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INSTITUTO DE MEDICINA SOCIAL

REDUÇÃO DE PESO NA PREVENÇÃO PRIMÁRIA DE ACIDENTE VASCULAR CEREBRAL

Cintia Chaves Curioni

Tese apresentada como requisito parcial para obtenção do grau de Doutor em Saúde Coletiva, Curso de Pós-graduação em Saúde Coletiva – área de concentração em Epidemiologia do Instituto de Medicina Social da Universidade do Estado do Rio de Janeiro.

Orientador: Renato Peixoto Veras
Co-Orientador: Charles André

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REDUÇÃO DE PESO NA PREVENÇÃO PRIMÁRIA DE ACIDENTE VASCULAR CEREBRAL

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“Se você quiser alguém em quem confiar, confie em si mesmo.
Quem acredita sempre alcança.”

Renato Russo

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Lista de Abreviaturas

AGE – Angiotensinogêneos

ASP – Proteína Estimulante de Acilação

AVC – Acidente Vascular Cerebral

CB – Receptores Canabinóides

CC – Circunferência da Cintura

DCV – Doenças Cardiovasculares

ECB – Endocanabinóides

FDA – Departamento de Administração de Drogas e Alimentos

HDL-c – Lipoproteína de Alta Densidade

IC – Intervalo de Confiança

IL-6 – Interleucina-6

IMC – Índice de Massa Corporal

LDL-c – Lipoproteína de Baixa Densidade

OMS – Organização Mundial da Saúde

PAI-1 – Inibidor de Plasminogênio ativado-1

SECB – Sistema Endocanabinóide

TNF-α - Fator de Necrose Tumoral α

Apresentação

Conforme o projeto de tese previamente aprovado pelo Departamento de Epidemiologia do Instituto de Medicina Social/ UERJ, esta tese inicialmente focava a redução de peso na prevenção primária do acidente vascular cerebral (AVC) e o panorama atual do AVC assim como das doenças cardiovasculares no Brasil. A revisão sistemática foi concluída, porém sem possibilidades de ter sido realizada a metanálise.

Durante o período do curso de Doutorado, permaneci um semestre na Universidade Heinrich-Heine de Düsseldorf – Alemanha, no grupo Cochrane de doenças endócrinas e metabólicas e por sugestão do coordenador do grupo, Dr. Bernd Richter, realizei outra revisão sistemática com possibilidade de agrupar os resultados com metanálise sobre o medicamento rimonabant no tratamento da obesidade. Droga que parece ser promissora no tratamento da obesidade e de fatores de risco cardiovascular.

Desta forma, esta tese apresenta a seguinte estrutura:

Seção 1: Incluindo - Introdução (1.1) - traçando um panorama geral sobre obesidade, AVC, a interação desses dois tópicos, mortalidade por doenças cardiovasculares no Brasil, sistema endocanabinóide, rimonabant; Justificativas do presente trabalho, assim como da realização dos artigos (1.2); Objetivos gerais e específicos da pesquisa (1.3).

Seção 2: A partir desta tese surgiram quatro artigos científicos já publicados internacionalmente (3) ou submetidos para publicação internacional. Os artigos são apresentados, em sua íntegra, no formato e no idioma solicitados pelas revistas às quais foram encaminhados. Como os artigos foram elaborados em inglês, optou-se por apresentá-los na seção de anexos, respeitando as normas de padronização de projetos e teses do Departamento de Epidemiologia do Instituto de Medicina Social/ UERJ. Desta forma, nesta seção são apresentados apenas os resumos ampliados, em português, de cada artigo incluído na tese.

Seção 3: Conclusões do presente estudo, onde são expostas algumas considerações acerca dos artigos apresentados.

Seção 4: Referências bibliográficas citadas na tese, sendo que as referências específicas de cada artigo encontram-se no final dos mesmos.

Seção 5: Incluindo - Anexo 1: Apresenta-se o primeiro artigo, cujo tema aborda: Declínio progressivo na mortalidade por AVC no Brasil de 1980-1982, 1990-1992 e 2000-2002 (*Progressive Decline in Stroke Mortality in Brazil From 1980 to 1982, 1990 to 1992, and 2000 to 2002*) publicado em "Stroke 2006 Nov;37(11):2784-9".

Anexo 2: Inclui o segundo artigo, cujo tema engloba: Declínio da mortalidade por doenças cardiovasculares no Brasil (*The decline of mortality from circulatory diseases in Brazil*, submetido à revista Panamericana de Salud Pública em agosto de 2007).

Anexo 3: Inclui o terceiro artigo, com o seguinte titulo: Redução de peso para prevenção primária de AVC em adultos com sobrepeso/obesidade (*Weight reduction for primary prevention of stroke in adults with overweight or obesity*) publicado em "Cochrane Database Systematic Reviews 2006 Oct 18; (4): CD006062".

Anexo 4: Inclui o quarto artigo, com o tema: Rimonabant para sobrepeso/ obesidade (*Rimonabant for overweight or obesity*) publicado em "Cochrane Database Systematic Reviews 2006 Oct 18; (4): CD006162".

Resumo/Abstract

Objetivo: Como as doenças cardiovasculares (DCV) constituem a principal causa de morte na maioria dos países e as tendências de mortalidade não se apresentam totalmente elucidadas nos países em desenvolvimento, torna-se adequado explorar a evolução da mortalidade das DCV, dando ênfase ao acidente vascular cerebral (AVC) no Brasil. Devido à prevalência de AVC e também devido à associação causal entre sobrepeso ou obesidade e AVC não ser clara, é importante avaliar o efeito da perda de peso na prevenção primária de AVC. Baseado no fato do rimonabant ser a primeira droga de uma nova classe de medicamentos promissora não apenas na redução de peso, mas por sua influência sobre os fatores de risco cardiovascular, torna-se pertinente estabelecer sua eficácia e segurança. **Método:** Inicialmente, para traçar um panorama sobre a epidemiologia das DCV no Brasil, com ênfase em AVC, foram realizados dois estudos com as tendências temporais de mortalidade por DCV ao longo das três últimas décadas, investigando as diferenças entre as regiões do país e entre indivíduos de diversas faixas etárias e de ambos os sexos, **(artigo I e II)**. Além disso, duas revisões sistemáticas foram realizadas: uma para avaliar o efeito da perda de peso na prevenção primária de AVC; a segunda para investigar o uso do medicamento rimonabant no tratamento da obesidade **(artigo III e IV**) **Resultados**: As taxas de mortalidade de AVC diminuíram substancialmente nas últimas três décadas, de 68,2 a 40,9 por 100 000 habitantes. Essa redução foi detectada em ambos os sexos de todas as faixas etárias, e nas diferentes regiões do país, sendo mais acentuadas nas regiões mais ricas **(artigo I)**. A mesma tendência foi observada nas demais DCV, que em geral apresentaram uma redução anual média de 3,9%. As maiores reduções foram encontradas para AVC (média de 4,0% ao ano) seguido por doença coronariana (média de 3,6% ao ano) **(artigo II)**. Não existem estudos avaliando o efeito da redução de peso na prevenção primária de AVC **(artigo III)**. Houve um efeito dose-resposta com o uso do rimonabant: comparado com placebo, 20 mg da droga produziu uma redução de peso maior (4,9 kg) em 4 ensaios clínicos com duração de 1 ano. Foram observadas melhoras nos marcadores de risco cardiovascular. Porém 5 mg comparado com placebo mostrou apenas uma redução de 1,3 kg a mais do peso. A maior dose também provocou maiores efeitos adversos. Perdas no seguimento foram de aproximadamente 40% **(artigo IV)**. **Conclusão:** Durante as últimas décadas, a mortalidade por DCV em geral e AVC diminiu consistentemente no Brasil, porém a magnitude do declínio variou de acordo com as diferenças socioeconômicas. Amplas intervenções poderiam ter mais êxito se planejadas de acordo com as desigualdades sociais e diferenças culturais. Os achados apontam para a necessidade da realização de ensaios

clínicos randomizados controlados avaliando a perda de peso na prevenção primária do AVC, devido à alta relevância dessa condição. Como intervenções não são totamente eficazes no tratamento da obesidade, a prevenção, englobando um conjunto articulado de ações, permanece a forma mais eficiente de controlá-la. O medicamento rimonabant apresentou modesta perda de peso, porém os resultados obtidos devem ser interpretados com cautela de acordo com as deficiências na qualidade metodológica apresentadas por todos os estudos. São necessárias pesquisas de alta qualidade para avaliar a eficácia e a segurança do rimonabant em períodos mais longos.
Palavras-chave: obesidade, perda de peso, doenças cardiovasculares, acidente vascular cerebral, mortalidade, séries temporais, rimonabant, revisão sistemática.

Objective: Cardiovascular diseases (DCV) are the leading cause of death in the world. Although mortality rates declined gradually in developed countries, the scenario is less clear in developing countries. We describe the trends in cardiovascular mortality in Brazil foccusing on stroke. Given the prevalence of stroke and the enormous health and economic cost of the disease, and the causal association between overweight or obesity and stroke is unclear, it is important to evaluate the effect of the weight loss in the primary prevention of stroke. Due to the fact that rimonabant is the first drug of a new class promising not only for weight reduction but also for the reduction of cardiovascular risk factors, it is important to establish its possible efficacy and safety. **Method:** Firstly, to better understand current epidemiological aspects of CVD in Brazil, focusing on stroke, two studies were carried out evaluating the secular trends of CVD mortality along the last three decades and possible differences according to social and regional disparities, gender and age distribution (articles I and II). Two systematic revisions were carried out: one evaluating the effect of weight loss in the primary prevention of stroke and the other investigating the use of rimonabant in the treatment of obesity (articles III and IV) **Results:** Stroke mortality rates decreased consistently in the last 3 decades, from 68.2 to 40.9 per 100 000 habitants. The reduction was detected in men and women and in all age strata being evident in all geopolitical regions of the Country, with the wealthiest regions exhibiting more marked reductions (article I). The same trend was observed for all CVD, with a mean annual reduction of 3.9%. The largest average decline found was for stroke (mean of 4.0% per year) followed by coronary disease (mean of 3.6% per year) (article II). There are no studies evaluating the effect of the weight reduction in the primary prevention of stroke (article III). The results concerning the drug rimonabant showed a dose-response effect: compared with placebo, 20 mg produced a greater weight loss (4.9 kg) in 4 clinical trials with 1 year of follow-up. Improvements in cardiomatabolic risk factors were also seen. However, 5 mg only led to a slightly increased weight reduction (1.3 kg more than placebo). Rimonabant 20 mg caused significantly more adverse effects. Attrition rates were approximately 40% (article IV). **Conclusion:** CVD and stroke consistently decreased in Brazil during the last decades. The reduction is in apparent relationship with indices of increasing social development. Broad interventions may be more succesful if planed according to social inequality and cultural differences. The findings point to the need of randomized controlled clinical trials specifically addressing the effects of weight loss in the primary prevention of stroke, due to the great importance of this condition. As interventions are not totally effective in the treatment of the obesity,

prevention remains the most valuable tool to control its harmful effects. Rimonabant could produce modest weight loss. Some caution with the observerd results should be take account since the studies presented some deficiencies in the methodological quality. More methodologically rigorous studies that are powered to examine efficacy and safety are required

Key-words: obesity, weight loss, cardiovascular disease, stroke, mortality, time series, rimonabant, systematic review.

