que tienen su origen en la infancia destacan el sobrepeso y la obesidad, las enfermedades cardiovasculares, ciertos tipos de cáncer, y la diabetes (WHO 2003). Un 60% de todas las muertes en el mundo se deben a estas enfermedades crónicas, no-transmisibles. Los factores de riesgo comunes a todas ellas son el tabaquismo, poca actividad física y una alimentación poco saludable (WHO 2003).

Desde la gestación y lactancia en los humanos, la adecuada nutrición materna es indispensable para evitar desenlaces adversos. Más tarde, al igual que en los adultos, la nutrición infantil es el factor ambiental más relevante que interactúa con la predisposición genética para el desarrollo del síndrome metabólico y, en consecuencia, del riesgo de enfermedad cardiovascular. Por lo tanto, en la vida intrauterina y en la infancia empiezan a tomar importancia tanto los factores protectores como los deletéreos para el desarrollo de enfermedades crónicas futuras. Por ejemplo, la lactancia materna, al contrario de la artificial, reduce el riesgo de enfermedades cardiovasculares (Singhal 2009). Es así como en estudios tanto observacionales como experimentales en recién nacidos pretérminos se demuestra que la lactancia materna reduce el riesgo cardiovascular al actuar en los principales componentes del síndrome metabólico (Singhal 2009). La aceleración postnatal del crecimiento como consecuencia de la sobrenutrición se asocia a disfunción endotelial, hipertensión arterial y mayor adiposidad. Existe la hipótesis de que dicha aceleración es producida por la sobrealimentación con lactancia artificial (Singhal 2009). Tanto los estudios en necropsias como mediciones ecográficas de la función vascular proporcionan pruebas del desarrollo de ateroesclerosis subclínica en niños pequeños y estas alteraciones vasculares se correlacionan con factores de riesgo cardiovascular más convencionales en la infancia (Berenson 1998).

Al mismo tiempo que sobre el anterior aspecto crece la evidencia, ésta es insuficiente y no consistente en el efecto que tienen en el desarrollo del niño las suplementaciones que ingieren las madres gestantes y las que lactan con ácidos grasos polinsaturados de cadena larga (*Long chain polyunsaturated Fatty Acids, LCPUFA*) (Jensen 2006). Se ha comprobado que dado que la formación de los LCPUFA a partir de Ácidos Grasos Esenciales en el inicio de la vida es limitada, los lactantes dependen del suministro exógeno de LCPUFA en la leche materna o en las leches artificiales suplementadas. Los LCPUFA son componentes estructurales de todos los tejidos y por lo tanto necesarios para el desarrollo y la salud humanos. Son elementos claves para la síntesis de la membrana celular y sus receptores y para la función de las organelas citoplasmáticas. Estos ácidos grasos se acumulan principalmente en el cerebro y la retina en el último trimestre de la gestación y en los primeros meses de vida. Si la dieta durante el inicio de la vida es deficiente en LCPUFA, se afecta el desarrollo neural estructural y funcional (Koletzco 2008). Sin embargo, a pesar de que la evidencia de que la efectividad de esta suplementación aun no es concluyente, proliferan los suplementos de LCPUFA de venta libre en muchos países (Jensen 2006).

En las etapas posteriores -la edad escolar y la adolescencia- los niños por lo general no se alimentan de manera adecuada en lo referente al frecuente y excesivo consumo de comida rápida y al déficit diario de frutas y verduras (Pomerlau 2006). En el Informe sobre la Salud en el Mundo 2002 de la Organización Mundial de la Salud (OMS) se calculó que la ingesta de escasa cantidad de frutas y verduras causa un 19% de los casos de cáncer gastrointestinal y un 31% de los casos de cardiopatía isquémica, produciendo 2,7 millones de muertes anuales en todo el mundo (el 5% del total) (WHO 2002). Estas cifras son preocupantes dadas las crecientes evidencias científicas que demuestran los efectos benéficos de las frutas y verduras para la salud y la prevención de enfermedades crónicas, incluyendo la de las deficiencias en micronutrientes (WHO 2002). Los factores de riesgo para dichas enfermedades provenientes de los estilos de vida se adoptan en la infancia. Las pautas de la alimentación como la adecuada ingesta de frutas y

verduras se desarrollan tempranamente y dejan su huella en la edad adulta (Kelder 1994, Lytle 2000).

Varias regiones del mundo en desarrollo están presentando una rápida transición demográfica y epidemiológica. En los países que experimentan estos cambios la dieta materno-infantil también se modifica. Los patrones de consumo tradicionales se han inclinado globalmente hacia el mayor consumo y capacidad de compra de alimentos de origen animal, alimentos con alto contenido en grasas principalmente hidrogenadas y aquellos que son procesados industrialmente. Es la llamada “Transición nutricional” (Uauy 2002, Popkin 2004, Popkin 2006). La comunicación y la industria alimenticia tienden a generar patrones similares de consumo y presionan por acceder y consumir en exceso comidas rápidas. Por ello, si el cambio en el patrón dietario se acompaña de sedentarismo y poca actividad física se potencia el exceso de tejido adiposo. Los datos recientes indican que hay una tendencia a que los hábitos de comportamiento poco saludables y las enfermedades no transmisibles conexas se concentran en las comunidades más pobres y contribuyen a las desigualdades sociales y económicas. El 66% de las defunciones atribuidas a las enfermedades no transmisibles se producen en los países en desarrollo, donde las personas afectadas son por término medio más jóvenes que en los países desarrollados (Uauy 2002).

En consecuencia, la inadecuada alimentación de los niños ha producido un incremento del sobrepeso y la obesidad a nivel mundial tanto en los países desarrollados como en los que están en vías de desarrollo (Wang 2006). La OMS define la obesidad y el sobrepeso como una acumulación anormal y excesiva de grasa que puede ser perjudicial para la salud y que se manifiesta por un exceso de peso y volumen corporales (WHO 2006). Este organismo considera la obesidad como la «epidemia del siglo XXI» por las dimensiones que ha adquirido a lo largo de las últimas décadas y por su impacto sobre la morbimortalidad, la calidad de vida y el gasto sanitario (WHO 2003). Además, el sobrepeso y la obesidad infantiles tienen una tendencia a persistir en la vida adulta (Guía de práctica clínica sobre la prevención y el tratamiento de la obesidad infantojuvenil 2009). La obesidad es considerada en sí misma como

una enfermedad crónica, pero también como un factor de riesgo para el desarrollo de otras enfermedades responsables de una elevada morbimortalidad en la edad adulta. Así, la obesidad infanto-juvenil se ha asociado con diabetes mellitus tipo 2, hipertensión arterial, dislipemias, cardiopatía isquémica, alteraciones osteoarticulares, insuficiencia venosa, accidentes cerebrovasculares, hiperuricemia y gota, apneas del sueño, insuficiencia respiratoria, trastornos psicológicos, esteatosis hepática, hernia de hiato y tumores malignos de diversa localización (colon, recto, próstata, ovarios, endometrio, mama y vesícula biliar). En la mujer, se ha asociado también con disfunción menstrual, síndrome de ovario poliquístico, infertilidad, aumento del riesgo perinatal e incontinencia urinaria (WHO 2003).

Por todo ello, existe una necesidad global de prevención de las enfermedades crónicas desde la infancia por medio de una nutrición adecuada (WHO 2002). En consecuencia, la nutrición del niño para evitar problemas en el desarrollo infantil y la prevención de los factores de riesgo se han constituido en una prioridad tanto en la clínica, mediante recomendaciones en las guías de práctica clínica (Gidding 2005, NICE 2006, Guía de práctica clínica sobre la prevención y el tratamiento de la obesidad infantojuvenil 2009), como en las políticas de sanidad pública, (Neira 2006). Ante la proliferación de publicaciones sobre el tema, los especialistas en nutrición humana y los profesionales de la salud requieren de una síntesis de la evidencia que guíe su trabajo, y de información de calidad en el diseño de programas para mejorar la nutrición materno-infantil.

En salud pública mejorar la nutrición desde la infancia se perfila como una estrategia potencial de prevención de las enfermedades crónicas y de hecho, ha sido adoptada y desarrollada por varios sistemas de salud (NICE 2006, Neira 2006). En este sentido, España impulsa, desde el año 2005, la Estrategia NAOS (Nutrición, Actividad física, prevención de la Obesidad y Salud), promovida por el Ministerio de Sanidad y Consumo dentro del Plan de Calidad. La Estrategia NAOS tiene como objetivo fomentar acciones de promoción de la alimentación saludable y de la práctica de actividad física en colaboración con

profesionales de la salud, municipios y comunidades autónomas, familias, los sectores educativo y empresarial (Neira 2005).

Por todo lo expuesto, es necesaria la revisión de la creciente evidencia científica para mejorar el balance de la alimentación de la madre y el niño y en la prevención desde la nutrición de las enfermedades crónicas del adulto. El empleo de la revisión de las investigaciones biomédicas en el ámbito nutricional infantil, cuando se elabora de manera sistemática y cuidadosa, permite guiar a los profesionales de la salud infantil en su práctica y a quienes toman decisiones sanitarias en políticas nutricionales.

Revisiones sistemáticas y guías de práctica clínica

Desde la década de 1980 se empezó a trabajar de manera más explícita para que tanto la Medicina como la práctica clínica estuvieran unidas a la evidencia. La amplia variabilidad en la práctica y el hecho de que muchas intervenciones no estaban apoyadas en información rigurosa llevó a un grupo de médicos de la Universidad de McMaster a generar un nuevo movimiento dentro de la enseñanza y práctica de la medicina, que denominaron Medicina Basada en la Evidencia (MBE) (Evidence-Based Medicine Working Group 1992, Djulbegovic 2009). Este movimiento plantea un método para la toma de decisiones en medicina y en los ambientes sanitarios consistente en la búsqueda y evaluación sistemáticas de información científica para que las decisiones en el campo sanitario sean eficientes, con mejores resultados, y menores costos y riesgos (Ruiz 2004).

Otro hecho relevante dentro del movimiento fue el desarrollo de herramientas que permiten la revisión sistemática de la bibliografía y la adopción de la evaluación crítica de la literatura científica como forma de graduar validez y su utilidad (Montori 2002). Si bien existe una variedad de definiciones de la MBE la formulada por Guyatt en el año 2000 establece que la MBE es: “la integración de la mejor evidencia obtenida de la investigación, con la experiencia clínica y los valores personales del paciente”. En esta definición se toma en cuenta el papel de la experiencia clínica y las necesidades del paciente (Montori 2002).

Este movimiento, que si bien se enfocaba inicialmente a las necesidades de información de los clínicos, se diseminó después hacia el campo de la salud pública. La pregunta que se formuló y que ha tratado de responderse fue: '¿qué intervenciones en salud pública son las que efectivamente funcionan?'. Teniendo en cuenta que existía una amplia variedad de intervenciones en salud pública en la literatura, se desarrollaron métodos y herramientas para las revisiones sistemáticas, principalmente de diseños experimentales (Mays 2005). Se ha propuesto el concepto de "Salud Pública Basada en la Evidencia", entendida como "el uso consciente, explícito y juicioso de la mejor evidencia en la toma de decisiones sobre la atención a comunidades y poblaciones en el campo de la protección de la salud, la prevención de la enfermedad y el mantenimiento y mejora de la salud" (Jenicek 1999).

Las revisiones sistemáticas son claves en la toma de decisiones clínicas y en la Salud Pública Basada en la Evidencia pues sintetizan de manera sistemática rigurosa y evalúan críticamente toda la información disponible sobre una determinado problema de salud y responden a una o múltiples preguntas, ya sean de intervenciones, terapéuticas, pronósticas o diagnósticas (Higgins 2008). Las revisiones sistemáticas se consideran actualmente como la mejor fuente de información disponible para la toma de decisiones y, dentro de la pirámide jerárquica de los diseños de estudios, se sitúan en lo más alto por ser la fuente más fiable. Se han definido como una revisión de una pregunta formulada de manera estructurada que usa métodos sistemáticos y explícitos para identificar seleccionar y evaluar críticamente investigación relevante y analizar los estudios incluidos en esa revisión (Higgins 2008). Si bien en clínica son los ensayos clínicos controlados la base principal de las revisiones sistemáticas, otros diseños pueden ser empleados en la evaluación de las actividades e intervenciones complejas en salud pública y promoción de la salud; este aspecto es el que se ha llamado "Evidencia en salud pública" (Jackson 2004, López 2008).

De forma paralela, desde hace poco más de dos décadas, algunos países han empezado a utilizar las guías de práctica clínica (GPC) con el objetivo de

mejorar la calidad de la asistencia sanitaria. Las GPC se definen como el conjunto de recomendaciones desarrolladas de manera sistemática con el objetivo de guiar tanto a los profesionales como a los pacientes en la toma de decisiones sobre qué intervenciones sanitarias son más adecuadas en el abordaje de una condición clínica específica, en circunstancias sanitarias concretas (Field 1990). Las GPC tienen como objetivo ayudar a los profesionales a asimilar, evaluar e implantar la cada vez mayor cantidad de evidencia científica disponible y las opiniones basadas en la mejor práctica clínica (Bonfill 2003). El propósito de formular recomendaciones explícitas es influir en la práctica clínica, por lo que éstas han de tener validez tanto interna como externa.

La proliferación actual de las GPC se debe, entre otras causas, a una mayor conciencia de la variabilidad de la práctica clínica, la existencia de tratamientos más eficaces, la mayor facilidad de acceso a la información biomédica por los profesionales y pacientes y a la necesidad de racionalizar los recursos en los sistemas de salud. En la estrategia de aumentar la transparencia en la provisión de servicios sanitarios, la formulación y las propuestas de la MBE han supuesto un estímulo y a la vez un apoyo metodológico para que al hablar de GPC se entienda, implícitamente, que se trata de que estén basadas en la evidencia científica (Bonfill 2003).

Las GPC se han consolidado como herramientas populares entre los clínicos pues abordan problemas de salud de forma global y amplia, sin centrarse únicamente en una intervención o método diagnóstico concreto, y por otra parte, integran grandes volúmenes de evidencia en un solo documento (Alonso 2007). Asimismo, las guías al llevar a cabo una revisión exhaustiva y estructurada de la literatura disponible sobre múltiples aspectos de un tema concreto, permiten la detección de lagunas de información sobre las que no existen revisiones sistemáticas previas o sobre las cuales, simplemente, no se dispone de la información o investigación necesaria para la toma de decisiones. Siempre que sea posible, las GPC se deben basar en revisiones sistemáticas de la literatura, pues éstas son las mejores herramientas para identificar y sintetizar la evidencia de la efectividad de las intervenciones (Alonso 2007). Sin

embargo el potencial de las guías para integrar información y lograr el mejor cuidado de los pacientes depende en gran parte del rigor de su elaboración y de un procedimiento de diseminación e implantación rigurosos (Wilson 1995). En la actualidad existe la necesidad de introducir y mejorar la metodología para desarrollar, implantar y evaluar GPC basadas en la evidencia (AGREE 2003).

Por lo tanto, si se tiene en cuenta que el principal producto de la atención sanitaria son las decisiones clínicas (Muir Gray 2003), el desarrollo de herramientas de síntesis crítica de la evidencia científica -como son las revisiones sistemáticas y las GPC- ha permitido la evaluación en un tiempo más razonable la creciente cantidad de información científica disponible en el campo de la clínica y de la salud pública y contribuir a decisiones clínicas mejor informadas.

Justificación de la propuesta

Actualmente se promocionan los suplementos con LCPUFA (*Long chain polyunsaturated Fatty Acids*) para varias condiciones clínicas. Entre ellas para lograr, a través de la lactancia materna, un desarrollo adecuado del bebé en los primeros meses de vida, periodo especialmente crítico pues estos ácidos grasos son esenciales e indispensables para la formación de estructuras neurales, principalmente la retina y el cerebro. En consecuencia, se han efectuado diversos estudios, con el fin de evaluar el efecto de la suplementación de LCPUFA sobre el desarrollo principalmente el psicomotor y el visual de los infantes. Los resultados de estos estudios no son consistentes y no han permitido determinar la conveniencia de esta suplementación para las madres que están lactando. Algunos estudios muestran efectos positivos y otros no detectan modificaciones (Koletzco 2008).

Los LCPUFA se pueden adquirir en distintas concentraciones sin receta en diversas partes del mundo. Una buena proporción de tiendas de suplementos las venden libremente y variados sitios web las promocionan (Jensen 2006) por lo tanto las madres que lactan preguntarán por la necesidad de esta suplementación y los clínicos tendrán que darles una adecuada respuesta. Los

expertos recomiendan una suplementación regular de LCPUFA durante la lactancia en madres de niños menores de 6 meses (Koletzco 2008) pero esta recomendación reciente se basa en consenso y no hay revisiones sistemáticas que apoyen sus conclusiones en una síntesis cuantitativa.

Con el aumento global de la prevalencia del sobrepeso y la obesidad infantiles quienes deciden de políticas de prevención y los clínicos requieren de herramientas donde existan recomendaciones fiables para el abordaje de esta enfermedad emergente. Por lo tanto, es necesario encontrar y evaluar la calidad de las GPC sobre el tema, más aun cuando no existe aún en la literatura disponible dicha evaluación. Aunque la información científica es más accesible que nunca, el gran volumen de información, la falta de tiempo y la necesidad de graduar la relevancia de la evidencia científica hacen necesaria la evaluación de las variadas GPC sobre prevención y tratamiento del sobrepeso y la obesidad infantil. Se tendrán en consecuencia GPC recomendadas y servirán como herramientas dirigidas al apoyo de la toma de decisiones clínicas.

La unidad temática de esta tesis doctoral se justifica entonces por la ausencia de revisiones sistemáticas sobre la suplementación con LCPUFA, la necesidad de actualizar las revisiones sobre la promoción del consumo de frutas y verduras en los escolares y contar con GPC de mayor calidad de elaboración en el aspecto del sobrepeso y la obesidad infantiles. La tesis permitirá disponer de herramientas cada vez más fiables y rigurosas para la información de la toma de decisiones en estos temas concretos de la nutrición materno-infantil en la perspectiva de lograr un adecuado balance nutricional en la infancia y en la prevención de las enfermedades crónicas del adulto.

OBJETIVOS

Objetivos

- Evaluar, de forma sistemática, la eficacia y la seguridad de la suplementación con LCPUFA (*Long chain polyunsaturated Fatty Acids*) en madres lactantes en el desarrollo de sus hijos.

- Revisar y evaluar, de forma sistemática, las GPC (Guías de práctica Clínica) sobre la prevención y el tratamiento del sobrepeso y obesidad infantiles.

- Evaluar, de forma sistemática, la efectividad de las intervenciones en el ámbito escolar para incrementar el consumo de frutas y verduras.

Trabajos presentados para la realización de la tesis:

1. Revisión sistemática sobre la eficacia de la suplementación con LCPUFA (*Long chain polyunsaturated Fatty Acids*) a madres lactantes en el crecimiento y desarrollo de sus hijos.

Delgado-Noguera MF, Calvache JA, Bonfill Cosp X. Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development. Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD007901. DOI: 10.1002/14651858.CD007901.pub2

2. Evaluación de las Guías de Práctica clínica para la prevención y tratamiento de la obesidad infantiles

Delgado-Noguera M, Tort S, Bonfill X, Gich I, Alonso-Coello P. Quality assessment of clinical practice guidelines for the prevention and treatment of childhood overweight and obesity. Eur J Pediatr. 2009 Jul;168(7):789-99

Otros artículos incluidos en los anexos

Anexo I: Efectividad de las intervenciones en el ámbito escolar para incrementar el consumo de frutas y verduras

- School-based interventions for promoting consumption on fruits and vegetables in primary school: a systematic review and metanalysis. (enviado a Preventive Medicine)

Anexo II: Otros

- Delgado M ¿Son útiles como textos las Guías de práctica Clínica? Rev Fac Cienc Salud. Univ Cauca. 2009; 11(3):53-56.

- Alonso-Coello P, Delgado-Noguera M, Tort S, Gich I, Bonfill X. Quality of guidelines on obesity in children is worrying. BMJ. 2008 Nov 11;337:a2474. doi: 10.1136/bmj.a2474. PubMed PMID: 19001488.

- Balcells E, Delgado-Noguera M, Pardo-Lozano R, Roig-González T, Renom A, González-Zobl G, Muñoz-Ortego J, Valiente-Hernández S,

Pou-Chaubron M, Schröder H. Soft drinks consumption, diet quality and BMI in a Mediterranean population. Public Health Nutr. 2010 Oct 19:1-7. [Epub ahead of print] PubMed PMID: 20955643

METODOLOGÍA

1. Revisión sistemática sobre los efectos en sus hijos de la suplementación con LCPUFA (*Long chain polyunsaturated Fatty Acids*) a madres lactantes

Estrategia de búsqueda

Para la realización de la revisión sistemática se llevó a cabo una búsqueda en el *Cochrane Pregnancy and Childbirth Group's Trials Register* (PCGBRT), MEDLINE, CENTRAL, CINAHL, EMBASE, GOOGLE SCHOOLAR y LILACS, limitando las mismas a los ensayos controlados aleatorizados y cuasi experimentales.

Dos revisores comprobaron las listas de referencias de todos los artículos recuperados a texto completo y a partir de revisiones y guías de práctica clínica identificados se buscaron potenciales estudios adicionales. Se buscaron ensayos adicionales por medio de correo electrónico con autores de los estudios encontrados.

Criterios de elegibilidad

Para la selección de estudios se tuvieron en cuenta todos los ensayos clínicos aleatorizados (ECA) o ensayos cuasialeatorios, con madres que estuvieran lactando, comparando la suplementación con LCPUFA con placebo, y que tuvieran como variables de resultado el desarrollo de su hijo: neurodesarrollo medido por distintas escalas (ejemplo: las escalas de Bayley o Gessell), escalas para el desarrollo motor (*Infant Planning Test*), Agudeza visual del bebé medido por diversas escalas (*Teller Acuity Card, Visual evoked potential* (VEP), *SWEEP-VEP*), crecimiento físico del niño en peso, talla y circunferencia cefálica, seguridad de la suplementación con LCPUFA, y satisfacción de la madre con la suplementación. Como criterio de exclusión se consideraron aquellos ECA que tuvieran como variable resultado mediciones bioquímicas. No se limitó la inclusión de los estudios por el idioma.

Extracción de datos

Dos revisores evaluaron de manera independiente los estudios para su inclusión, recuperamos los estudios relevantes, extrajimos la información necesaria sobre la población, intervención, variables de resultado señaladas, y aspectos metodológicos de los estudios incluidos. En ambas fases (recuperación y evaluación) los desacuerdos se resolvieron por consenso entre los revisores, y en caso de persistir el desacuerdo se consultó al tercer autor.

Evaluación de la validez interna

Se recogió la información metodológica necesaria para la evaluación de la validez interna (Higgins 2008) en los siguientes ítems: existencia y método de generación de la secuencia de aleatorización, método de ocultamiento de la misma, cegamiento de los responsables del seguimiento de los pacientes, evaluadores de los eventos (variables de resultado); número y razones para las pérdidas (*lost to follow-up*). La evaluación del riesgo total de sesgo se llevó a cabo en una tabla resumen de los resultados por medio del sistema GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) (Guyatt 2005).

Análisis cuantitativo de los datos

Los resultados se presentaron como la diferencia estandarizada de medias en 5 áreas del neurodesarrollo: atención, desarrollo del lenguaje, habilidad para resolver problemas, desarrollo psicomotor y desarrollo motor, en la agudeza visual y en mediciones del crecimiento de la talla, en el peso y en el perímetro cefálico. Los estudios variaron en la duración del seguimiento de tal manera que se establecieron evaluaciones de los resultados en tres periodos: hasta los 12 meses, de 12 a 24 meses y después de los 24 meses de vida del niño. Si dentro de estas categorías se encontraban estudios y si la heterogeneidad no era importante ($I^2 > 50\%$), se combinaban en metanálisis. Se estableció este estimador, I^2, que representa la proporción total de la variación entre los estudios atribuible a su heterogeneidad y no al propio azar (Higgins 2008). Se

hizo análisis de sensibilidad para analizar la variabilidad en la estimación global del efecto eliminando los ensayos clínicos con alto riesgo de sesgo.

Los análisis se llevaron a cabo siguiendo el principio de intención de tratar, incluyendo en el denominador a los pacientes en el brazo del estudio al que fueron aleatorizados. Se utilizó el programa Review Manager 5.0 (The Cochrane Collaboration, 2008) para analizar los datos de cada resultado utilizando el modelo de efectos aleatorios (Higgins 2008). Todos los estimadores globales fueron calculados con intervalos de confianza al 95%.

2. Evaluación de las Guías de práctica Clínica (GPC) sobre prevención y tratamiento del sobrepeso y la obesidad infantiles.

Identificación de las Guías

Se identificaron GPC pertinentes a la prevención y tratamiento del sobrepeso y la obesidad infantiles desde enero de 1998 hasta agosto de 2007. Se restringió la búsqueda a los idiomas inglés, francés y castellano. La estrategia para buscar en los metabuscadores como TRIP Database (*Turning Research into Practice*), y en los organismos compiladores o *Clearinghouses* fue emplear la palabra "*obesity*" u "*overweight*" de tal manera que la búsqueda fuera inicialmente sensible. Con el objetivo de no dejar pasar por alto alguna GPC también se buscó en los sitios elaboradores donde la búsqueda se especificó adicionando a "*obesity*" las palabras "*childhood*", "*children*", "*adolescen*t".

Para MEDLINE (a través de PubMed), la búsqueda se basó en un algoritmo que combinó los principales términos relacionados con el tema de la GPC, junto con un filtro para identificar este tipo de documentos: (*obesity AND Practice Guideline[pt] OR Guideline[pt] OR guideline*[ti] OR consensus[ti]*), con los límites: "*published in the last 5 years, only items with abstracts, Humans, Practice Guideline, English, French, Spanish, Systematic Reviews, Preschool*

Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years). Además, en *Querys* se buscó con la estrategia (*obesity children*) *AND systematic(sb*).

Selección de las Guías

Se consideraron para su inclusión los documentos en los que existieran recomendaciones para la práctica clínica para niños y adolescentes. Se excluyeron publicaciones secundarias a las GPC, revisiones sistemáticas, revisiones que fueran hechas por un solo autor y documentos de evaluación de tecnologías. No se descartaron los documentos donde coexistieran recomendaciones para niños y adultos y donde las recomendaciones se hicieran sobre políticas comunitarias, servicios de salud o de salud pública.

Evaluación de las Guías

Las guías encontradas se evaluaron guiándose en los dominios señalados por el instrumento AGREE (*Appraisal of Guidelines Research and Evaluation*) (AGREE 2003) que presenta un marco de referencia sistemático para el análisis de los componentes que establecen la calidad, la elaboración y la documentación del proceso para desarrollar una guía. Las seis áreas de calidad que mide el instrumento AGREE son: (1) alcance y objetivo, con 3 ítems, (2) participación de los implicados, con 4 ítems, (3) rigor en la elaboración, con 7 ítems, (4) claridad y presentación, con 4 ítems, (5) aplicabilidad, con 3 ítems, y (6) independencia editorial, con 2 ítems. Cada ítem se presenta en una escala Likert de cuatro puntos donde la puntuación 4 significa estar fuertemente de acuerdo y la puntuación 1 estar muy en desacuerdo. Este es un instrumento que ha sido validado internacionalmente y ha sido adoptado por organizaciones de investigación, gestión sanitaria y agencias de evaluación de tecnologías sanitarias (Oxman 2006, AGREE 2003). Cada guía fue calificada de manera independiente por tres evaluadores. Las puntuaciones de los distintos dominios se calcularon sumando todos los puntos de los ítems individuales de un dominio y estandarizando el total según la siguiente fórmula: (puntaje obtenido - mínimo puntaje posible) / máximo puntaje

posible - mínimo puntaje posible). El máximo puntaje posible para cada dominio sería el número de preguntas multiplicado por el número de calificaciones de 4 por los revisores y el mínimo puntaje posible sería el número de preguntas multiplicado por el número de calificaciones de 1 por los revisores. AGREE estipula que la guía se califique de acuerdo a estos puntajes como muy recomendada, recomendada con condiciones o modificaciones, podría no recomendarse o ser no-recomendada.

Análisis

Llevamos a cabo un análisis descriptivo de cada dominio. El promedio de 50% se determinó como punto de corte para establecer la proporción de GPC que estaban sobre o bajo ese límite de referencia. Se calculó el Coeficiente de Correlación Intraclase (CCI) con el 95% de confianza como un indicador global del grado de acuerdo entre los tres revisores. El CCI se ha aceptado como la mejor medida para establecer el grado de acuerdo para datos continuos (Kramer 1981). Describe la proporción del grado de acuerdo que proviene de las diferencias de los evaluadores.

3. Revisión sistemática sobre las intervenciones en el ambiente escolar para incrementar el consumo de frutas y verduras.

Estrategia de búsqueda

Para la realización de esta revisión sistemática se llevó a cabo una búsqueda en MEDLINE, CENTRAL, CINAHL y EMBASE, limitando la misma a los ensayos controlados aleatorizados y no aleatorizados. Se incluyeron también ensayos en clúster, series de tiempo interrumpidas y estudios controlados antes-después. Los ensayos en clúster podían incluir estudios que compararan programas escolares versus no programa y podían ser diseños en clúster, es decir que emplean más las escuelas o los salones de clase que individuos como unidad de análisis.

Tres revisores comprobaron los resúmenes que produjo la estrategia de búsqueda y eligieron los artículos que podrían ser relevantes. Estos fueron recuperados a texto completo y a partir de ellos y las revisiones sobre el tema se revisaron las listas de referencias para identificar potenciales estudios adicionales.

Criterios de elegibilidad

Para la selección de estudios se tuvieron en cuenta todos los ECA o ensayos controlados aleatorizados o no, ensayos clínicos en clúster, series de tiempo interrumpidas y estudios controlados antes-después, que compararan intervenciones en escolares (5- >12 años) versus la no-intervención o un programa distinto. Las intervenciones podían ser cambios en el currículo de las escuelas, educación en salud, procedimientos por medio del Internet, telefonía o de multimedia, estrategias en las cafeterías escolares o en el ambiente escolar, iniciativas de escuelas amigables, programas de nutrición infantil o servicios de comidas a las escuelas e iniciativas de los gobiernos. Las intervenciones podían incluir a los padres o maestros (educadores) y/o cuidadores que promocionaran el consumo de frutas y/o verduras. Las variables de resultado fueron incremento en raciones/día, gramos/día u otra medida del consumo de frutas y/o verduras que proporcionaran los estudios. No se limitó la inclusión de los estudios por el idioma ni por países de procedencia.

Extracción de datos

Tres revisores evaluaron de manera independiente los estudios para su inclusión, y extrajimos la información necesaria sobre la población, intervención, variables de resultado señaladas, y aspectos metodológicos de los estudios incluidos. En ambas fases los desacuerdos se resolvieron por consenso entre los revisores. En caso de que los estudios no hubieran tomado en cuenta el efecto de la unidad de análisis en la población estudiada se corregía la muestra según la propuesta de Higgins (Higgins 2008).

Evaluación de la validez interna

Se recogió la información metodológica necesaria para la evaluación de la validez interna por medio de una herramienta desarrollada y validada por el proyecto "*The Effective Public Health Practice*" (Thomas 2004). Esta herramienta de evaluación consta de 6 criterios que evalúan: sesgo de selección, el ocultamiento de la asignación, manejo adecuado de los posibles confundentes, cegamiento, métodos de recolección de la información, y número y razones para las pérdidas durante el seguimiento (Ver apéndice 1). Por otra parte clasifica los estudios de intervención en ensayos controlados aleatorizados (*Randomysed controlled trials*) cuando la forma de aleatorización es explícita y en ensayos controlados (*Controled Clinical Trials*) cuando no lo es.

Para que un estudio fuese calificado en la calidad metodológica como "fuerte", 4 de los 6 criterios de la mencionada herramienta debían haber sido evaluados como fuertes y no haber tenido ninguna calificación de los criterios como débil. Si dos de ellos fueran calificados como "débiles", el estudio era evaluado como tal. Se tomaron en cuenta para la extracción de datos y los análisis los estudios que fueron calificados en la evaluación metodológica final como "fuertes" o "moderados". Las diferencias en la calificación se resolvieron por medio de la discusión.

Para la estimación del tamaño del efecto se tomó en cuenta los procedimientos planteados por Knai (Knai 2006): Diferencias en la ingesta de frutas y verduras entre los grupos (Intervenido y control) o Diferencias entre los grupos en el seguimiento.

Análisis cuantitativo de los datos

Los estudios que aleatorizaron unidades en clúster (escuelas o salones de clases), pero que no tomaron en cuenta ese procedimiento en el efecto para el análisis de los datos, se volvieron a analizar. Con el fin de evitar la sobreestimación del tamaño de la muestra, se utilizó el análisis propuesto por

Higgins (Higgins 2008). Para este objetivo, se redujo el tamaño de cada estudio en su “tamaño efectivo de la muestra” utilizando un coeficiente de correlación (CCI) de 0,02 como una estimación de la variabilidad relativa intragrupal y entre los grupos. El valor del CCI fue elegido porque se utilizó en el estudio de Baranowski 2003 y se extrapoló a otros estudios que no registraban ese valor. Se llevó a cabo un análisis de sensibilidad con un valor de CCI de 0,05, el valor normal máximo de la CCI para estos estudios, pero no hubo diferencias significativas en los efectos de las intervenciones.

Se hicieron distintas comparaciones por el tipo de intervención encontradas como patrón común en los estudios (Acceso libre a frutas y verduras por los escolares/ frutas y verduras subsidiadas para las escuelas), intervenciones con varios componentes, denominadas multicomponentes o complejas e intervenciones que promocionaban el consumo de frutas y verduras por medio de Internet o juegos electrónicos de mesa). Se llevó a cabo el análisis de subgrupos por tipo de diseño del estudio. La heterogeneidad se estimó mediante el estadístico I2. Se estableció que si se encontraba una alta heterogeneidad (I2> 70%), se realizaría una síntesis narrativa. En caso contrario, se estimarían los efectos combinados de las intervenciones por medio de metanálisis de efectos aleatorios en RevMan 5.0 para cada tipo de intervención, y también para cada subgrupo. Todos los estimadores globales fueron calculados con intervalos de confianza al 95%.

RESULTADOS

Revisión sistemática sobre la eficacia de la suplementación con LCPUFA (*Long chain polyunsaturated Fatty Acids*) a madres lactantes en el crecimiento y desarrollo de sus hijos.

Delgado-Noguera MF, Calvache JA, Bonfill Cosp X. Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development. Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD007901. DOI: 10.1002/14651858.CD007901.pub2

Factor de Impacto: 5.65 (2009)

Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development (Review)

Delgado-Noguera MF, Calvache JA, Bonfill Cosp X

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[Intervention Review]

Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development

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ABSTRACT

Background

Long chain polyunsaturated fatty acids (LCPUFA), especially docosahexaenoic acid (DHA), are the most abundant fatty acids in the brain and are necessary for growth and maturation of the brain and retina. LCPUFA are named "essential" because they cannot be synthesised efficiently by the human body and come from maternal diet. It remains controversial whether LCPUFA supplementation to breastfeeding mothers is beneficial for the development of their infants.

Objectives

To assess the effectiveness and safety of supplementation with LCPUFA in breastfeeding mothers in the cognitive and physical development of their infants as well as safety for the mother and infant.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (November 2009), CENTRAL (2009, Issue 2), PubMed (1966 to July 2009), EMBASE (1974 to June 2009), CINAHL (1984 to June 2009), LILACS (1982 to June 2009), Google Scholar (June 2009) and reference lists of published narrative and systematic reviews.

Selection criteria

Randomised controlled trials or cluster-randomised controlled trials evaluating the effects of LCPUFA supplementation on breastfeeding mothers and their infants.

Data collection and analysis

Two review authors independently assessed eligibility and trial quality and performed data extraction.

Main results

We included six randomised controlled trials involving 1280 women. We found no significant difference in children's neurodevelopment: language development (standardised mean difference (SMD) -0.14, 95% confidence interval (CI) -0.49 to 0.20; two trials, 349 participants); intelligence or problem-solving ability (two trials, 817 participants; SMD -0.22, 95% CI -0.23 to 0.66); psychomotor development (SMD 0.34, 95% CI -0.11 to 0.78; two trials, 279 participants); motor development (SMD 0.08, 95% CI -0.13 to 0.29; two trials, 349 participants); in child attention there was a significant difference (SMD 0.50, 95% CI 0.24 to 0.77; one study). For child visual acuity there was no significant difference (SMD -0.06, 95% CI -0.26 to 0.14; three trials, 401 participants). For growth, there were significant differences in length (MD -0.75 cm, 95% CI -1.38 to -0.12; two trials, 834 participants) and head circumference (MD 0.69 cm, 95% CI 0.35 to 1.02; one trial, 244 participants). One study reported a significant difference in infant allergy (risk ratio (RR) 0.12, 95% CI 0.02 to 0.95). We found no significant difference in one trial evaluating postpartum depression (SMD 0.15, 95% CI -0.11 to 0.41).

Authors' conclusions

Based on the limited evidence that we found, LCPUFA supplementation did not appear to improve children's neurodevelopment or visual acuity. In two studies, LCPUFA supplementation was associated with increased head circumference. Currently, there is insufficient evidence to support or refute the practice of giving LCPUFA supplementation to breastfeeding mothers in order to improve infant growth and development.

PLAIN LANGUAGE SUMMARY

Long chain polyunsaturated fatty acid supplements for mothers who breast feed

Long chain polyunsaturated fatty acids (LCPUFA) are abundant in the brain and are necessary for growth and maturation of a young infant's brain and the retina of the eye. These particular fatty acids include docosahexaenoic acid (DHA) and are said to be 'essential' because the human body is not efficient in producing them. This means that infants who are breastfeeding obtain the fatty acids from their mothers' diet, mainly from fish oil and ocean fish.

This review of six randomised clinical trials showed that supplementing a mother's diet with LCPUFA during the pregnancy and the first four months after birth did not improve the child's neurodevelopment in terms of problem solving ability or intelligence, psychomotor or motor development. In language development at 12 to 24 months and at five years in child attention, weak evidence was found (one study) favouring the supplementation. The age of the children at the last neurodevelopment assessment was seven years. A total of 1280 women from high-income countries were included in the six included trials but our individual analyses were based on fewer numbers of trials and women. The children's visual acuity was not clearly different at 12 months of age compared with children of the control groups of mothers who received supplements of olive, soybean or corn oils. More evidence is needed.

BACKGROUND

Growth of the fetus and small infants, and in particular of the brain, is exceptionally fast during the last trimester of pregnancy and the first year of life and depends on the quality of the environment around them as well as maternal nutrition (Grantham-McGregor 2007).

The World Health Organization recommends that children should be exclusively breastfed until six months of age and emphasises the importance of lactating women's nutrition. A deterioration in their nutritional status can produce a shortfall in some nutrients in breast milk and, therefore, in their offspring (Hoddinot 2007; Horta 2007). Breastfeeding has a demonstrated benefit on child development. Breast milk may help child development through its nutrients, especially through the essential fatty acids (Hoddinot 2007; Walker 2007).

Special emphasis has been placed on lipid fraction of breast milk which represents the main source of energy for children breastfeeding. Some of these lipids, long chain polyunsaturated fatty acids (LCPUFA), are named "essential" because they can not be synthesised efficiently by the human body and come from mater-

nal diet. Interest has focused on them because they are involved in the development of nervous system tissue (Jensen 2006; Tinoco 2007).

Lipids in breast milk are the main energy suppliers (40% to 55% of total energy intake) for an appropriate growth. LCPUFA are the most abundant fatty acids in the brain and are necessary for growth and maturation of the brain and retina (Koletzco 2008; Simmer 2008a). The most important ones are arachidonic acid (20:4 (n-6) (AA)) and particularly, docosahexaenoic acid (22:6 (n-3) (DHA)). AA is involved in several pathways of activation through the cell membrane receptors (Cell Signalling Pathway) and is a precursor of eicosanoids, products of remarkable physiological activity as prostaglandins and leukotrienes, in several key cellular processes (McCann 2005). DHA is the most abundant fatty acid in the brain and an important component of brain cell membranes and retina. Its known functions are neurogenesis, neurotransmission and protection against oxidative agents in the brain and retina (Fleith 2005; Innis 2007). They are accumulated in the brain tissue mainly during the second half of pregnancy and during the first two years of life (McCann 2005). In terms of safety, the current recommendation is consumption of one to two portions of sea fish per week, including fatty fish, which is a good source of LCPUFA. This intake of fatty fish rarely exceeds the tolerable intake of environmental contaminants (Koletzko 2007). A international consensus recommends that pregnant and lactating women should ingest a DHA intake of 200 mg per day (Koletzco 2008).

DHA and AA are not widely distributed in foods and are not present in vegetable oils and fats, but are present in the fat of certain sea fish. These fish are the primary, and almost exclusive, exogenous source. It is transferred during pregnancy through the placenta, and after birth through breast milk. Breast milk provides both AA and DHA. The level of AA is relatively constant, whereas the level of DHA is variable and depends on maternal dietary habits, culture and lifestyle (Agostoni 2005; Koletzco 2008). The concentration of DHA in maternal serum decreases significantly after childbirth and depends on maternal intake, so that a diet rich in DHA determines higher levels in breast milk (Jensen 2006; Tinoco 2007), in a dose-dependent relationship (Gibson 1997). DHA supplementation during lactation increases breast milk DHA content and is more effective in raising breast milk DHA content than supplementation limited to pregnancy only (Jensen 2006).

Experimental studies have used LCPUFA supplemented formula during the period of lactation in children, and measured results of their development in terms of visual acuity, language and psychomotor development. Two Cochrane reviews conclude that, based on the existing evidence, routine LCPUFA supplementation formula cannot be recommended in term infants (Simmer 2008a) and no clear long-term benefits are evident for preterm infants receiving formula supplemented with LCPUFA infants (Simmer 2008b). Observational studies have shown that breastfed infants have higher concentrations of DHA than those who are fed with formula (Innis 2007), while there were several observations on the improvement of neurodevelopment among infants who have been breastfed compared with those who have received formula (Agostoni 2005) containing DHA and AA. It has also been shown that a high concentration of DHA in breast milk is associated with a low prevalence of postpartum depression (Llorente 2003).

Therefore, researchers and clinicians have hypothesised that giving LCPUFA supplementation to lactating mothers may affect children's neurodevelopment, visual acuity and growth. Recent experimental studies have given LCPUFA supplementation to breastfeeding mothers of exclusively breastfed term newborns, but some of these studies included a limited number of individuals. In some, there were more than 20% losses to follow-up, therefore, the results are inconsistent and do not provide strong evidence (Jensen 2005; Lauritzen 2004; McCann 2005). Therefore, this systematic review aims to establish whether supplementary LCPUFA is beneficial for both lactating mothers and their infants.

OBJECTIVES

To assess the effectiveness and safety of supplementation with LCPUFA in breastfeeding mothers in the cognitive and physical development of their infants, as well as the safety for the mother and the infant.

METHODS

Criteria for considering studies for this review

Types of studies

All published and unpublished randomised controlled trials or cluster-randomised controlled trials evaluating the effects of LCPUFA supplementation on breastfeeding mothers and their infants during the postpartum period.
We excluded quasi-randomised trials.

Types of participants

Breastfeeding women receiving LCPUFA supplementation in the postpartum period.

Types of interventions

LCPUFA: AA and/or DHA supplementation to breastfeeding mothers compared with any control group (placebo, no supplementation).

Both groups should receive the same co-intervention, if any.
The following trials were not eligible for inclusion:

1. trials reported exclusively biochemical outcomes.

Types of outcome measures

Primary outcomes

Child neurodevelopment outcomes measured by different scales (e.g. Bayley scale, including the Mental Development Index (MDI) and Psychomotor Development Index (PDI); Gesell scale for gross motor development (Infant Planning Test); or as specified in the original trial reports).

Secondary outcomes

1. Child visual (acuity) development measures (Teller Acuity Card, Visual Evoked Potential (VEP), SWEEP-VEP visual acuity determination) or as specified in the original trial reports.
2. Child's physical growth: weight, length and head circumference in centimetres.
3. Safety of supplementation with LCPUFA to mothers and babies (considered as environmental contamination of supplementation).
4. Mothers' views about or satisfaction with their diets (as defined by trial authors).

Time to outcome assessment

We assessed study outcomes at short term (12 months), medium term (12 to 24 months) and long term (beyond 24 months).

Search methods for identification of studies

Electronic searches

We contacted theTrials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (November 2009).
The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.
Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.
In addition, we searched CENTRAL (2009, Issue 2), PubMed (1966 to July 2009), EMBASE (1974 to June 2009) and CINAHL (1984 to June 2009) using the search strategies detailed in Appendix 1, Appendix 2, Appendix 3 and Appendix 4.
We searched in LILACS (1982 to June 2009) (Appendix 5) and Google Scholar (June 2009) (Appendix 6).

Searching other resources

We searched reference lists of published narrative reviews or related papers. We also contacted authors to provide data.
We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors, Mario Delgado (MD) and Andrés Calvache (AC) assessed independently for inclusion all the potential studies identified as a results of the search. We resolved any disagreement through discussion or, if required, consulted a referee, Xavier Bonfill (XB).

Data extraction and management

We designed a standard form to extract data. For eligible studies, two review authors (MD, AC) extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third person (XB). We entered data into Review Manager software (RevMan 2008) and checked for accuracy.
When information regarding any of the above is unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors (MD, AC) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). We resolved any disagreement by discussion or by involving a referee (XB).

(1) Sequence generation (checking for possible selection bias)

For each included study we described the methods used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We classified the methods as:

- adequate (any truly random process, e.g. random number table; computer-generated random numbers);
- inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear (insufficient information about the sequence generation process to permit judgement).

(2) Allocation concealment (checking for possible selection bias)

For each included study, we described the method used to conceal the allocation sequence in sufficient detail and determined whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment.
We classified the methods as follows:

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

We described for each included study all the methods used, if any, to blind study participants and personnel from knowing which intervention the participants received. We also provided information on whether the intended blinding was effective. Where blinding was not possible, we assessed whether the lack of blinding was likely to have introduced bias. We assessed blinding separately for different outcomes or classes of outcomes.
We classified the methods as follows:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We described for each included study and for each outcome or class of outcomes the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. We obtained missing data from the authors whenever possible. We assessed methods as:

- adequate (less than 20% of missing data);
- inadequate (greater than 21% of missing data);
- unclear.

(5) Selective reporting bias

For each included study we described how we, as well as our findings, examined the possibility of selective outcome reporting bias. We classified the methods as:

- adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear (no details provided).

(6) Other sources of bias

We assessed whether each study was free of other problems that could put it at risk of bias:

- yes;
- no;
- Unclear.

(7) Overall risk of bias

We made explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings.

Measures of treatment effect

Dichotomous data

For dichotomous data (safety of supplementation with long chain polyunsaturated fatty acids to mothers and babies), we presented results as summary risk ratios with 95% confidence intervals.

Continuous data

For continuous data (child neurodevelopment scales, child visual acuity measures, child physical growth, rating of mother postpartum depression), we used the mean difference if outcomes were measured in the same way between trials. We used standardised mean difference to combine trials measuring the same outcome, but using different methods.

Unit of analysis issues

We included cluster-randomised trials in the analysis along with individually randomised trials. We adjusted their standard errors using the methods described in the *Handbook,* using an estimate of the intra cluster correlation co-efficient (ICC derived from the trial (if possible), or from another source. If ICCs from other sources were used, we have reported this and conducted sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we planed to synthesise the relevant information. We considered it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of the intervention and the choice of randomisation unit is considered to be unlikely.

We have also acknowledged heterogeneity in the randomisation unit and performed a separate meta-analysis.

Dealing with missing data

We noted the levels of attrition for included studies. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all the outcomes, as far as possible we carried out analysis on an intention-to-treat basis, i.e. we was attempt to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. When I^2 was greater than 50%, we conducted a random-effects analysis.

Assessment of reporting biases

Where we suspected reporting bias, we attempted to contact study authors asking them to provide missing outcome data. Where this is not possible, and the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results by a Sensitivity analysis.

Data synthesis

We carried out statistical analysis using Review Manager software (RevMan 2008). We used fixed-effect inverse variance meta-analysis for combining data where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. Where there is clinical or methodological heterogeneity between studies, sufficient to suggest that treatment effects may differ between trials, we used the random-effects analysis to perform the meta-analysis.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses for the primary outcome.

1. Term/preterm status.
2. Type of polyunsaturated fatty acids.
3. Mother's nutritional status at trial entry (adequate/inadequate).

Sensitivity analysis

We carried out sensitivity analysis to analyse variability of global effect estimation, in order to modify the incorporation of the clinical trials to analysis, according to its methodological quality (low bias risk versus moderate or high risk) and discussing why studies have a larger influence on the estimate.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Searches in the databases yielded 1151 references. The search of the Cochrane Pregnancy and Childbirth Group's Trials Register (PCGBRT, November 2009), CENTRAL (2009, Issue 2), PubMed (1966 to July 2009), EMBASE (1974 to June 2009), CINAHL (1984 to June 2009), LILACS (1982 to June 2009), Google Scholar (June 2009) and reference lists of published narrative and systematic reviews retrieved 65, 157, 379, 254, 78, 0 and 218 reports, respectively. We selected six studies from the search of the reference lists of trials and reviews. There were 1062 irrelevant references. From them we excluded 37 duplicates. After applying the inclusion and exclusion criteria, we excluded 36 studies and included six studies (24 reports).

Included studies

We identified six randomised studies (1280 women), assessing the clinical effects of fatty acid supplementation to lactating mothers on development and growth of their children. We did not find studies evaluating outcomes in preterm infants. All the included trials used a randomised clinical trial design and the studies came from high-income countries. We have provided full details of the six included studies in the Characteristics of included studies table. Lauritzen 2004 was conducted in Denmark and women were recruited from the Danish National Birth Cohort (Olsen 2001).

Jensen 2005 was developed in United States. Helland 2001 was developed in Norway, and Gibson 1997, Lucia 2007, and Furuhjelm 2009 were conducted in Australia, Germany, and Sweden, respectively.

All the studies were funded by governmental and private organisations. Market Biosciences provided the LCPUFA in the Australian and United States studies and BASF in the Danish studies. Peter Møller, Avd. Orkla ASA, and Aktieselskabet Freia Chocoladefabriks Medicinske Fond funded the Norway study. The supplements were donated by Nestle in Germany study. The Swedish study was financed by government funds and GlaxoSmithKline.

The 1280 women were healthy lactating mothers, without pregnancy complications, who were intending to breastfeed their children. Their children were born at term (37 to 43 weeks' gestation), they were healthy and without malformations, and were fed mainly by exclusive breastfeeding.

The experimental intervention used in the Lauritzen 2004 study consisted of 1.5 grams of LCPUFA, 800 mg of DHA+600 mg of eicosapentaenoic acid. Furuhjelm 2009 used 1.1 gr of DHA+1.6 gr eicosapentaenoic acid. Jensen 2005 and Lucia 2007 each used 200 mg of DHA. DHA at various concentrations (200 to 1300 gr) was used in Gibson 1997. Helland 2001 used 10 ml of cod liver oil.

Placebo consisted of olive oil in Lauritzen 2004; soybean oil and corn oil in Jensen 2005; only corn oil in Helland 2001; and soy oil in Furuhjelm 2009 and Lucia 2007. The nature of the placebo was not reported in Gibson 1997.

The intervention was initiated in pregnancy in Helland 2001, Lucia 2007 and Furuhjelm 2009 and continued during the breastfeeding period. In Lauritzen 2004, Jensen 2005 and Gibson 1997 the intervention was initiated postpartum and during the first four months after birth.

We identified no trials of supplementation of other fatty acids (alfa-linoleic or linolenic) being given to lactating mothers.

The outcomes assessed on the included trials were neurodevelopment and visual acuity; growth related to weight, length and head circumference. Infant blood pressure, infant allergy and maternal depression were also reported. Jensen 2005 did not provide data of anthropometric measurements.

We considered five areas of neurodevelopment to assess this primary outcome: language development (Jensen 2005; Lauritzen 2004); intelligence or problem solving ability (Helland 2001; Jensen 2005; Lauritzen 2004); psychomotor development (Gibson 1997; Jensen 2005), motor development (Jensen 2005; Lauritzen 2004) and child attention (Jensen 2005).

For the visual acuity outcome there were three short-term studies (Gibson 1997; Jensen 2005; Lauritzen 2004) but no data in relation to medium- and long-term outcomes.

For the child's physical growth outcome, there were three studies (Helland 2001; Lauritzen 2004; Lucia 2007) that reported weight, length and head circumference (short-, medium- and long-term data).

To assess the outcomes, different measurements were used: for language development; Jensen 2005 used CLAMS (Clinical Linguistic and Auditory Milestone Scale) and Lauritzen 2004 used the CDI scale (MacArthur Communicative Development Inventory-vocabulary production (number of words) at 24 months).

For the outcome Intelligence or Problem Solving ability, Helland 2001 used Kaufmann Assessment Battery for Children; Jensen 2005 used the Clinical Adaptative Test; and Lauritzen 2004 used the Infant Planning Test. For Psychomotor development, both Gibson 1997 and Jensen 2005 used the Bayley Scales of Infant Development. For motor development, Jensen 2005 used Gesell Gross Motor Scale and Lauritzen 2004 used the child's age of sitting without support. For evaluation of child attention, the Leíter international Performance Scale was used (Jensen 2005).

Visual acuity outcomes were measured in different ways: Gibson 1997 used the VEP and Sweep VEP. Lauritzen 2004 and Jensen 2005 used Teller Acuity Cards, Sweep VEP and VEP (For a detailed description of visual acuity-assessment methods see Simmer 2008a).

For measurements of growth in weight, length and head circumference, Helland 2001, Lauritzen 2004 and Lucia 2007 used scales in grams and centimetres, respectively.

We found no trials that reported outcomes about safety of supplementation. Jensen 2005 reported maternal depression and Furuhjelm 2009 reported infant allergy. For the outcome postpartum depression Jensen 2005 used self-rating measures. For assessment of allergia, Furuhjelm 2009 used the skin prick test, determination of IgE antibodies and clinical examination. These results were considered as secondary effects of the intervention under study, and added to secondary outcomes.

Excluded studies

We excluded 36 trials and created a Characteristics of excluded studies table, giving reasons for exclusion. We excluded trials because the study was not a clinical trial; the intervention was not a LCPUFA; the authors reported only biochemical data; or the reports were abstracts of unpublished randomised controlled trials.

Risk of bias in included studies

Based on *Cochrane Handbook for Systematic Reviews of Interventions* criteria, Furuhjelm 2009, Helland 2001, Jensen 2005, Lauritzen 2004 and Lucia 2007 were evaluated as presenting low risk of bias. The randomisation was performed with adequate sequence generation. the trials were blinded, and allocation concealment was carried out. Furuhjelm 2009, Helland 2001, Jensen 2005 and Lauritzen 2004, described withdrawals in different steps of follow-up. Follow-up rates ranged from 40% to 80%. There were no differential losses to follow-up between intervention and control groups. In Lucia 2007 the differential losses were unclear. Helland

2001 and Jensen 2005 did not report data on infant growth at the first year.

Gibson 1997 was evaluated as high risk of bias. Gibson 1997 had low power due to the small sample size, as well as 50% losses to follow-up.

We have included a summary of the risk of bias assessments for the included trials in the Characteristics of included studies table, in the methodological quality graph (Figure 1) and in the methodological quality summary (Figure 2).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

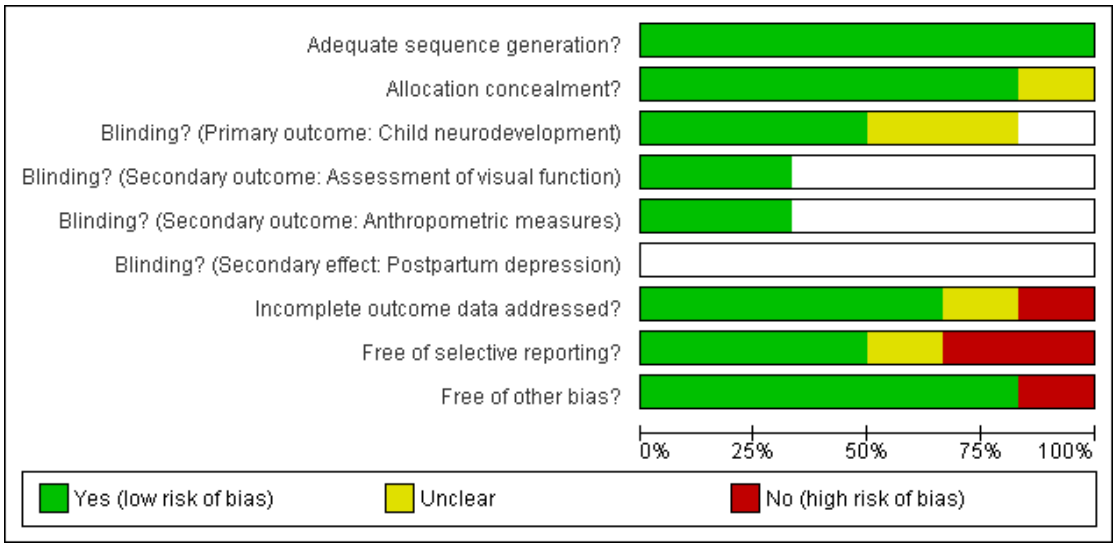
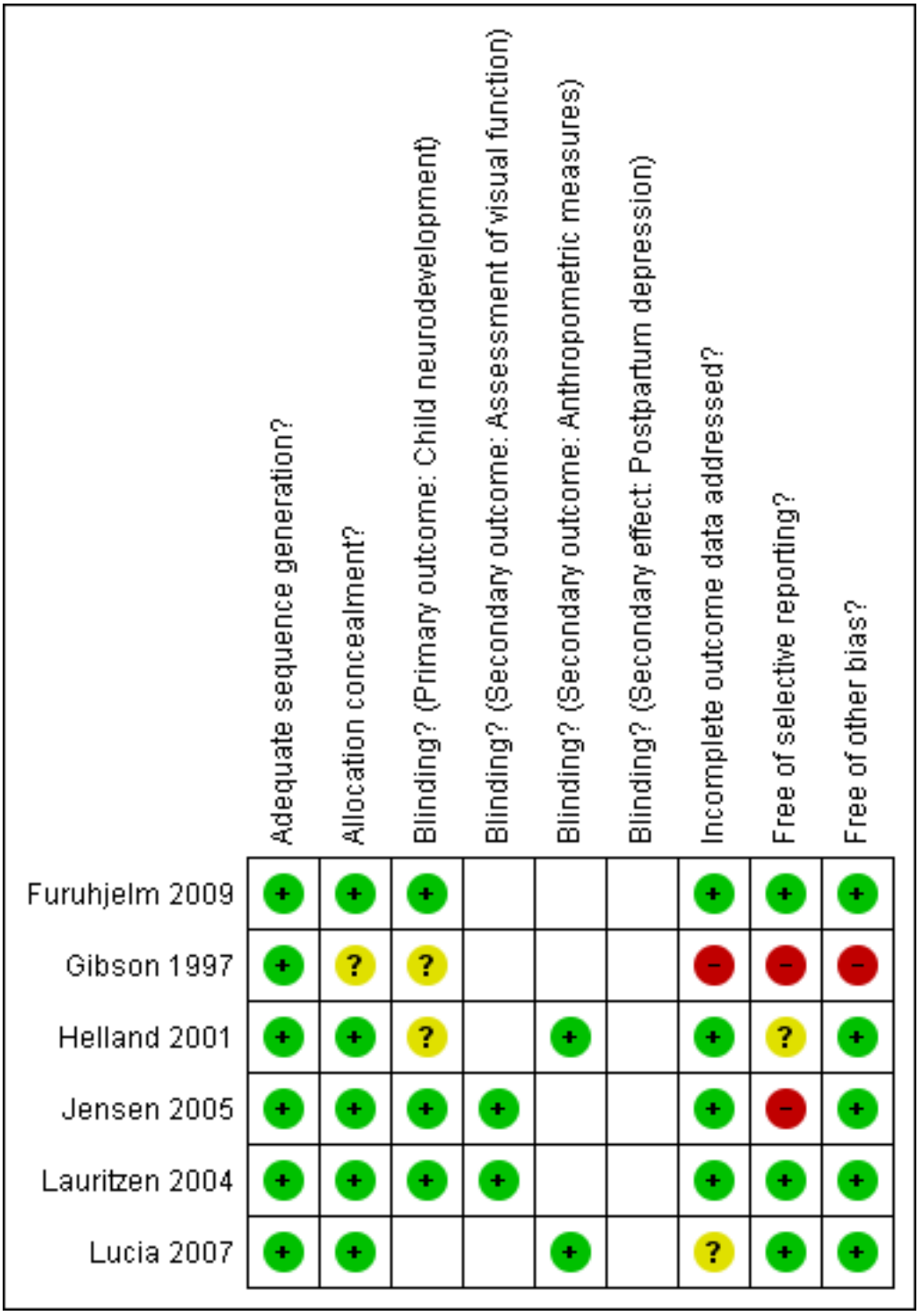


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Effects of interventions

1. Primary outcome - neurodevelopment

For this outcome we considered five areas of neurodevelopment: language development, intelligence or problem solving ability, psychomotor development, motor development and child attention.

For the pooled analysis of these studies, we performed a random-effects model meta-analysis and expressed the result as standardised mean difference (SMD), because different instruments were used to measure the neurodevelopment and the postpartum depression in studies.

Language development

(Analysis 1.1)

Up to 12 months (Subgroup 1.1.1)

Only one study with 227 participants (Jensen 2005) reported data for this outcome. No significant differences were found between LCPUFA supplementation and control groups (SMD -0.14, 95% confidence interval (CI) -0.40 to 0.12).

12 to 24 months (Subgroup 1.1.2)

One study with 122 participants (Lauritzen 2004) reported this outcome. Significant differences were found between LCPUFA supplementation and control group (SMD -0.41, 95% CI -0.77 to -0.05).

Beyond 24 months (Subgroup 1.1.3)

Two studies providing data from 349 participants (Jensen 2005; Lauritzen 2004) were included in the meta-analysis. No significant differences were found between LCPUFA supplementation and control groups (SMD -0.14, 95% CI -0.49 to 0.20). Heterogeneity between studies was not significant (Chi^2 =2.5, P = 0.11; I^2 = 60%).

Intelligence or problem solving ability

(Analysis 1.2)

Up to 12 months (Subgroup 1.2.1)

Two studies with 712 participants (Helland 2001; Lauritzen 2004) reported this outcome and were included in the meta-analysis. No significant differences were found between LCPUFA supplementation and control groups (SMD -0.12, 95% CI -0.34 to 0.11). Heterogeneity between studies was not significant (Chi^2 = 2.5, P = 0.21; I^2 = 37%).

12 to 24 months (Subgroup 1.2.2)

One study with 227 participants (Jensen 2005) reported data for this outcome. No significant differences were found between LCPUFA supplementation and control groups (SMD -0.09, 95% CI -0.35 to 0.17).

Beyond 24 months (Subgroup 1.2.3)

Two studies with 817 participants (Helland 2001; Jensen 2005) reported this outcome and were included in the meta-analysis. No significant differences were found between LCPUFA supplementation and control groups (SMD 0.22, 95% CI -0.23 to 0.66). Heterogeneity between studies was significant (Chi^2 = 2.5, P = 0.004; I^2 = 88%).

Psychomotor development

(Analysis 1.3)

Up to 12 months (Subgroup 1.3.1)

No studies reported data for this subgroup.

12 to 24 months (Subgroup 1.3.2)

One study with 52 participants (Gibson 1997) reported data for this outcome. No significant differences were found between LCPUFA supplementation and control groups (SMD -0.11, 95% CI -0.75 to 0.54).

Beyond 24 months (Subgroup 1.3.3)

A meta-analysis was conducted including two trials with 279 participants (Gibson 1997; Jensen 2005). No significant differences were found between LCPUFA supplementation and control groups (SMD 0.34, 95% CI -0.11 to 0.78). Heterogeneity between studies was not significant (Chi^2 = 1.89, P = 0.17; I^2 = 47%).

Motor development

(Analysis 1.4)

Up to 12 months (Subgroup 1.4.1)

A meta-analysis was conducted including two studies with 349 participants (Jensen 2005; Lauritzen 2004). No significant differences were found between LCPUFA supplementation and control groups (SMD 0.08, 95% CI -0.13 to 0.29). Heterogeneity between studies was not significant (Chi² =1.43, P = 0.23; I² = 30%).

12 to 24 months (Subgroup 1.4.2)

No studies reported data for this subgroup.

Beyond 24 months (Subgroup 1.4.3)

One study with 227 participants (Jensen 2005) reported data for this outcome. No significant differences were found between LCPUFA supplementation and control groups (SMD -0.15, 95% CI -0.41 to 0.11).

Child attention

(Analysis 1.5)

Up to 12 months (Subgroup 1.5.1)

No studies reported data for this subgroup.

12 to 24 months (Subgroup 1.5.2)

No studies reported data for this subgroup.

Beyond 24 months (Subgroup 1.5.3)

One study with 227 participants (Jensen 2005) reported data for this outcome at five years. Significant differences were found between LCPUFA supplementation and control groups in favour of experimental group (SMD 0.50, 95% CI 0.24 to 0.77).

2. Secondary outcomes

Visual acuity

(Analysis 1.6)

Three studies reported data for this outcome at 12 months (short term) (Gibson 1997; Jensen 2005; Lauritzen 2004). A total of 401 participants were included in a meta-analysis. No significant differences were found (SMD -0.06, 95% CI -0.26 to 0.14). Heterogeneity between studies was not significant (Chi² = 1.4, P = 0.5; I² = 0%).

No data were reported for this outcome for medium and long term.

Physical growth

(Analysis 1.7, Analysis 1.8 and Analysis 1.9)

Children's physical growth was measured by weight, length and head circumference. Helland 2001 and Lauritzen 2004 assessed these outcomes at short term. In the medium term physical growth was evaluated only by Lucia 2007 (117 participants). Long-term outcomes were presented in Helland 2001 and Lauritzen 2004 (834 participants).