Seção 1

1.1. Introdução

1.1.1. Doenças Cardiovasculares

As doenças cardiovasculares (DCV) de alta prevalência e alta taxa de morbidade e mortalidade na maioria dos países representam elevados custos sociais e econômicos.

Nos países desenvolvidos têm sido bem documentado o aumento histórico e o recente declínio da mortalidade por DCV (Lopez 1993; Murray 1994; Thom 1992). A identificação dos principais fatores de risco através de estudos populacionais e estratégias efetivas de controle que combinam educação para a comunidade e tratamento de indivíduos de alto risco contribuíram para a queda nas taxas de mortalidade (inclusive doença coronariana e doença vascular cerebral) nos países industrializados (Lopez 1993).

Embora os países em desenvolvimento contribuam para uma maior parte da carga global de DCV, o agravamento da epidemia desta condição há duas ou três décadas gerou menor discussão e até mesmo menor ação relacionada à saúde pública dentro destes países (Lopez 1993; Whelton 1995). Foi estimado que 5.3 milhões de mortes que ocorreram em países desenvolvidos em 1990 foram atribuíveis as DCV, enquanto que para os países em desenvolvimento a estimativa foi de 8 a 9 milhões (Lopez 1993).

O processo de transição epidemiológica está ainda em andamento no Brasil, onde a mortalidade por doenças infecciosas e desnutrição diminuiu continuamente ao longo dos últimos 70 anos (notadamente entre 1930 e 1985), e a mortalidade cardiovascular aumentou até inicio dos anos 70 e depois de um período de estabilidade aparente entre 1970 e 1985, exibe um declínio gradual semelhante ao que aconteceu em países desenvolvidos em décadas prévias (Prata 1992).

Em países em desenvolvimento, a alta taxa de mortalidade pode ser atribuída ao envelhecimento desta população e pela alta prevalência dos fatores de risco clássicos para DCV como hipertensão, tabagismo, dislipidemia, diabetes e obesidade (Erdine 2004, Fagerstrom 2002, WHO 2000, Liu 2004, de Sereday 2004).

Em países da América do Norte, Europa Ocidental e Australia um substancial declínio tem sido observado nas taxas de mortalidade das DCV (Ergin 2004, Levi 2002, Reid 2005,

Kesteloot 2006). Na América Latina há menos informações disponíveis. No Brasil, o mesmo fenômeno de diminuição nas taxas parece estar começando a acontecer (Oliveira 2005, Mansur 2001). Entre os fatores que contribuem para a diminuição das taxas de mortalidade podemos citar uma melhora nas condições econômicas da população e um possível maior controle de fatores de risco, como por acesso a medicamentos para hipertensão arterial e diabetes mellitus.

Estudos de tendência da mortalidade por doenças cardiovasculares mostram que apesar do Brasil ter apresentado um aumento no número absoluto de mortes nos últimos 30 anos, houve uma redução anual na taxa de mortalidade de DCV de aproximadamente 3,9% por 100 000 habitantes (Curioni, não publicado). Esta redução é evidenciada em todas as regiões do país, sendo maior nas regiões mais ricas. Tais diferenças podem refletir o impacto de alguns fatores, incluindo estilo de vida (atividade física, tabagismo, hábitos dietéticos), assim como detecção e controle de fatores de risco clássicos como hipertensão e diabetes e diferenças em cuidados hospitalares (Curioni, não publicado).

Alguns fatores podem, no futuro, conduzir a um aumento relativo no número de mortes cardiovasculares como o aumento da prevalência de diabetes e obesidade (Brasil, MS 2004, Sartorelli 2003). Em geral, países em desenvolvimento enfrentam problemas de custos proibitivos e, portanto deve ser dada grande ênfase em estratégias de prevenção primária efetivas ara fatores de risco cardiovasculares (Gyarfas 1996).

1.1.2. Acidente Vascular Cerebral

As DCV constituem a principal causa de mortalidade no Brasil, sendo as doenças cerebrovasculares, a primeira causa de morte nesse grupo.

Apesar de seu declínio nos últimos anos, o AVC ainda é a terceira causa de morte em vários países do mundo e também a principal causa de incapacitação física e mental. Mundialmente, três milhões de mulheres e dois milhões e meio de homens morrem por AVC a cada ano (WHO 2004).

Durante o século 20 houve uma redução significativa nas taxas de mortalidade de AVC nos Estados Unidos e muitos outros países desenvolvidos. Dados dos países em

desenvolvimento são menos abundantes, porém alguns países também parecem mostrar um declínio nas taxas de mortalidade (Radishauskas 2005, Sarti 2000).

No Brasil, a taxa de mortalidade de AVC diminuiu constantemente nos últimos 20 anos ou mais. Essa redução foi evidenciada em homens e mulheres de faixa etária maior que 25 anos e abrange todas as regiões geopolíticas do país, com as regiões mais ricas exibindo taxas iniciais mais altas e reduções mais acentuadas na taxa de mortalidade. (André 2006). Tal redução não parece ser completamente explicada pelo controle dos fatores de risco clássicos em indivíduos de alto risco, avanços tecnológicos, ou melhorias em cuidado, mas pode, em parte, refletir uma melhoria nas condições gerais de saúde no Brasil. O progressivo envelhecimento da população tende, porém, a conduzir-nos a um aumento progressivo no número total de mortes atribuíveis ao AVC e doenças cardiovasculares nas próximas décadas.

O AVC, com base na definição simples, porém epidemiologicamente útil da organização mundial da saúde (OMS), é caracterizado pelo "rápido desenvolvimento de sinais clínicos focais de distúrbio da função cerebral, durando mais que 24 horas ou levando à morte, sem outra causa aparente a não ser aquela de origem vascular." Portanto, o AVC pode ser compreendido como um sofrimento do tecido cerebral causado por redução da oferta de sangue e seus constituintes vitais (oxigênio, glicose) a uma determinada área do cérebro, por mecanismo isquêmico (obstrução arterial ou redução do débito cardíaco) ou hemorrágico (ruptura de artéria no parênquima encefálico ou espaço subaracnóideo). Esta lesão (geralmente focal, mas por vezes extensa) tem como conseqüência básica a perda ou diminuição das respectivas funções. Manifesta-se de diversas formas. A mais comum é a paralisia ou fraqueza da metade da face e membros de um lado do corpo (hemiplegia), porém um grande número e combinação de outros déficits podem surgir – por exemplo, alterações da fala, sensibilidade, comportamento, campo visual. Casos mais graves podem evoluir com formação de edema cerebral e hipertensão intracraniana; ou afetar diretamente estruturas responsáveis pelo controle de funções vitais – respiração, circulação, levando à morte do indivíduo.

Existem basicamente dois tipos de AVC: isquêmico e hemorrágico. O tipo isquêmico (infarto cerebral) é mais freqüente, constituindo 70 a 80% dos casos de AVC. As lesões hemorrágicas tendem a associar-se a maiores taxas de letalidade (André 2005).

Devido à limitação das opções para o tratamento efetivo do AVC, um grande número de pacientes afetados padecerá por seqüelas neurológicas e graus variados de limitação funcional. Isto torna a correta identificação de fatores de risco e a implantação de estratégias eficientes de prevenção da doença fundamentais para a redução expressiva da mortalidade e conseqüências nefastas dos AVC.

Embora tenham ocorrido importantes avanços nos métodos terapêuticos, o tratamento ainda permanece distante de ser satisfatório (de Freitas 2001). Portanto esforços devem focar na prevenção. A prevenção do AVC é baseada no combate aos fatores de risco. Quanto à classificação, os fatores de risco para AVC podem ser divididos de acordo com potencial para modificação (Goldenstein 2001):

1º grupo - aqueles não suscetíveis à modificação, ditos fatores não-modificáveis que incluem idade (Brown 1996; Wolf 1992); sexo (Brown 1996); raça/etnia (Sacco 1998); e história familiar (Kiely 1993). Embora estes fatores não sejam modificáveis, eles identificam os indivíduos que apresentam maior risco de AVC e aqueles que podem se beneficiar da prevenção rigorosa ou tratamento de fatores de risco ditos modificáveis (Sacco 1997).

2º grupo - os que podem ser modificados ou atenuados por mudanças nos hábitos ou por medicamentos, denominados fatores modificáveis que já estão bem estabelecidos. Incluem: em primeiro lugar, a hipertensão arterial (Wolf 1999); e também o tabagismo (Kool 1993); níveis elevados de colesterol total e especialmente LDL-c ou baixos níveis de HDL-c (Brown 2004); Diabetes Mellitus (Kannel 1979); fibrilação atrial (Laupacis 1998); estenose da carótida assintomática (O'Leary 1992); doenças valvares e outras cardiopatias (Di Pasquale 1998).