Child weight

For children's weight at short term, a total of 712 participants were included in a meta-analysis. No significant differences were found between LCPUFA supplementation and control groups (MD 0.24 kg, 95% CI -0.07 to 0.55). Heterogeneity between studies was not significant (Chi² = 0.42, P = 0.13; I² = 0%). In medium term, no significant differences were found between LCPUFA supplementation and control group (MD -0.56 kg 95% CI -0.64 to 0.48). For the long term data, a total of 834 participants were included in a meta-analysis. No significant differences were found (MD 0.22 kg, 95% CI -0.13 to 0.57). Heterogeneity between studies was not significant (Chi² = 2.71, P = 0.26; I² = 26%).

Child length

For length at short term (up to 12 months), 712 participants were included in a meta-analysis. Supplementation with LCPUFA had no significant effect on children (MD 0.00 cm, 95% CI -0.31 to 0.31). Heterogeneity between studies was not significant (Chi² = 1.97, P = 0.16; I² = 49%).

In the medium term, no significant differences were found between LCPUFA supplementation and control groups in one study involving 117 participants (MD 0.10 cm 95% CI -0.12 to 0.32). For the long-term data, significant differences were found in favour of the control group in two studies involving 834 participants (MD -0.75 cm, 95% CI -1.38 to -0.12). Heterogeneity between studies was not significant (Chi² = 2.21, P = 0.33; I² = 9%).

Head circumference

In a meta-analysis of two studies (712 participants), supplementation with LCPUFA had a no significant effect on the head circumference of children at short term (MD 0.19 cm, 95% CI -0.04 to 0.41). Heterogeneity between studies was significant (Chi² = 2.44, P = 0.12; I² = 59%). In contrast, for the long-term data, significant differences were found on one study (244 participants) in favour of the experimental group (MD 0.69 cm, 95% CI 0.35 to 1.02). In the medium term, significant differences were found between LCPUFA supplementation and control group in one study (117 participants) (MD -0.70 cm 95% CI -0.56 to 0.84).

Safety of supplementation with LCPUFA to mothers and babies

No trials reported this outcome.

Mother's views or satisfaction

We no found trials that reported data on mother's views or satisfaction.

Other non-prespecified secondary outcomes

(Analysis 1.10, Analysis 1.11)

Postpartum depression

Postpartum depression was evaluated by Jensen 2005. No significant difference was found (SMD 0.15, 95% CI -0.11 to 0.41).

Infant allergy

Infant allergy was evaluated by Furuhjelm 2009. Significant differences were found between LCPUFA supplementation and control groups (risk ratio (RR) 0.12, 95% CI 0.02 to 0.95).

Subgroup analysis

There were insufficient data to perform the planned subgroup analysis; these will be carried out in subsequent updates of this review, as data become available.

Sensitivity analysis

We performed a sensitivity analysis, removing Gibson 1997 from primary outcome psychomotor development because this study had a high risk of bias. Significant differences were found between LCPUFA supplementation and control groups (SMD 0.49, 95% CI 0.22 to 0.75). This study is considered at high risk of bias and may be one potential explanation for the heterogeneity (47%).
We removed Gibson 1997 from secondary outcome visual acuity. No significant difference was found (SMD -0.08, 95% CI -0.30 to -0.14). Heterogeneity between studies was not significant (Chi^2 = 1.08, P = 0.30; I^2 = 7%) (Analysis 1.6).

DISCUSSION

It has been recognised that LCPUFA are important nutrients, with biologically plausible and potential benefits in child growth and development. The fetus and the newborn should receive LCPUFA in amounts sufficient to guarantee visual and cognitive development. The main source of LCPUFA, particularly DHA, during the first six months of life is breast milk. DHA concentration in breast milk depends on the mother's diet (Jensen 2006; Koletzco 2008; McCann 2005).

Researchers have hypothesised that for lactating mothers, LCPUFA supplementation might have significant effects on children's neurodevelopment, visual acuity and growth. This systematic review was designed to evaluate the efficacy of LCPUFA supplementation to lactating mothers compared with placebo in development of their children.

Summary of main results

We included data from six trials (1280 participants) and were unable to identify a significant effect of LCPUFA on child development or visual acuity. We included trials in which LCPUFA began the during pregnancy and continued in the period of breastfeeding, as well as trials where LCPUFA did not commence until the period of breastfeeding. In the next update of this review, we will include a subgroup analysis based on the timing of the onset of LCPUFA supplementation (during or after pregnancy).
The meta-analysis showed no significant and consistent effects of supplementation with LCPUFA in different areas of neurodevelopment as psychomotor development and motor development.
After a sensitivity analysis, removing Gibson 1997, we found a significant difference in psychomotor development at long term favouring the experimental group, based on only one trial (Jensen 2005).
The age of the children at the last neurodevelopment assessment was seven years. One study (Lauritzen 2004) showed significant differences in language development (12 to 24 months) and Jensen 2005 showed significant differences in child attention (at five years) favouring the intervention group.
For visual acuity was measured up to 12 months. Regarding growth, assessments were made in children from 12 months to seven years follow-up (Lauritzen 2004). The supplementation lasted for four months. Visual acuity was a secondary outcome in this review. The meta-analysis at short term showed no evidence of effectiveness with supplementation on visual acuity. It is striking that studies did not measure visual acuity in the longer term.
The analyses of growth at long term was significant and it favoured the control group in terms of length. We found significant differences at medium and long term in head circumference, favouring the experimental group. The largest circumference at birth has been reported in a meta-analysis of trials exploring the potential beneficial effects of supplementation of pregnant women with LCPUFA on fetal growth. The study also found also a higher birthweight in the intervention group (Szajewska 2006).

Regarding the secondary effects, in postpartum depression one study (Jensen 2005) showed no significant effects of supplementation with LCPUFA. For infant allergy, the intervention decreased

the risk of allergy sensitisation during of first year of life (Furuhjelm 2009).

Overall completeness and applicability of evidence

This review did not find sufficient evidence to sustain the recommendation of supplementing LCPUFA to lactating mothers. The results of our review are consistent with the suggestions of Cheatham 2006 and McCann 2005 who concluded that, in order to achieve appropriate neurological and visual development, it is necessary to test different amounts of LCPUFA supplementation, and measurement methods must be homogeneous, sensitive, and specific for the different areas of neurodevelopment. The development outcomes must be measured in longer term, involving preschool and school children. Because maternal DHA status is often diverse and inadequate (Brenna 2007; Torres 2009), and there are different patterns of ocean fish intake, the natural source of LCPUFA (Welch 2002), it seems appropriate to conduct studies in different regions of the world.
Mothers participating in the trials came from high-income countries. Moreover, they were healthy women with no-risk pregnancies, so the external validity is limited.

Quality of the evidence

While the characteristics of mothers participating in the various studies were similar, trials used different doses of DHA and AA, varying from the current recommendations for breastfeeding mothers (Koletzco 2008) to an amount five times higher in the Danish studies (Furuhjelm 2009; Lauritzen 2004). Trials showed variation in terms of measurement and age at which the neurodevelopment and visual acuity were assessed. However, growth measurements were made, as expected, in a standard fashion.
Five of the six trials had low risk of bias. Although losses of participants to follow-up were greater than 20%, the trials were rigorous in their methodology. When we carried out a sensitivity analysis we found one study (Jensen 2005) with significant differences between the experimental and control groups.
A strength of this review is the organisation of the neurodevelopment outcomes in five areas and at different times of evaluation.

AUTHORS' CONCLUSIONS

Implications for practice

Our review did not find strong evidence that supplementation improves the areas of child development. The absence of sound evidence regarding LCPUFA supplementation contrasts with the recommendations of a consensus expert (Koletzco 2008) and a usual clinical practice in many countries.

LCPUFA supplementation is currently being promoted and may be purchased without prescription in different doses and different formulations in various regions all over the world. Large proportions of supplement stores and web sites promote consumption (Jensen 2006), so users ask about the need for this supplementation.

Therefore, based on the available evidence, we do not recommend supplementation with LCPUFA in breastfeeding mothers to improve infant growth and development.

Implications for research

Is necessary to perform the subgroup analysis based on timing of onset of supplementation (pregnancy or postpartum). These will be carried out in subsequent updates of this review, as data become available.

Further prospective trials with sufficient statistical power and longer follow-up periods are needed to further evaluate the effects of supplementation with LCPUFA to lactating mothers in the parameters of development in children, mainly in the area of psychomotor, language and attention development where we found a study that favouring the experimental group. It is necessary to take into account that variations in measurements make analysis and interpretation of the results difficult. Therefore, it is desirable to standardise the techniques, using in future studies those with proven sensitivity and specificity to facilitate the procedures. Studies should include mothers and children from different latitudes due to variability in diets and doses of DHA. More studies are necessary for the assessment the effectiveness of LCPUFA supplementation in breastfeeding woman in infant allergy and postpartum depression.

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As part of the pre-publication editorial process, this review has been commented on by two peers (an editor and referee who is external to the editorial team), a member of the Pregnancy and Childbirth

Group's international panel of consumers and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by year of study]*

Gibson 1997

Methods	Randomised trial.
Participants	Adelaide, Australia. 52 "Mothers of term infants (> 37 weeks' gestation) who intended to breastfeed for at least 12 weeks". Criteria of eligibility: Quote: "All infants were healthy, appropriate weight for gestation and had Apgar scores greater than 7 at 5 minutes post birth".
Interventions	Intervention group: DHA-rich algal oil.The oil contained 43% DHA, 1% n-6 PUFA, 38% saturates and 18% monounsaturated. 0.2, 0.4, 0.9 or 1.3 gr DHA/day. Control group: placebo (not stated). Duration of intervention:12 weeks. Duration of following: 12 months.
Outcomes	Neurodevelopmental status measured by Bayley MDI and PDI. Visual acuity measured by VEP 12 weeks and 16 weeks.
Notes	"Financial support was provided by Martek Biosciences, MD, USA and the National Health and Medical Research Council, Australia."

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "..These mothers were randomised to receive one of five doses".
Allocation concealment?	Unclear	Not stated.
Blinding? Primary outcome: Child neurodevelopment	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	No	Inadequate. For the first outcome, assessment of visual function, 26/52 (50%) were excluded for difficult behaviour at 12 weeks. Quote: "...the large number of exclusions from the VEP acuity determinations reduced the power of the study raising the possibility of a type II error. The number of exclusions was greater than expected at 12 weeks of age which may have been due to the fact that some infants may not have developed binocularity at this age so that some children may have had difficulty focusing on the monitor".

Gibson 1997 (*Continued*)

		50%, rate of lost for assessment of visual function. The greater proportion of missed follow-up occurred in the short term.
Free of selective reporting?	No	No data about child growth outcome.
Free of other bias?	No	Small number of participants.

Helland 2001

Methods	Randomised trial. Blinded. Helland 2001 is the main study with three publications at different times with same outcomes.
Participants	Norway. 590 (intervention group: 301, control group 289). Criteria of eligibility: healthy women with single pregnancy, 19-35 years of age, with intention to breastfeed. Exclusion criteria of newborns: premature, asphyxia, infections, anomalies that required special attention.
Interventions	Intervention group: 10 ml of cod liver oil per day. Control group: 10 ml of corn oil. Duration of intervention: 17-19 weeks of pregnancy to 3 months postpartum. Duration of following: 12 months (Helland 2001); 4 years (Helland 2003); 7 years (Helland 2008).
Outcomes	1. Helland 2001 reports cognitive function at 6 and 9 months; weight, length and head circumference at birth and 12 months. 2. Helland 2003 reports measure of intelligence (IQ) at 4 years. 3. Helland 2008 reports measure of intelligence (IQ) and weight, length and head circumference at 7 years.
Notes	"This study was financed by grants from Peter Møller, Avd. Orkla ASA, and "Aktieselskabet Freia Chocoladefabriks Medicinske Fond".

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Done. Quote: "The study was randomized and double-blinded, and the randomization was performed by a computer program".
Allocation concealment?	Yes	
Blinding? Primary outcome: Child neurodevelopment	Unclear	Quote in Helland 2001, 2003 and 2008: "The study was .. double-blinded". But in

Helland 2001 (*Continued*)

		Helland 2001 says: "The participants were assessed by one of the authors (L.S.) administering the Fagan Test of Infant Intelligence at 27 and 39 weeks of age".
Blinding? Secondary outcome: Anthropometric measures	Yes	Quote: "The study was ...double-blinded".
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	No data of weight, length and head circumference at 12 months.
Free of other bias?	Yes	

Lauritzen 2004

Methods	Randomised trial. Blinded. Lauritzen 2004 is the main study with eight publications at different times and with different outcomes.
Participants	Denmark. Participants were selected from cohort of Danish women Olsen 2001. 122 (intervention group:62, control group 60) exclusive breastfeeding women with a term delivery. Criteria of eligibility: uncomplicated pregnancy, prepregnancy BMI < 30 kg/m^2, absence of metabolic disorders, intention to breasted for a least 4 months. Newborns healthy, term, singleton, weight adequate for gestational age and Apgar > 7 at 5 minutes.
Interventions	Intervention group: 4.5 gr of fish oil with a content of 1.5 gr of n-3 LCPUFA per day in capsules. Control group: olive oil in capsules. Reference group: 64 mothers with high fish intake. Duration of intervention: 4 months postpartum. Duration of following: 4 months (Lauritzen 2004); 2 years (Lauritzen 2005a); 2.5 years (Ulbak 2004, Lauritzen 2005); 7 years (Asserhoj 2009).
Outcomes	1. Lauritzen 2004 reports infant visual acuity at 4 months. 2. Ulbak 2004 reports infant's blood pressure at 2.5 years. 3. Lauritzen 2005 reports infant's growth at 2.5 years. 4. Lauritzen 2005a reports infant's developmental outcomes at 2 years. 5. Asserhoj 2009 reports infant's blood pressure and growth at 7 years.
Notes	"This study was financed by FØTEK-The Danish Research and Development Program for Food and Technology and BASF Aktiengesellschaft".

Risk of bias

Lauritzen 2004 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Done. Quote: "After birth, the women with fish intakes below the 50th percentile were randomly assigned to a supplementation group by a randomization schedule prepared by a person uninvolved in the study."
Allocation concealment?	Yes	Quote: "Owing to the non-identical appearance of the capsules for the two groups, a person who was not otherwise involved in the project handled the capsules in order to avoid breaking the blinding of the investigators".
Blinding? Primary outcome: Child neurodevelopment	Yes	Quote: "...Thus, with respect to formulation as well as blinding of mothers and investigators".
Blinding? Secondary outcome: Assessment of visual function	Yes	
Incomplete outcome data addressed? All outcomes	Yes	Lost > 20% in both groups by similar reasons.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Jensen 2005

Methods	Randomised trial, blinded. Jensen (2005) is the main study with eight publications.
Participants	USA 227 (intervention group: 114; control group: 113) exclusive breastfeeding women with a term delivery. Eligibility criteria: healthy mothers: 18 to 40 years, with term infants, 2500 g to 4200 g.
Interventions	Intervention group: DHA (DHA Algal oil) 200 mg/day for 4 months. Control group: soy and corn oil. Time of intervention: 4 months. Time of following: 30 months (Jensen 2005); 4 months (Llorente 2003); 5 years (Jensen 2004).

Outcomes	1. Jensen 2005 reports neurodevelopmental status measure by Bayley Scale at 12, 30 months. Attention measure by Sustained Attention Subtest of the Leíter International Performance Scale (Jensen 2005) 2. Jensen 2004 reports visual acuity measure by Teller Acuity Card and VEP at 4 and 8 months. Attention at 5 years. 3. Llorente 2004 reports postpartum depression measure at 4 months. Jensen 1999a, Jensen 1999b, Jensen 2001, Voigt 1998 and Voigt 2000 are previous abstracts of primary study of Jensen 2005 published in supplements. Jensen 2000 reports fatty acid composition of breast milk lipids and infant plasma phospholipids.
Notes	Funding by Departament of Agriculture. Martek Biosciences Corp. Mead Johnson.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "Women who qualified were assigned randomly in a double-masked manner with a computer-generated randomisation scheme".
Allocation concealment?	Yes	Quote: "to receive 1 of 2 identical capsules daily for 4 mo".
Blinding? Primary outcome: Child neurodevelopment	Yes	Quote: "... Women who qualified were assigned randomly in a double masked manner with the use of a computer-generated randomization scheme, to receive 1 of 2 identical capsules daily for 4mo, starting within 5 d after delivery" It is unclear for outcome evaluation but we consider it unlikely that the lack of blindness of the outcomes is a source of bias.
Blinding? Secondary outcome: Assessment of visual function	Yes	
Incomplete outcome data addressed? All outcomes	Yes	Lost > 20% in both groups by similar reasons. The greater proportion of missed follow-up occurred in the short term.
Free of selective reporting?	No	Growth measures (weight, length and head circumference) not provided.
Free of other bias?	Yes	

Lucia 2007

Methods	Randomised trial. Blinded.
Participants	Germany. 144 recruited during pregnancy (at delivery: intervention group 43, control group 74). Criteria of eligibility: exclusion criteria of mothers: lactose intolerance, diabetes, smoking increase risk of premature delivery, multiple pregnancy, allergy to cow milk protein, consumption of alcohol. Exclusion criteria of infants: premature, major malformations, hospitalised for more than one week.
Interventions	Intervention group: "basic supplement with FOS and DHA (200 mg) prepared from fish oil". Control group: "basic supplement containing vitamins and minerals"; second control group: "basic supplement plus the prebiotic, FOS (4.5 g). Duration of intervention: during pregnancy 21 week-three months into lactation. Duration of follow-up: 21 months.
Outcomes	Length, weight and head circumference.
Notes	An author belongs to Nestle Nutrition Institute.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "Prospective mothers were randomized by a computer program and allocated to one of three groups."
Allocation concealment?	Yes	
Blinding? Secondary outcome: Anthropometric measures	Yes	Quote: "The identity of supplements was blinded to the subjects, support staff and investigators".
Incomplete outcome data addressed? All outcomes	Unclear	At time of birth, 27/144 "had been lost to follow-up". For the final assessment at 21 months 61/144 were available. No data about differences between the groups in withdrawals.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Furuhjelm 2009

Methods	Randomised trial. Blinded.
Participants	Sweden. 145 pregnant women with antecedents of allergy (intervention group 70, control group 65).
Interventions	Intervention group: capsules with 1.1 gr of DHA; 1.6 gr of EPA. Control group: soy oil capsules. Duration of intervention: 25 week of pregnancy to 3 months postpartum. Duration of follow-up: 12 months.
Outcomes	"risk of allergy sensitization during of first year of life" measures by Skin prick test, IgE levels and clinical examinations.
Notes	"The study was supported financially by Medical Research Council of Southeast Sweden (FORSS), The Otsergotland County Council, The Ekhaga Foundation, Swedish Asthma and Allergy Association, The Swedish Research Council for Environment, Agricultural Sciences and Spatial Planning (FORMAS), The Swedish Society of Medicine and Glaxo Smith Kline, Sweden."

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"The mothers were randomly allocated to dietary supplementation either with x-3 fatty acids (x-3 group) or placebo".
Allocation concealment?	Yes	"The producer performed the block randomization".
Blinding? Primary outcome: Child neurodevelopment	Yes	For the outcome risk of allergy sensitization: Quote: "The research nurses, the Paediatricians and the person performing the laboratory analyses were blinded during the intervention and follow-up." For the evaluation of allergy: Quote: "One possible flaw in our study may be the incomplete blinding due to belching with fish taste reported by some mothers in the x-3-supplemented group."
Incomplete outcome data addressed? All outcomes	Yes	117/145 mothers "were followed up in accordance with the study plan".
Free of selective reporting?	Yes	
Free of other bias?	Yes	

BMI: body mass index
EPA: eicosapentaenoic acid

FOS: fructooligosaccharide
LCPUFA: long chain polyunsaturated fatty acids
MDI: Mental Development Index
PDI: Psychomotor Development Index
VEP: visual evoked potential

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anderson 2005	Excluded because the intervention (Trans fatty acids) was not a LCPUFA.
Bergmann 2008	Excluded because this trial reports exclusively biochemical outcomes.
Bertschi 2005	Excluded because the intervention (Alpine butter) was not a LCPUFA.
Boris 2004	Excluded because this trial reports exclusively biochemical outcomes.
Cant 1991	Excluded because the intervention (Linoleic and gamma-linolenic acids) was not a LCPUFA.
Craig-Schmidt 1984	Excluded because the intervention (Hydrogenated fat) was not a LCPUFA.
Doornbos 2009	Excluded because the purpose of the study was different to purpose of the review. The only outcome is the prevention of postpartum depression.
Dunstan 2007	Excluded because the participants were only pregnant women and reporting exclusively biochemical outcomes.
Fidler 2000	Excluded because this trial reports exclusively biochemical outcomes.
Hasin 2007	Excluded because the intervention (Isomer of conjugated linoleic acid) was not a LCPUFA.
Hauner 2009	Excluded because the intervention (c9, t11-18:2 or t10, c12-18:2) was not a LCPUFA.
Hawkes 2002	Excluded because this trial reports exclusively biochemical outcomes.
Helland 1998	Excluded because this trial reports exclusively biochemical outcomes.
Helland 2006	Excluded because this trial reports exclusively biochemical outcomes.
Henriksen 2008	Excluded because the intervention was supplementation of human milk to preterm infants, not to their mothers.
Kaapa 1986	Excluded because this trial reports exclusively biochemical outcomes.
Kitz 2006	Excluded because the interventions of study (Gamma-linolenic acid) was not a LCPUFA.
Makrides 1996	Excluded because this trial reports exclusively biochemical outcomes.

(*Continued*)

Makrides 2002	Excluded because the intervention (egg yolk) was not a LCPUFA; the participants were infants not breast-feeding mothers.
Makrides 2009	Excluded because de participants were preterm infants with enteral feeds.
Masters 2002	Excluded because the intervention (Isomers of octadecadienoic acid) was not a LCPUFA.
Mellies 1978	Excluded because the intervention (varying maternal dietary cholesterol and phytosterol) was not a LCPUFA.
Mellies 1979	Excluded because the intervention (varying maternal dietary fatty acids) was not a LCPUFA.
Mosley 2007	Excluded because the intervention (Conjugated linoleic acid) was not a LCPUFA.
Palmer 2005	Excluded because the intervention (cooked and raw egg consumption) was not a LCPUFA.
Park 1999	Excluded because the intervention (high-fat dairy product) was not a LCPUFA.
Potter 1976	Excluded because the type of study. This study was not a randomised controlled trial.
Ritzenthaler 2005	Excluded because the intervention (conjugated linoleic acid) was not LCPUFA supplementation.
Scopesi 2008	Excluded because the type of study. This study was not a randomised controlled trial.
Shahin 2006	Excluded because the intervention (margarine and butter consumption) was not a LCPUFA.
Smithers 2008	Excluded because the participants were not lactating mothers.
Smithers 2008a	Excluded because the participants were not lactating mothers.
Tanaka 2009	This study compared the cognitive function of preterm babies who were breastfeeding with those who were formula-fed.
Van Goor 2009	Excluded because this trial reports exclusively biochemical outcomes.
Warstedt 2009	Excluded because the participants were only pregnant women and reporting exclusively biochemical outcomes.
Weseler 2008	Excluded because this trial reports exclusively biochemical outcomes.

LCPUFA: long chain polyunsaturated fatty acids

DATA AND ANALYSES

Comparison 1. Fatty acid supplementation versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Language development	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Up to12 months	1	227	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.40, 0.12]
1.2 12 to 24 months	1	122	Std. Mean Difference (IV, Random, 95% CI)	-0.41 [-0.77, -0.05]
1.3 Beyond 24 months	2	349	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.49, 0.20]
2 Intelligence or problem solving ability	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Up to 12 months	2	712	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.34, 0.11]
2.2 12 to 24 months	1	227	Std. Mean Difference (IV, Random, 95% CI)	-0.09 [-0.35, 0.17]
2.3 Beyond 24 months	2	817	Std. Mean Difference (IV, Random, 95% CI)	0.22 [-0.23, 0.66]
3 Psychomotor development	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Short term 12 months	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
3.2 Medium term 12 to 24 months	1	52	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.75, 0.54]
3.3 Beyond 24 months	2	279	Std. Mean Difference (IV, Random, 95% CI)	0.34 [-0.11, 0.78]
3.4 Beyond 24 months (excluding Gibson 1997)	1	227	Std. Mean Difference (IV, Random, 95% CI)	0.49 [0.22, 0.75]
4 Motor development	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Short term 12 months	2	349	Std. Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.13, 0.29]
4.2 Medium term 12-24 months	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.3 Long term beyond 24 months	1	227	Std. Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.41, 0.11]
5 Child attention	1	227	Std. Mean Difference (IV, Random, 95% CI)	0.50 [0.24, 0.77]
5.1 Short term 12 months	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
5.2 Medium term 12 to 24 months	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
5.3 Long term beyond 24 months	1	227	Std. Mean Difference (IV, Random, 95% CI)	0.50 [0.24, 0.77]
6 Child visual acuity	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Visual acuity 12 months (short term)	3	401	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.26, 0.14]
6.2 Visual acuity 12 months (excluding Gibson 1997)	2	349	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.30, 0.14]
6.3 Visual acuity 12 to 24 months (medium term)	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
6.4 Visual acuity beyond 24 months (long term)	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
7 Child weight	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Short term 12 months	2	712	Mean Difference (IV, Fixed, 95% CI)	0.24 [-0.07, 0.55]
7.2 Medium term 12 to 24 months	1	117	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-0.64, -0.48]
7.3 Long term beyond 24 months	2	834	Mean Difference (IV, Fixed, 95% CI)	0.22 [-0.13, 0.57]

8 Child length	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Short term 12 months	2	712	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.31, 0.31]
8.2 Medium term 12 to 24 months	1	117	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.12, 0.32]
8.3 Long term beyond 24 months	2	834	Mean Difference (IV, Fixed, 95% CI)	-0.75 [-1.38, -0.12]
9 Child head circumference	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Short term 12 months	2	712	Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.04, 0.41]
9.2 Medium term 12 to 24 months	1	117	Mean Difference (IV, Fixed, 95% CI)	0.70 [0.56, 0.84]
9.3 Long term beyond 24 months	1	244	Mean Difference (IV, Fixed, 95% CI)	0.69 [0.35, 1.02]
10 Postpartum depression	1	227	Std. Mean Difference (IV, Random, 95% CI)	0.15 [-0.11, 0.41]
11 infant allergy	1	117	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.02, 0.95]

Analysis 1.1. Comparison 1 Fatty acid supplementation versus placebo, Outcome 1 Language development.

Review: Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development

Comparison: 1 Fatty acid supplementation versus placebo

Outcome: 1 Language development

Study or subgroup	Fatty acids N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Up to12 months							
Jensen 2005	114	100.6 (14.6)	113	102.5 (13.2)		100.0 %	-0.14 [-0.40, 0.12]
Subtotal (95% CI)	**114**		**113**			**100.0 %**	**-0.14 [-0.40, 0.12]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.02 (P = 0.31)							
2 12 to 24 months							
Lauritzen 2004	62	54 (37)	60	71 (45)		100.0 %	-0.41 [-0.77, -0.05]
Subtotal (95% CI)	**62**		**60**			**100.0 %**	**-0.41 [-0.77, -0.05]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.24 (P = 0.025)							
3 Beyond 24 months							
Jensen 2005	114	106.8 (15.2)	113	106.6 (14.9)		56.2 %	0.01 [-0.25, 0.27]
Lauritzen 2004	62	242 (170)	60	297 (147)		43.8 %	-0.34 [-0.70, 0.01]
Subtotal (95% CI)	**176**		**173**			**100.0 %**	**-0.14 [-0.49, 0.20]**
Heterogeneity: Tau² = 0.04; Chi² = 2.50, df = 1 (P = 0.11); I² =60%							
Test for overall effect: Z = 0.81 (P = 0.42)							

Analysis 1.2. Comparison 1 Fatty acid supplementation versus placebo, Outcome 2 Intelligence or problem solving ability.

Review: Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development

Comparison: 1 Fatty acid supplementation versus placebo

Outcome: 2 Intelligence or problem solving ability

Study or subgroup	Fatty acids N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Up to 12 months							
Helland 2001	301	55.5 (3.8)	289	56.2 (3.5)		70.7 %	-0.19 [-0.35, -0.03]
Lauritzen 2004	62	4.5 (3.1)	60	4.3 (3.6)		29.3 %	0.06 [-0.30, 0.41]
Subtotal (95% CI)	**363**		**349**			**100.0 %**	**-0.12 [-0.34, 0.11]**
Heterogeneity: Tau² = 0.01; Chi² = 1.58, df = 1 (P = 0.21); I² =37%							
Test for overall effect: Z = 1.03 (P = 0.30)							
2 12 to 24 months							
Jensen 2005	114	109 (10.7)	113	110 (10.8)		100.0 %	-0.09 [-0.35, 0.17]
Subtotal (95% CI)	**114**		**113**			**100.0 %**	**-0.09 [-0.35, 0.17]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.70 (P = 0.49)							
3 Beyond 24 months							
Helland 2001	301	106.4 (7.4)	289	102.3 (11.3)		52.6 %	0.43 [0.27, 0.59]
Jensen 2005	114	98.1 (9)	113	98.3 (8.7)		47.4 %	-0.02 [-0.28, 0.24]
Subtotal (95% CI)	**415**		**402**			**100.0 %**	**0.22 [-0.23, 0.66]**
Heterogeneity: Tau² = 0.09; Chi² = 8.35, df = 1 (P = 0.004); I² =88%							
Test for overall effect: Z = 0.95 (P = 0.34)							

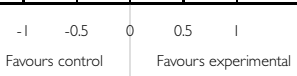
Analysis 1.3. Comparison 1 Fatty acid supplementation versus placebo, Outcome 3 Psychomotor development.

Review: Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development

Comparison: 1 Fatty acid supplementation versus placebo

Outcome: 3 Psychomotor development

Study or subgroup	Fatty acids N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Short term 12 months							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Medium term 12 to 24 months							
Gibson 1997	40	98 (19)	12	100 (15)		100.0 %	-0.11 [-0.75, 0.54]
Subtotal (95% CI)	**40**		**12**			**100.0 %**	**-0.11 [-0.75, 0.54]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.33 (P = 0.74)							
3 Beyond 24 months							
Gibson 1997	40	100 (17)	12	100 (15)		31.1 %	0.0 [-0.65, 0.65]
Jensen 2005	114	116.8 (15.2)	113	108.4 (18.9)		68.9 %	0.49 [0.22, 0.75]
Subtotal (95% CI)	**154**		**125**			**100.0 %**	**0.34 [-0.11, 0.78]**
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 1.89$, df = 1 (P = 0.17); $I^2 = 47\%$							
Test for overall effect: Z = 1.49 (P = 0.14)							
4 Beyond 24 months (excluding Gibson 1997)							
Jensen 2005	114	116.8 (15.2)	113	108.4 (18.9)		100.0 %	0.49 [0.22, 0.75]
Subtotal (95% CI)	**114**		**113**			**100.0 %**	**0.49 [0.22, 0.75]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.62 (P = 0.00029)							



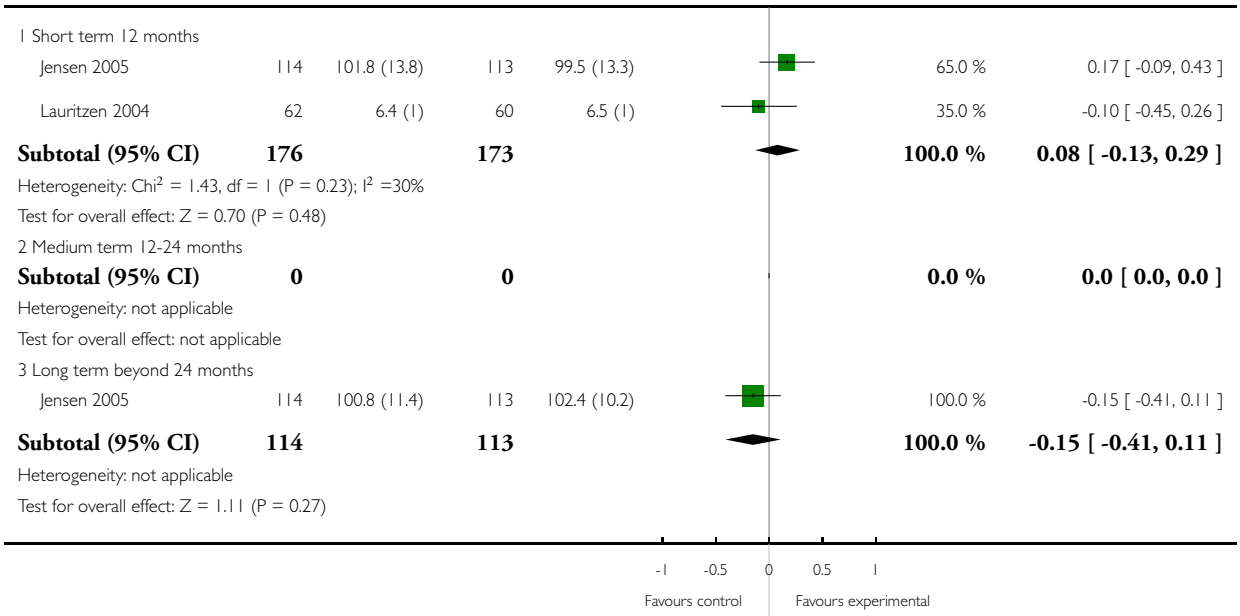
Analysis 1.4. Comparison 1 Fatty acid supplementation versus placebo, Outcome 4 Motor development.