3º grupo - também modificáveis, porém que não estão ainda bem estabelecidos. Inclui a obesidade (Walker 1996; Rexrode 1997); o uso de álcool (Gorelick 1989); o uso de anticoncepcionais (Bushnell 1999) e o sedentarismo (Kiely 1994). Existem ainda várias outras causas menos freqüentes de AVC, como doenças inflamatórias das artérias (Jander 1998); o uso de drogas como a cocaína (Sloan 1998); e doenças do sangue, principalmente distúrbios da coagulação sangüínea (Folsom 1999).

A incidência de AVC na população varia de acordo com idade, sexo, e raça/etnia. Notavelmente, a idade tem sido identificada como o mais importante determinante da incidência de AVC. Para cada acréscimo de 10 anos, após a idade de 55 anos, a taxa de AVC mais que dobra em homens e mulheres (Wolf 1992, Broderick 1998). Devido ao fato de que o AVC desproporcionalmente afeta o idoso, é antecipado que o AVC, como problema de saúde pública nas próximas décadas, aumentará concomitante com o envelhecimento da população. Em geral, a taxa de incidência de AVC nos homens é aproximadamente 30% maior que nas mulheres. Entre indivíduos mais jovens, porém, a incidência de AVC entre homens e mulheres é aproximadamente a mesmo. Nas faixas mais avançadas de idade (por exemplo, nona década), o número de mulheres vítimas de AVC excede o número de homens apesar de uma incidência menor. Isto se deve à maior longevidade das mulheres (Elkind 2003).

O excesso de peso é um fator de risco bem documentado para doença coronariana (Willett 1995; Manson 1990; Rimm 1995; Hubert 1983). A associação entre obesidade e AVC não está bem estabelecida. A obesidade está, porém fortemente associada a fatores que podem ocasionar o AVC, como hipertensão e diabetes mellitus (Stamler 1991; Colditz 1990).

1.1.3. Obesidade

Atualmente existe uma grande preocupação sobre o aumento do risco de doenças cardiovasculares e outras doenças induzidas pelo ganho de peso excessivo pela população.

A prevalência da obesidade vem aumentando em praticamente todas as populações de todas as faixas etárias mundialmente. Atualmente é considerada como um dos mais graves problemas de saúde pública, por contribuir de forma significativa para o aumento da incidência de diversas causas de morbi-mortalidade, substituindo preocupações mais tradicionais como a desnutrição e as doenças infecciosas (WHO 2000). Setenta milhões de brasileiros (40% da população) apresentam algum grau de excesso de peso, sendo 17,5 milhões obesos, representando 10% da população. O número de pessoas com sobrepeso ou obesidade no Brasil aumentou mais de 50% em um período de 30 anos. (Brasil, MS 2004).

A obesidade é uma doença crônica multifatorial que se desenvolve devido à interação do genótipo com o ambiente. A compreensão de como e por que a obesidade se

desenvolve é incompleta, mas seu mecanismo envolve a integração de fatores sociais, comportamentais, culturais, fisiológicos, metabólicos e genéticos (NHLBI - Clinical Gdlns 1998).

De forma pragmática, a obesidade refere-se a um excesso de gordura corporal ou adiposidade. O índice de massa corporal (IMC), ou peso em quilogramas por altura em metro ao quadrado, é um índice de peso relativo à altura que possui elevada correlação com a adiposidade, mas que não quantifica a adiposidade corporal total nem dá informações sobre a distribuição regional de gordura. Está se tornando evidente que diferentes grupos étnicos apresentam proporções diferentes de massa magra e gorda e equivalente IMC e que a magnitude de múltiplas co-morbidades associadas com alto IMC também pode diferir entre diferentes grupos étnicos por razões que podem refletir o impacto de interações ambiental–genéticas. (Deurenberg 1998; Swinburn 1999).

Os adultos com um IMC de 18.5 a 24.9 kg/m² são classificados como sendo de peso normal, baseados em análises internacionais de impacto de saúde de diferentes IMC em homens e mulheres. O sobrepeso é definido como IMC entre 25 – 29.9 kg/m² e obesidade como IMC superior a 30 kg/m² (WHO 2000).

A obesidade está associada ao desenvolvimento de diversas doenças, incluindo hipertensão (Brown 2000; Dyer 1989), diabetes tipo II (Medalie 1974; Ohlson 1985), doenças coronarianas (Willet 1995; NIHCD 1985), acidente vascular cerebral (Rexrode 1997; Walker 1996; Hubert 1983), osteoartrite (Cicuttini 1996; Hart 1993), apnea do sono e problemas respiratórios (Chua 1994) e ainda alguns tipos de câncer (endométrio, mama, próstata e cólon) (Chu 1991; Schottenfeld 1992).

A presença de excesso de gordura abdominal é um fator de risco independente de morbidades associadas. A circunferência da cintura (CC) é uma medida antropométrica simples para avaliar o conteúdo de gordura abdominal. A razão cintura-quadril também tem sido utilizada para mensurar a gordura abdominal, porém a CC tem sido considerada como um melhor marcador para avaliar o conteúdo de gordura abdominal. Uma circunferência aumentada da cintura, em pacientes com IMC variando entre 25 e 34.9 kg/m², está associada a maior risco de doenças cardiovasculares, assim como diabetes tipo II e hipertensão. (NHLBI - Clinical Gdlns 1998)

De acordo com a OMS, os riscos de complicações metabólicas são aumentados quando a CC é superior a 94 cm (homens) e 80 cm (mulheres) e muito aumentados quando maior que 102 cm (homens) e 88 cm (mulheres). (Lean 1995; Han 1995; WHO 2000).

Em adultos com um padrão de obesidade abdominal, onde existe uma distribuição preferencial de adipócitos dentro da parede abdominal e tecidos intra-abdominais, o risco de DCV parece ser maior (Donohue 1987; Lean 1998; Lemieux 2000). O padrão de distribuição de gordura vem se destacando como um perigoso fator de risco, independente da faixa de IMC (Han 1995).

1.1.4. Obesidade como fator de risco para AVC

O papel da obesidade no desenvolvimento do AVC é mediado através de efeitos intermediários no desenvolvimento de hipertensão, dislipidemia e diabetes mellitus. Porém mecanismos adicionais podem ser considerados para explicar esta associação.

Obesidade abdominal é associada com disfunção endotelial que é um marcador precoce de doença vascular aterosclerótica generalizada. A obesidade também pode resultar em ativação plaquetária por mecanismos que incluem inflamação, peroxidação lipídica e hiperviscosidade. Estes fatores podem promover aterosclerose generalizada e trombose aguda que resultam em AVC (Solorte 1997; Davi 2002).

Alguns investigadores propõem um risco aumentado de eventos isquêmicos com o aumento dos níveis de fatores protrombóticos, como o inibidor de plasminogênio ativado-1 (PAI-1) e fibrinogênio (De Pergola 1997; Morange 1999; Juhan-Vague 2000). Aumento nos níveis de proteína-C reativa também pode representar um papel nessa associação (Visser 1999; Hak 1999).

Obesidade é acompanhada por inflamação generalizada, caracterizada por aumento nos níveis plasmáticos de proteína C reativa assim como pela produção de citocinas por monócitos, linfócitos e outras células imunes (Ouchi 2003). Os mecanismos que conduzem a essas mudanças permanecem ainda não esclarecidos. A presença da obesidade tem sido associada com disfunção endotelial e vascular, o que fornece uma explicação parcial de como a obesidade pode conduzir a doenças cardiovasculares (Fruhbeck 2004; Ekmekci 2006; Matsuzawa 2006). O mecanismo pelo qual a obesidade gera desordens

vasculares é desconhecido. Alterações da função imune podem constituir o elo entre obesidade, desordens vasculares e fatores de risco para aterosclerose (Channon 2002). Além disso, dados recentes mostram que adipócitos, assim como outras células presentes no tecido adiposo, são capazes de lançar numerosos fatores vasoativos que conduzem à doença cardiovascular em indivíduos obesos. Estas substâncias derivadas dos adipócitos produzem efeitos significativos no sistema imune e modificam assim a inflamação.

Entre tais substancias, denominadas adipocinas, destacam-se o fator de necrose tumoral-alfa (TNF-α), a interleucina-6 (IL-6), o PAI-1, a resistina, leptina, adiponectina, a proteína estimulante de acilação (ASP) e os angiotensinogêneos (AGE). Na obesidade, os depósitos de gordura corporal estão aumentados, apresentando elevada expressão das adipocinas, proporcional ao maior volume das células adiposas (Savage 2001; Winkler 2003; Rexrode 2003). As adipocinas que participam na regulação da homeostase vascular são os AGE e os PAI-1.

O TNF-α e a IL-6 são fatores contribuintes para a produção de proteínas de fase aguda pelos hepatócitos, causando aumento nos níveis circulantes de proteína C reativa e de fibrinogênio que são associados à doença cardiovascular (Lemieux 2001; Hotamisligil 1995; Heinrich 1990).

Os mecanismos que podem relacionar a obesidade com AVC não são claros e são controversos. Em resumo, as adipocinas, podem claramente modular as funções imune e vascular, ambas representando um papel crítico na morbi-mortalidade cardiovascular. São necessários mais estudos para esclarecer os mecanismos entre a interação entre o sistema imune e as células vasculares em doenças envolvendo a obesidade.

Há uma incidência crescente de AVC nos indivíduos obesos, especialmente na presença de hipertensão, diabetes ou hipercolesterolemia. A obesidade aumenta o risco de doenças que favorecem o desenvolvimento de AVC. É possível diminuir a incidência do AVC reduzindo a prevalência dos fatores de risco na população; identificando e tratando os indivíduos com "alto risco". Deste modo, a redução de peso em pessoas com sobrepeso/obesidade é recomendada devido ao aumento das co-morbidades associadas, que podem contribuir com o surgimento do AVC (de Freitas, 2001).

Estudos prospectivos demonstram associação positiva entre obesidade e AVC: o “The

Honolulu Heart Program" associou o IMC com maior risco de AVC entre homens não fumantes (Abott 1994). O "Framingham Heart Study", demonstrou uma associação entre maior peso e AVC em mulheres, mas não em homens (Hubert 1983). O "Nurses' Health Study" mostrou que mulheres com alto IMC apresentaram risco aumentado de AVC isquêmico, mas não após ajuste para hipertensão, diabetes e dislipidemia (Rexrode 1997). Outros estudos também demonstram uma associação positiva entre obesidade e AVC (Jood 2004; Kurth 2002; Milionis 2003; Song 2004; Benfante 1994).

Em contraste, outros estudos têm fracassado em demonstrar associação entre obesidade e risco de AVC em mulheres e homens (Folsom 1990; Lapidus 1984; Larsson 1984; Lindestrom 1993; Stokes 1987; Njølstad 1996).

1.1.5. Perda de Peso

A redução e a manutenção do peso, como parte de um programa de modificação de estilo de vida, permanecem a base do tratamento em pessoas com obesidade e doença cardiovascular.

Perda de peso clinicamente significativa é definida como uma perda de 5–10% de peso inicial ou aproximadamente 5–10 kg, e está associada com melhorias significativas em níveis de lipídios, controle glicêmico e da pressão arterial (Oster 1999; Blackburn 1995; Goldstein 1992). Estes efeitos, além dos efeitos diretos de perda de peso, têm um potencial para reduzir a morbi-mortalidade de DCV. Deste modo podem ajudar no controle das doenças que são agravadas pela obesidade e podem também diminuir a probabilidade do desenvolvimento das doenças cardiovascular.

Os métodos tradicionais para promover perda de peso enfocam a redução da ingestão calórica através de dietas hipo-calóricas ou hipo-lipídicas, aumento no gasto energético por aumento nos níveis de atividade física, e modificação comportamental. Para crianças e adultos moderadamente obesos, as combinações de exercício e dieta oferecem muito mais flexibilidade para conseguir um balanço calórico negativo e a subseqüente perda de gordura corporal do que o exercício ou a dieta isoladamente. O acréscimo de exercício a um programa de controle ponderal facilita a perda de gordura, muito mais do que quando essa perda depende quase totalmente da restrição alimentar (Brownell 1982; Brownell 1986; Di Pietro 1995; Miller 1991; Pavlou 1989; Racette 1995; Wadden 1995). Curioni e Lourenço (2005), em uma metanálise avaliando a efetividade de intervenções de dieta e

exercício em longo prazo, demonstraram que a associação de dieta e exercício físico pode promover maior perda de peso ao fim da intervenção comparando apenas com dieta. Após um ano do fim da intervenção, a perda de peso ainda é maior para este grupo, sendo compatível com benefícios clinicamente relevantes. Porém, a efetividade destes métodos para redução de peso é limitada, ambas intervenções estudadas apresentaram recuperação parcial de 50% da perda de peso.

Numerosas outras intervenções para perda de peso estão disponíveis, incluindo cirurgia para redução da ingestão alimentar por diminuição do intestino delgado ou gastroplastia, suplementos de vitaminas e minerais, substituições de refeições, terapias farmacológicas e diversas terapias alternativas.

A terapia farmacológica como um reforço para dieta e mudanças de estilo de vida pode melhorar a perda de peso em longo prazo. O medicamento anti-obesidade idealmente deve apresentar três características importantes. Primeiro, deveria causar sustentada perda de peso clinicamente significativa e reduzir a morbi-mortalidade relacionada com a obesidade. Segundo, a relação risco - beneficio da droga deve ser favorável. E por último, o custo é uma consideração importante porque a obesidade é uma condição que desproporcionalmente afeta pessoas de baixa classe socioeconômica. Pacientes com IMC maior que 30 kg/m² ou maior que 27 kg/m² com alguma morbidade associada são elegíveis para o tratamento farmacoterápico.

Terapias farmacológicas atualmente aprovadas para perda de peso dividem-se em duas categorias: medicamentos supressores do apetite, que diminuem a ingestão alimentar reduzindo o apetite ou aumentando a saciedade; e medicamentos que modificam o metabolismo, provocando diminuição da absorção de nutriente (Yanovski 2002). Os dois tipos de medicamentos são caros, e podem apresentar efeitos colaterais (por exemplo, boca seca, constipação, insônia, enxaquecas, urgência fecal, flatulência e absorção reduzida de vitaminas gordura-solúvel). Orlistat e Sibutramina são os únicos medicamentos aprovados para uso em longo prazo. Novos medicamentos estão atualmente sendo desenvolvidos clinicamente, sendo o rimonabant o único em estágios avançados de investigação.

As intervenções de perda de peso em pessoas com sobrepeso ou obesidade podem ser associadas com flutuações de peso (weight cycling). Existem evidências que esta condição pode estar associada com aumento de risco de morbidades, especialmente doenças

cardiovasculares (Ernsberger 1996).

1.1.6. Sistema Endocanabinóide (SECB) e Rimonabant

A obesidade e as doenças cardiovasculares representam um grave problema de saúde pública, como descrito anteriormente. Alguns fatores de risco cardiovascular podem modificar-se favoravelmente, em especial com terapia farmacológica, sendo o caso da hipertensão arterial, das dislipidemias e do diabetes mellitus tipo 2 (Psaty 1997; Pearson 2005; Van Gaal 2003). No entanto, atualmente existem opções limitadas de terapias farmacológicas para tratar outros potenciais fatores de risco cardiovascular como o tabagismo e a obesidade.

A manipulação do SECB através do bloqueio de receptores de canabinóide é um novo método que pode beneficiar o tratamento da obesidade.

Constituem o SECB os receptores canabinóides (CB), os endocanabinóides (ECB) e as enzimas que catalisam sua síntese e degradação (Cota (1) 2003). O SECB, devido a suas diversas ações fisiológicas, tem emergido durante a última década como um atrativo farmacológico para o tratamento não somente da obesidade e tabagismo, como também de outros fatores de risco cardiovascular associados a estas alterações.

Cannabis sativa tem sido utilizada por milênios como fonte de fibra e óleo, e também como fonte de drogas (maconha e hashish) (Gelfand 2006). Esta planta contém mais de 60 canabinóides, dos quais se destaca o Δ9-tetrahidrocannabinol (Howlett 2004).

Os canabinóides naturais e sintéticos atuam sobre dois tipos de receptores CB1 e CB2 que tem seus próprios ligantes endógenos: os ECB. O CB1 é o mais abundante receptor de membrana-ligados-a-proteína G no cérebro, enquanto o CB2 está presente nas células do sistema imunológico (Di Marzo 2004; Di Marzo 2005). Os ECB de interesse em relação ao apetite são os 2-araquidonoilglicerol e a n-araquidonoiletanolamina (anandamida).

Por serem sintetizadas primordialmente (mas não exclusivamente) nas células neuroniais, os ECB vêm sendo considerados como neuro-transmissores não clássicos, já que não se armazenam nas vesículas sinápticas, e sim são produzidos e liberados “a partir da demanda” (Pagotto 2005).

A liberação dos ECB ocorre em resposta à despolarização da membrana e ao fluxo de cálcio dentro da célula, tal como ocorrem com os neuro-transmissores clássicos, para logo se unir a seu receptor e posteriormente ser desativado através de mecanismos de recaptação e de degradação enzimática (Pagotto 2005).

A união dos ECB a seu receptor CB1 (ativação dos receptores) causa a inibição da adenilatociclase, diminuição dos níveis de AMPc, abertura dos canais de K+, hipo-polarização celular e o fechamento dos canais de Ca++, impedindo sua entrada na célula (Rodríguez de Fonseca, 2005).

Entre as diversas regiões do sistema nervoso central na qual se expressa o receptor CB1, merece destaque o hipotálamo, pois é a estrutura relacionada com a regulação da energia e apetite. Os receptores CB1 também se localizam em órgãos periféricos relacionados com o mesmo fenômeno como o trato gastro-intestinal, o fígado, o músculo esquelético e o tecido adiposo (Engeli 2005).

Efeitos Cardiovasculares do sistema endocanabinóide:

Em animais de laboratório, a administração aguda de um endocanabinóide produz uma resposta hemodinâmica trifásica característica: uma taquicardia breve e vagalmente mediada e hipotensão; uma resposta pressora igualmente breve; e uma resposta vasodepressora dominante e prolongada (Varga 1995).

Efeitos Metabólicos:

Receptores canabinóides e ligantes estão presentes em altas concentrações em todos os tecidos que apresentam um papel importante na regulação de ingestão alimentar, ou seja, tecido adiposo, sistema límbico e hipotálamo. Algumas evidências agora apontam para um papel dos endocanabinóides na regulação do metabolismo e composição corporal, aumentando impulso orexigênico e lipogênese periférica. (Cota (2) 2003). A administração de agonista de CB1 induz hiperfagia em roedores (Jamshidi 2001; Kirkham 2002) e antagonistas de CB1 previne superalimentação compensatória em ratos forçados a inanição. Por outro lado, administração de leptina suprime a síntese de endocanabinóides (Di Marzo 2001). Igualmente ratos com deficiência de receptores CB1 exibiram um fenótipo magro, mesmo sendo alimentados com dieta rica em gorduras para promover obesidade, primariamente em conseqüência de redução de calorias espontaneamente (Cota (2) 2003). Endocanabinóides são considerados também como sendo centrais no papel da adição e em comportamentos de recaídas (De Vries 2005).

As evidências que apóiam o envolvimento dos endocanabinóides no controle da ingestão alimentar têm encorajado estudos com o uso de antagonistas dos receptores CB1 contra a obesidade. Rimonabant (SR-141716A) foi sintetizada e descrita em 1994 por Rinaldi-Carmona et al.

Estudos com roedores demonstraram que o rimonabant foi associado com uma redução na ingestão alimentar e uma perda de peso de aproximadamente 4% (Di Marzo 2001).

Ratos, com deficiência do receptor CB1 não demonstraram nenhuma perda de peso sugerindo um mecanismo específico de perda de peso mediado por CB1. Inicialmente, rimonabant diminui o apetite, porém estes efeitos são transitórios. Durante a continuação da terapia, ocorre hiperfagia, porém a perda de peso continua. A maior parte da perda de peso é acompanhada por uma depleção de 50% nas reservas de gordura. Animais tratados com rimonabant exibem níveis de glicose e insulina de plasmático mais baixo, assim como melhora na resistência insulínica (Ravinet Trillou 2003) Tais achados também sugerem que somente a ingestão alimentar não pode responder pela perda de peso sustentada durante tratamento com rimonabant.