Review: Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development

Comparison: 1 Fatty acid supplementation versus placebo

Outcome: 4 Motor development

Study or subgroup	Fatty acids N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Short term 12 months							
Jensen 2005	114	101.8 (13.8)	113	99.5 (13.3)		65.0 %	0.17 [-0.09, 0.43]
Lauritzen 2004	62	6.4 (1)	60	6.5 (1)		35.0 %	-0.10 [-0.45, 0.26]
Subtotal (95% CI)	**176**		**173**			**100.0 %**	**0.08 [-0.13, 0.29]**
Heterogeneity: Chi^2 = 1.43, df = 1 (P = 0.23); I^2 =30%							
Test for overall effect: Z = 0.70 (P = 0.48)							
2 Medium term 12-24 months							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
3 Long term beyond 24 months							
Jensen 2005	114	100.8 (11.4)	113	102.4 (10.2)		100.0 %	-0.15 [-0.41, 0.11]
Subtotal (95% CI)	**114**		**113**			**100.0 %**	**-0.15 [-0.41, 0.11]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.11 (P = 0.27)							



Analysis 1.5. Comparison 1 Fatty acid supplementation versus placebo, Outcome 5 Child attention.

Review: Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development

Comparison: 1 Fatty acid supplementation versus placebo

Outcome: 5 Child attention

Study or subgroup	Fatty acids N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Short term 12 months							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Medium term 12 to 24 months							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
3 Long term beyond 24 months							
Jensen 2005	114	46.5 (8.9)	113	41.9 (9.3)		100.0 %	0.50 [0.24, 0.77]
Subtotal (95% CI)	**114**		**113**			**100.0 %**	**0.50 [0.24, 0.77]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.73 (P = 0.00019)							
Total (95% CI)	**114**		**113**			**100.0 %**	**0.50 [0.24, 0.77]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.73 (P = 0.00019)							

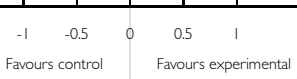
Analysis 1.6. Comparison 1 Fatty acid supplementation versus placebo, Outcome 6 Child visual acuity.

Review: Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development

Comparison: 1 Fatty acid supplementation versus placebo

Outcome: 6 Child visual acuity

Study or subgroup	Fatty acids N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Visual acuity 12 months (short term)							
Gibson 1997	40	0.72 (0.09)	12	0.71 (0.06)		9.6 %	0.12 [-0.53, 0.76]
Jensen 2005	114	9.4 (0.23)	113	9.4 (0.21)		59.0 %	0.0 [-0.26, 0.26]
Lauritzen 2004	62	0.62 (0.08)	60	0.64 (0.09)		31.5 %	-0.23 [-0.59, 0.12]
Subtotal (95% CI)	**216**		**185**			**100.0 %**	**-0.06 [-0.26, 0.14]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.40$, df = 2 (P = 0.50); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.61 (P = 0.54)							
2 Visual acuity 12 months (excluding Gibson 1997)							
Jensen 2005	114	9.4 (0.23)	113	9.4 (0.21)		64.1 %	0.0 [-0.26, 0.26]
Lauritzen 2004	62	0.62 (0.08)	60	0.64 (0.09)		35.9 %	-0.23 [-0.59, 0.12]
Subtotal (95% CI)	**176**		**173**			**100.0 %**	**-0.08 [-0.30, 0.14]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.08$, df = 1 (P = 0.30); $I^2 = 7\%$							
Test for overall effect: Z = 0.75 (P = 0.45)							
3 Visual acuity 12 to 24 months (medium term)							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
4 Visual acuity beyond 24 months (long term)							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							

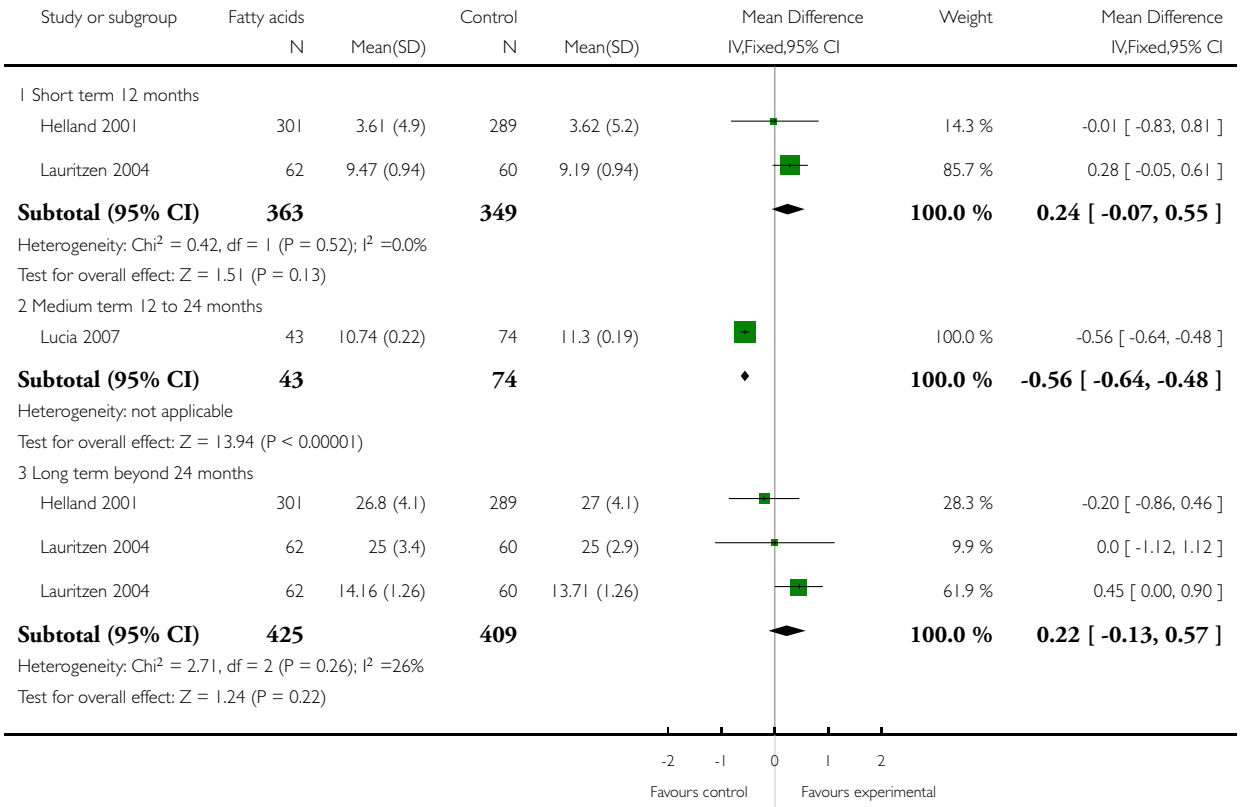


Analysis 1.7. Comparison 1 Fatty acid supplementation versus placebo, Outcome 7 Child weight.

Review: Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development

Comparison: 1 Fatty acid supplementation versus placebo

Outcome: 7 Child weight

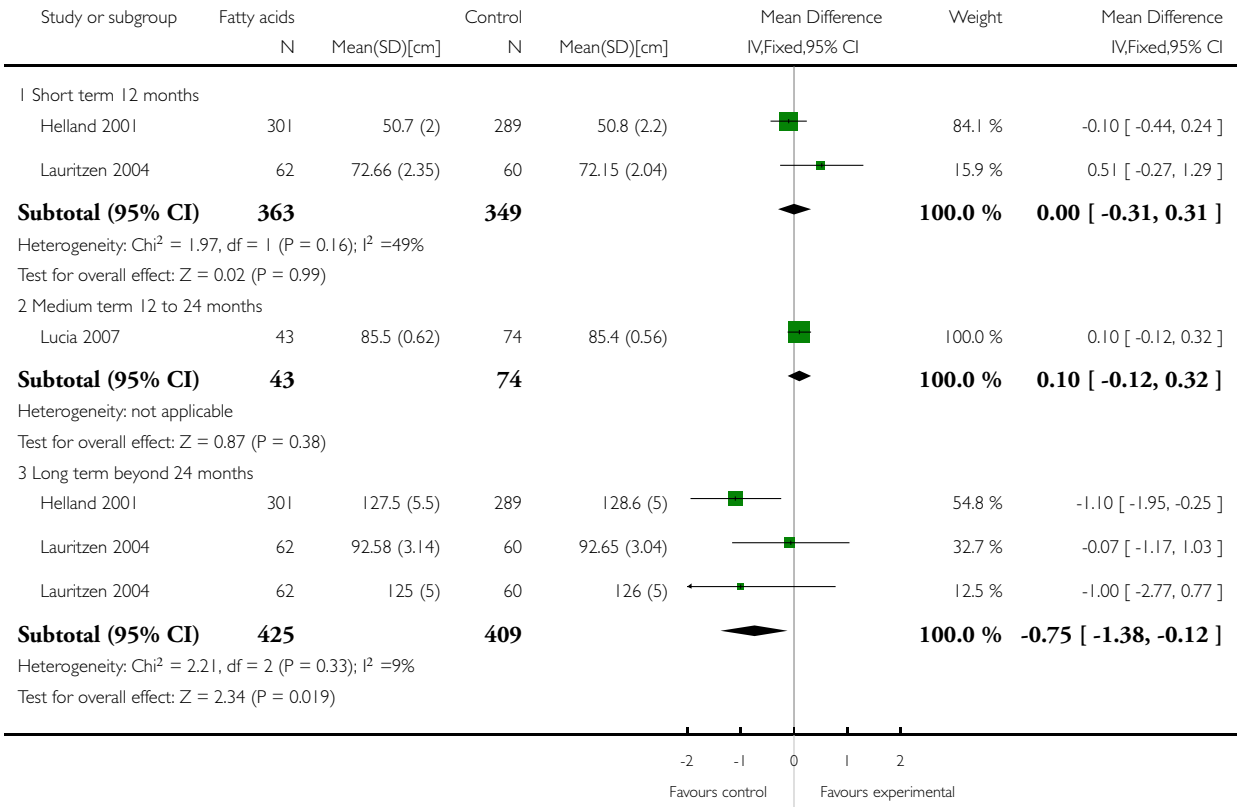


Analysis 1.8. Comparison 1 Fatty acid supplementation versus placebo, Outcome 8 Child length.

Review: Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development

Comparison: 1 Fatty acid supplementation versus placebo

Outcome: 8 Child length



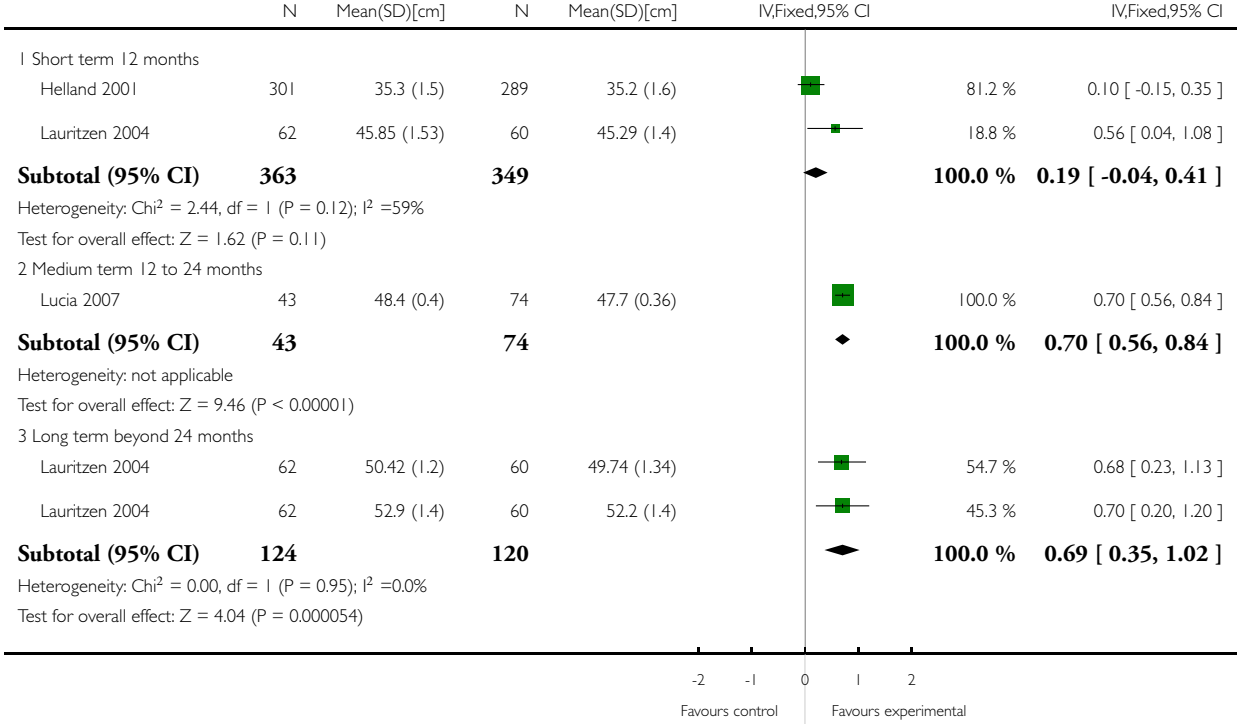
Analysis 1.9. Comparison 1 Fatty acid supplementation versus placebo, Outcome 9 Child head circumference.

Review: Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development

Comparison: 1 Fatty acid supplementation versus placebo

Outcome: 9 Child head circumference

Study or subgroup	Fatty acids N	Mean(SD)[cm]	Control N	Mean(SD)[cm]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Short term 12 months							
Helland 2001	301	35.3 (1.5)	289	35.2 (1.6)		81.2 %	0.10 [-0.15, 0.35]
Lauritzen 2004	62	45.85 (1.53)	60	45.29 (1.4)		18.8 %	0.56 [0.04, 1.08]
Subtotal (95% CI)	**363**		**349**			**100.0 %**	**0.19 [-0.04, 0.41]**
Heterogeneity: Chi^2 = 2.44, df = 1 (P = 0.12); I^2 =59%							
Test for overall effect: Z = 1.62 (P = 0.11)							
2 Medium term 12 to 24 months							
Lucia 2007	43	48.4 (0.4)	74	47.7 (0.36)		100.0 %	0.70 [0.56, 0.84]
Subtotal (95% CI)	**43**		**74**			**100.0 %**	**0.70 [0.56, 0.84]**
Heterogeneity: not applicable							
Test for overall effect: Z = 9.46 (P < 0.00001)							
3 Long term beyond 24 months							
Lauritzen 2004	62	50.42 (1.2)	60	49.74 (1.34)		54.7 %	0.68 [0.23, 1.13]
Lauritzen 2004	62	52.9 (1.4)	60	52.2 (1.4)		45.3 %	0.70 [0.20, 1.20]
Subtotal (95% CI)	**124**		**120**			**100.0 %**	**0.69 [0.35, 1.02]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%							
Test for overall effect: Z = 4.04 (P = 0.000054)							

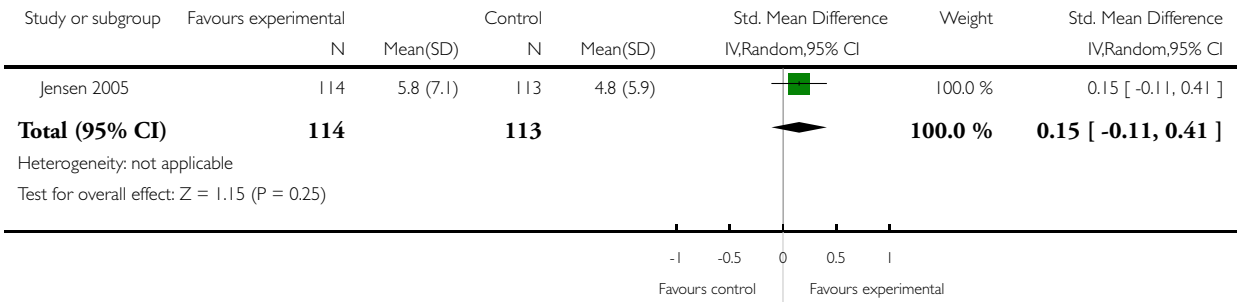


Analysis 1.10. Comparison 1 Fatty acid supplementation versus placebo, Outcome 10 Postpartum depression.

Review: Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development

Comparison: 1 Fatty acid supplementation versus placebo

Outcome: 10 Postpartum depression

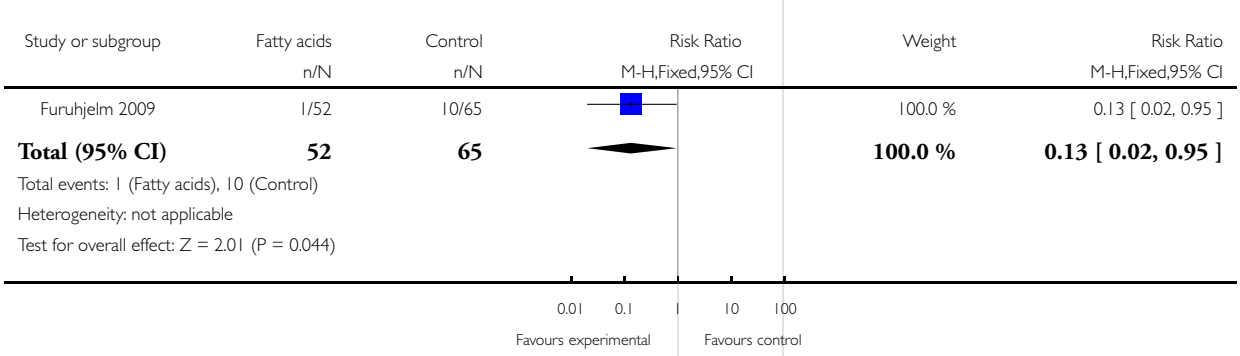


Analysis 1.11. Comparison 1 Fatty acid supplementation versus placebo, Outcome 11 infant allergy.

Review: Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development

Comparison: 1 Fatty acid supplementation versus placebo

Outcome: 11 infant allergy



APPENDICES

Appendix 1. CENTRAL search strategy

The Cochrane Central Register of Controlled Trials (CENTRAL) (2009, Issue 2)

#1 MeSH descriptor Lactation explode all trees
#2 MeSH descriptor Breast Feeding explode all trees
#3 lactation OR breast-fe* OR breastfe* OR breast-milk OR breastmilk OR breastfeed* OR breast-feed* OR lactating mother* OR lactating woman OR lactating women
#4 #1 OR #2 OR #3 OR #4
#5 MeSH descriptor Fatty acids explode all trees
#6 fatty acid*
#7 omega 3
#8 LCPUFA* OR PUFA* OR LC n-3
#9 docosahexaenoic acid* OR docosahexanoic acid* OR eicosapentaenoic acid* OR eicosapentanoic acid*
#10 MeSH descriptor Fish oils explode all trees
#11 fish oil*
#12 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR#11
#13 #4 and #12

Appendix 2. PubMed search strategy

(1966 to July 2009)
#1 Lactation[MeSH]
#2 lactation[tiab]
#3 "Breast Feeding"[MesH]
#4 breast-fe*[tiab] OR breastfe*[tiab]
#5 breast-milk[tiab] OR breastmilk[tiab]
#6 breastfeed*[tiab]
#7 breast-feed*[tiab]
#8 lactating mother*[tiab]
#9 lactating woman[tiab]
#10 lactating women[tiab]
#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12 "Fatty Acids"[MesH]
#13 fatty acid*[tw]
#14 omega 3[tw]
#15 LCPUFA*[tw]
#16 LC n-3 FA*[tw]
#17 PUFA*[tw]
#18 docosahexaenoic acid*[tiab] OR docosahexanoic acid*[tiab] OR docosahexenoic acid*[tiab]
#19 eicosapentaenoic acid*[tiab] OR eicosapentanoic acid*[tiab] OR eicosapentenoic acid*[tiab]
#20 "Fish Oils"[MesH]
#21 fish oil*[tiab]
#22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #11 and #22
#24 randomized controlled trial [pt]
#25 controlled clinical trial [pt]
#26 randomized [tiab]
#27 placebo [tiab]
#28 drug therapy [sh]
#29 randomly [tiab]

#30 trial [tiab]
#31 groups [tiab]
#32 #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31
#33 animals [mh] not (humans [mh] and animals [mh])
#34 #23 AND #32
#35 #34 NOT #33

Appendix 3. EMBASE search strategy

(1974 to June 2009, via OVID)

1 exp LACTATION/
2 lactation.ti,ab.
3 exp Breast Feeding/
4 (lactation OR breast-fe* OR breastfe* OR breast-milk OR breastmilk OR breastfeed* OR breast-feed* OR lactating mother* OR lactating woman OR lactating women).ti,ab.
5 1 or 2 or 3 or 4
6 exp Fatty Acid/
7 fatty acid*.mp.
8 omega 3.mp.
9 (LCPUFA* or LC n-3 FA* or PUFA*).mp.
10 (docosahexaenoic acid* or docosahexanoic acid* or docosahexenoic acid*).ti,ab
11 (eicosapentaenoic acid* or eicosapentanoic acid* or eicosapentenoic acid*).ti,ab.
12 exp Fish Oil/
13 fish oil*.ti,ab.
14 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15 5 and 14
16 Clinical trial/
17 Randomized controlled trials/
18 Random Allocation/
19 Single-Blind Method/
20 Double-Blind Method/
21 Cross-Over Studies/
22 Placebos/
23 Randomi?ed controlled trial$.tw.
24 RCT.tw.
25 Random allocation.tw.
26 Randomly allocated.tw.
27 Allocated randomly.tw.
28 (allocated adj2 random).tw.
29 Single blind$.tw.
30 Double blind$.tw.
31 ((treble or triple) adj blind$).tw.
32 Placebo$.tw.
33 Prospective Studies/
34 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35 Case study/
36 Case report.tw.
37 Abstract report/ or letter/
38 35 or 36 or 47
39 34 not 38
40 animal/ not human/

41 15 and 39
45 41 not 40

Appendix 4. CINAHL search strategy

(1984 to June 2009, via Ovid)
1 exp LACTATION/
2 lactation.ti,ab.
3 exp Breast Feeding/
4 (lactation OR breast-fe* OR breastfe* OR breast-milk OR breastmilk OR breastfeed* OR breast-feed* OR lactating mother* OR lactating woman OR lactating women).ti,ab.
5 1 or 2 or 3 or 4
6 exp Fatty Acid/
7 fatty acid*.mp.
8 omega 3.mp.
9 (LCPUFA* or LC n-3 FA* or PUFA*).mp.
10 (docosahexaenoic acid* or docosahexanoic acid* or docosahexenoic acid*).ti,ab
11 (eicosapentaenoic acid* or eicosapentanoic acid* or eicosapentenoic acid*).ti,ab.
12 exp Fish Oil/
13 fish oil*.ti,ab.
14 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15 5 and 14
16 exp prognosis OR exp study design OR random:.mp.
17 15 and 16

Appendix 5. LILACS search strategy

(1982 to June 2009)
First block
((Pt ENSAIO CONTROLADO ALEATORIO OR Pt ENSAIO CLINICO CONTROLADO OR Mh ENSAIOS CONTROLADOS ALEATORIOS OR Mh DISTRIBUICAO ALEATORIA OR Mh MÉTODO DUPLO-CEGO OR Mh MÉTODO SIMPLES-CEGO) AND NOT (Ct ANIMALS AND NOT (Ct HUMANO AND Ct ANIMALS)) OR (Pt ENSAIO CLÍNICO OR Ex E05.318.760.535$) OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh PLACEBOS OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR (Mh PROJETOS DE PESQUISA) AND NOT (Ct ANIMALS AND NOT (Ct HUMANO AND Ct ANIMALS)) OR (Ct ESTUDO COMPARATIVO OR Ex E05.337$ OR Mh SEGUIMENTOS OR Mh ESTUDOS PROSPECTIVOS OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct ANIMALS AND NOT (Ct HUMANO AND Ct ANIMALS))) AND NOT Mh ANIMALS
Second block
Mh Eicosapentaenoic Acid OR Mh Docosahexaenoic Acids OR Mh Fatty Acids OR Mh Fish oils OR AB LC-PUFA OR AB omega-3 OR AB acido oleico
Third block
Mh Breast feeding OR Mh Lactation OR Mh Milk Human OR AB breast-fe$ OR breastfe$
Block 1 AND Block 2 AND Block 3

Appendix 6. GOOGLE SCHOLAR search strategy

We use a simple search strategy with the next phrase. We restrict the strategy with the addition of hyphen (-animals) to search humans only.
Lactation Breast Feeding Breast milk Fatty acids Fish oils Docosahexaenoic Acids Eicosapentaenoic Acid Clinical Trial Randomized Controlled Trials -animals
Searched June 2009

HISTORY

Protocol first published: Issue 3, 2009

Review first published: Issue 12, 2010

CONTRIBUTIONS OF AUTHORS

Mario Delgado conceived, designed and wrote the protocol and the review, and provided a methodological, clinical and policy perspective. Andres Calvache searched, evaluated references for the background section and wrote the review. Xavier Bonfill commented on the content of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of Cauca, Popayán, Colombia.
- Iberoamerican Cochrane Centre, Spain.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. **Definition of third secondary outcome.** Safety was considered as environmental contamination of supplementation.

2. **Non-prespecified secondary outcomes.** We added two new secondary outcomes: postpartum depression and infant allergy.

3. **Search methods for identification of studies.** We added a search in reference list of published narrative reviews or related papers and we sent emails to authors who had not reported some data.

Evaluación de la calidad de las guías sobre la prevención y tratamiento del sobrepeso y obesidad infantiles

Delgado-Noguera M, Tort S, Bonfill X, Gich I, Alonso-Coello P. Quality assessment of clinical practice guidelines for the prevention and treatment of childhood overweight and obesity. Eur J Pediatr. 2009 Jul;168(7):789-99

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Factor de Impacto: 1.63 (2009)

Eur J Pediatr
DOI 10.1007/s00431-008-0836-5

ORIGINAL PAPER

Quality assessment of clinical practice guidelines for the prevention and treatment of childhood overweight and obesity

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Received: 19 June 2008 / Accepted: 4 September 2008

Abstract
Background The prevalence of childhood overweight and obesity is increasing at dramatic rates in children and adolescents worldwide. Clinical practice guidelines (CPGs) are "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances." Their objective is to provide explicit recommendations for clinical practice based on current evidence for best practice in the management of diseases.
Materials and methods The aim of this study was to identify and assess the quality of CPGs for the prevention and treatment of obesity and overweight in childhood. We developed a search to identify CPGs published between January 1998 and August 2007. We considered for inclusion documents that provided recommendations for clinical practice referring to children and adolescents. Three independent appraisers assessed the quality of the1 CPGs using the AGREE (Appraisal of Guidelines Research and Evaluation) instrument. We identified 376 references and selected 22 for further assessment.
Results The overall agreement among reviewers using the intraclass correlation coefficient was 0.856 (95% confidence interval [CI] 0.731–0.932). Six of the 22 initial guidelines were recommended and a further eight were recommended with conditions or provisos. We concluded that the number of documents with recommendations on the prevention and treatment of childhood obesity published during the 10-year study period was considerable, but only a few of them could be considered as high quality. CPGs were deficient in areas such as applicability, editorial independence and rigor in development.
Conclusion Due to the increasing burden of obesity among children and the potential for long-term comorbidities, clinicians need to be critical in assessing the rigor of how these are developed and their appropriateness for use in the clinician's own practice. There is a need to improve the methodology and the quality of CPGs on childhood obesity to help clinicians and other decision-makers to tackle this disease.

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Keywords Guidelines · Overweight · Obesity · AGREE · Child · Adolescent

Background

Obesity is presently one of the most challenging public health problems in the developed world and it is also a growing concern in developing countries [47]. In the European Union, the prevalence of childhood obesity and overweight has tripled since 1980 [48]. In the United States, the prevalence of overweight in children and adolescents presents a continuous increase in the last several decades [34].

Several socio-demographic factors are associated with changes in dietary habits and lifestyle. Traditional diets are being replaced by fast food and physical activity is decreasing both during work and leisure time. Furthermore, children and adolescents now spend more time in sedentary activities, such as watching TV, surfing the Internet or playing video games [48].

Clinical practice guidelines (CPGs) have been described as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" [22]. Their objective is to provide explicit recommendations for clinical practice and reduce inadequate variations in order to optimise results, minimise risks and promote cost-effective practice [50]. However, the potential of CPGs to improve the use of resources and patient care largely depends on the rigor of their development and dissemination and the implementation strategy [6, 51].

One of the main limitations of CPGs is that recommendations may be erroneous or biassed due to the incomplete compilation or inadequate interpretation of scientific evidence. Limitations may also be the result of CPG development teams having biassed opinions or only considering results from a clinical point of view. Furthermore, often, CPGs do not consider the balance between benefits and harms, quality of life, the potential cost implications or efficient use of resources. Such limitations may not only lead to potential risks for patients but also may also confuse physicians or public health professionals and contribute to medical errors [51].

All CPGs should be externally evaluated and fully assessed prior to implementation to assure that they are of high quality. For this purpose, the AGREE (Appraisal of Guidelines Research and Evaluation) instrument is the most accepted international [6] and validated tool [2, 10]. The AGREE instrument was developed by an international group of researchers and is used to assess the quality of clinical guidelines [2, 10].

To our knowledge, there is no published assessment of guidelines quality regarding this topic. We conducted this study in order to assess the quality of the available guidelines in the field of the prevention and treatment of childhood overweight and obesity.

Methods

Identification of guidelines

We searched databases for CPGs on the prevention and treatment of childhood overweight and obesity published from January 1998 to August 2007. The keywords initially used in the search engine TRIP (Turning Research into Practice) database and guidelines compiler entities or clearinghouses were "obesity" and "overweight" (so that the search would be initially sensitive). We also searched the main guideline developer websites by adding the keywords "childhood," "children" and "adolescent" to the term "obesity." The clearinghouses and guidelines developers websites searched can be observed in the Appendix 1.

Separately, we completed our search checking MEDLINE (through PubMed) combining the above terms with a filter (obesity AND (Practice Guideline (pt) OR Guideline (pt) OR guideline*(ti) OR consensus (ti). We restricted the search to documents that were published in the last ten years, included an abstract and were written for children and adolescents. The search was restricted to the English, French and Spanish languages.

Selection of guidelines

We considered as guidelines those documents that provided clinical practice recommendations for children and adolescents and collected all related documents and supporting materials. We excluded systematic reviews because these publications are one of the sources for developing CPGs, single-author documents and any publications, such as summaries, developed from CPGs.

Evaluation of guidelines

Scope and purpose

We assessed whether the CPGs found were about screening, prevention or treatment of childhood obesity, whether they focussed on children and adults or children only, and if their recommendations were only clinical or included public health and community issues and health policies as well.

Quality assessment

We determined whether guidelines were evidence-based or not. Guidelines were considered to be evidence-based if they reported a search strategy (including at least one database) that classified the quality of the evidence and graded the strength of recommendations.

We used the AGREE instrument to appraise the quality of CPGs [2, 41]. This instrument provides criteria to assess the quality of clinical guidelines. These criteria mainly concern the methods used for developing the guideline and the quality of the reporting. It provides an assessment of the predicted validity of a guideline; that is, its likelihood to achieve the intended outcome [35, 45].

This instrument consists of 23 key items organised in six domains: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence. Each item is rated on a four-point Likert scale such as: 4 'Strongly Agree', 3 'Agree', 2 'Disagree' and 1 'Strongly Disagree'. The scale measures the extent to which a criterion (item) has been fulfilled. The investigators had experience in CPG development. In order to improve the quality of the data collection, we pilot-tested the evaluation with several guidelines. Three authors (a paediatrician (MD) and two family physicians (ST, PA)) independently rated each of the items of the six domains of the AGREE instrument in every CPG identified.

We obtained the results for each domain by summing up all of the scores for the individual items in a domain and then standardising as follows: (obtained score − minimum possible score)/(maximum possible score − minimum possible score). The maximum score for each domain was the number of questions multiplied by the number of reviewers multiplied by the number of scores of 4 (strongly agree). The minimum score was the number of questions multiplied by the number of reviewers multiplied by the number of scores of 1 (strongly disagree). The minimum standardised score for each domain was, therefore, 0% and the maximum was 100%.

The final component of the AGREE instrument involves a recommendation regarding the use of the guidelines in practice as "recommended," "recommended (with provisos or exceptions)," "would not recommend" or "unsure," depending on the number of items and domains if the score was >60%, 30–60% and <30%, respectively. In our review, each appraiser made a judgement based on the guideline as a whole, as well as the rating of individual items. Finally, appraisers reached an agreement by consensus (Table 2) [41].