Alguns estudos de fase III com o antagonista do receptor CB1, rimonabant, estão em andamento e alguns resultados já foram publicados. O objetivo destes estudos é a avaliação do papel do rimonabant no manejo da obesidade, manutenção da perda de peso, prevenção da recuperação do peso após perda de peso inicial e melhora dos fatores de risco relacionados à obesidade, como diabetes e dislipidemia.

1.2. Justificativa

Como descrito na introdução, o presente trabalho foi motivado pela inconsistência observada nos resultados dos estudos esclarecendo o papel da perda de peso na prevenção primária do AVC. Devido ao fato da maioria dos estudos relacionados com a obesidade avaliarem apenas os marcadores de fator de risco de doenças cardiovasculares, torna-se imperiosa a investigação de estudos que avaliem os efeitos da perda de peso diretamente sobre a morbidade cardiovascular, avaliando seus potenciais benefícios e riscos.

É oportuno realizar uma revisão sistemática e, se possível, integrar seus resultados com metanálise, para investigar os principais estudos que relatam redução de peso em longo prazo, para discutir seu papel na prevenção primária do acidente vascular cerebral. Além disso, a avaliação crítica e sistemática da produção neste campo pode permitir a compreensão das inconsistências observadas nos achados dos diferentes estudos, levando às sugestões úteis para o desenvolvimento de futuras pesquisas.

Devido às DCV constituírem a principal causa de morte na maioria dos países, estando as tendências de mortalidade bem descritas nos países desenvolvidos, mas ainda não totalmente elucidadas nos países em desenvolvimento, torna-se adequado explorar a evolução da mortalidade das DCV, dando ênfase ao AVC no Brasil, explorando as diferenças de acordo com sexo, idade e regiões.

Baseado no fato que o rimonabant é a primeira droga de uma nova classe de medicamentos que parece reduzir peso e melhorar fatores de risco para DCV, torna-se pertinente avaliar os estudos clínicos existentes para estabelecer a eficácia e segurança desse medicamento.

1.3. OBJETIVOS

1.3.1. Objetivo Geral

Avaliar a evolução das taxas de mortalidade das DCV, com ênfase no AVC no Brasil; avaliar o efeito da redução do peso, através de diversos tipos de intervenção para o tratamento da obesidade, na prevenção primária de AVC; e avaliar a eficácia e segurança do medicamento Rimonabant no tratamento da obesidade.

1.3.2. Objetivos Específicos

Artigo I - Avaliar a evolução das taxas de mortalidade de AVC no Brasil no período inicial (3 primeiros anos) das 3 últimas décadas, explorando possíveis diferenças de acordo com idade e sexo e entre as diferentes regiões geopolíticas do país.

Artigo II - Avaliar a evolução das taxas de mortalidade das principais doenças cardiovasculares no Brasil no período de 1980 a 2003, explorando possíveis diferenças de acordo com idade e sexo entre as diferentes regiões geopolíticas do país.

Artigo III - Avaliar o efeito da perda de peso na prevenção primária de AVC em adultos com sobrepeso ou obesidade através de uma revisão sistemática com ensaios clínicos randomizados comparando qualquer intervenção para redução de peso incluindo como desfecho a incidência de um primeiro AVC.

Artigo IV - Avaliar os efeitos do rimonabant em indivíduos com sobrepeso e obesidade através de uma revisão sistemática com ensaios clínicos randomizados comparando intervenções com rimonabant incluindo como desfechos medidas de peso corporal, efeitos adversos e fatores de risco cardio-metabólicos.

Seção 2

Artigos

Originalmente, os artigos foram escritos em inglês de acordo com as normas exigidas pelas revistas na qual foram submetidas. A seguir os artigos serão apresentados de forma resumida em português e a íntegra é apresentada em anexo.

2.1. Artigo I

Título: Declínio progressivo na mortalidade por AVC no Brasil de 1980-1982, 1990-1992 e 2000-2002.

André C, Curioni CC, da Cunha CB, Veras R..

***Stroke*. 2006; 37:2784-2789**

Introdução

Nos Estados Unidos e em outros países desenvolvidos houve uma redução significativa nas taxas de mortalidade durante o século XX. Dados dos países em desenvolvimento são menos abundantes, porém em alguns países também tem sido detectado um declínio nas taxas (Radishauskas 2005; Sarti 2000).

No Brasil, em análises específicas de algumas regiões, também demonstra uma redução nas taxas de mortalidade (Lolio 1993; Lotufo 2004). Informações sobre mortalidade cardiovascular dos anos 60 e 70 no Brasil são difíceis de serem encontradas, porém um declínio mais recente pode ter ocorrido (de Pádua 2003). Desigualdades nas mortalidades cardiovasculares e de AVC podem ser encontradas no Brasil considerando as discrepâncias encontradas nas condições socioeconômicas e na saúde entre as diferentes regiões geopolíticas.

Disparidades regionais em mortalidade por AVC no Brasil não foram estudadas previamente. O presente estudo avalia a evolução das taxas brasileiras de mortalidade de AVC durante os períodos iniciais das últimas três décadas e explora as possíveis diferenças de acordo com idade e sexo e entre as diversas regiões geopolíticas, com suas grandes disparidades socioeconômicas.

Métodos

O número de óbitos de AVC foi obtido do Sistema de Informações de Mortalidade brasileiro. As taxas de mortalidade foram calculadas para estimativas da população derivados dos censos feitos em 1980, 1991 e 2000. Todas as taxas foram padronizadas pela idade através do método direto, utilizando a população de 1980 como padrão.

As taxas de mortalidade padronizadas para cada década correspondem aos valores médios dos três primeiros anos de cada período, exemplo, para a década de 80: 1980, 1981 e 1982. Tal procedimento se torna necessário para atenuar eventuais e inesperadas oscilações. A distribuição das faixas etárias é apresentada de acordo com o sistema da Organização Pan Americana de Saúde. A evolução das taxas de mortalidade também foi explorada nas cinco regiões brasileiras.

Foi utilizado o modelo regressão de Poisson para verificar as mudanças ocorridas na taxas. Para o modelo, foi utilizado o número de óbitos e a correspondente população estratificada por ano, região, idade e sexo. Mudanças na tendência das taxas de mortalidade padronizadas foram adicionalmente testadas para possíveis interações entre sexo, faixa etária e regiões. Os resultados são apresentados para analisar os resultados nos períodos iniciais de 1990 e 2000 comparados com 1980. Para todas as analises estatísticas, um p-valor de 00,5 foi considerado estatisticamente significativo. Todas as análises foram realizadas com ajuda do software SAS (Stokes 2000).

Resultados

As taxas de mortalidade padronizadas diminuíram consistentemente entre 1980 a 1982 e 2000 a 2002: de 68.2 para 40.9 por 100 000 habitantes. Usando a taxa de 1980 como referência, houve una redução de risco (RR) de 30% (95% IC, 30% a 31%) em 1990 e 55% (95% IC, 55% a 56%) em 2000 (P=0.001 para ambas as medidas).

A redução proporcional de mortalidade de AVC foi evidente para homens e mulheres, sendo mais destacado entre homens. O declínio também foi observado em todas as faixas etárias. Uma interação entre sexo e idade foi detectada, com um declínio mais evidente na população masculina jovem (até 45 anos) e para mulheres de todas as outras faixas etárias (p = 0.001 para todos os achados).

Uma redução foi observada em todas as regiões geopolíticas. As regiões mais ricas (sul e sudeste) exibiram taxas iniciais mais altas e também reduções mais acentuadas durante o período de estudo. Os achados foram confirmados pelo modelo de regressão de Poisson na qual a menor redução foi encontrada na região nordeste: 41% (95% IC, 40% a

42%). Os valores correspondentes para as outras regiões foram: norte, 52% (95% IC, 51% a 52%); centro este, 53% (95% IC, 53% a 54%); sul, 57% (95% IC, 56% a 57%); e sudeste, 59% (95% IC, 58% a 59%).

Porém, o número total de mortes relacionado ao AVC no Brasil tem aumentado continuamente nas últimas 3 décadas: de 79.862 em 1980 a 1982 a 101.625 em 2000 a 2002. Este aumento reflete principalmente o envelhecimento progressivo da população brasileira.

Conclusão

Houve uma redução consistente na mortalidade de AVC entre 1980 e 2000 no Brasil. A redução foi mais acentuada nas regiões mais desenvolvidas. Essa redução não parece ser completamente explicada por controle de fatores de risco clássicos em indivíduos de alto risco, avanços tecnológicos, ou melhorias em cuidado de AVC agudo, mas pode em parte refletir melhoria nas condições gerais de saúde no Brasil. O envelhecimento progressivo da população, porém, conduzirá a um aumento progressivo no número total de mortes atribuível ao AVC e doenças cardiovasculares nas próximas décadas.

2.2. Artigo II

Título: Declínio da mortalidade por doenças cardiovasculares no Brasil

Curioni C, Cunha CB, Veras R, André C.

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Introdução

A alta taxa de mortalidade por causas cardiovasculares em países em desenvolvimento (estimada em 9 milhões em 1990 e com aumento esperado para 19 milhões em 2020) (Murray 1996) pode ser explicada pelo aumento da idade média para óbitos e das taxas de prevalência dos fatores clássicos de risco de doenças cardiovasculares como hipertensão, tabagismo, dislipidemia, diabete e obesidade (Erdine 2004; Fagerstrom 2002; WHO 2000; Liu 2004; de Sereday 2004).

Foi observado um importante declínio na mortalidade cardiovascular em países desenvolvidos (Ergin 2004; Levi 2002; Reid 2005; Kestloot 2006). O mesmo já pode estar começando no Brasil (Oliveira 2005; Mansur 2001). Vários fatores podem contribuir para a redução da incidência e da taxa de mortalidade por doenças cardiovasculares, inclusive AVC e doença coronariana. Entre tais fatores, podem-se incluir aqueles que afetam a população inteira ou grande parte dela, como uma melhora gradual nas condições econômicas e um maior acesso a drogas usadas no tratamento dos principais fatores de risco, como hipertensão e diabetes.