Statistical analysis

We performed a descriptive statistical analysis for each domain. A weighted mean of 50% was determined to establish the proportion of CPGs that scored above this level in each domain. We calculated the intra-class correlation coefficient (ICC) with a 95% confidence interval (CI) as an overall indicator of agreement among the reviewers for each of the 23 items of the AGREE instrument. The ICC has been accepted as the best measure for continuous data. It describes the proportion of the total variation explained by differences among observers. The total variance of their measurements is due to three sources: differences between observers, differences of individuals (in this case, CPGs) and unexplained variation. According to the scale proposed by Landis and Koch, the degree of agreement between 0.01 and 0.20 is slight, from 0.21 to 0.40 is fair, from 0.41 to 0.60 is moderate, from 0.61 to 0.80 is substantial and from 0.81 to 1.00 is very good [24]. All analyses were performed using the statistical package SPSS version 9.0.

Results

Literature search

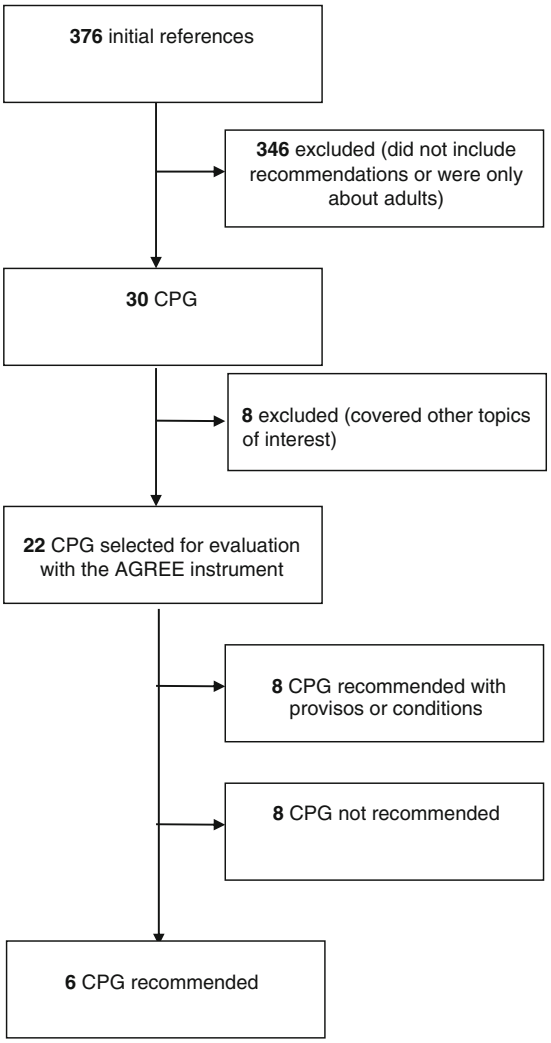
Of 376 references identified for possible inclusion, 346 were excluded as they did not provide recommendations or concerned only adults. A total of 30 documents were, thus, considered for inclusion [1, 4, 5, 7–9, 11, 13, 15–17, 20–22, 25–32, 36, 38–40, 44, 46, 49]. Five references were rejected as they were nutritional guidelines [17, 31–33, 44], recommendations to promote cardiovascular health [49] and for measuring the height and weight of children [14] and two reviews, one based on a previous CPG [15] and the other on anti-obesity drugs for adults [28] (Fig. 1).

Of the 22 selected CPGs, seven were from the United States, five from the United Kingdom, three from Canada, two from Malaysia and four from Singapore, Spain, Australia and France, respectively. The final one was the result of an international consensus [40]. Nearly half of the CPGs focussed on children and adolescents only, whereas the other half also considered adults. In relation to the scope of the CPGs, nine were about prevention and treatment, eight about prevention only and five about treatment. Half of the 22 CPGs were considered as evidenced-based according to our a priori criteria (Table 1).

Appraisal of guidelines

The overall ICC value among reviewers was very good (0.856; 95% CI 0.731–0.932). The results for e standardised domain of each domain of the AGREE instrument are as follows (Table 2):

Scope and purpose The score for this domain reflects the degree to which the overall objectives of the guideline,



CPG: clinical practice guidelines, AGREE: Appraisal of Guidelines Research and Evaluation

Fig. 1 Identification and evaluation of clinical practice guidelines for the prevention and treatment of the childhood overweight and obesity. CPG = clinical practice guidelines; AGREE = Appraisal of Guidelines Research and Evaluation

the clinical questions covered and the patients to whom the guideline was meant to apply were specifically described. The mean score for the selected CPGs was 68.4% and five of the guidelines scored below 50%.

Stakeholder involvement This domain evaluates the degree to which the guideline represents the views of its intended users. The aspects assessed include the composition of the guideline development group (specifically, if individuals from all relevant professional groups were represented), whether consumers' experiences and expectations informed the development of the guideline, whether the target users of the guideline were well-defined and whether the guideline was piloted among end-users. The mean score was 33.7%, with 14 of the CPGs scoring below 50%, suggesting a poor involvement of stakeholders in the guideline development. In only three of the 22 CPGs (9.1%) were consumers peer-reviewers and in two (9.1%), the consumers could be considered as authors. Nevertheless, all relevant professional groups were represented in most of them (73%).

Rigor of development This domain assures that the following issues were taken into account: systematic search methods for evidence; the criteria for selecting the evidence and the methods used to formulate the recommendations; an explicit link between the recommendations and the supporting evidence; description of health benefits; side effects and risks when formulating the recommendations; external revision of the guideline by experts prior to publication; and provision of a procedure for updating the guideline. The mean score for this domain was just 35.1%. Once again, 14 documents scored under 50% and did not mention any database in their search strategy. Over 50% of them did not include a system to evaluate the quality of the evidence or grade the strength of recommendations. All told, most of the documents (82.6%) included references within the text.

Clarity and presentation This domain describes the clarity of the guidelines and whether the recommendations are specific and unambiguous, the different management options are clearly presented, if key recommendations are easily identifiable and whether the guideline was supported with tools for its application. The mean score obtained by the guidelines was just over 50% (58.5%) and eight of 22 guidelines scored under 50%. Ten (45%) included a quick reference guideline, four (18.2%) a patient information section and only three (13.6%) had tools for their application.

Applicability This domain evaluates issues that are pertinent to guideline implementation. More specifically, it considers organisational barriers, cost implications and monitoring criteria. The mean score in this case was a low 24.5%. Sixteen scored under 50% and just five (22.7%) suggested or included indicators within to monitor their impact.

Editorial independence This domain evaluates the presence of conflicts of interest, specifically whether the guideline was editorially independent from the funding body and whether potential conflicts of interest were reported for the members of the guideline development group. The mean score was 45.1%. Most guidelines (12 of 22), scored under 50% and only seven (31.8%) had an explicit statement about the potential conflicts of interest.

Table 1 Clinical practice guidelines (CPGs) on the prevention and treatment of childhood overweight and obesity

Title	Country	Organisation	Year of publication	Population	Evidence-based/ consensus-based	Prevention/ treatment
Canadian clinical practice guidelines on the management and prevention of obesity in adults and children [26]	Canada	Canadian Medical Association (CMAJ)	2007	Adults/ children	Evidence	Prevention/ treatment
Prevention and management of obesity (mature adolescents and adults) [21]	United States	Institute for Clinical Systems Improvement (ICSI)	2005	Adults/ children	Evidence	Prevention
Childhood obesity. Recommendations of the Nutrition Committee of the Spanish Association of Pediatrics [25]	Spain	Spanish Pediatrics Association	2006	Children	Consensus	Prevention
Active healthy living: prevention of childhood obesity through increased physical activity [11]	United States	American Academy of Pediatrics. (AAP); Council on Sports Medicine and Fitness and Council on School Health	2006	Children	Consensus	Prevention
Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children [30]	United Kingdom	National Institute for Health and Clinical Excellence (NICE)	2006	Adults/ children	Evidence	Prevention
Primary prevention of childhood obesity [36]	Canada	Registered Nurses' Association of Ontario (RNAO)	2005	Children	Evidence	Prevention
Screening and interventions for childhood overweight [46]	United States	U.S. Preventive Services Task Force (AHRQ)	2005	Children	Evidence	Treatment
Overweight in children and adolescents: pathophysiology, consequences, prevention, and treatment [13]	United States	American Heart Association (AHA)	2005	Children	Consensus	Prevention/ treatment
Consensus statement: childhood obesity [40]	International	Obesity Consensus Working Group	2005	Children	Consensus	Prevention/ treatment
Overweight children and adolescents: a clinical report of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition [4]	United States	North American Society for Pediatric Gastroenterology, Hepatology and Nutrition	2005	Children	Consensus	Prevention/ treatment
Guidelines for the management of obesity in secondary care [9]	Northern Ireland, United Kingdom	Clinical Resource Efficiency Support Team (CREST)	2005	Adults/ children	Consensus	Treatment
Preventing childhood obesity [8]	United Kingdom	British Medical Association (BMA) Board of Science	2005	Children	Consensus	Prevention
Overweight, obesity and physical inactivity [7]	Canada	British Columbia Medical Association, British Columbia Ministry of Health	2005	Adults/ children	Consensus	Prevention/ treatment

Table 1 (continued)

Title	Country	Organisation	Year of publication	Population	Evidence-based/ consensus-based	Prevention/ treatment
Management of obesity in childhood [20]	Malaysia	Health Technology Assessment Unit, Malaysia	2004	Children	Evidence	Prevention/ treatment
Obesity [39]	Singapore	Singapore, Ministry of Health	2004	Adults/ children	Evidence	Treatment
Clinical practice guidelines on management of obesity [27]	Malaysia	Malaysia, Ministry of Health	2004	Adults/ Children	Evidence	Treatment
Storing up problems. The medical case for a slimmer nation [37]	United Kingdom	Royal College of Physicians of London	2004	Adults/ Children	Consensus	Prevention/ treatment
Managing obesity in children and adolescents [1]	France	Agence Nationale d'Accréditation et d'Évaluation en Santé (ANAES)	2003	Adults/ Children	Evidence	Prevention/ treatment
Guidelines for childhood obesity prevention programs: promoting healthy weight in children [5]	United States	Weight Realities Division of the Society for Nutrition Education	2003	Children	Consensus	Prevention
Prevention of pediatric overweight and obesity [23]	United States	American Academy of Pediatrics (AAP). Committee of Nutrition	2003	Children	Consensus	Prevention
Management of obesity in children and young people [38]	Scotland, United Kingdom	Scottish Intercollegiate Guidelines Network (SIGN)	2003	Children	Evidence	Prevention/ treatment
Clinical practice guidelines for the management of overweight and obesity in children and adolescents [29]	Australia	National Health and Research Council (NHMRC)	2003	Children	Evidence	Treatment

Overall recommendation Regardless of the fact that 11 (50%) of the guidelines included were initially considered to be evidence-based, following the formal evaluation with the AGREE instrument, we finally recommend six [21, 26, 29, 30, 36, 38] out of the 22 CPGs evaluated, that is, less than one third (27.3%). Eight [1, 4, 8, 13, 27, 37, 39, 46] are recommended with provisos and the remaining eight [5, 7, 9, 11, 20, 23, 25, 40] are not recommended (Table 2).

Discussion

Since 2003, a significant number of guidelines on the prevention and treatment of overweight and obesity in childhood have been published worldwide, particularly in the US and the UK. Nevertheless, these guidelines generally have significant limitations. This is reflected by the fact that, in our study, half of the 22 CPGs found were considered to be evidence-based. Previously, the National Guideline Clearinghouse (NGC) undertook a guideline synthesis of six prominent overweight and obesity guidelines in children and adolescents. This publication included a comparison of major recommendations and explored areas of agreement and disagreement [28].

Our evaluation based on the AGREE instrument showed that only six out of the 22 guidelines could be recommended and applied. These six documents had a well-defined, concise scope and purpose, rigorous methodology, clear presentation and explicit editorial independence and would be useful to health-care providers. Nevertheless, we acknowledge that these well-developed and well-structured CPGs are, in many cases, context-specific and their recommendations might require adaptation prior to use in other contexts. Higher quality guidelines were generally developed by institutions with important resources, highly skilled staff and a long tradition in this field, such as the

Table 2 AGREE domain-standardised scores for CPGs on the prevention and treatment of childhood overweight and obesity and overall recommendation

Guideline	Scope and purpose[1]	Stakeholder involvement[2]	Rigor of development[3]	Clarity of presentation[4]	Applicability[5]	Editorial independence[6]	Overall recommendation
Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children. NICE [30]	85	72	92	92	85	100	Recommended
Canadian clinical practice guidelines on the management and prevention of obesity in adults and children [26]	89	58	86	83	74	100	Recommended
Primary prevention of childhood obesity. RNAO [36]	100	58	83	94	52	67	Recommended
Prevention and management of obesity (mature adolescents and adults). ICSI [21]	89	58	68	83	70	72	Recommended
Management of obesity in children and young people. SIGN [38]	85	50	67	81	52	94	Recommended
Clinical practice guidelines for the management of overweight and obesity in children and adolescents. NHMRC [29]	96	67	86	81	11	72	Recommended
Obesity. Singapore MH [39]	74	61	48	78	22	22	Recommended with provisos or alterations
Screening and interventions for childhood overweight. AHRQ [46]	96	22	62	47	4	61	Recommended with provisos or alterations
Storing up problems. The medical case for a slimmer nation [37]	67	53	14	64	30	17	Recommended with provisos or alterations
Preventing childhood obesity. BMA [8]	78	19	14	67	19	22	Recommended with provisos or alterations
Managing obesity in children and adolescents. ANAES [1]	59	25	30	56	7	39	Recommended with provisos or alterations
Clinical practice guidelines on management of obesity. Malaysia MH [27]	89	25	19	61	0	22	Recommended with provisos or alterations
Overweight children and adolescents: a clinical report of the North	70	31	13	31	4	39	Recommended with provisos or alterations

Table 2 (continued)

Guideline	Scope and purpose[1]	Stakeholder involvement[2]	Rigor of development[3]	Clarity of presentation[4]	Applicability[5]	Editorial independence[6]	Overall recommendation
American Society for Pediatric Gastroenterology, Hepatology and Nutrition [4]							
Overweight in children and adolescents: pathophysiology, consequences, prevention, and treatment. AHA [13]	56	0	13	39	0	72	Recommended with provisos or alterations
Guidelines for the management of obesity in secondary care. CREST [9]	56	31	2	53	89	11	Not recommended
Management of obesity In childhood. Malaysia MH [20]	56	8	40	28	0	33	Not recommended
Prevention of pediatric overweight and obesity. AAP [23]	48	31	5	42	0	39	Not recommended
Guidelines for childhood obesity prevention programs: promoting healthy weight in children [5]	78	19	6	17	0	28	Not recommended
Overweight, obesity, and physical inactivity [7]	37	11	11	69	0	17	Not recommended
Active healthy living: prevention of childhood obesity through increased physical activity [11]	33	22	5	25	15	33	Not recommended
Childhood obesity. Recommendations of the Nutrition Committee of the Spanish Association of Pediatrics [25]	33	14	0	53	0	22	Not recommended
Consensus statement: childhood obesity [40]	30	6	8	42	4	11	Not recommended
Mean	68.4	33.7	35.1	58.5	24.5	45.1	

[1] Degree to which the overall objectives of the guideline and the clinical questions covered
[2] Degree to which the guideline represents the views of its intended consumers
[3] To what extent systematic methods for formulating the recommendations were taking into account
[4] Clarity of the guidelines and whether the recommendations are specific and unambiguous
[5] Evaluation of guideline implementation issues
[6] Evaluation of the presence of conflicts of interest

National Institute for Health and Clinical Excellence (NICE) [30] or the Scottish Intercollegiate Guidelines Network (SIGN) [38].

Only two of the six domains included in the AGREE instrument had a mean score over 50%, these being "Scope and purpose" and "Clarity of presentation." In the latter, although half of the guidelines had a quick reference guide or summary to facilitate the identification of key recommendations, less than 20% had specific guidance for patients. As in similar evaluations of CPGs in other fields

[3, 12, 18, 19], the lowest scores were obtained in the "Stakeholder involvement" and "Applicability" domains, signalling the difficulties and the complexity of involving consumers in guideline development and the lack of a tradition of guideline implementation, monitoring or cost consideration. Only five of the six documents included cost-effectiveness data or potential indicators for their evaluation. The domain "Editorial independence" also obtained a low score, with just over 30% of the guidelines including details about potential conflicts of interest.

Of most concern regarding the 22 guidelines identified was the low score obtained in the "Rigor of development" domain, indicating that many of the recommendations were based on unsound grounds and far from an evidence-based approach. The generally low quality of CPGs has been previously reported in paediatrics [6] and other fields [3, 12, 18, 19]. Nearly half of the documents did not report the databases searched or a structured approach to evaluate the quality of the evidence or grade the strength of recommendations. This lack of a rigorous and systematic evaluation of the best available evidence is a major drawback and could lead to unreliable or even harmful recommendations for patients [51].

Guidelines are widely accepted as useful tools for medical practitioners to improve patient care [50]. In the paediatric field, guidelines can help ensure that overweight and obesity be considered as a chronic condition with potential co-morbidities that should be diagnosed, followed and managed according to sound recommendations based on the best available evidence. Guidelines should be developed rigorously to improve their uptake and to foster patient care and safety. According to a US survey [16], paediatricians, like other physicians, are probably more likely to adhere to clinical guidelines if they are clear, evidence-based, easy to consult, realistic in alignment with clinical practice and improve clinical results. Most paediatricians concur that guidelines can improve patient care when they are flexible and not used punitively. Thus, the external, objective and standardised evaluation of existing guidelines, such as that undertaken in this review, provides useful and practical information to all potential users of guidelines on obesity in childhood.

A strong point of this review is the broad focus of our systematic search for documents in Medline (using a sensitive filter), guideline search engines, compiler entities and guideline developers' sites. Guidelines are not often published in biomedical journals and their search requires a multifaceted strategy, despite the existence of extremely useful search engines, such as the TRIP database [43]. Our work was not limited to publications in English, but also considered those in French and Spanish, providing a more representative international view. Furthermore, the high degree of agreement found in the independent evaluations by our three reviewers strengthens our confidence in the results.

Guidelines that follow the methodology proposed by the AGREE instrument [42] have a better chance of rigorous development. Nevertheless, the use of the AGREE instrument has some potential drawbacks. First of all, most of the criteria are based on theoretical assumptions rather than on empirical evidence. Furthermore, it assesses the likelihood of achieving an intended outcome, but it does not determine the guidelines' impact on patient outcomes. The validity of the overall assessment of the guidelines is another potential limitation of the AGREE instrument. Although the reviewers were instructed to consider the domain scores when making a decision about whether or not to recommend the guidelines, no clear rules were established as to how to weigh the differing domains. In light of this, a new project is currently underway by several members of the original consortium of international researchers to further refine the AGREE instrument [42]. The overall objective is to conduct research to better establish its psychometric properties, including validity, and to test its utility. If appropriate, a revised version of the instrument will be presented.

As in other healthcare fields, improvement is needed in the quality of CPGs for obesity and overweight in childhood. In order to make the needed shift happen, in practice, guideline producers should, when developing or updating guidelines, adhere more closely to the AGREE instrument. Finally, due to the increasing burden of obesity among children and the potential for long-term co-morbidities, clinicians need to have access to key recommendations from the best available guidelines, be critical of how these are developed and consider their appropriateness for use in their own clinical practice.

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Appendix 1

The sites searched for the identification of clinical practice guidelines are listed in this appendix.

Generic databases or search engines:

- PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmedov/entrez)
- Pubgle (http://www.pubgle.com/buscar.htm)
- TRIP database (http://www.tripdatabase.com)

Compiler entities, registries or clearinghouses:

- National Guideline Clearinghouse (http://www.guideline.gov/)
- CMA Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp)
- NHS (http://www.nhsdirect.nhs.uk/)
- GuíaSalud (http://www.guiasalud.es)

Guidelines developers:

- AHRQ (http://www.ahrq.gov/)
- ACP (http://www.acponline.org/index.html/)
- ICSI (http://www.icsi.org)
- NHMRC Guidelines Group (http://www.nhmrc.gov.au/)
- New Zealand Guidelines Group (http://www.nzgg.org.nz/)
- RCP Guidelines (http://www.rcplondon.ac.uk/college/ceeu/search/)
- SIGN (http://www.sign.ac.uk)
- NICE (http://www.nice.org.uk/)

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DISCUSIÓN

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Actualmente asistimos a un cambio con tendencias globales en la nutrición humana y por lo tanto en la infantil. Es la llamada transición nutricional, caracterizada por el consumo de mayor proporción de calorías provenientes de la grasa tanto vegetal como animal y de bebidas azucaradas al mismo tiempo que se ingiere más proteínas de origen animal. Estos cambios ocurren incluso en regiones (América Central, Suramérica y el Caribe) cuyos problemas nutricionales hasta 1980 se centraban en la desnutrición y en las enfermedades parasitarias. La transición nutricional produce modificaciones en la composición corporal, incrementando la proporción de grasa y por lo tanto el incremento de la prevalencia de las enfermedades crónicas relacionadas con la nutrición, como el sobrepeso, la obesidad y las enfermedades cardiovasculares (Lucas 2006).

Desde que el foco prioritario se centró hace dos décadas más en el impacto de la nutrición en la salud que en los requerimientos nutricionales, se dispone de un nuevo cuerpo de conocimientos para entender los efectos biológicos de la nutrición así como para la prevención primaria de enfermedades crónicas mediante la intervención nutricional desde la infancia. Incluso el concepto de prevención primaria se ha ampliado desde la reducción del riesgo de la enfermedad hacia la optimización del potencial de neurodesarrollo (Popkin 2006). Al mismo tiempo, es creciente la evidencia sobre el impacto a largo plazo de los desbalances de la nutrición en periodos sensibles o críticos sobre la estructura y función del organismo, el denominado *Programming* o programación metabólica (Lucas 2006, Wells 2009). Si bien la investigación inicial en la programación metabólica se centró en el periodo perinatal, no está restringida a ese periodo pues la forma de alimentación y los patrones de crecimiento durante la infancia se asocian más tarde con el riesgo de sobrepeso, obesidad y enfermedades cardiovasculares (Maynard 2003, Ness 1997). Estos hechos han llevado a reconocer que la nutrición debe ser vista en términos de intervención terapéutica que influye en la salud a distintos plazos y

por consiguiente, así, con esta concepción, este campo necesita de investigación primaria y de revisión formal (Lucas 2006).

Si se tiene en cuenta que la transición nutricional ha traído consigo un rápido incremento de la prevalencia de la obesidad infantil y sus comorbilidades en los países desarrollados y en las naciones emergentes (Adair 2005, Popkin 2006), es importante llevar a cabo una síntesis de la investigación basada en evidencias principalmente de ensayos clínicos aleatorizados, -que reducen en lo posible la confusión y por lo tanto establecen con mayor validez la causalidad-, que evalúen tanto las intervenciones nutricionales que prevengan la aparición de las enfermedades crónicas del adulto como la calidad de las GPC donde están las recomendaciones sobre el tema para quienes hacen estrategias preventivas y las políticas en nutrición y para los clínicos que deben prevenir y tratar el sobrepeso y la obesidad infantil.

En otras palabras, la síntesis de las evidencias en el campo de la nutrición infantil permite a quienes toman decisiones en salud poder establecer políticas de manera informada, estructurada y rigurosa. Al clínico la síntesis le facilita la evaluación de los efectos de las intervenciones de una manera más rápida y puede ser más crítico a la hora de interpretarla y aumentar su confianza en las recomendaciones a sus pacientes.

Por ello el compendio de publicaciones de esta tesis doctoral evaluó la calidad de la evidencia disponible, los efectos encontrados y la factibilidad de varios aspectos de la nutrición materno-infantil: los efectos en los hijos de la suplementación a las madres lactantes con LCPUFA (*Long chain polyunsaturated Fatty Acids*) y la evaluación de la calidad de las GPC para la prevención y tratamiento del sobrepeso y la obesidad infantiles. Así mismo, también se valoró la eficacia de las intervenciones para promover el consumo de frutas y verduras en ambientes escolares. De esta manera, estos aspectos de la nutrición infantil son evaluados en el presente trabajo desde la metodología de la medicina basada en la evidencia.

Efectos sobre el crecimiento y desarrollo de sus hijos de la suplementación con LCPUFA a madres lactantes

Se identificaron seis estudios realizados en países desarrollados con 20 reportes cuya población estuvo constituida por madres sanas, sin embarazo complicado y con intenciones de lactar a sus hijos. De los seis, cuatro iniciaron la suplementación durante la gestación y la continuaron durante el periodo de la lactancia. La revisión sistemática no demostró efectos significativos en el neurodesarrollo. Para facilitar el análisis, al encontrar que los estudios a menudo presentaban evaluaciones en distintas áreas del desarrollo infantil y múltiples evaluaciones en el tiempo, los resultados se dividieron en cinco áreas del neurodesarrollo (desarrollo del lenguaje, habilidad para resolver problemas, desarrollo psicomotor, desarrollo motor y atención) y en tres periodos de seguimiento: corto plazo (hasta el primer año de la vida del niño); mediano plazo (hasta los dos años) y largo plazo (después de los dos años). No obstante estas variaciones en los estudios y la variedad en las mediciones, se objetivó una moderada heterogeneidad entre los ensayos clínicos. El metanálisis se llevó a cabo en cuatro de las cinco áreas: desarrollo del lenguaje, desarrollo psicomotor, habilidad para resolver problemas y desarrollo motor sin demostrar en ninguna de ellas un efecto combinado significativo. (Anexo III, Tabla 1)

De manera individual, después de hacer el análisis de sensibilidad, retirando uno de los estudios que tenía alto riesgo de sesgo, se encontró que había una diferencia significativa en el largo plazo a favor del grupo suplementado en relación al desarrollo psicomotor. En ese plazo, el mismo estudio mostró un efecto semejante en la atención del niño (Jensen 2005) y otro estudio (Lauritzen 2004) encontró diferencias significativas en el desarrollo del lenguaje.

En el siguiente resultado de la revisión, el desarrollo visual de los niños, se encontraron tres estudios en el corto plazo sin heterogeneidad entre ellos, cuyo metanálisis no mostró diferencias significativas entre el grupo de madres suplementadas y el que no recibía suplementos (Anexo III, Tabla 1).

Respecto al crecimiento de los niños, no hubo diferencias entre los dos grupos en el peso pero en el perímetro cefálico y en la talla el metanálisis de dos estudios en el largo plazo (Lauritzen 2004, Helland 2001) mostró que el crecimiento fue significativamente menor en la talla y mayor en estos dos parámetros en el grupo suplementado. El incremento del perímetro cefálico también ha sido reportado en una revisión sistemática con metanálisis que evaluaba esta medida en los hijos recién nacidos de madres suplementadas con LCPUFA durante el embarazo (Szajewska 2006). También se reportó en Lauritzen 2004, a los siete años de edad de los niños, que tanto la tensión arterial sistólica como la diastólica se elevaron en el grupo suplementado (3.8mm de Hg y 2.3mm de Hg, respectivamente). En Furuhjelm 2009, se reportó disminución del riesgo de alergia en los niños en el grupo suplementado. Respecto a los efectos en las madres, el efecto de la suplementación con LCPUFA en la depresión posparto no fue significativo en el análisis combinado de dos estudios.

En la revisión no se encontraron datos respecto a la seguridad de la suplementación, tomándola como la posible contaminación con Mercurio de las fuentes de suplementos. El número de ensayos clínicos por variable de resultado osciló entre uno y tres en el caso de las áreas de desarrollo y crecimiento infantiles y fueron tres los estudios en el caso del desarrollo visual. En cuanto a los efectos secundarios la información disponible fue escasa.

Hay varias situaciones actuales que atañen a la suplementación de las madres con LCPUFA. Su fuente natural en madres lactantes es la grasa de algunos peces oceánicos y su ingesta tiene una amplia variabilidad geográfica de tal manera que la concentración en la leche materna depende de la cantidad de LCPUFA ingerida por la madre (Torres 2009, Brenna 2007). Por otra parte, los suplementos con LCPUFA se utilizan de manera global y amplia con venta libre en muchos países (Jensen 2006). Los efectos de su carencia en niños, los potenciales efectos en su neurodesarrollo y en otras áreas, como la modulación del sistema inmune y la prevención del síndrome metabólico, han hecho que

paneles de expertos recomienden su suplementación a las madres lactantes (Koletzco 2008).

Así mismo se ha generado un estímulo para una activa investigación en ese campo (Agostoni 2008) porque se considera que los factores nutricionales llamados ahora funcionales como los LCPUFA, durante el inicio del desarrollo humano, tienen efectos a largo plazo sobre la salud y en los riesgos de morbilidad y mortalidad en la etapa adulta.

Pero a la luz de esta revisión, dado el limitado número de ensayos clínicos aleatorizados encontrados y que no encuentra diferencias significativas consistentes entre los grupos, sería preferible esperar más estudios con mediciones a largo plazo y en distintas regiones geográficas que tienen diferentes niveles de consumo de pescado para recomendar la suplementación en madres que lactan para mejorar el desarrollo y crecimiento de sus hijos. También es relevante señalar que la revisión encuentra un aumento de la circunferencia cefálica y disminución de la talla en los niños de los grupos suplementados, efectos que deben estudiarse.

Cabe la posibilidad que las recomendaciones actuales sean de utilidad en las regiones geográficas donde el consumo de pescado, fuente natural de LCPUFA, no es habitual entre las mujeres que lactan, pero es necesario que las recomendaciones tengan bases suficientes y adecuadas en ensayos clínicos a plazos más largos que den información adicional.

En general, la calidad de la información en esta revisión puede ser considerada como moderada por provenir del escaso número encontrado de ensayos clínicos aleatorizados con calidad igualmente moderada. Por ello, es probable que estudios posteriores, suficientes y con mediciones más uniformes y exactas de los eventos del neurodesarrollo que aumentarían la uniformidad y validez de los resultados, tengan un importante impacto en la confianza en la estimación del efecto disponible y sirvan de base para recomendaciones de suplementación con LCPUFA en mujeres lactantes que tengan en cuenta los beneficios y los potenciales efectos como los detectados en uno de los ensayos

clínicos de esta revisión y cuyo significado no es claro (Asserhoj 2009). Las revisiones Cochrane como es el caso de ésta actualizan sus búsquedas periódicamente después de la primera publicación (The Cochrane Collaboration 2008). En aquel momento es posible que nueva evidencia permita hacer un análisis de subgrupos con aquellas madres que iniciaron la suplementación desde la gestación y la continuaron durante la lactancia y con aquellas que sólo fueron suplementadas en este último periodo.

Entre las fortalezas de esta revisión se encuentra haber organizado la información acerca del efecto de la suplementación en las madres lactantes en cinco áreas del neurodesarrollo y en distintos tiempos de evaluación de tal manera que los resultados tuvieran una mayor comprensibilidad y utilidad para los lectores. Otra fortaleza radica en que es la primera revisión sistemática sobre el tema que culmina en un análisis cuantitativo. Las limitaciones proceden del escaso número de estudios encontrados y de su grado de evidencia moderada. También las limitaciones provienen de las dificultades para contactar a uno de los autores de un ensayo clínico. Dado que tenía múltiples reportes, algunos en resúmenes de congresos, era de importancia aclarar datos faltantes o si se estaban llevando a cabo estudios con seguimientos más largos a partir del estudio inicial.

Calidad de las Guías de Práctica Clínica para la prevención y tratamiento del sobrepeso y la obesidad infantiles

Desde 1998 un número significativo de guías sobre el tema han sido publicadas por diversos países, principalmente en Estados Unidos y Reino Unido, sobre prevención y tratamiento del sobrepeso y la obesidad infantil. De las 376 referencias identificadas se seleccionaron 22 GPC. Las entidades financiadoras de las guías correspondieron a entidades públicas en la mitad de los casos y en la otra mitad a asociaciones científicas. En cuanto al enfoque 34.7% de las GPC lo hicieron tanto en tratamiento como en prevención, 34.7% en prevención y 21.7% en tratamiento únicamente. Aproximadamente la mitad

de las GPC estaban dirigidas exclusivamente a niños o adolescentes; las restantes a niños y a adultos.

La mitad de las GPC fueron consideradas como basadas en la evidencia. De los seis dominios del instrumento AGREE (*Appraisal of Guidelines Research and Evaluation)* con el que se valoró su calidad, solamente dos, "Enfoque y propósito" y "Claridad de la presentación", tuvieron una puntuación por encima del 50%. Aunque la mitad de las GPC proveían de un apartado breve para los pacientes con el fin de identificar las recomendaciones más importantes, solo cuatro de ellas contaban con guías específicas para los pacientes.

Lo más preocupante fue la puntuación baja (poco más del 35%) obtenida en el dominio de "Rigor en la elaboración" lo que indica que muchas de las recomendaciones no se basaron en la evidencia. Casi la mitad de los documentos no informaron sobre las bases de datos buscadas ni ofrecieron un plan estructurado para evaluar la calidad de la evidencia o el grado de la fuerza de las recomendaciones.

Si bien las diferencias entre las directrices internacionales encontradas sobre el manejo del sobrepeso y la obesidad presente en las GPC podrían reflejar de alguna manera las variaciones de la estructura de los servicios de salud de los países, de los recursos y de la cultura (Kipping 2008), éstas pueden explicarse con mayor contundencia por los cimientos poco sólidos y escasamente basados en una evaluación exhaustiva y estructurada de la calidad de la mejor evidencia disponible y ser, por lo tanto, incluso deletéreas para los pacientes.

Este hecho también se ha encontrado en otras evaluaciones de la calidad de guías con el instrumento AGREE, tanto en pediatría (Boluyt 2005) como en otros campos clínicos (Arnau 2006, Cranney 2002, Graham 2001, Harpole 2003). Sorprende que sólo cerca de la mitad de los documentos en estudio mostraran de manera explícita las bases de datos consultadas y un sistema de recomendaciones. Este hecho no es una muestra de transparencia y podría generar desconfianza en los profesionales sanitarios en el momento de aplicarlas.

Una guía que haya seguido la metodología del instrumento AGREE tiene más probabilidades de haber tenido una elaboración rigurosa (AGREE 2003). En el caso del sobrepeso y la obesidad infantiles seis de las guías (27.3%) que se recomiendan podrían emplearse con razonable confianza, con la salvedad de que han sido elaboradas para ser aplicadas en contextos sociales y sanitarios específicos.

Es reconocida la utilidad de las GPC como una de las herramientas en el trabajo médico para mejorar la calidad del cuidado de la salud (Woolf 1999). En el campo del sobrepeso y la obesidad infantiles las GPC tienen el potencial de influir en el personal sanitario en la visión y manejo de estas condiciones como entidades crónicas que se deben diagnosticar y seguir de manera adecuada, y manejar de acuerdo a directrices apropiadas que provengan de la mejor evidencia. Por lo tanto, las guías deben ser elaboradas con rigor y calidad para evitar que los médicos no las usen y para garantizar la seguridad y la calidad de atención a los pacientes. Este aspecto es importante para los médicos pues según una encuesta sobre el empleo de las GPC hecha a pediatras de Estados Unidos, éstos respondieron mayoritariamente que su uso sería más probable si las guías eran claras, basadas en evidencia, fáciles de seguir y si fueran percibidas como viables en la práctica y demostraban resultados clínicos positivos. La mayoría de los pediatras encuestados dijeron además que las GPC pueden mejorar el cuidado del paciente cuando son flexibles, se elaboran e implementan sin el objetivo de reducir costos o cuando no solamente se implementan para evitar punibilidad (Flores 2000).

Entre las fortalezas de esta revisión se encuentra una búsqueda exhaustiva de las principales bases de datos con documentos en inglés, castellano y francés. Por otro lado la evaluación independiente por parte de los tres revisores con un alto grado de acuerdo (ICC 0.85 IC95% 0.71-0.93), mejora la confianza en los resultados y aporta importantes enseñanzas de cara a la elaboración de futuras guías. Las limitaciones del estudio provienen del mismo instrumento de evaluación que no está diseñado para evaluar la calidad de las recomendaciones sino para evaluar el proceso del desarrollo de la guía y la

manera cómo ese proceso esta reportado (AGREE 2003). Otra de las posibles limitaciones radica en la dificultad en la búsqueda de las GPC y en la localización de manera sistemática a pesar de herramientas valiosas como TRIP Database, un metabuscador que clasifica los documentos encontrados por diseños de investigación, en este caso GPC y por países elaboradores (TRIP Database 2010). Esta dificultad radica en que algunas de las guías se presentan como documentos que no se publican habitualmente en revistas indexadas, están incompletas o publicadas de manera parcial en la web o, -menos frecuentemente-, no son accesibles a menos que se pague por ellas. No obstante nuestra búsqueda fue sistemática incluyendo la consulta de metabuscadores, *clearing houses*, instituciones elaboradoras y consulta con una estrategia de búsqueda en Medline.

En concreto, en vista de la tendencia creciente y global de la prevalencia del sobrepeso y la obesidad infantiles y dado que tienen una fuerte tendencia a persistir en la vida adulta, contar con herramientas de calidad para que tanto los clínicos e instituciones y los pacientes afronten el problema es fundamental. Sin embargo, el potencial de las guías para mejorar el uso de los recursos y el cuidado de los pacientes depende en gran parte del rigor de su elaboración y de un procedimiento de diseminación e implantación rigurosas. Sobre la base de esta revisión recomendamos que las futuras GPC sobre el tema tengan en cuenta para su elaboración el instrumento AGREE.

En la misma línea de investigación de la tesis se evaluó la efectividad de las intervenciones en el ámbito escolar para incrementar el consumo de frutas y verduras. Para tal efecto se llevó a cabo una revisión sistemática mostró que a nivel general la mayoría de las encontradas son efectivas en el incremento de la cantidad consumida, dando consistencia a las revisiones sistemáticas anteriores sobre el tema (Knai 2006, de Sa 2009). Knai encontró en su revisión un aumento del consumo de frutas y verduras en un rango de +0.3 a 0.99. Se encontraron además varias revisiones narrativas previas con búsquedas y enfoques limitados (French 2003, Howerton 2007).

Después de aplicar los criterios de elegibilidad, se seleccionaron 18 estudios que fueron considerados intervenciones en clúster pues aleatorizaron grupos, en este caso clases o escuelas, más que individuos. Las intervenciones tuvieron lugar en países desarrollados y fueron variadas como cabía esperar en las denominadas intervenciones complejas en el campo de la salud pública que a menudo están constituidas por varios componentes. También podía esperarse una elevada heterogeneidad entre los estudios proveniente de la variación de las intervenciones, de la medición de los resultados y de los contextos.

Para dar claridad a los resultados y facilitar los análisis, se organizaron las intervenciones en tres clases: intervenciones que empleaban juegos de mesa, videos o Internet, intervenciones provenientes de programas de gobiernos donde se ofrecía o se subsidiaba frutas y verduras a las escuelas e intervenciones con varios componentes o multicompontes que involucraban maestros, familia, ambiente escolar o cambios en los currículum escolares como por ejemplo la participación de los alumnos en las actividades de preparación culinaria de las frutas y las verduras, el uso de modelos que promocionaran el consumo de frutas y verduras como héroes de comic, o la participación en la intervención del personal de los comedores y de personas de la comunidad. Se hicieron, además, subgrupos según el tipo de diseño, ensayos controlados aleatorizados o ensayos clínicos controlados.

Se encontraron tres estudios cuyas intervenciones estaban basadas en video, videojuegos o Internet. Se llevó a cabo un metanálisis de dos estudios con similar diseño y sin heterogeneidad entre ellos que mostró efectividad en incrementar el consumo de frutas y verduras en la población de escolares. La calidad de los estudios fue moderada. Si se tiene en cuenta que la edad escolar es una edad en la que el juego cumple un destacado papel vital y de aprendizaje en la vida de los niños (Horne 1995), que las prácticas alimenticias de los niños en edad escolar pueden ser maleables y que tienen el potencial de ser influidas por situaciones que ellos encuentren divertidas, -entre ellas los

juegos y personajes de comic-, en los ordenadores ya sean por multimedia o Internet, esta clase de intervención debe promoverse y recomendarse. (Anexo III, Tabla 2)

En cuanto a las intervenciones multicomponentes se encontraron 11 estudios de calidad moderada. Se llevó a cabo un análisis combinado entre ensayos controlados aleatorizados ya que la heterogeneidad encontrada estuvo por debajo de los límites preestablecidos. El efecto a favor de los grupos intervenidos fue cercano al nivel de significancia (Standarized Mean Difference 0.00; IC95% -0.08, 0.17). (Anexo III, Tabla 3). En los ensayos clínicos controlados no se llevó a cabo un metanálisis por la alta heterogeneidad encontrada.

A escala general, el efecto hallado en las revisiones previamente mencionadas es consistente con el de la presente revisión, si bien en aquellas no se llegó a realizar metanálisis. Una vez analizados los efectos al nivel según el tipo de intervención sólo mostraron efectividad significativa en aquellas intervenciones que empleaban computadores con juegos de mesa o videos si bien las intervenciones con multicomponentes tuvieron una efectividad cercana al nivel de significancia. Existe la posibilidad de que al combinar solamente resultados de los estudios por tipo de diseño y por calidad, el efecto de las intervenciones multicomponentes sea menor pero más real. Futuros estudios con adecuado diseño, que tomen en cuenta el efecto clúster, pueden añadir más confianza en la efectividad de las intervenciones con multicomponentes. El efecto encontrado en esta revisión en el consumo de frutas y verduras por los escolares resalta el hecho del requerimiento infantil de un ambiente adecuado y favorable, motivación y apoyo para consumir más frutas y verduras y llegar a la cantidad de 400 grs. al día o a las 5 porciones al día que en la actualidad se recomiendan (WHO 2002, Thomas 2003).

Por último, los tres estudios hallados de intervenciones que promovían el consumo de frutas y verduras por medio de subsidios o de acceso libre a las frutas y las verduras no mostraron efectos significativos a favor de la

intervención y fueron de calidad moderada. Dos de ellos, ensayos controlados aleatorizados, se combinaron en metanálisis pues su heterogeneidad era baja, pero su efecto combinado no fue significativo (Anexo III Tabla 4). A la luz de este hallazgo, parece que los niños en la edad escolar no solo necesitan un acceso más fácil o libre a las frutas y las verduras sino que también requieren de motivación, de ambientes estimulantes y de modelos para incrementar el consumo (Knai 2006). A la par se encuentran en la literatura datos crecientes sobre la necesidad de intervenciones que eviten barreras u opciones que impidan el consumo de frutas y verduras o que eviten el consumo de comida calóricamente densa (*junk food*). Por lo tanto, se debe tender a estimular y promover ambientes escolares adecuados para hacer elecciones sanas (*healthy food*) en cuanto a su alimentación (Thomas 2003).

Con esta revisión se afianza el hecho de que las escuelas son ambientes convenientes y adecuados para intervenir y moldear las conductas sanas alimenticias de los niños que tienen el potencial de persistir en la etapa adulta y por lo tanto reducir la creciente epidemia de sobrepeso y obesidad en los países desarrollados y los que están en la transición nutricional y contribuir en mediano y largo plazo a la reducción de la prevalencia de las enfermedades crónicas que tienen raíces en la infancia y (Briefel 2009). Las conductas sanas alimenticias, denominadas "*Healthy Eating*", se promueven en estrategias para la prevención de enfermedades crónicas como la diseñada por la OMS (WHO 2003).

En los estudios primarios, se objetivaron limitaciones importantes en el diseño, la mayoría asociados con la ausencia de información explícita sobre la forma de aleatorización y el mecanismo de ocultación de la secuencia de la misma. También fue notorio que muchos estudios no tomaron en cuenta el error proveniente de la unidad de análisis o "*unit of analysis error*" que consiste en no tomar en cuenta para el tamaño muestral el hecho de que en las intervenciones en clúster no aleatorizan individuos sino grupos de individuos, en este caso salones de clase o escuelas. En este tipo de estudios existe la posibilidad de un sesgo de selección porque los grupos no se forman por la asignación al azar, sino más bien a través de alguna conexión física, social, geográfica o de

otro tipo entre sus miembros. Por lo tanto los ensayos en clúster requieren de un mayor tamaño de muestra porque la correlación entre los miembros de la agrupación reduce la potencia global del estudio (Higgins 2008). El error proveniente de la unidad de análisis se corrigió en la presente revisión y constituye en una de las fortalezas de la revisión.

Los estudios primarios tampoco ofrecieron sus resultados de manera explícita y homogénea, elevando el nivel de dificultad en la extracción de los datos. Es por lo tanto recomendable que futuros trabajos adopten guías de información como CONSORT que ya se ha extendido a los estudios de intervención en clúster (Campbell 2004).

En el futuro sería además importante probar la efectividad de las intervenciones con juegos de mesa/videos o Internet, que han demostrado ser consistentemente efectivas en las revisiones sistemáticas, en los países emergentes donde la transición nutricional también reclama bases sólidas para políticas en la prevención de la epidemia de sobrepeso y obesidad que los aqueja (Uauy 2002).

Una posible limitación de esta revisión es no haber llevado a cabo una búsqueda en la literatura gris o no publicada, lo que puede inducir a un sesgo de publicación. Sin embargo, el sesgo puede ser pequeño pues se revisaron las listas de referencias de los estudios primarios y se logró captar estudios adicionales. En futuras actualizaciones de la revisión se puede hacer una estrategia de búsquedas en esa clase de literatura. Entre las fortalezas de esta revisión se encuentra en ser la primera revisión sistemática sobre el tema que termina en un análisis combinado y cuantitativo de los datos por tipo de intervención y por tipo de diseño de investigación y el haber tomado en cuenta el tamaño efectivo de la muestra (*effective sample size*) para los cálculos de los efectos de las intervenciones, lo que a su vez produce una mayor validez de los resultados de la revisión pues varias de las revisiones previas no habían corregido ese error o no lo hacían explícito.

Como conclusión, cabe recordar que el principal objetivo de la investigación epidemiológica en nutrición es proporcionar la mejor evidencia posible para apoyar el entendimiento de su papel en las causas y la prevención de las enfermedades. Entre las fortalezas de la presente tesis destaca el haber analizado y actualizado las evidencias actuales relacionadas tanto con la prevención como con el manejo de diversas condiciones en el campo de la nutrición infantil. Asimismo, el haber seguido una metodología lo más adecuada posible en las tres revisiones, tratando al mismo tiempo de organizar de manera clara la información existente. Sin embargo, la tesis no está exenta de algunas debilidades que provienen del escaso número de ensayos clínicos encontrados, de la calidad moderada de la evidencia y de las características propias del instrumento AGREE.

CONCLUSIONES

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1. La evidencia de un efecto benéfico de la suplementación con LCPUFA (*Long chain polyunsaturated Fatty Acids*) a madres lactantes respecto al placebo es escasa sobre el crecimiento y desarrollo de sus hijos y por lo tanto no se recomienda la mecionada suplementación. Dado que los LCPUFA son nutrientes que pueden tener potenciales beneficios en el desarrollo infantil, futuros estudios deben contar con mediciones más uniformes, ser llevados a cabo en plazos más largos, y deben evaluar los posibles efectos secundarios. También es necesario realizar el análisis de subgrupos de los ensayos clínicos encontrados según el periodo de suplementación (gestación y lactancia, y solamente lactancia).

2. La calidad de las GPC (Guías de Práctica Clínica) sobre la prevención y tratamiento de la obesidad infantil no es suficientemente adecuada. Es necesario mejorar la calidad de las GPC sobre el tema pues son herramientas de utilidad para confrontar esta condición que afecta de manera creciente a la población infantil. Las nuevas GPC sobre el tema deben ser elaboradas con el rigor metodológico propuesto por el instrumento AGREE (*Appraisal of Guidelines Research and Evaluation*). .

3. Las intervenciones para aumentar el consumo de frutas y verduras en el ámbito escolar son efectivas. El efecto encontrado es consistente en términos generales con revisiones anteriores. A nivel particular, sólo demostraron efectividad aquellas intervenciones que usaron los computadores con juegos de mesa o videos. Existen algunos aspectos metodológicos que deben mejorarse en futuros estudios: mostrar sus resultados de manera explícita y homogénea, tomar en cuenta el efecto clúster y reportar adecuadamente la manera de aleatorización. También es necesario que se realicen intervenciones en países de medianos ingresos pues la evidencia existente hasta ahora proviene de áreas desarrolladas.

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ANEXOS

Anexo I. Revisión sistemática sobre la efectividad de las intervenciones en el ámbito escolar para incrementar el consumo de frutas y verduras.

Delgado Noguera MF, Tort S, Martínez MJ, JA, Bonfill Cosp X. ***School-based interventions for promoting consumption on fruits and vegetables in primary school: a systematic review.*** En revision en Preventive Medicine.

ABSTRACT

Objective
To assess the effectiveness of school-based interventions designed to increase fruit and vegetable (FV) consumption in children aged between 5-12 years.

Methods
We conducted a systematic review of randomised clinical trials (RCTs) and controlled clinical trials (CCTs) to evaluate primary school-based interventions. We performed a search in MEDLINE, EMBASE, CINAHL and CENTRAL and checked references from published articles. Data were extracted from the trials that received a strong or moderate methodology quality rating. We pooled the results and stratified the analysis according to the type of intervention (free/subsidized FV, multicomponent interventions, and computer-based interventions) and study design. We performed a meta-analysis using a random effects model in RevMan 5.0.

Results
The search identified 1683 studies. Eighteen were included and all were cluster studies. Twelve were RCTs and six were CCTs. Most studies did not describe the randomisation method and did not take the cluster's effect into account in the analysis. Pooled results of two RCTs (606 participants) of computer-based interventions showed effectiveness in improving consumption of FV [Standardized Mean Difference (SMD) 0.33 (95% CI 0.16, 0.50)]. No significant differences were found in the pooled analysis of seven RCTs (4800 participants) of multicomponent interventions [SMD 0.00 (95% CI -0.08, 0.17)] or in the combined results of two RCTs (1536 participants) evaluating free/subsidized FV interventions [SMD 0.02 (95% CI -0.08, 0.12)].

Conclusions
Our meta-analysis shows that computer-based interventions were effective in increasing FV consumption, multicomponent interventions point out a trend towards effectiveness, although this result was not statistically significant. Free/subsidized FV interventions were not effective. Improvements in methodology are needed in future cluster studies in order to learn more about the effectiveness of interventions to improve FV intake in primary school children.

Keywords: systematic review; fruit; vegetables; schools; children; randomised controlled trials; controlled clinical trials.

INTRODUCTION

Both developed and developing countries are confronting chronic disease challenges related to nutrition transition and increase in obesogenic environments[1]. The increase of overweight and obesity, and the subsequent growth in chronic disease prevalence have sounded the alarm bells.[1-2] Proposed actions include improving the consumption of fruit and vegetables (FV) in children and adolescents [2-3]. The benefits of including FV in the habitual diet are well established.[2-4] Daily consumption of 400 grams/day starting from childhood can prevent chronic diseases in the future such as cardiovascular diseases, overweight and obesity,[3-5] as well as certain types of cancer and micronutrient deficiencies.[3,6] However, international data show that the consumption of FV is insufficient both in adults and children, and their low intake is among the top 10 risk factors contributing to attributable mortality.[3-4]

Food habits and preferences are established in childhood and tend to be maintained into adult life, as shown in longitudinal studies.[8, 9] As children spend much of their time in school and many of their lifestyle factors and behaviours are established in this environment, schools are a logical setting for implementing interventions to improve the consumption of FV, [10-12] and to help to achieve a long-term impact on the reduction of chronic illnesses that can be prevented from infancy.[2]

Interventions to promote consumption of FV in schools are varied. Some of them are based on free provision of FV at school[10] whereas others are focused on changes in the school environment[13] and on determinants of FV consumption such as knowledge and skills, and the involvement of parents and teachers.[10, 12] Some school-based interventions to promote consumption of FV contain several components, such as nutritional education, media campaigns, food services, and involvement of parents and teachers, that may act independently or interdependently to generate an effect.[14]

The aim of this study was to systematically review the effectiveness of interventions promoting consumption of FV in primary school children.

METHODS

In this review we included all randomised controlled trials (RCTs) and all controlled clinical trials (CCTs) that promoted consumption of FV in the primary school setting. Both types of trials could include studies with a cluster design, where the unit of analysis is a group instead of an individual.

Studies were identified through a search in electronic databases: MEDLINE (through PubMed) (1966 – October 2009), CENTRAL (The Cochrane Library 2009, Issue 3), CINAHL (1982 – October 2009) and EMBASE (1980 – October 2009). Search strategies were adapted according to the requirements of individual databases. Search terms were: randomised controlled trial, controlled clinical trial, random allocation, randomised, randomly, trial, placebo, school, health promoting programme, intervention, school-based intervention, school-based, school health services, child nutrition ciences, fruit, vegetables, salad, juice. Relevant articles were hand searched for any additional references. There were no language restrictions. Three reviewers (MD, MJM, ST) independently reviewed titles and abstracts and selected the papers.

We included all school-based interventions that studied environmental school change strategies, health education approaches and computer games in attempts to increase FV consumption. We did not exclude studies that jointly evaluated interventions to promote FV and increase physical exercise. Interventions could be delivered by any staff in the school environment that promoted or influenced changes in FV consumption in children aged 5 to 12 years. In all studies the primary outcome considered was FV intake. We included all studies that measured FV consumption at the end of follow-up, and all studies that compared FV consumption at the end of study with baseline. We extracted data using standardised forms based on the RevMan 5.0 table of study characteristics.[15]

The methodological quality of selected studies was assessed by three of the authors (MD, MJM, ST). The quality of primary studies was tested using the Quality Assessment Tool for Quantitative Studies (QATool**)** from the Effective Public Health Practice Project of Ontario.[16] We extracted and analysed only data from studies with a strong or moderate quality.

Statistical Analysis

Changes in FV consumption were stratified into three groups according to the type of intervention: free or subsidized FV distribution at school, computer-based approaches and multicomponent strategies consisting of more than one approach.

Data were pooled when possible. The effect of the intervention was measured as a standardised mean difference (SMD) with a 95% confidence interval (95% CI). We used SMD because the primary outcome was continuous and we expected some variability in the way outcomes were measured. We analysed subgroups by stratifying studies according to the design (RCT or CCT). When data on FV consumption was given in grams and could not be combined with the other studies, we calculated the mean difference (MD) (95% CI).

Studies with a cluster design were assessed for unit of analysis error that may occur when such trials do not take clustering into account.[17-19] We corrected for this error following the guidelines of the Cochrane Handbook.[20] We thus reduced the size of each trial to its effective sample size using an Intracluster Correlation Coefficient (ICC) of 0.02 to estimate the relative variability within and between clusters (Table 1).

We estimated heterogeneity between studies using the variability percentage (I^2). If no substantial heterogeneity was identified (I^2<70%), we estimated pooled treatment effects using a random effects meta-analysis in RevMan 5.0.[15]

RESULTS

Literature Search

Of the 1683 references identified, 1582 were excluded as they did not meet all the inclusion criteria. A total of 101 studies were considered for inclusion. Four additional articles were added from lists of references. Of these 105 studies, 53 were excluded and 52 were examined in full text. Of these, 25 were excluded as they did not meet our eligibility criteria, 27 were obtained in full text and 18 were finally included (Figure 1).

Characteristics of the studies

The QATool was applied to the 27 studies evaluated in full text. Five were rated as strong quality, thirteen moderate and nine weak. In the trials rated as weak,[21-29] study design, selection bias and blinding were the main weakness and these studies were excluded. In the 18 remaining (graded as strong or moderate), twelve were classified as RCTs[30-41] and six were classified as CCTs.[42-47]

The follow-up of the studies ranged from five weeks to three years. Twelve of the eighteen studies had follow-up of less than a year. Four studies were performed in low socio-economic status populations in high-income countries [35, 38-40]. Table 1 summarised study characteristics. Most of the study interventions were guided by the constructs of Social Cognitive Theory.[48]

All 18 studies included groups of individuals and were thus considered cluster trials. Five of the 18 did not take into account the effect of cluster sample size (27.2%). Table 1 shows the effective sample size, which was recalculated for those studies that did not take this effect into account.

Effects of interventions

Data were pooled by type of intervention and design (Table 2).

Free/subsidized FV

Three studies compared groups that received free/subsidized FV with groups that received no intervention. Two of these, Bere [33] and Moore et al's [35] were RCTs. Bere's intervention provided subsidized FV. At the end of the second year, this intervention showed an increase in consumption of +0.59 servings of FV per day. Moore's intervention established a subsidized fruit tuck shop for one year, but the consumption of FV did not increase. A pooled analysis of these two studies (1536 participants) found no significant differences between intervention and control groups (SMD 0.02, 95% CI -0.08, 0.12; I^2=0%).

The third study, (Ransley et al.[46]) was a CCT. The intervention consisted of giving each student one piece of FV daily for two years. With this intervention, fruit intake increased by +0.2 servings after three months, but the effect dropped back to +0.1 servings at seven months, and returned to baseline in the second year. (Figure 2)

Computer-based interventions

We found three trials that used computer approach in their interventions, compared with no intervention. Amaro [30] and Baranowski et al's studies [32] were RCTs. Horne et al's study [45] was a CCT. Horne found significant differences in the consumption of FV (MD 25.0 grs FV, 95% CI 24.5, 25.4).

Pooled analysis was performed with the two RCTs with 606 participants. Significant differences were found between intervention and control groups (SMD 0.33, 95% CI 0.16, 0.50; I^2=0%). (Figure 3)

Multicomponent interventions

Eleven trials used a multicomponent approach compared to no intervention. The multicomponent interventions targeted the school educational/curriculum components,[31, 36-37,39-40,42-44] school environment modification [36-37,41,44] and involved teachers[39-40,42,47] and parents.[34, 36, 41-44] Sahota[40] and Taylor et al's studies[47] interventions also had a physical exercise component. The interventions performed by Taylor[47] and Gortmaker et al's studies[44] extended to community members outside the school environment.

The studies by Baranowski,[31] Mangunkusumo,[34] Perry,[36] Perry,[37] Reynolds,[39] Sahota[40] and Te Velde et al's[41] were RCTs. Except for the trial of Mangunkusumo et al's, the consumption of FV increased with the interventions in all these studies. Pooled analysis was performed with these seven trials (4800 participants). No significant differences were found between multicomponent interventions and control groups (SMD 0.00, 95% CI -0.08, 0.17; I^2=50%) (Figure 4).

The studies of Auld,[42] Friel,[43] Gortmaker[44] and Taylor et al's[47] were CCTs. These studies showed an increase in the consumption of FV and provided data from 1404 participants. Heterogeneity between these studies was 71%, so we did not perform a pooled analysis.

Other comparisons

Reinaerts[38] conducted a RCT to compare an intervention distributing free FV at school twice a week with a multicomponent programme focused on nutritional education in the classroom and with parental involvement. Both the free distribution and the multicomponent programme were effective in increasing consumption of fruit by +0.2 portions.

DISCUSSION

This systematic review included 18 trials that investigated the effectiveness of interventions to promote FV intake in primary-school children. All the studies were conducted in developed countries, although some of them were performed in low socio-economic status populations in high-income countries. Our meta-analysis shows that computer-based interventions were effective in increasing the consumption of FV, while free/subsidized interventions and multicomponent interventions did not achieve results.

Interventions to promote FV intake in children have been studied in nine previous reviews. However, seven of these studies were either limited to English language papers[6], were not systematic[13], or evaluated interventions in only one region or in one country[49-53]. The remaining two papers were systematic reviews that evaluated interventions in school-age children to promote FV consumption, but they did not perform a meta-analysis[10, 11]. The authors of these two reviews concluded that all interventions to promote FV consumption had some effectiveness but we could not confirm this finding in our review. There are two possible explanations for this. The first is related to the fact that not all the studies were included in the meta-analysis, mainly because CCTs presented a high heterogeneity. We consider that the CCTs probably had a selection bias. The second explanation is related to the fact that 27.2% of the studies did not take the cluster effect into account to calculate the sample size. When we corrected for cluster effect, sample size was reduced and statistical power was not sufficient to detect differences between groups.

We found that computer-based RCT interventions were effective in increasing FV intake in the primary school setting. This is not surprising as young children learn best through play and computer games motivate via amusement.[54] In the pooled analysis of two studies we also found that free/subsidized FV interventions were not effective in increasing consumption of FV. This finding seems to emphasize the fact that motivation could be a factor in FV consumption.

Overall, the studies included in this review had a moderate quality. All of them took measures to avoid selection bias and control confounding factors, and data collection about FV consumption was adequate. However, only two studies clearly disclosed the randomisation method and only one study clearly described the intervention blinding, which is a challenge in

this type of study, due to the nature of the intervention.[55-56] CONSORT guideline for cluster randomised trials should be considered in planning this kind of trials.[17]

Another characteristic of the studies included in the review is that most had a follow up of less than one year and this was a too short period to determine the sustainability of the interventions's effect. As information about sustainability of effects is crucial for decision makers, we suggest that future studies should be designed with a longer follow up period. [56-57]

Our review is limited by the design of the studies as their sample size was insufficient to determine differences between groups in many cases. The selection bias in CCTs also limited the internal validity of findings. External validity of results was also limited due to the fact that all the studies were conducted only in developed countries.

In conclusion, the main results of our systematic review were that computer-based interventions were effective to increase FV consumption among primary school children. Multicomponent interventions showed a trend towards an increase in FV consumption but this was not statistically significant. Free/subsidized interventions did not show any effectiveness. Improvements in methodology are needed in studies of this type. Future RCTs should include a longer follow up, take the design effect into account, and clarify the method of randomisation. Studies from developing nations are needed to contribute to our knowledge concerning the effectiveness of interventions to improve FV intake in childhood.

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Authors´ contributions

MD drafted the manuscript; MD, MJM, ST screened and reviewed the articles, and took part in quality assessment and data extraction; MJM, ST helped to draft the manuscript; XB discussed and provided feedback on the final version of the review.

List of abbreviations

FV: Fruits and vegetables; RCT: Randomised Controlled Studies; CCT: Controlled Clinical Trials; SMD: Standardised Mean Difference; MD: Mean Difference; ICC: Intracluster Correlation Coefficient; I^2: Measure used to quantify heterogeneity.

Competing interests

The authors declare that they have no competing interests.