Estudos recentes de tendências de mortalidade de doenças cardiovasculares no Brasil analisaram apenas dados específicos de cidades ou regiões ou doenças específicas (Lolio 1986; Lolio 1995; Lotufo 1998). Análises detalhadas que explorem eventuais discrepâncias entre diversos grupos de doenças ainda não foram realizadas. Também, ainda não foram estudadas possíveis disparidades regionais. Diferenças na distribuição de mortalidade cardiovascular são prováveis considerando as grandes discrepâncias nas condições socioeconômicas e de saúde em todo o país.

O objetivo deste estudo é apresentar a evolução das taxas de mortalidade dos principais grupos de doenças cardiovasculares no Brasil no período entre 1980 e 2003,

explorando possíveis diferenças de acordo com idade e sexo entre as diversas regiões geopolíticas que exibem evidentes disparidades socioeconômicas.

Métodos

O número de óbitos por causas cardiovasculares foi obtido através do Sistema de Informação de Mortalidade do Brasil. Foram obtidos dados para todos os óbitos por doenças cardiovasculares em geral e para os 4 maiores grupos de doenças - doença coronariana, AVC, complicações de hipertensão (essencialmente doença cardíaca e renal), e outras causas.

Foram calculadas as estimativas de taxa de mortalidade, expressas como o número de óbitos para 100 000 habitantes, para as estimativas da população derivadas de censos brasileiros realizados em 1980, 1991, 1996 e 2000. Todas as taxas foram padronizadas pela idade através do método direto, utilizando a população de 2000 como padrão.

A evolução da taxa de mortalidade cardiovascular foi estratificada por sexo, faixa etária e região. Foram feitas correções para causas de morte mal definidas, devido à alta proporção, embora declinante no Brasil (por exemplo, 21,5% de mortes em 1980 vs. 5,1% em 1999) (Mello Jorge 2002).

Tendências para mortalidade de doenças cardiovasculares - total e dos 4 grupos de doenças - durante o período de 1980 a 2003 no Brasil separadamente para cada sexo, faixa etária, e regiões geopolíticas foram analisadas pelo Modelo de Regressão Binomial Negativa. Este modelo foi adotado devido à alta dispersão encontrada nos dados analisados (Kleinbaum 1998).

O modelo é representado por: $Log\ (taxa\ do\ evento) = \alpha + \beta * Year + \varepsilon$, onde α indica intercepto; β, coeficiente angular; e ε, erro randômico.

Foram realizados modelos para cada estrato das variáveis consideradas. A mudança percentual média anual (AAPC) para as taxas de doença foi obtida utilizando a seguinte fórmula: $100\ [\exp(\beta) - 1]$.

Para todas as análises estatísticas, um valor de $p < 0,05$ foi considerado como estatisticamente significativo. Todas as análises foram feitas com o auxílio do software estatístico SAS para Windows 9 (Stokes 2000).

Resultados

O número total de óbitos por doenças cardiovasculares no Brasil aumentou continuamente durante o período estudado. O número médio de óbitos aumentou 45%

entre 1980 e 2003; com uma tendência semelhante para todos os 4 grupos de doenças. Este aumento reflete principalmente o envelhecimento progressivo e o crescimento da população brasileira.

Apesar disto, a taxa de mortalidade padronizada diminuiu constantemente no Brasil entre 1980 e 2003 para todos os grupos de doenças: taxas de mortalidade cardiovasculares totais exibiram uma redução anual média de 3.9% por 100 000 habitantes. AVC exibiu a taxa de mortalidade mais alta entre as doenças cardiovasculares; mas também apresentou o maior declínio anual - 4.0% por 100 000 habitantes; taxas relacionadas à doença coronariana apresentaram uma redução anual de 3.6% por 100 000 habitantes.

Para ambos os sexos, foi observada uma tendência declinante estatisticamente significativa para taxas do total das doenças cardiovasculares e dos 4 subgrupos de doenças ($P < 0.0001$). O declínio percentual anual médio foi semelhante entre homens e mulheres em todos os grupos de doenças. AVC foi a principal causa de morte em mulheres em 1980 e ainda em 2003. Doença coronariana desde 1999 ultrapassou o AVC como principal causa de morte cardiovascular em homens brasileiros.

Foi observada uma diminuição nas taxas de mortalidade em todas as faixas etárias. Um declínio mais acentuado foi evidenciado na população mais jovem (até 45 anos), porém todos os estratos sofreram um grande declínio nos últimos 24 anos ($P < 0.0001$ para todos os achados). A mortalidade relacionada a complicações da hipertensão na população mais idosa (> 75 anos) representou uma exceção, com taxas que aumentaram ligeiramente (média 0.4% por ano) ao longo do período estudado.

Ocorreu uma redução nas taxas de mortalidade em todas as regiões geopolíticas. A região Norte exibiu reduções mais acentuadas durante o período do estudo; porém este achado deve ser interpretado com cautela desde o aumento paralelo no fluxo migratório de outras regiões brasileiras ocorrido entre 1980 e 1991 resultando numa expansão demográfica muito superior à média naquela região (Moreira 2000). Excluindo a Região Norte, as regiões mais ricas (Sul e Sudeste) exibiram taxas iniciais de mortalidade de doenças cardiovasculares mais altas e também maiores reduções ao longo do tempo em relação às outras regiões menos desenvolvidas. Tendências na mesma direção foram observadas para AVC e doença coronariana.

Conclusão

Durante um período de 24 anos, a mortalidade por DCV no Brasil diminuiu progressivamente nas mulheres e nos homens de todas as faixas etárias, porém a magnitude do declínio variou de acordo com diferenças socioeconômicas regionais. Além disso, com o aumento progressivo no número total de óbitos anuais por DCV esperado nas próximas décadas, deveriam ser incentivados maiores esforços de prevenção. Considerando a associação observada entre condições socioeconômicas e mortalidade cardiovascular, grandes intervenções poderiam ter mais êxito se planejadas de acordo com as desigualdades sociais e diferenças culturais.

2.3. Artigo III

Título: Redução de peso para prevenção primária de acidente vascular cerebral (AVC) em adultos com sobrepeso e obesidade

Curioni C, André C, Veras R,

***Cochrane Database Syst Rev.* 2006 Oct 18;(4):CD006062. Review.**

Introdução

Descrição da condição

Obesidade

De acordo com a Organização Mundial de Saúde, obesidade é uma doença crônica multifatorial com freqüência crescente em muitos países, podendo ser caracterizada como uma epidemia de grande preocupação (WHO 2000). Obesidade é uma condição de excesso de gordura corporal que pode ter importantes conseqüências na saúde. Sobrepeso e obesidade parecem estar associados com maior morbidade, como hipertensão arterial, diabetes, doença coronariana, AVC, osteoartrite, apnea do sono, problemas respiratórios e alguns tipos de câncer (Clinical Gdlns 1998). A gordura abdominal é melhor correlacionada com aumento de mortalidade e risco de desordens como diabetes, dislipidemia, hipertensão e doenças cardiovasculares (Donahue 1987; Ducimetiere 1986; Lapidus 1984; Larsson 1984; Ohlson 1985; Remexe 1985).

Acidente Vascular Cerebral

AVC é a terceira causa de morte em países desenvolvidos atrás de doença coronariana e câncer e a principal causa de séria incapacitação em longo prazo. A maioria dos países em desenvolvimento também apresenta uma tendência crescente em mortalidade de AVC (Balaguer Vintro 2004).

Devido às opções limitadas para tratar os pacientes acometidos por AVC, o reconhecimento de fatores de risco e esforços preventivos permanecem a melhor forma para reduzir a prevalência de AVC. Fatores de risco e marcadores de risco para um primeiro AVC normalmente são classificados de acordo com seu o potencial para modificação (modificáveis, não modificáveis, potencialmente modificáveis) (Goldstein 2001).

AVC e Obesidade

A obesidade é reconhecida como um fator de risco modificável para doenças cardiovasculares, especialmente doença isquêmica do coração. A associação causal entre obesidade e AVC está menos clara. A obesidade aumenta o risco para hipertensão, diabetes e dislipidemia (Brown 2000; Dyer 1989; Ford 1997; Larsson 1981; Ohlson 1985). Com base apenas nessas associações, obesidade poderia estar relacionada a um aumento do risco de AVC. Porém, estudos documentando o impacto específico da obesidade ou sobrepeso em AVC mostram resultados heterogêneos.

Prevenção de AVC

Prevenção primária de AVC inclui modificações de estilo de vida (aumento de atividade física, interrupção de tabagismo, redução de consumo de álcool) e medidas para controlar pressão sanguínea, níveis de colesterol, diabete e fibrilação atrial. Prevenção primária é particularmente importante porque mais que 70% de AVC são eventos primários (Goldstein 2001). Devido à obesidade contribuir para outros fatores de risco associados com AVC, promover perda de peso e manutenção de um "peso" saudável pode ser considerado como uma alta prioridade.

Como a intervenção atua

A redução e a manutenção de peso como parte de um programa de modificação de estilo de vida, permanecem a base do tratamento em pessoas com sobrepeso ou obesidade. Intervenções de redução de peso incluem: dieta, exercício, intervenções psicológicas ou comportamentais, farmacoterapia, cirurgia e terapias alternativas (Clinical Gdlns 1998). Uma perda de peso de 5% a 15% do peso inicial pode ser associada com melhorias significantes em níveis de lipídeos, controle glicêmico e da pressão arterial (Douketis 2005). Estes efeitos poderiam ter o potencial para reduzir a incidência de morbi-mortalidade cardiovascular. Desta forma, a perda de peso pode ajudar no controle de doenças exacerbadas pelo sobrepeso ou obesidade e também pode diminuir a probabilidade de se adquirir estas doenças.

Efeitos adversos da intervenção

As intervenções de perda de peso em indivíduos com sobrepeso ou obesos podem estar associadas a flutuações de peso.

Por que é importante fazer esta revisão

Não existe nenhuma revisão sistemática que avalie o papel de tratamento de obesidade na prevenção de um primeiro AVC (prevenção primária). Não está claro se existe

evidência científica que comprove rigorosamente a recomendação da redução de peso para prevenir AVC.

O Objetivo desta revisão é avaliar o efeito da redução de peso na prevenção primária de AVC em adultos com sobrepeso e obesidade.

Métodos

Critérios para considerar estudos para essa revisão:

Ensaios clínicos controlados randomizados, incluindo adultos diagnosticados com sobrepeso ou obesidade, comparando qualquer intervenção para redução de peso. As medidas de desfecho incluem: incidência de um primeiro AVC, mortalidade e qualidade de vida.

Estratégias de busca

As seguintes fontes eletrônicas foram incluídas no processo de busca: The Cochrane Library, MEDLINE, EMBASE e LILACS. Para aumentar a abrangência da revisão, banco de dados de *ongoing trials*, listas de referência de estudos e revisões sobre o tema também foram consultadas.

Seleção de Estudos

Dois autores (CC e CA) independentemente avaliaram títulos, resumos e palavras-chave dos estudos identificados pelas estratégias de busca. O texto completo foi avaliado quando:

(1) incluíram pacientes com sobrepeso ou obesidade;

(2) apresentaram uma intervenção de perda de peso;

(3) avaliaram um ou mais desfechos relevantes.

Detalhes da metodologia planejada para avaliação dos estudos são encontrados na íntegra no Anexo III

Resultados

Para achar todos os estudos possíveis, uma estratégia de busca foi desenvolvida com um equilíbrio entre integralidade e precisão. Após conferir os resultados da busca, nenhum ensaio clínico foi elegível para inclusão. Na tentativa de encontrar estudos, a estratégia de busca foi readaptada. Novamente, nenhum estudo foi encontrado. Duas buscas adicionais foram realizadas, porém, nenhum estudo pôde ser incluído.

Como descrito no protocolo, buscou-se a melhor fonte de evidência científica disponível, através de ensaios clínicos controlados randomizados. Após não terem sido encontrados estudos, houve a tentativa de identificar estudos de coorte prospectivos. Uma estratégia de busca foi desenvolvida para identificar este tipo de estudo observacional. Infelizmente, não foi detectado nenhum estudo de coorte investigando os efeitos da perda de peso em AVC em adultos.

Conclusão

Existem dados insuficientes para se fazer recomendações práticas sobre os efeitos de redução de peso em pessoas com sobrepeso ou obesidade na incidência de AVC.

2.4. Artigo IV

Título: Rimonabant para obesidade ou sobrepeso

Curioni C, André C

***Cochrane Database Syst Rev.* 2006 Oct 18;(4):CD006162. Review.**

Introdução

Descrição da condição

A prevalência da obesidade e sobrepeso vem aumentando em taxas alarmantes em países industrializados e em número significativo de países em desenvolvimento (WHO 2000). Este problema é associado com uma grande variedade de conseqüências de saúde que representam um grande custo nos sistemas de saúde e, também pode afetar de forma substancial a qualidade de vida dos indivíduos afetados.

A obesidade se refere a um excesso de gordura corporal. O índice de massa corporal (IMC; em kg/m2) é amplamente reconhecido como um índice de peso-para-altura que tem uma alta correlação com adiposidade. O IMC de 25-29 kg/m² é classificado como sobrepeso e um IMC maior que 30 kg/m² reflete obesidade (WHO 2000).

A presença de excesso de gordura abdominal é um preditor independente de diabetes tipo 2, dislipidemia, hipertensão, e doença cardiovascular (NHLBI 1998), que vem sendo demonstrado por vários estudos (Donahue 1987; Ducimetiere 1986; Lapidus 1984; Larsson 1984; Ohlson 1985; Remexe 1985).

Descrição da intervenção

A obesidade é uma condição que requer tratamento. Tratamento significa, em primeiro lugar, redução de peso. Existe forte evidência que a perda de peso (5% a 15% do peso corporal) em indivíduos obesos reduz fatores de risco associados com obesidade (NHLBI 1998).

Métodos tradicionais para promover perda de peso enfocam redução da ingestão calórica com dietas, aumento do gasto energético por aumento da atividade física, e modificação comportamental. Numerosas outras intervenções são disponíveis, incluindo farmacoterapia, cirurgia para reduzir consumo alimentar e terapias alternativas.

A terapia medicamentosa deve ser considerada em pacientes obesos e com sobrepeso com um IMC maior que 27 kg/m², particularmente na presença de comorbidades ou uma circunferência de cintura aumentada quando intervenções como terapia comportamental,

dieta e exercício não resultaram na perda de peso desejada (NHLBI 1998). Entretanto, medicamentos sempre devem ser associados com terapias não-farmacológicas.

Os Medicamentos aprovados para obesidade podem ser divididos em duas categorias:

(1) Inibidores de absorção intestinal de gorduras, na qual o único agente disponível é orlistat.

(2) Drogas que agem na supressão do apetite. Um exemplo desta categoria inclui sibutramina.

Atualmente, vários outros medicamentos estão em estágio de desenvolvimento clínico. A maioria destas drogas está em fases iniciais de desenvolvimento. Rimonabant é a única droga em fase avançada de resultados.

Como a intervenção pode atuar

Rimonabant é um antagonista seletivo do receptor canabinóide-1 (CB-1) que tem sido investigado devido sua eficácia em reduzir peso corporal e fatores de risco associados em pacientes obesos (Bonner 2005). O receptor CB-1 apresenta um papel na regulação do apetite e peso corporal. O sistema endocanabinóide (EC) consiste em receptores de canabinóide e endocanabinóides, assim como enzimas que catalisam sua biossíntese e degradação (Di Marzo 2005). Estímulos farmacológicos de receptores CB1 por administração sistêmica da planta estimulam a ingestão alimentar, até mesmo em animais saciados (Colombo 1998; Rowland 2001; Simiand 1998).

A administração do primeiro antagonista seletivo de CB1 (rimonabant) atenuou estimuladores da ingestão alimentar e reduziu o consumo de alimentos saborosos (tais como doces) e a ingestão de alimentos em animais privados de alimentos (Rinaldi-Carmona 2004; Werner 2003). Rimonabant tem mostrado reduzir a ingestão alimentar, fome e peso corporal em homens com sobrepeso e obesidade após sete dias de tratamento (Vickers 2005).

Ensaios clínicos fase III estão agora em desenvolvimento para testar o uso do rimonabant na perda de peso em longo prazo. Quatro ensaios clínicos (RIO (rimonabant em obesidade) EUA, RIO-Europa, RIO-diabetes e RIO-Lipideos) envolvendo 6000 pacientes sugerem que rimonabant 20 mg comparado com placebo produz uma perda de peso de aproximadamente 5 kg. Nenhum grande efeito colateral foi relatado; porém, com a ampla distribuição de receptores CB1 dentro do corpo, é possível que a droga possa afetar vários sistemas (Halford 2006).

Por que é importante fazer esta revisão

Não existe nenhuma revisão sistemática que avalie a eficácia e também os possíveis efeitos adversos do rimonabant em pessoas com sobrepeso ou obesas. Dada a prevalência de sobrepeso e obesidade, é importante estabelecer o possível impacto do rimonabant em pessoas que sofrem destas condições.

Método

Critérios para considerar estudos para essa revisão:

Ensaios clínicos randomizados controlados, incluindo adultos diagnosticados com sobrepeso ou obesidade, comparando rimonabant com placebo, associado ou não a outra intervenção nos dois grupos; com outra intervenção farmacológica ou não farmacológica. As medidas primárias de desfecho incluem: mudança no peso e na circunferência abdominal, morbidades e efeitos adversos; e as secundárias: mortalidade, mudanças em fatores de risco cardio-metabólicos e qualidade de vida.

Estratégias de busca

As seguintes fontes eletrônicas foram incluídas no processo de busca: The Cochrane Library, MEDLINE, EMBASE e LILACS. Para aumentar a abrangência da revisão, banco de dados de *ongoing trials*, listas de referência de estudos e revisões sobre o tema também foram consultadas.

Seleção de estudos

Dois autores (CC e CA) independentemente avaliaram títulos, resumos e palavras-chave dos estudos identificados pelas estratégias de busca. O texto completo foi avaliado quando:

(1) incluíram pacientes com sobrepeso ou obesidade;

(2) apresentaram rimonabant como intervenção;

(3) avaliaram um ou mais desfechos relevantes.

Extração dos dados

A extração dos dados também foi realizada de forma independente pelos dois revisores utilizando um formulário padrão para a transcrição dos dados. Diferenças na extração e entrada dos dados entre os revisores foram resolvidas mediante discussão e reavaliação do artigo original.

Avaliação da qualidade dos estudos

Dois revisores avaliaram a qualidade metodológica dos estudos independentemente por critérios de análise individual de qualidade dos artigos (CC e CA). Estudos não foram excluídos somente com base na baixa qualidade.

Análise dos dados

Para analisar a magnitude do efeito da intervenção nos desfechos contínuos foram utilizadas diferenças de médias ponderadas com intervalo de confiança (IC) de 95% para os valores pós-intervenção ou para as diferenças entre os valores do *baseline* e pós-intervenção. Para as variáveis dicotômicas o tamanho do efeito da intervenção foi expresso como razão de chances (OR) e seu respectivo IC de 95%.

A heterogeneidade foi avaliada através de teste qui-quadrado, com um nível de significância de 0.1 devido ao baixo poder deste teste. Também foi utilizado o teste I2, onde valores de 50% ou mais indicam heterogeneidade.

Análises de sensibilidade foram realizadas para explorar a influência de alguns fatores no tamanho de efeito.

Resultados

Descrição dos Estudos

Quatro estudos preencheram os critérios estabelecidos para inclusão. A duração da intervenção foi de 12 meses para três e 24 meses para um deles. Foram envolvidos 6625 pacientes no total e as intervenções encontradas foram placebo, rimonabant 5mg e rimonabant 20mg em associação com dieta hipocalórica.

Todos os estudos demonstraram alguma deficiência de acordo com o critério de qualidade avaliado, envolvendo randomização, sigilo de alocação, mascaramento, cálculo de poder do estudo, descrição de perdas de seguimento e intenção de tratamento.