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Table 1. Characteristics of included studies

Study	Design/ Quality	Theoretical framework	Participants	Effective sample size	Data collection	Intervention and duration	Results
Amaro 2006, Italy	RCT/moderate	Nutrition knowledge-based approach; behaviourally focused nutrition education	2 class in intervention group, 1 class in control. 188 children in intervention group, 103 in control	173/ 63	Knowledge and preference questionnaire	Kaledo. A board game for nutritional-education. Nutrition knowledge of Mediterranean diet 6 months	Increase in vegetable consumption of +0.7 FV portions per week. (P<0.01)
Auld 1999, USA	CCT / moderate	Social cognitive theory; Piaget's cognitive development theory	2 schools in intervention group, 2 in control. 316 children in intervention group and 331 in control	239/ 250	Plate waste assessment, food record, survey on knowledge and attitudes about FV	Multicomponent (curricula, teacher training, parent education, food preparation, community volunteers). 4 months	Increase in servings of FV per week in +0.35 (P<0.001)
Baranowski 2000, USA	RCT/ moderate	Social cognitive theory	8 schools in intervention group, 8 incontrol. 625 children in intervention group and 625 in control	245/ 245	7-day food record	Gimme 5. Multicomponent (school curricula, media campaign, food service, family). 12 sessions carried out over 6 weeks in 3 consecutive years	Increase in servings of FVin +0.2/day
Baranowski 2003, USA	RCT /moderate	Social cognitive theory	13 schools in intervention group, 13 in control. 785 children in	224/ 221	4-day food record using Food Intake Recording Software System	Squire's test. Interactive multimedia formatted game	Increase in servings of FVin +1.0/day

			intervention group and 793 control		(FIRSSt) Twice per week for 5 weeks		
* Bere 2005, Norway	RCT/moderate	Government school fruit subscription programme	9 schools in intervention group, 10 in control. 286 children in intervention, 231 in control	286/ 231	1-day FVrecord	Educational intervention/free distribution of fruit the first year, the second with a cost. 2 years	Increase in servings of FVin +0.6/day (P=0.03)
Friel 1999, Ireland	CCT/ moderate	Social cognitive theory	8 schools in intervention group, 3 in control. 453 children in intervention group, 468 in control	148/ 153	5-day food diary, also assessed knowledge and preferences	'Hearty Heart and Friends': school-based program with materials for the classroom: assessment of nutritional knowledge, preferences and behaviour. Parent involvement. 5 times per week for 10 weeks	Increase in servings of FVin +1.0/day (P<0.01)
Gortmaker 1999, USA	CCT /moderate	Social cognitive theory	6 schools in intervention group, 8 in control. 173 children in intervention group, 163 in control	173/ 163	Food frecuency questionnaire and 24-hours recall	'Eat Well and Keep Moving'. School fruit subscription programme: classroom, school environment, family/community component 2 years	Increase in servings of FVin +0.36/day (95%CI 0.10, 0.62)
Horne 2009, Ireland	CCT /moderate	Conditional and learning process.	1 schools in intervention group, 1 in control. 228 children in intervention	43/ 39	Direct weight of FV consumed	`Food Dudes´ Intervention. A six episode video "Food Dude": letters/homepacks. Rewards. 1 year	Increase of FV intake of +25 grs/ (95% CI 24.5, 25.4)

			group, 207 in control				
Mangunkusumo 2007, Netherlands	RCT/strong	Behavioural change theory	16 class in intervention group, 14 in control. 263 children in intervention group, 223 in control,	201/ 171	Internet-administered questionnaire	Counselling-tailored internet advice, nutrition counselling by nurse. 3 months	Increase of FV intake was not significant.
Moore 2008, United Kingdom	RCT / strong	Theoretical framework not well established.	22 schools in intervention group, 21 control. 1091children in intervention group, 811 in control	585/ 434	Computerised 24-hour recall questionnaire	Fruit tuck shops throughout one academic year 1 year	Increase of +0.05 in FVconsumption (not significant)
*Perry 1998, USA	RCT / moderate	Social cognitive theory	12 schools in intervention group, 12 in control. 212 children in intervention group, 212 in control	212/ 212	Health behaviour questionnaire, 24-hour food record, lunch-room observation	5-A Day Power Plus. Multicomponent intervention: behavioural curricula, parental involvement/education, school services changes, industry involvement and support. 5 times per week for 10 weeks	Increase in +0.49 servings of FVper day
*Perry 2004, USA	RCT/moderate	Social cognitive theory	26 schools in intervention group, 12 in control. 584 children in intervention group, 584 in control	584/ 584	Observations by trained staff	'Cafeteria-based intervention', events to promote consumption of FV. 2 years	Increase in +0.17 servings of FV
Ransley 2007,	CCT	Governmental	53 schools in	1586/	Child and diet	One portion of fruit or vegetable	Increase in +0.2

United Kingdom	/ moderate	programme for implementing 5-A Day strategy.	intervention group, 45 in control. 3380 children in intervention group, 3199 in control	1324	evaluation tool	provided per child on each school day. 10 months	servings of FVat 2 months; +0.1 at 7 months. At 2 years no changes
*Reinaerts 2007, Netherlands	RCT / moderate	Governmental programme of free distribution of fruit-vegetables/ Intervention mapping-Health promotion programmes	3 schools in intervention group, 3 in control. 270 children in intervention group, 208 in control	270/ 208	24-hour food recall	Group 1: Free FVdistribution programme. Group 2: Multicomponent: classroom curricula and parental involvement 1 year	Increase in +0.2 servings of FVwith both interventions
Reynolds 2000, USA	RCT/ strong	Social cognitive theory	14 schools in intervention, 14 control. 849 children in intervention, 849 in control	392/ 392	Children: 24- hour recall and cafeteria observation. Parents: food frequency questionnaire	'High 5 project' Multicomponent: classroom, curriculum, family, food service, physical education. 2 years	Increase in +1.0 servings of FVper day
Sahota 2001, United Kingdom	RCT/strong	Social cognitive theory	5 schools in intervention group, 5 in control. 314 children in intervention group, 322 in control	260/ 266	24-hour recall, 3-day food diary	APPLES Multicomponent: (teacher training, curriculum, tuck shops, physical education) 1 year	Increase in +0.3 servings of FVper day (95% CI 0.2, 0.4)
Taylor 2007, New Zealand	CCT / moderate	Community-based intervention	4 schools in intervention group, 3 in control. 302 children in	115/ 103	3-day food questionnaire	Multicomponent with community active communicators, resources for teachers, physical exercise and interactive card game.	Increase in +0.8 servings of fruits/ per 3 day

			intervention group, 270 in control			1 year	(95% CI 0.5, 1.1)
Te Velde 2008, Norway, Netherlands, Spain	RCT/ moderate	Social-ecological theory	32 schools inintervention group, 32 in control. 1115 children in intervention group, 991 in control	671/597	Pro-children Questionnaire	Free piece of fruit. Multicomponent: 'Pro Children': classroom, school, family involvement, curriculum components. 2 years	Increase in +62 grs. in FVper day consumption at second year of follow-up

* Studies with previous correction for effective sample size. RCT: Randomised Controlled Clinical Trial. CCT: Controlled Clinical trial. F/V: fruit and vegetables

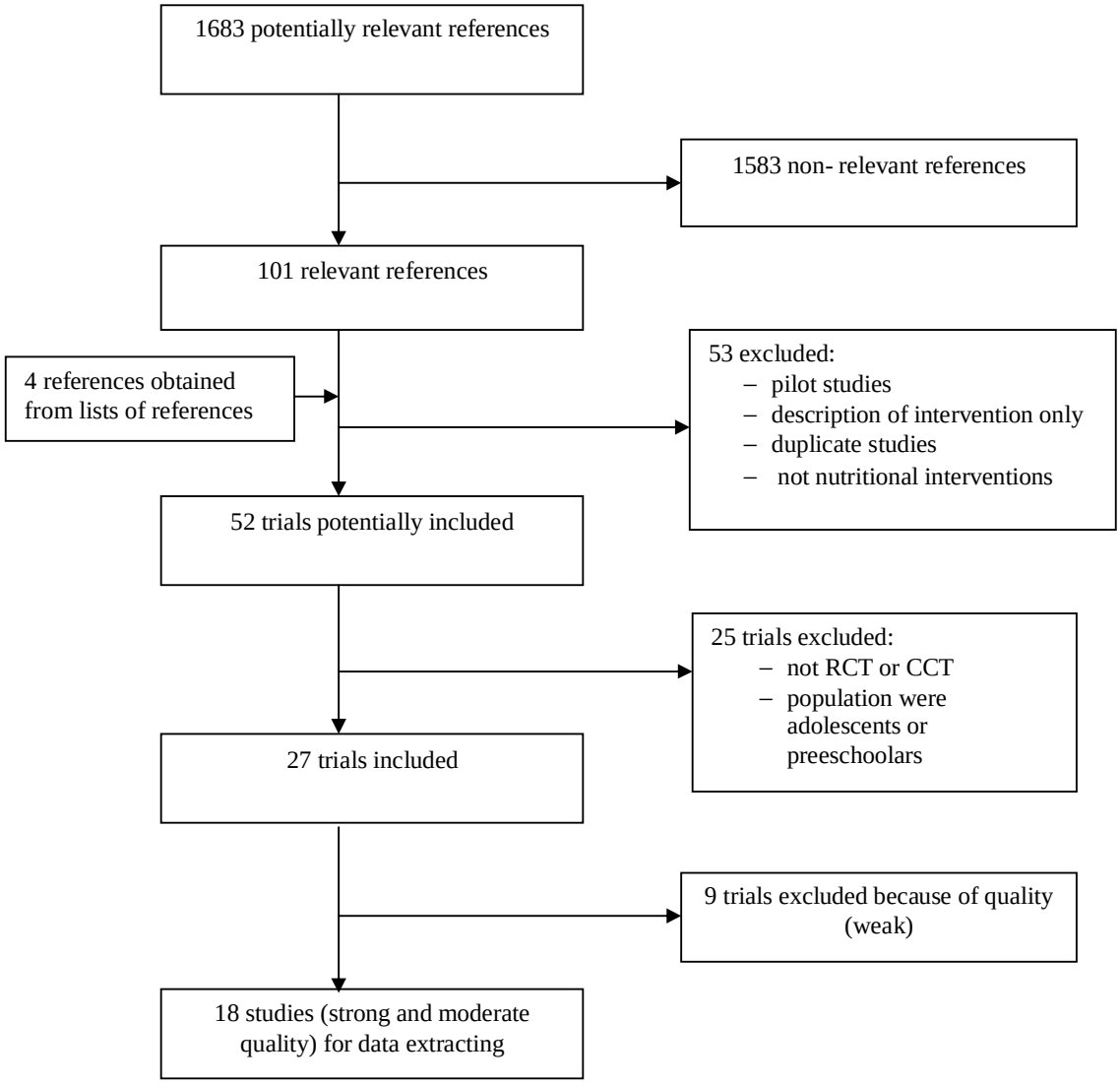
Table 2. Summary of results of consumption of fruit and vegetables (FV) by intervention type

Study	Results
Computer-based interventions	
Amaro 2006	SMD 0.33 (95% CI 0.16, 0.50)*
Baranowski 2003	
Horne 2009	Increase of 25 grs in consumption of FV from baseline (95% CI 24.5, 25.4)
Multicomponent interventions	
Baranowski 2000	SMD 0.00 (95% CI -0.08, 0.17)*
Mangunkusumo 2007	
Perry 1998	
Perry 2004	
Reynolds 2000	
Sahota 2001	
Te Velde 2008	
Auld 1999	Increased consumption of FV from +0.35 to +1.0 servings
Friel 1999	
Gortmaker 1999	
Taylor 2007	
Free or subsidized programmes	
Bere 2005	SMD 0.02 (95% CI -0.08, 0.12)*
Moore 2008	
Ransley 2007	Increase in +0.2 servings of FV at 2 months; +0.1 at 7 months. No changes at 2 years
Other comparisons	

Reinaerts 2007	Increase in consumption of fruit by +0.2 portions with both interventions at 1 year

SMD: standardised mean difference
*Pooled analysis

Fig. 1 Flow chart of study selection



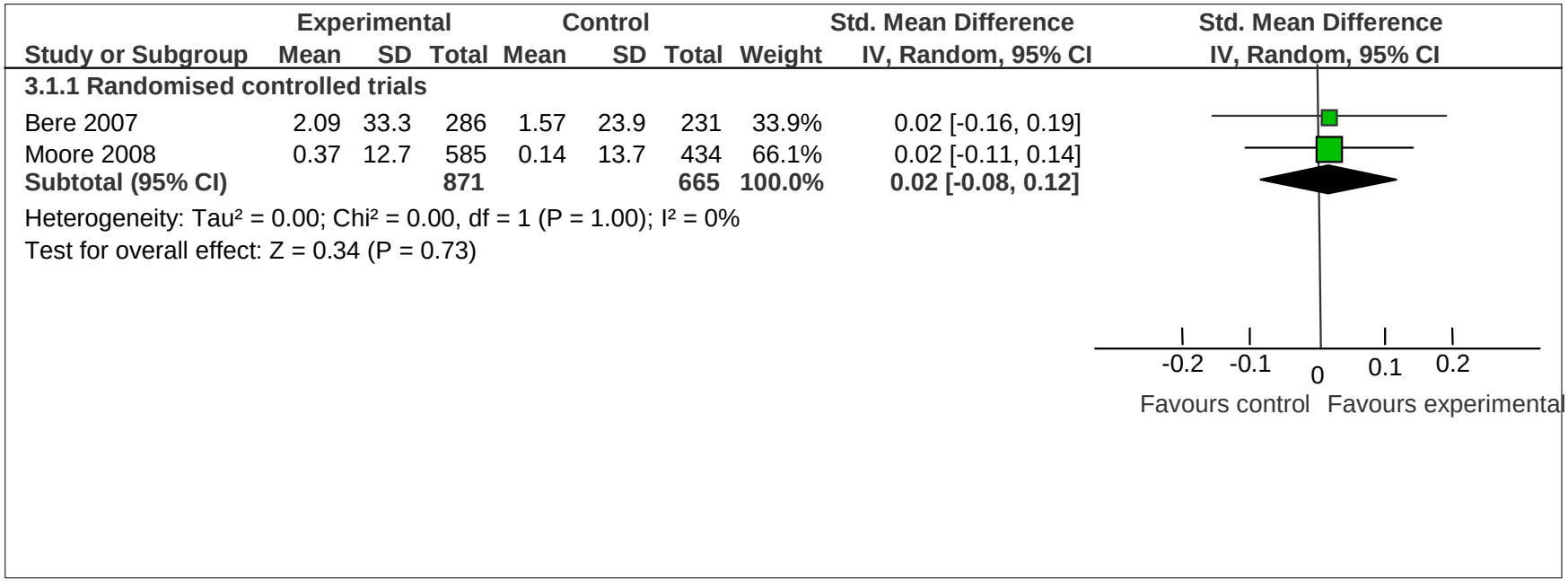


Fig. 2. Meta-analysis of free/subsidized FV programmes

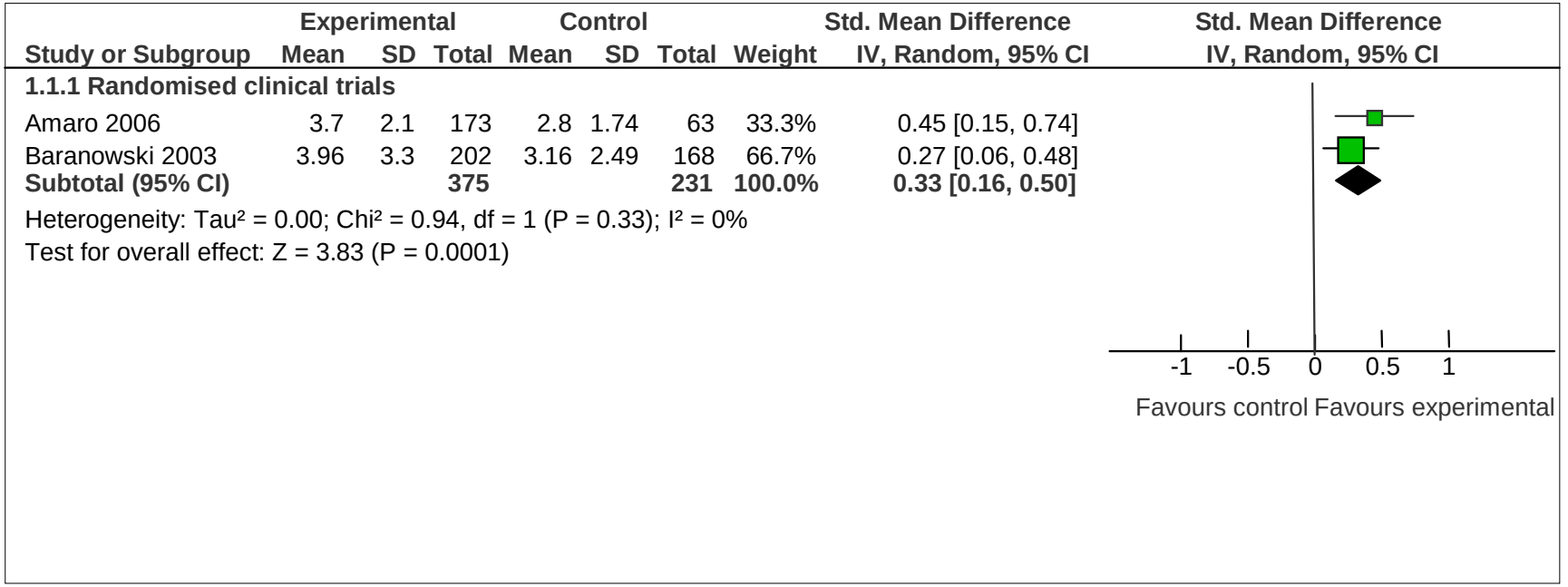


Fig. 3. Meta-analysis of board games/computer-based interventions

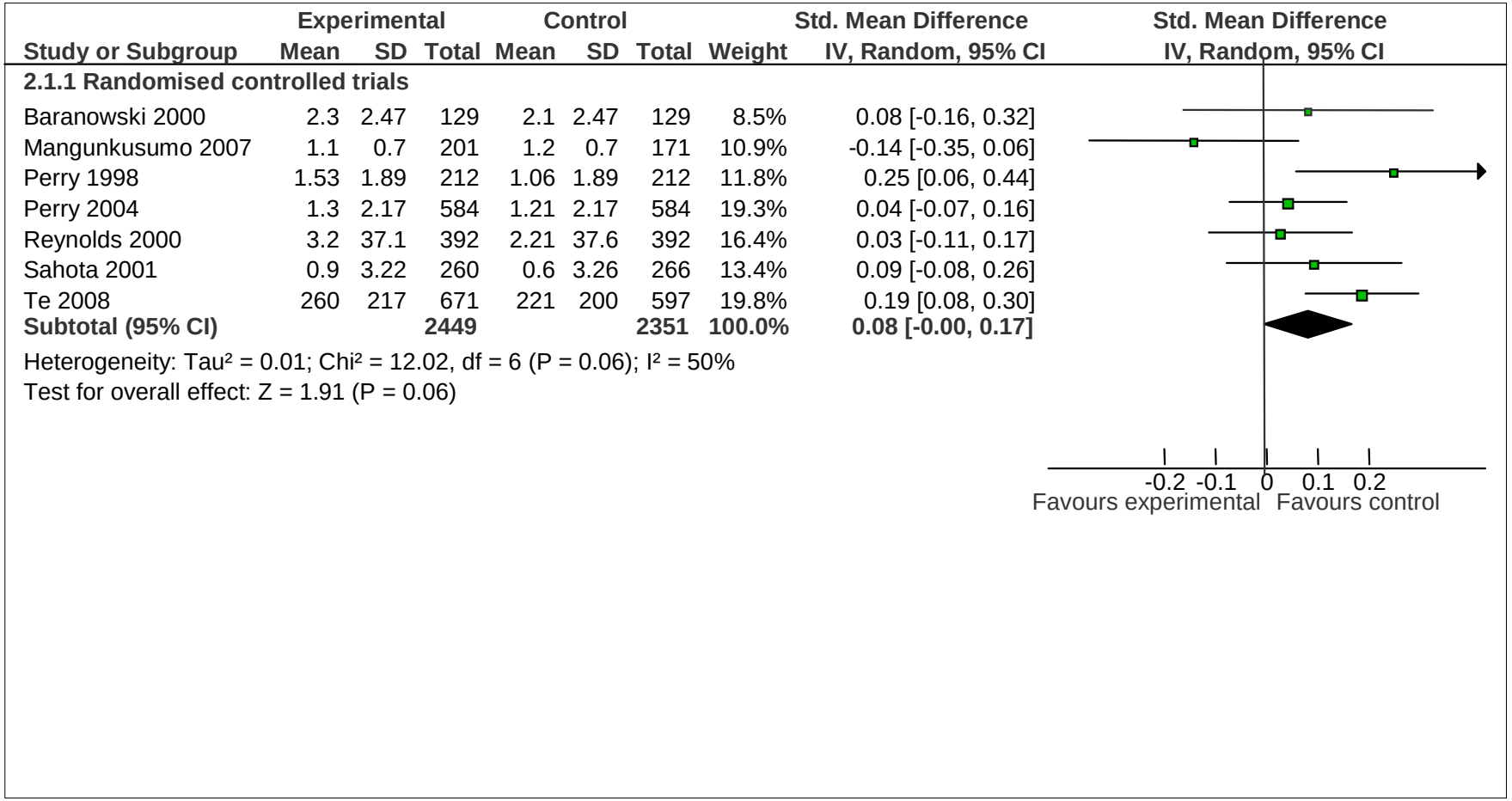


Fig. 4. Meta-analysis of multicomponent interventions

Anexo II.. Otros

- Alonso-Coello P, Delgado-Noguera M, Tort S, Gich I, Bonfill X. Quality of guidelines on obesity in children is worrying. BMJ. 2008 Nov 11; 337:a2474. doi: 10.1136/bmj.a2474. PubMed PMID: 19001488

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LETTERS

LAKE COUNTY MUSEUM/CORBIS

DEPRESSION AND ASSISTED DYING

Euthanasia and depression: no surprise

Nobody should be surprised at the prevalence of depression and anxiety in Oregon patients requesting physician assisted suicide.[1] This was the pattern of euthanasia's expansion in Holland—a movement for relief of unbearable suffering in terminal cases became a means of termination for those whose problems were often more existential, or psychological, than physical.

In Holland the critical case in law and ethics was the Chabot case, in which a divorced woman with clinical depression after the death of a son asked for, and received, euthanasia.[2] In another case, a request for euthanasia by a young woman with anorexia later was granted.

A retrospective study of deaths attributed to Dr Jack Kevorkian found none with end stage disease and several in whom necropsy revealed no clear organic dysfunction.[3] Again, what was publicly proclaimed as an end to suffering became a matter of termination of people whose physical or psychological suffering was not correctly palliated or treated.

Depression attends generally to cases of physical limit and chronic disease. The focus on euthanasia rather than on treatment, and state support for palliative and psychological treatment makes premature physician assisted death a default option.[4] This ignores in the name of autonomy a wealth of evidence that argues that most of those with chronic limits and progressive conditions may, after an initial period of anxiety and depression, find a worthiness to life so long as physical and psychological treatment is provided.[5] It similarly ignores the potential for fruitful life with both aggressive palliative care and psychological support.

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Competing interests: None declared.

1 Ganzini L, Goy ER, Dobscha SK. Prevalence of depression and anxiety in patients requesting physicians' aid in dying: cross sectional survey. *BMJ* 2008;337:a1682. (8 October.)
2 Transcript summary of prosecution against Boudewign Chabot. Docket No 478-1993. 16 September 1993.
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Psychiatric review is mandatory in Australia

Ganzini and colleagues' finding that 3 of the 18 Oregonians who received a prescription for a lethal drug met caseness criteria for depression raises concerns about the state's Death with Dignity Act, which demands a psychiatric review only if "concern exists that the patient has a psychiatric disorder."[1]

We know that depression is common in the terminally ill and that depression may be successfully treated in this population. We know that depression may impair a person's capacity when requesting physician assisted suicide, and we know that non-psychiatrically trained physicians are poor at detecting depression. We also know that these four facts are true for delirium in patients who are terminally ill.

There is a strong argument for including mandatory psychiatric review in any legislation that enables physician assisted death, to detect and protect those who would not have requested assistance to die had they not been depressed or delirious.[2] This safeguard was included in the Australian Northern Territory's Rights of the Terminally Ill Act 1995 and has also been included in recent attempts at legislative reform in Victoria.

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1 Ganzini L, Goy ER, Dobscha SK. Prevalence of depression and anxiety in patients requesting physicians' aid in dying: cross sectional survey. *BMJ* 2008;337:a1682. (8 October.)
2 Ryan CJ. Velcro on the slippery slope: the role of psychiatry in active voluntary euthanasia. *Australian and New Zealand Journal of Psychiatry* 1995;29:580-5.

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Depression in terminal illness

The article from Oregon raises questions about the relevance of depression in those who are dying.[1] It is perhaps not surprising that anyone facing death might be depressed. One might almost say it is normal. But depression is not a psychotic disorder, and there is no reason to assume that a depressed person is not rational and therefore perfectly capable of making an informed decision about assisted suicide.

Those who are so anxious to identify depression will presumably also wish to treat it. This raises questions of patient autonomy since the patient has probably not complained of depression and may therefore not wish to be treated. In any case, treatment takes time, and may produce side effects if drugs are used. Is this really appropriate in a dying patient, who does not have much time?

And what exactly is the point of treatment? Is it to make sure that the patient is happy about his or her impending death? Is that a realistic or desirable therapeutic approach? Doesn't it rather impose further medication and expectations on a patient who is already suffering greatly?

Why do people find it so difficult to accept that some people may wish to end their suffering, and may require assistance to do so, and that this is their inalienable right? Oregon has done excellent pioneering work which needs to be followed by similar legislation elsewhere. If the option of physician assisted suicide is available very few people will actually take it, and some will be so reassured by the fact that it is an option that they will never request it. To offer it is the only humane approach to intolerable suffering, if we really do claim to have a civilised society.

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1 Ganzini L, Goy ER, Dobscha SK. Prevalence of depression and anxiety in patients requesting physicians' aid in dying: cross sectional survey. *BMJ* 2008;337:a1682. (8 October.)

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OBESITY IN CHILDREN

Quality of guidelines on obesity in children is worrying

Kipping and colleagues argue that the differences between international guidelines on managing obesity reflect variations in the structure of health services, resources, culture, and behaviour between countries.[1] However, a more worrying explanation is the poor quality of clinical practice guidelines.

We recently conducted a systematic review of 22 guidelines for preventing and treating obesity and overweight in childhood,[2] assessing quality with the AGREE instrument.[3] Their quality was generally low. Only two of the six domains included in the AGREE instrument (scope and purpose and clarity of presentation) had a mean score over 50%. Although half of the guidelines had a quick reference guide or summary to identify key recommendations, only four had specific guidance for patients.

Of most concern was the low score (just over 35%) obtained in the rigour of development domain, indicating that many of the recommendations were based on unsound grounds and far from an evidence based approach. Nearly half of the documents did not report the databases searched or a structured approach to evaluate the quality of the evidence or grade the strength of recommendations. We would recommend and apply only six of them.

When developing or updating guidelines on obesity in children, developers should adhere more closely to the AGREE instrument.

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ASSESSING COMPLEX INTERVENTIONS

Guidelines perpetuate inappropriate methods

The guidelines for research in complex systems conflate complex with complicated.[1]

Complex systems and interventions are most appropriately viewed as non-linear, which implies that they cannot be understood by reducing them to their component parts. Outcomes are never an end in themselves but simply a further reiteration of an ongoing process where a more appropriate focus is the interaction of system variables from which patterns emerge that are not always predictable.

A large systems literature ignored by the guidelines has addressed all these problems in a much greater depth, particularly in soft systems thinking.[2] Realistic evaluation offers alternative methodological approaches,[3] and complexity theory itself has much to offer.[4]

Lakatos has suggested that research programmes in a discipline change with time but develop to form a protective belt of auxiliary theories that defend the fundamental and unassailable core.[5] The centrality of the randomised controlled trial continues to be protected in this way. Therefore inappropriate methodologies are perpetuated and the development of more relevant approaches to research in complex systems are inhibited.

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Importance of behaviour in interventions

Many simple interventions are actually complex, so the guidance on developing and evaluating complex interventions is applicable more generally than might have been thought in the past.[1]

The nature of behavioural instructions can influence the recipients' intentions to adhere to and their success in adhering to their intended actions.[2] The behavioural instruction in patient information leaflets is an integral part of a simple drug intervention. Recovery from surgery can be influenced by the information or instructions given.[3] In unblinded trials, as in most trials of surgical interventions, the effects of behavioural instruction are likely to interact with the treatment being evaluated.

Behavioural instruction delivered through a patient information leaflet can be standardised and effects of variation can, in principle, be tested using randomised designs. However, behavioural instruction (or other behaviour change techniques) delivered by a physician, surgeon, or pharmacist may be tailored but is usually not measured, reported, or controlled. This may confound the effects of other components of the intervention.

Almost all interventions delivered by clinicians or research staff (or patients themselves) are complex, in that their effects are influenced by measurable behaviours performed by the recipient or the deliverer. Trials methodology can be enhanced if these components are identified, reported, measured, standardised (at the appropriate level[4]), and tailored (to recipient and context).

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RESEARCH METHODS AND REPORTING

EQUATOR Network collates resources for good research

The new *BMJ* section on how to do and write up research will help to produce more reliable health research literature.[1] The EQUATOR Network, a new international initiative, also promotes clear, accurate, and transparent reporting of health research.[2]

The EQUATOR website (www.equator-network.org/) pulls together available reporting guidelines, making them easy to find and use, and also refers to other resources, training courses, and meetings concerned with reporting health research. It is a valuable source for anyone interested in improving the quality of scientific publications.

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¿SON ÚTILES COMO TEXTOS LAS GUÍAS DE PRÁCTICA CLÍNICA?

Mario Delgado Noguera*

RESUMEN

Este ensayo pretende ilustrar las ventajas de las GPC (Guías de Práctica Clínica) sobre los textos tradicionales como herramientas de enseñanza de las enfermedades más comunes en medicina. Su propósito es ampliar el conocimiento de las GPC, de sus instituciones elaboradoras y generar un debate sobre la posible función de las GPC como textos en algunas circunstancias clínicas.

Palabras clave: *(DECS): Libros de Texto como Asunto, Guías de Práctica Clínica como Asunto, Materiales de enseñanza, Educación médica.*

ABSTRACT

This paper illustrates the advantages of CPG (Clinical Practice Guidelines) on the traditional texts as teaching tools for the most common diseases in medicine. Its purpose is to increase awareness of the GPC, its institutions, processors and generate debate on the possible role of CPG as texts in some clinical circumstances.

Key Words: (*DECS): Textbooks as Subject, Clinical Practice Guidelines as Topic, Teaching materials, medical education*.

Los cambios muy rápidos que se están produciendo en las variadas disciplinas que nutren las ciencias de la salud obligan a no desdeñarlos y hacen necesario apropiar herramientas para elegir entre el amplio compás de lo novedoso, lo útil tanto para la práctica clínica como para la enseñanza.

En las ciencias de la salud se desarrollan y refinan tecnologías de modo numeroso y veloz. Estos avances se han producido particularmente en los últimos tres decenios y se han hecho para ayudar a los clínicos a tomar decisiones basadas en investigación (1). Al mismo

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tiempo se produce nueva información de manera acelerada. Entre otros aspectos, la velocidad de los cambios con los que las facultades de ciencias de la salud se enfrentan día a día dependen de de aquellos que se producen en la informática, en el acceso más fácil a Internet y a beneficiarse de su fuerza democratizadora y las destrezas en la red de los jóvenes estudiantes que ingresan a las facultades de medicina con información masiva pero no seleccionada.

En el paradigma científico occidental se considera un buen principio no aceptar ningún hecho hasta que acople con un sistema establecido. De esta manera, el profesional de la salud debe buscar la respuesta a su pregunta clínica en diagnóstico, pronóstico o tratamiento, principalmente en los estudios hechos en humanos con suficiente validez interna y externa para contribuir a tomar una decisión segura sobre el problema que busca (2). Por fortuna con la Medicina Basada en la Evidencia (MBE) se cuenta con un sistema y un método para abordar esos cambios y que se expande en la formación de nuevos profesionales, en la práctica clínica y en la gestión de los servicios. Hasta hace algunos años, hablar o debatir sobre la MBE parecía exótico; ahora es un método que ha ganado amplia aceptación.

Uno de las acciones que promueve la MBE es la síntesis de manera sistemática de la investigación en salud, y su diseminación en forma de revisiones sistemáticas. Estas son a su vez una de las principales bases para las recomendaciones del Guías de Práctica Clínica (GPC).

Las GPC son recomendaciones desarrolladas de forma sistemática para ayudar tanto al profesional de la salud como al paciente a tomar las decisiones adecuadas en circunstancias clínicas específicas (3,4). Uno de los mayores cambios en la elaboración de las GPC es que no solamente son los profesionales de la salud quienes las hacen sino que son los pacientes o las organizaciones de ellos también hacen parte de la formulación de las recomendaciones (5). La elaboración, implementación y diseminación de las GPC son responsabilidades de las autoridades de salud y de las organizaciones profesionales. Su propósito no es funcionar como un standard de atención sino, como su nombre lo indica, ser una guía para la práctica basada en la evidencia existente hasta ese momento sobre la situación de salud de un paciente particular en un contexto específico (6).

Las GPC “representan un intento de síntesis de grandes volúmenes de conocimiento en un formato conveniente y listo para ser usado por quienes participan en la toma de decisiones sobre la salud” (7). Además de los médicos y otros profesionales que prestan directamente el servicio, también se benefician de ellas los administradores y políticos del sector y los usuarios, es decir, los pacientes y sus familias.

Los libros de texto han sido tradicionalmente el primer puntal en la formación de los profesionales de la salud. Incluso desde organismos internacionales como la OPS (Organización Panamericana de la Salud) se promueve su adquisición bajando sus costos y favoreciendo su accesibilidad con puntos de venta en las facultades de salud. La mayoría de los estudiantes de medicina en distintos países americanos se han formado con ellos y con los también tradicionales apuntes de clase. Ejemplos clásicos en medicina clínica son los textos de Medicina Interna de Harrison y Cecil, de Pediatría de Nelson y el Manual Merck.

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Si bien los libros de texto siguen siendo de mucha utilidad cuando se busca información rápida sobre una enfermedad, un asunto de la epidemiología general o de la etipatogenia de una entidad, aspectos principalmente diagnósticos o terapéuticos pueden haberse situado rápidamente fuera de actualidad dada la aparición de los nuevos estudios asequibles principalmente a través de Internet y disponibles por PubMED. Muchas de las recomendaciones que surgen de los textos provienen del razonamiento fisiopatológico y no de experiencias con pacientes.

Los textos al revisar una enfermedad toman en cuenta variadas preguntas para responder y lo hacen de un modo no sistemático, produciendo información que por lo general no es la evidencia necesaria para tomar una decisión. Muchas veces se confía en uno o más autores para la revisión de determinada enfermedad que cumplen la función de expertos en el tema y cuyos métodos para llevarla a cabo rara vez se hacen explícitos y por lo tanto no son replicables. Se corre el riesgo de que los autores introduzcan en su revisión estudios que a priori ellos consideren acordes con la teoría que tengan y defiendan. Es conocida la anécdota del premio Nobel Linus Pauling sobre su hipótesis que defendía con entusiasmo de que la vitamina C ayudaba a vivir más y mejor. Para argumentar la defensa en sus publicaciones solo elegía los ensayos clínicos que apoyaban su teoría (8). A semejanza de la postura del nóbel, el experto en el tema, al escribir su revisión narrativa, puede solo elegir la literatura médica que apoye su teoría.

Por su parte las GPC cuando están hechas de manera adecuada[*], hacen recomendaciones basadas en revisiones sistemáticas y en ensayos clínicos preferentemente sobre los distintos tópicos de enfermedades frecuentes y de impacto. Son desarrolladas por instituciones de salud gubernamentales reconocidas como la británica NICE (9) (*National Institute for Health and Clinical Excellence*) o privadas como el estaudinense ICSI (10) (*Institute for Clinical Systems Improvement*) o pueden serlo por sociedades científicas o por paneles de expertos.

La propuesta que hago es ampliar el empleo de las GPC y que funcionen a la manera de los textos en la enseñanza del pre y el postgrado en las facultades de medicina y otras áreas de la salud. Si las GPC provienen de sitios reconocidos y han sido evaluadas satisfactoriamente, tienen la ventaja de su actualidad y de provenir de un trabajo sistemático y por lo tanto generar una confianza razonable sobre sus recomendaciones. A su vez, ahorran mucho trabajo y tiempo en buscar la evidencia en ensayos o revisiones sistemáticas y tienen un interesante desarrollo ético al haber tomado en cuenta la opinión de los pacientes.

Muchas GPC evalúan los aspectos diagnósticos donde la controversia y la variabilidad de la elección de las pruebas diagnósticas pueden resultar desconcertantes tanto para el clínico como para el paciente. Las GPC en este caso tendrían la posibilidad de ayudar a racionalizar el gasto en salud porque elige una alternativa diagnóstica que evita el uso de

[*] Para evaluar la calidad de una GPC se han desarrollado instrumentos validados como AGREE. The AGREE collaboration (2003) Appraisal of Guidelines for Research & Evaluation [AGREE] Instrument. En: http://www.agreecollaboration.org/pdf/aitraining.pdf

otras que no son apropiadas o que contribuyen en poco en la aclaración de la enfermedad en estudio.

Varias de ellas también toman a su vez aspectos preventivos a la vez que terapéuticos de tal manera que el aspecto preventivo que muchas veces puede parecer no ser relevante en los ambientes terciarios de atención, toma su debida importancia al de momento establecer el pronóstico y la posterior alta del paciente a su ambiente cotidiano.

Pueden ser la base, además, del desarrollo o la actualización de protocolos de los distintos servicios hospitalarios. Sin embargo, las GPC pueden provenir de instituciones públicas, sociedades científicas y de países donde los sistemas de salud tienen cobertura, organización, vigilancia, gestión sólidas y presupuesto del Estado –como en los estados de bienestar europeos donde la salud como derecho es la regla- y por lo tanto debe ser estudiada su aplicabilidad en el contexto.

Si el problema es el hallazgo de las GPC en Internet la solución se está facilitando pues se han desarrollado sitios de búsqueda y metabuscadores que ayudan la labor del estudiante y del profesor en resolver la pregunta inicial para apoyarse en la decisión que se tomará con un paciente: ¿Sobre esta posible enfermedad del paciente existe una GPC? Uno de los sitios de la red que facilitan la búsqueda de guías es TRIP database (*Turning Research Into Practice*) (11), un poderoso motor que discrimina por tema o enfermedad GPC, ensayos clínicos, revisiones sistemáticas, estudios diagnósticos y pronósticos. Tiene filtros para las referencias en PubMED, filtros por especialidad y filtros por tipo de publicación especialmente hecha para síntesis de literatura. Actualmente se está desarrollando la versión en español de este motor (12).

El encuentro y aplicación de la GPC adecuada para un problema específico puede ayudar a la cooperación y reciprocidad entre estudiante y profesor en el empleo de técnicas interactivas de aprendizaje y de este modo ampliar las destrezas de uso de conceptos y búsqueda en la maraña informativa de Internet, algunos de los principios básicos de una buena enseñanza (13).

Este ensayo ha pretendido ilustrar algunas ventajas de las GPC sobre los textos tradicionales como herramienta de enseñanza de las enfermedades más comunes en medicina. La metodología del desarrollo de las guías puede encontrarse en el sitio web de SIGN (14) (*Scottish Intercollegiate Guidelines Network*), una entidad escocesa que genera GPC de calidad y que aporta desarrollos metodológicos en el área (Figura 2) y en GuíaSalud, el sitio de las GPC del Sistema Nacional de Salud de España (15). La evaluación de esta iniciativa podría llevarse a cabo con un estudio cuasi-experimental de series temporales donde por periodos académicos y por áreas de un departamento clínico, se empleen los textos tradicionales y las GPC de manera intermitente, midiendo por el rendimiento con los exámenes y las calificaciones habituales. Se tiene la ventaja de la existencia de registros previos y confiables de calificaciones (16).

Un debate académico sobre los pros y los contras de esta propuesta parece ser necesario y productivo.

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Soft drinks consumption, diet quality and BMI in a Mediterranean population

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Abstract

Objectives: Evidence of the effects of soft drinks consumption on BMI and lifestyle in adult populations is mixed and quite limited. The aim of the present study was to determine the association of soft drinks consumption with BMI and lifestyle in a representative Mediterranean population.

Design: Two independent, population-based, cross-sectional (2000 and 2005) studies. Dietary intake was assessed using a validated FFQ. Weight and height were measured.

Setting: Girona, Spain.

Subjects: Random sample of the 35- to 74-year-old population (3910 men and 4285 women).

Results: Less than half (41·7 %) of the population consumed soft drinks; the mean consumption was 36·2 ml/d. The prevalence of sedentary lifestyle increased with the frequency of soft drinks consumption ($P = 0·025$). Daily soft drinks consumption significantly increased the risk of low adherence to the Mediterranean diet (OR = 0·57, 95 % CI 0·44, 0·74 *v.* top tertile of Mediterranean diet score). Multiple linear regression analyses, controlled for potential confounders, revealed that an increment in soft drinks consumption of 100 ml was associated with a 0·21 kg/m^2 increase in BMI ($P = 0·001$). Only implausibly low reports of energy consumption showed a null association between soft drinks consumption and BMI.

Conclusions: Soft drinks consumption was not embedded in a healthy diet context and was positively associated with BMI and sedentary lifestyle in this Mediterranean population.

Keywords
Sugar-sweetened beverages
BMI
Lifestyle
Mediterranean diet

The obesity epidemic is one of the most important challenges for public health policy. The prevalence of excessive weight strongly affects cardiovascular health[1,2] and contributes to a tremendous economic burden of public health[3]. An increasing trend of obesity has been observed during the last decade not only in the USA but also in Europe, and particularly in Spain[4]. Between 1995 and 2000, BMI increased by about 1 kg/m^2 in men and women at the population level in north-east Spain[5].

The increase in excessive weight is accompanied by concomitant lifestyle changes, such as in diet and physical activity[6]. Total energy intake has increased during the past 20 years in the USA, a trend driven mainly by an increase in carbohydrate consumption[7]. The daily energy contribution from soft drinks increased from 1000 kJ (239 kcal) to 1230 kJ (294 kcal) over the past decade among adult North American soft drinks consumers[8,9]. In Spain, daily soft drinks consumption has

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also increased, albeit slightly, from 44·8 ml (79 kJ/18·8 kcal) in 1991 to 72·4 ml (127 kJ/30·4 kcal) in 2001[10].

Although still inconclusive, the main body of evidence associating soft drinks consumption with BMI comes from American studies focusing on children and adolescents[11–14]. Our knowledge of the impact of soft drinks consumption on BMI in the adult population is limited[15], particularly where the consumption is low, as in Mediterranean populations. Lifestyle differs by population and culture, and therefore the underlying dietary pattern and leisure-time physical activity involving soft drinks might vary and might have different impacts on the association of soft drinks consumption with BMI. Indeed, one might speculate that soft drinks consumption might not produce detrimental health outcomes within the context of a high-quality diet such as the Mediterranean diet. Furthermore, energy misreporting is a common problem in nutritional studies and, if not controlled for, results in biased findings about the impact of diet on BMI[16,17].

The aim of the present study was to analyse the association of soft drinks consumption with BMI and the risk of obesity, controlling for lifestyle and low energy reporting, in a representative Mediterranean population.

Materials and methods

Study participants

Data were obtained from population-based cross-sectional surveys conducted in Girona (Spain) in 2000 and 2005. These surveys of randomly selected, free-living men and women included 3058 persons aged 25–74 years in 2000 and 6352 persons aged 35–80 years in 2005. Response rates for the two surveys were 71·0 % and 71·5 %, respectively. All survey participants aged 35 to 74 years (n 8195) were included in the present study. After excluding persons with extremely low reported energy intake (<3347 kJ/<800 kcal) and extremely high value for BMI (>60 kg/m^2) or reported energy consumption (corresponding to a physical activity level >2·4, which exceeds the established upper limit[18] for strenuous work or highly active leisure behaviours), 3593 men and 3508 women were included for analysis.

The protocol was approved by the local ethics committee (CEIC-IMAS, Barcelona, Spain) and all participants were sent the results of their examination.

Anthropometric measurements

A precision scale was used for weight measurement, with subjects in underwear. Readings were rounded to the nearest 200 g. Height was measured in the standing position and measurements rounded to the nearest 5 mm. BMI was determined as weight divided by height squared (kg/m^2).

Dietary assessment

Standard structured questionnaires administered by trained personnel were used to obtain information on demographic and socio-economic variables, medical history, diet and lifestyle factors, including tobacco smoking and alcohol consumption. Food consumption and nutrient intake were measured by a 168-item validated FFQ[19] administered by a trained interviewer. The optical readable FFQ asked for usual intake over the past year of specific foods and alcoholic and non-alcoholic beverages. Participants were asked to describe their average frequency of consuming each item, using ten categories ranging from 'almost never' to '6 times/day'. Instead of standard questions on portion size based on weight or volume, the FFQ used specific medium servings, defined by natural (e.g. one orange, one slice of bread) or household units (e.g. one spoon, one cup, one glass). The FFQ included one item on soft drinks consumption ('1 can of sugar-sweetened carbonated soda: Coca Cola, Fanta or similar, but not light'). Therefore, in the current study the term 'soft drinks consumption' is limited to sugar-sweetened carbonated beverages.

Measurement of diet quality

Overall diet quality was measured as adherence to the Mediterranean dietary pattern, using the Mediterranean diet score (MDS). Higher scores indicate higher adherence to the Mediterranean diet. Distribution values were calculated for all dietary components of the FFQ. The resulting MDS ranged from 10 to 30.

This operative variable for the analysis of associations between diet quality and health outcomes is calculated according to the tertile distribution of food consumption, with the exception of red wine. For cereals, fruits, vegetables, legumes, fish, olive oil and nuts, the lowest tertile is coded as 1, medium as 2 and the highest as 3. The score is inverted for meat and dairy products, with the highest tertile coded as 1 and the lowest as 3. Moderate red wine consumption (up to 20 g) is included as a favourable component in the MDS, with a score of 3. Exceeding this upper limit or reporting no red wine consumption was coded as 0.

BMR was calculated using the predictive equations based on sex, age and body weight recommended by FAO/WHO/United Nations University[20]. If the quotient of reported energy intake divided by the predicted BMR was <1·2, this was considered as energy under-reporting.

Other measurements

Leisure-time physical activity was measured by the Minnesota Leisure-Time Physical Activity Questionnaire and administered by a trained interviewer. This questionnaire has been previously validated for Spanish men and women[21,22]. Sedentary lifestyle was defined as leisure-time physical activity of less than 30 min/d.

Information on smoking habits was obtained by structured interview. Participants were categorized as non-smokers or current smokers.

Maximum education level attained was elicited and recorded for analysis as primary school, secondary school and post-secondary school.

PHN Public Health Nutrition

Table 1 General characteristics of the study population according to frequency of soft drinks consumption*: random sample of the 35- to 74-year-old population (3910 men and 4285 women), Girona, Spain

	Soft drinks non-consumers (*n* 4141)		Soft drinks consumers (*n* 2960)		
	% or Mean	95 % CI or SD	% or Mean	95 % CI or SD	*P*
Women (%)	52·2	51·7, 54·7	44·1	42·3, 45·9	<0·001
Age (years)	57·1	10·3	50·4	10·5	<0·001
Total energy intake (MJ/d)	9·6	2·6	10·5	2·7	<0·001
Low energy reporters† (%)	23·3	22·2, 24·5	16·2	14·9, 17·6	<0·001
Dietary energy density‡	1·23	0·32	1·38	0·32	<0·001
BMI (kg/m^2)	27·8	4·5	27·3	4·5	0·009
LTPA (MET × min/d)	307·9	324·7	296·9	311·9	0·031
Smokers (%)	20·5	19·2, 21·8	28·2	26·6, 29·7	<0·001
Alcohol consumption (g/d)	11·5	17·2	12·1	19·8	0·369
Educational level§ (%)	41·3	39·8, 42·8	53·6	51·8, 55·3	<0·001

LTPA, leisure-time physical activity; MET, metabolic equivalent task.
*Results are expressed as percentage of subjects and 95 % confidence interval or mean and standard deviation. Significance of *P* between soft drinks consumers and soft drinks non-consumers was determined by the Student *t* test (continuous variables) or logistical regression analysis (categorical variables).
†Energy intake:BMR <1·2.
‡Energy density was calculated as energy intake from all foods consumed (kcal) divided by weight of foods consumed (g); 1 kcal = 4·184 kJ.
§More than primary school.

Energy density was defined as the amount of energy (kJ) in a given weight of food (g).

Statistical analysis

Differences in continuous variables were compared using the Student *t* test. The χ^2 test was used for categorical variables. General linear modelling procedures (PROC GLM) in the SAS statistical software package version 9·1 (SAS Institute Inc., Cary, NC, USA) were used to estimate lifestyle, anthropometric and socio-economic variables according to categories of soft drinks consumption. For continuous variables, polynomial contrast was calculated to determine *P* for linear trend.

Multiple linear regression models were fitted (PROC REG procedure in SAS version 9·1) to determine the confounder-controlled association of soft drinks consumption and BMI, and produced a normal distribution of data. Multiple linear regression analysis, stratified by energy misreporting, was performed to determine the impact of energy under-reporting on the association between soft drinks consumption and BMI.

Multiple logistic regression analysis (PROC LOGISTIC procedure in SAS version 9·1) was used to assess the relationship of daily soft drinks consumption (200 ml/d) and diet quality (tertile distribution of the MDS). Differences were considered significant if $P < 0·05$.

Results

Less than half of the population (41·7 %) consumed soft drinks. Mean daily consumption of soft drinks consumers was 86·2 ml; monthly, weekly and daily frequency of soft drinks consumption was 55·5 % (19·0 ml/d), 27·7 % (77·9 ml/d) and 16·8 % (326·4 ml/d), respectively.

The association of soft drinks consumption with BMI, obesity and lifestyle was quite similar for both sexes. For this reason we present non-stratified results, adjusted for sex as appropriate.

Soft drinks consumers were younger, more highly educated and less prone to under-report total energy intake. They reported higher energy intakes, spent less time in leisure-time physical activity, smoked more and had a lower BMI than non-consumers (Table 1). Age decreased across frequencies of soft drinks consumption (Table 2). After controlling for sex and age, higher frequency of soft drinks consumption was associated with higher BMI and higher prevalence of sedentary lifestyle and obesity (Table 2).

Soft drinks consumption was directly associated with energy intake, energy density and intakes of carbohydrates, pastry/sweets and high-fat dairy products (Table 3). A decrease occurred across categories of soft drinks consumption in the ratio of unsaturated to saturated fat and intakes of protein, total fat, fibre, olive oil, low-fat dairy products, fish, vegetables, fruits, nuts, poultry/rabbit and legumes (Table 3).

Multiple linear regression analysis – adjusted for sex, age, educational status, leisure-time physical activity, energy intake, smoking, alcohol consumption and energy under-reporting – revealed that a 100 ml increment in soft drinks consumption was associated with an increase of 0·213 kg/m^2 in BMI ($P < 0·001$; Table 4). This association was unchanged in both magnitude and direction in plausible energy reporters but was attenuated in low energy reporters. Multivariate ANOVA adjusted for sex and age revealed a positive association of soft drinks consumption across BMI categories (normal weight, overweight and obese; $P < 0·001$). Participants with normal weight consumed 31·2 ml/d whereas their obese

Table 2 General characteristics of the population by frequency of soft drinks consumption*: random sample of the 35- to 74-year-old population (3910 men and 4285 women), Girona, Spain

	No consumption (*n* 4141)		Monthly (*n* 1644)		Weekly (*n* 820)		Daily (*n* 496)		*P* for linear trend
	% or Mean	95 % CI	% or Mean	95 % CI	% or Mean	95 % CI	% or Mean	95 % CI	
Sex (% men)	46·8	45·3, 48·3	49·3	46·9, 51·7	61·2	57·8, 64·6	69·0	64·6, 73·3	<0·001
Age (years)	57·1	56·8, 57·4	51·0	50·5, 51·5	49·0	48·3, 49·7	50·1	49·2, 51·0	<0·001
BMI (kg/m^2)	27·5	27·4, 27·7	27·6	27·4, 27·8	28·2	27·8, 28·5	28·1	27·7, 28·5	0·001
Obesity† (%)	25·6	24·3, 27·0	26·7	24·5, 28·8	29·3	26·2, 32·3	30·2	26·3, 34·1	0·007
Overweight‡ (%)	44·1	42·6, 45·7	44·1	41·7, 48·5	45·1	41·7, 48·5	45·3	40·9, 49·6	0·551
LTPA (MET × min/d)	303	293, 313	309	294, 324	303	281, 325	285	257, 313	0·280
Sedentary lifestyle§ (%)	32·4	31·0, 33·9	30·2	27·9, 32·5	33·4	30·2, 36·7	39·5	35·3, 43·6	0·025
Smokers (%)	23·7	22·4, 25·0	21·8	19·8, 23·8	23·3	20·5, 26·1	30·5	26·8, 34·1	0·175
Alcohol consumption (g)	10·4	10·0, 10·9	9·8	9·1· 10·5	8·7	7·7, 9·7	9·6	8·4, 10·9	0·093
Educational level‖ (%)	45·4	44·0, 46·9	52·3	50·0, 54·6	44·6	41·3, 47·9	37·9	33·7, 42·1	0·075

LTPA, leisure-time physical activity; MET, metabolic equivalent task.
*Results are expressed as percentage of subjects or mean and 95 % confidence interval. Sex- and age-adjusted ANOVA was used to estimate variables according to frequency of soft drinks consumption.
†BMI ≥ 30 kg/m^2.
‡BMI = 25·0–29·9 kg/m^2.
§Less than 30 min LTPA/d.
‖More than primary school.

Table 3 Age- and sex-adjusted daily food and nutrient intakes by category of soft drinks consumption*: random sample of the 35- to 74-year-old population (3910 men and 4285 women), Girona, Spain

	No consumption (0 ml; *n* 4141)		Monthly (19·0 ml; *n* 1644)		Weekly (77·9 ml; *n* 820)		Daily (326·4 ml; *n* 496)		*P* for linear trend
	Mean or %	95 % CI	Mean or %	95 % CI	Mean or %	95% CI	Mean or %	95 % CI	
Energy (MJ)	9·7	9·6, 9·8	10·1	9·9, 10·2	10·4	10·2, 10·6	10·9	10·7, 11·1	<0·001
Energy from soft drinks (MJ)	0	–	0·03	0·02, 0·04	0·13	0·12, 0·14	0·56	0·55, 0·57	<0·001
Energy density†	1·25	1·24, 1·26	1·32	1·30, 1·33	1·36	1·33, 1·38	1·39	1·36, 1·42	<0·001
Energy under-reporting‡ (%)	23·9	22·6, 25·1	19·1	17·1, 21·0	17·5	14·7, 20·3	14·2	10·6, 17·8	<0·001
Carbohydrate§ (%)	40·9	40·7, 41·2	40·5	40·2, 40·9	41·9	41·4, 42·4	44·4	43·8, 45·1	<0·001
Protein§ (%)	17·9	17·9, 18·0	17·6	17·4, 17·7	17·3	17·1, 17·4	16·4	16·2, 16·7	<0·001
Fat§ (%)	40·8	40·7, 41·1	41·8	41·5, 42·2	41·2	40·7, 41·6	39·9	39·1, 40·3	<0·001
Unsaturated:saturated fat	2·30	2·28, 2·31	2·22	2·19, 2·25	2·14	2·11, 2·19	2·18	2·14, 2·24	<0·001
Dietary fibre (g/4·18 MJ)	12·3	12·1, 12·4	11·3	11·1, 11·5	10·7	10·4, 11·0	10·2	9·9, 10·6	<0·002
Vegetables (g/4·18 MJ)	226	222, 230	204	198, 210	191	182, 200	181	171, 192	<0·001
Fruits (g/4·18 MJ)	207	203, 212	184	178, 192	176	166, 186	164	151, 176	<0·001
Legumes (g/4·18 MJ)	23·7	23·2, 24·2	21·8	21·0, 22·6	21·6	20·5, 22·8	21·4	20·0, 22·9	0·005
Cereals (g/4·18 MJ)	75·2	74·2, 73·6	75·0	73·4, 76·6	75·9	73·6, 78·1	74·1	71·1, 76·9	0·568
Fish (g/4·18 MJ)	35·5	34·9, 36·1	33·9	32·9, 34·9	32·1	30·7, 33·5	29·8	28·0, 31·6	<0·001
Red meat/sausages (g/4·18 MJ)	45·9	45·3, 46·6	48·7	47·7, 49·9	49·1	47·6, 50·7	47·4	45·4, 49·3	0·167
Poultry/rabbit (g/4·18 MJ)	19·5	19·1, 20·0	18·2	17·4, 18·9	17·6	16·6, 18·7	16·9	15·5, 18·2	<0·001
Olive oil (g/4·18 MJ)	11·8	11·6, 12·0	11·6	11·2, 12·0	10·5	10·0, 11·0	10·3	9·7, 11·0	<0·001
Low-fat dairy (g/4·18 MJ)	78·3	75·6, 81·0	67·3	63·1, 71·5	61·7	55·8, 67·7	51·4	43·8, 59·1	<0·001
High-fat dairy (g/4·18 MJ)	57·2	55·1, 59·4	59·4	56·1, 62·8	66·8	62·1, 71·6	64·5	58·2, 70·5	0·006
Pastry/sweets (g/4·18 MJ)	22·1	21·5, 22·8	25·6	24·5, 26·6	29·1	27·6, 30·5	30·1	28·3, 31·9	<0·001
Nuts (g/4·18 MJ)	6·4	6·2, 6·7	6·0	5·6, 6·4	5·2	4·7, 5·8	4·4	3·7, 5·1	<0·001

*Results are expressed as mean or percentage of subjects and 95 % confidence interval. Sex- and age-adjusted ANOVA was used to estimate variables according to frequency of soft drinks consumption.
†Energy density was calculated as energy intake from all foods consumed (kcal) divided by weight of foods consumed (g); 1 kcal = 4·184 kJ.
‡Energy intake:BMR <1·2.
§Percentage of total energy intake.

peers drank 42·4 ml/d ($P = 0·003$). Additionally controlling for energy intake, leisure-time physical activity, smoking, educational level, diet quality and energy under-reporting attenuated this association slightly (P for linear trend = 0·007; soft drinks consumption by normal weight *v.* obese participants: 32·2 ml/d *v.* 41·5 ml/d; $P = 0·021$). Figure 1 shows the association of soft drinks consumption with overall diet quality, defined by MDS. Adherence to a healthy diet decreased with daily soft drinks consumption ($P < 0·001$).

Discussion

Soft drinks consumption was directly associated with BMI. Stratifying by implausibly low and plausible energy reporters revealed a significant association of soft drinks consumption and BMI in plausible reporters but not in under-reporters. Furthermore, daily soft drinks consumption was associated with low diet quality.

Soft drinks consumption in the USA constitutes 7·1 % of total energy intake[23]. In contrast, in the present population

Table 4 Regression coefficient and 95 % confidence interval of the association between soft drinks consumption and BMI* among a random sample of the 35- to 74-year-old population (3910 men and 4285 women), Girona, Spain

	BMI (kg/m^2)		
	Regression coefficient	95 % CI	*P*
All participants (*n* 7101)†			
Soft drinks (100 ml)‡	0·213	0·112, 0·313	<0·001
Plausible energy reporter (*n* 5585)§			
Soft drinks (100 ml)‡	0·218	0·114, 0·322	<0·001
Low energy reporter (*n* 1512)§			
Soft drinks (100 ml)	0·185	−0·142, 0·512	0·267

*Multiple linear regression models were fitted to analyse the association of soft drinks consumption and BMI.
†Adjusted for sex, age, leisure-time physical activity, educational level, smoking, alcohol consumption, diet quality (Mediterranean diet score), energy (energy from soft drinks excluded) and energy under-reporting (energy intake:BMR <1·2).
‡100 ml corresponds to 0·5 drinks/d.
§Adjusted for sex, age, leisure-time physical activity, educational level, smoking, alcohol consumption, diet quality (Mediterranean diet score) and energy (energy from soft drinks excluded).

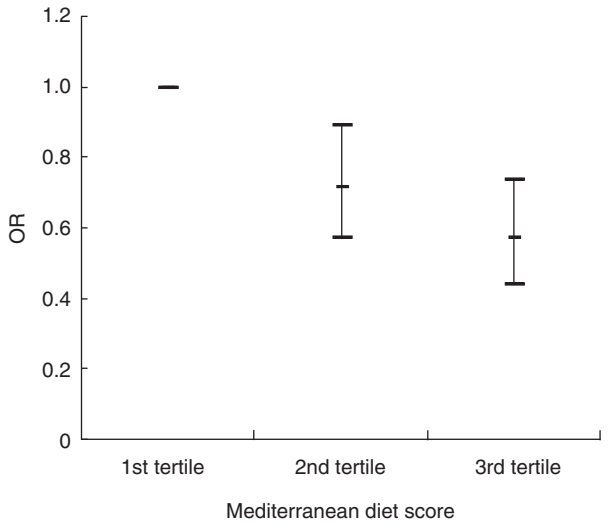

Fig. 1 Odds ratio and 95 % confidence interval of daily soft drinks consumption and adherence to the Mediterranean diet (tertile distribution of the Mediterranean diet score) among a random sample of the 35- to 74-year-old population (3910 men and 4285 women), Girona, Spain. Odds ratios were adjusted for sex, age, leisure-time physical activity, educational level, smoking, alcohol consumption, diet quality (Mediterranean diet score), energy (energy from soft drinks excluded) and energy under-reporting (energy intake:BMR <1·2). *P* for linear trend = 0·001

soft drinks consumption can be considered low, since it contributes only 61 kJ (14·5 kcal) to total energy intake (0·6 % of the total energy supply). Furthermore, the average daily amount (86·8 ml) reported by soft drinks consumers falls within the range of the recently proposed tolerable intake of soft drinks[24]. The Mediterranean dietary pattern is associated with favourable health outcomes[25–27]. It is conceivable that soft drinks consumption at these amounts is unlikely to replace healthy food choices in this context. Furthermore, moderate soft drinks consumption as part of a healthy lifestyle should not affect weight gain, cardiovascular health or BMI. However, our data showed that frequent soft drinks consumption increased the risk of low adherence to the Mediterranean diet and was associated with a cluster of unhealthy food preferences. The observation that unhealthy food choices are associated with soft drinks consumption is in line with previously published reports from younger populations[28,29].

In the present population there was a positive association, controlled for potential confounders, between soft drinks consumption and BMI. Limited evidence from other cross-sectional and prospective epidemiological studies in adult populations, particularly from the USA, has indicated a modest positive association[11–15]. Chen *et al.* reported a significant weight loss associated with a reduction of 1 serving of soft drinks per day after 18 months[15]. A recently published Spanish study of male and female university alumni found a significant positive association between soft drinks consumption and weight gain among adults who had gained more than 3 kg weight in the 5 years before the study[30]. In the present study, a 100 ml increment in soft drinks consumption was associated with an increase of 0·21 kg/m^2 in BMI. Although the magnitude of the association is modest, the fact that it derives from a single food item, rather than a complex dietary pattern, reflects a considerable impact on BMI in this population. The association of BMI and soft drinks consumption was only slightly attenuated after controlling for overall diet quality. This finding indicates that soft drinks consumption affects BMI independently of the magnitude of diet quality as measured by adherence to the Mediterranean diet. Even within the context of an overall healthy diet, soft drinks consumption adversely affects BMI.

Several mechanisms linking soft drinks consumption and weight gain have been proposed[31]. The predominant evidence points to an imbalance in energy intake, as soft drinks mediate less satiation and low satiety[32]. In the present population, higher soft drinks consumption was not associated with energy compensation in the overall diet. By definition, excess energy intake through soft drinks consumption without compensatory energy expenditure is a formula for weight gain in the long run.

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Unfortunately, energy under-reporting is a common problem for the analysis of associations between diet and health outcomes, particularly BMI[16,17]. It has been shown that obese subjects tend to selectively under- or overestimate selected foods[16,17]. In the present study, prevalence of low energy reporting decreased with frequent soft drinks consumption. Thus, it was not surprising that soft drinks consumption was positively associated with BMI in plausible reporters but exhibited a null association in those who reported low energy consumption. Our results indicate that controlling for energy under-reporting is essential to avoid bias in the association of foods or diet and BMI.

A limitation of the present study's cross-sectional design is that causality cannot be drawn between the variables studied. Misreporting is an acknowledged source of measurement error in prospective or retrospective methods of dietary assessment using self-reported food intake records. Furthermore, total consumption of sugar-sweetened drinks is underestimated in this population because the term 'soft drink' did not include non-carbonated sugar-sweetened beverages. The strengths of the present study include the relatively large sample size, the population-based design and the consideration of potential confounders in the analysis, including physical activity, smoking, socio-economic status and energy under-reporting.

In conclusion, frequent consumers of soft drinks tended towards a more sedentary lifestyle and a cluster of unhealthy dietary habits. The risk of low adherence to the Mediterranean diet increased significantly with daily soft drinks consumption. Higher BMI was found in more frequent consumers of soft drinks as compared with their non-consuming peers, after controlling for several potential confounders. Low energy reporters showed a null association between soft drinks consumption and BMI, indicating that energy misreporting is a strong potential confounder for analysis of the relationship between soft drinks consumption and BMI.

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Anexo III.. Tablas

Tabla 1. Tabla GRADE: Valoración del efecto de la suplementación a madres lactantes con LCPUFA (*Long Chain Polyunsaturated Fatty Acids*) en el crecimiento y desarrollo de sus hijos

Patient or population: **Lactating mothers**
Intervention: **LCPUFA versus placebo**

Outcomes	Illustrative comparative risks* (95% CI) Corresponding risk **Fatty acid supplementation versus placebo**	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Language development - Beyond 24 months Follow-up: 24 months	The mean Language development - Beyond 24 months in the intervention groups was **0.14 standard deviations lower** (0.49 lower to 0.2 higher)	349 (2 studies)	**moderate**	SMD -0.14 (-0.49 to 0.2)
Psychomotor development - Beyond 24 months Follow-up: 24 months	The mean Psychomotor development - Beyond 24 months in the intervention groups was **0.34 standard deviations higher** (0.11 lower to 0.78 higher)	279 (2 studies)	**moderate**	SMD 0.34 (-0.11 to 0.78)
Motor development - Short term 12 months Follow-up: 12 months	The mean Motor development - Short term 12 months in the intervention groups was **0.08 standard deviations higher** (0.13 lower to 0.29 higher)	349 (2 studies)	**moderate**	SMD 0.08 (-0.13 to 0.29)
Child visual acuity - Visual acuity 12 months (short term) Follow-up: 12 months	The mean Child visual acuity - Visual acuity 12 months (short term) in the intervention groups was **0.06 standard deviations lower** (0.26 lower to 0.14 higher)	401 (3 studies)	**moderate**	SMD -0.06 (-0.26 to 0.14)

SMD: Standarized Mean Difference; CI: Confidence Interval.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Tabla 2. Tabla GRADE: Valoración del efecto de las intervenciones con ordenadores en el consumo de frutas y verduras en niños escolares

Patient or population: **Childs on primary school.**
Settings: **Schoolar setting**
Intervention: **computers**
Comparison: **control**

Outcomes	Illustrative comparative risks* (95% CI) Corresponding risk **Computers**	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Fruits/vegetables servings - Randomysed clinical trial	The mean Portions of F/V - Randomysed clinical trial in the intervention groups was **0.59 standard deviations higher** (0.08 to 1.1 higher)	1054 (3 studies)	**moderate**	SMD 0.59 (0.08 to 1.1)
Fruits/vegetables servings – Controled clinical trial	The mean Portions of F/V - Controled clinical trial in the intervention groups was **24.76 standard deviations higher** (20.86 to 28.67 higher)	82 (1 study)	**low**	SMD 24.76 (20.86 to 28.67)

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Tabla 3. Tabla GRADE: Valoración del efecto de las intervenciones con multicomponentes en el consumo de frutas y verduras en niños escolares

Patient or population: **Childs on primary school.**
Settings: **Schoolar setting**
Intervention: **Multicomponent**
Comparison: **control**

Outcomes	Illustrative comparative risks* (95% CI) Corresponding risk **Multicomponent**	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Fruits/vegetables servings - Randomysed controlled trials	The mean Portions of F/V - Randomysed controlled trials in the intervention groups was **0.08 standard deviations higher** (0 to 0.17 higher)		4800 (7 studies)	**moderate**	SMD 0.08 (0 to 0.17)
Fruits/vegetables servings – Controled Clinical Trial	The mean Portions of F/V - Controled Clinical Trial in the intervention groups was **0.23 standard deviations higher** (0.03 to 0.43 higher)		1404 (4 studies)	**moderate**	SMD 0.23 (0.03 to 0.43)

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Tabla 4. Tabla GRADE: Valoración del efecto de las intervenciones que promueven el ibre acceso o el subsidio en el consumo de frutas y verduras en niños escolares

Patient or population: **Childs on primary school.**
Settings: **Schoolar-setting**
Intervention: **Free subscription of FV**
Comparison: **control**

Outcomes	Illustrative comparative risks* (95% CI) Corresponding risk **Free subscription**	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Fruits/vegetables servings - Randomysed controlled trials	The mean Raciones de frutas/verduras - Randomysed controlled trials in the intervention groups was **0.02 standard deviations higher** (0.08 lower to 0.12 higher)	1536 (2 studies)	**moderate**	SMD 0.02 (-0.08 to 0.12)
Fruits/vegetables servings - Controled clinical trial	The mean Raciones de frutas/verduras - Controled clinical trial in the intervention groups was **0.03 standard deviations higher** (0.04 lower to 0.09 higher)	3929 (1 study)	**moderate**	SMD 0.03 (-0.04 to 0.09)

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.