Mudanças nos desfechos primários

Comparando rimonabant 20 mg com placebo, excluindo o estudo Rio-diabetes, os dados agrupados mostraram uma redução de peso de 4.9 kg (IC 95% -5,3 a -4,5). Na comparação entre rimonabant 5 mg e placebo, o efeito foi uma redução de peso de 1.3 kg para o rimonabant excluindo o estudo Rio-Norte-América (IC 95% -1,6 a -0,9). Comparando as duas intervenções, houve uma redução de peso de 3.3 kg para o grupo com rimonabant 20 mg (IC 95% -3,7 a -2,9).

A redução da cintura foi de -3.8 cm (IC 95% -4,3 a -3,4) para o grupo de rimonabant 20 mg comparando com placebo e de -1,2 cm (IC 95% -1,7 a -0,7) para o grupo de rimonabant 5mg comparado com placebo.

Comparando com placebo, o grupo com rimonabant 20 mg apresentou maiores efeitos colaterais, e não houve diferença comparando o grupo rimonabant 5 mg com placebo. O mesmo resultado foi encontrado para descontinuação do tratamento devido a efeitos colaterais.

Como desfechos secundários, maiores mudanças foram detectadas no grupo rimonabant 20 mg nos marcadores cardio-metabólicos avaliados (mudanças na pressão arterial e no perfil lipídico).

Nenhum estudo apresentou resultados de avaliação de qualidade de vida, mortalidade e custos.

Conclusão

Implicações para prática

Esta revisão sugere que o uso de rimonabant após um ano de intervenção pode produzir modesta perda de peso de aproximadamente 5%. Algumas cautelas com os resultados observados devem ser consideradas de acordo com as deficiências na qualidade metodológica apresentadas por todos os estudos. Estudos com seguimento após o fim do tratamento e mais rigor na qualidade metodológica desta nova droga devem ser realizados antes de podermos fazer recomendações definitivas em relação ao papel deste medicamento no tratamento de pacientes obesos.

Implicações para pesquisa

São necessárias pesquisas de alta qualidade para avaliar a eficácia e a segurança do rimonabant em períodos mais longos de seguimento. Estudos com cálculo adequado de poder do estudo devem incorporar princípios apropriados incluindo métodos de alocação, randomização, mascaramento, minimização de perdas.

Seção 3

Conclusões

Esta seção foi elaborada com o objetivo de salientar alguns aspectos gerais relacionados ao conjunto dos estudos que compõem a tese e também de apresentar algumas reflexões sobre a importância do tema estudado.

As principais conclusões do presente trabalho de tese incluem:

Não existem ensaios clínicos randomizados avaliando a redução de peso na incidência de AVC;

Ocorreu um declínio progressivo nas taxas de mortalidade por DCV e AVC no Brasil nas últimas três décadas em ambos os sexos, regiões e faixas etárias;

O medicamento rimonabant, indicado como promissor para o tratamento da obesidade e de fatores de risco cardiovascular, produz uma perda de peso modesta; estudos com maior rigor metodológico são necessários para avaliar de forma precisa os riscos e benefícios desse novo medicamento.

No âmbito da pesquisa, tem-se a expectativa que esta tese contribua para realçar a lacuna que existe na literatura sobre a avaliação de desfechos de morbidade cardiovascular quando se avaliam intervenções de perda de peso.

O presente estudo não conseguiu identificar artigos que avaliassem os efeitos da redução de peso em pessoas com sobrepeso ou obesidade na incidência de AVC. No momento existem evidências insuficientes para se fazer recomendações práticas da influência do peso em tal doença.

A perda de peso intencional pode melhorar ou prevenir muitos dos fatores de riscos da obesidade associados às doenças cardiovasculares, como níveis pressóricos, lipídicos e de glicose, porém são necessários estudos avaliando esta intervenção diretamente sobre morbidade de AVC, uma vez que flutuações no peso podem estar associadas com risco cardiovascular.

No momento existem estudos em desenvolvimento avaliando intervenções de perda de peso em desfechos cardiovasculares: o estudo "Swedish Obesity Subjects (SOS)" examina o efeito da intervenção de peso-perda através de cirurgia em um longo prazo (10 anos) na morbi-mortalidade em mais de 2000 pacientes obesos; o estudo "Sibutramine Cardiovascular Outcomes Trial (SCOUT)", tem como objetivo primário examinar o efeito da sibutramina em associação com um programa de intervenção de estilo de vida na morbi-mortalidade cardiovascular em aproximadamente 9000 indivíduos com sobrepeso ou obesidade sob risco de um evento cardiovascular; e o estudo "Comprehensive

Rimonabant Evaluation Study of Cardiovascular ENDpoints and Outcomes (CRESCENDO)" avalia os efeitos do rimonabant nos desfechos cardiovasculares. Esses estudos irão fornecer informações importantes no tratamento da obesidade na morbi-mortalidade das doenças cardiovasculares.

O presente estudo demonstrou que tanto as taxas de AVC como as de doenças cardiovasculares vêm apresentando um importante declínio nas últimas décadas. Porém o número absoluto tem aumentado continuamente no mesmo período, provavelmente devido ao envelhecimento da população. Uma vez que o tratamento das doenças cerebrovasculares não é eficaz e acessível para todos os pacientes, a prevenção continua sendo o melhor método para diminuir a prevalência de AVC. A prevenção primária é particularmente importante porque mais de 70% dos eventos de AVC são primários.

Associando a obesidade ao AVC, uma vez que a eficácia das intervenções para perda de peso não estão comprovadas, a melhor estratégia continua sendo a prevenção da obesidade. Como exemplo, no presente estudo foi avaliado uma intervenção medicamentosa para o tratamento da obesidade - rimonabant, sendo verificado que seu efeito de perda de peso não difere muito das outras drogas já aprovadas. Além disso, tais efeitos na perda de peso são equiparáveis aos produzidos apenas por dieta e exercício. Não existe tratamento considerado "padrão-ouro" e a indicação deve ser baseada em critérios individuais.

Por ser uma doença de proporções alarmantes mundialmente, deve haver cautela na indicação de novos tratamentos, principalmente medicamentosos. Indicações devem ser baseadas em estudos que provem eficácia e segurança. A revisão sistemática com rimonabant apresentada nessa tese foi realizada antes de sua aprovação em qualquer país. Mostrou-se com bases nos estudos realizados que nenhuma indicação segura poderia ser feita. Infelizmente apenas nos Estados Unidos, o departamento de administração de drogas e alimentos (FDA) exigiu maiores informações sobre segurança em um número maior de indivíduos como exigência para sua aprovação.

Deve ser ressaltado que o estudo envolvendo o medicamento rimonabant, foi realizado com três estudos publicados em jornais científicos e um publicado apenas em anais de congresso (RIO-diabetes). Após o término da revisão sistemática, este estudo foi publicado com maiores detalhes em jornal científico, o que poderia influenciar os resultados de algumas análises. Futuras atualizações dessa revisão permitirão a inclusão deste estudo além de novas análises sobre esse medicamento.

Diante deste cenário, estratégias de saúde pública visando o controle da obesidade via tratamento, empregadas com algum sucesso para outros problemas de saúde, parecem ineficientes, seja pela magnitude do problema, pela baixa eficácia dos tratamentos disponíveis, ou ainda pelos custos proibitivos que representariam.

Por fim, ressalta-se que estratégias de ação sanitária devem ser focadas na prevenção, que requer um conjunto articulado de ações que, ao mesmo tempo, protejam, promovam e apóiem estilos de vida saudáveis, com destaque para a alimentação equilibrada e para a atividade física regular. Uma política consistente de prevenção da obesidade deve incluir não só ações de caráter educativo e informativo (como campanhas veiculadas por meios de comunicação de massa), como também medidas legislativas (por exemplo, o controle da propaganda de alimentos não saudáveis, especialmente os dirigidos ao público infantil), tributárias (isentando alimentos saudáveis e onerando os preços dos não saudáveis), treinamento e reciclagem de profissionais de saúde, medidas de apoio à produção e comercialização de alimentos saudáveis.

Seção 4

Referências Bibliográficas

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Seção 5

5. Anexos

5.1. Anexo I – Progressive decline in stroke mortality in Brazil from 1980 to 1982, 1990 to 1992 and 2000 to 2002

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Progressive Decline in Stroke Mortality in Brazil From 1980 to 1982, 1990 to 1992, and 2000 to 2002

Charles André, Cíntia Chaves Curioni, Cynthia Braga da Cunha and Renato Veras

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Progressive Decline in Stroke Mortality in Brazil From 1980 to 1982, 1990 to 1992, and 2000 to 2002

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Background and Purpose—We describe the trends in stroke mortality in Brazil during 3 decades and investigate their differences according to regional disparities, sex, and age distributions.

Methods—Official data on mortality and population estimates were retrieved to calculate standardized mortality rates (with the 1980 Brazilian population as a reference) in 6 age strata and in the 5 political regions for the initial period (3 first years) of the 1980, 1990, and 2000 decades. Data were corrected for undefined causes of death. The Poisson model was used to estimate risk reduction during the 3 decades and to study the interaction between those rates and sex, age strata, and regions.

Results—The stroke standardized mortality rate decreased consistently in the last 20 years, from 68.2 to 40.9 per 100 000 habitants. This reduction paralleled a decrease in total cardiovascular mortality rates in the same period, from 208.2 to 126.1 per 100 000 habitants. The reduction in stroke standardized mortality rate was detected in men and women and in all age strata. The reduction was evident in all geopolitical regions of the country, with the wealthiest regions' exhibiting higher initial rates and more marked standardized mortality rate reductions. The risk of dying of stroke in the period 2000 to 2002 was 0.45 (95% CI, 0.44 to 0.45) of that found in the period 1980 to 1982.

Conclusions—The risk of dying of stroke in Brazil declined dramatically between the initial period in the early 1980s and the early 2000s. The decline was especially marked in the most developed regions and may reflect an improvement in general health conditions during the study period. **(*Stroke*. 2006;37:2784-2789.)**

Key Words: stroke ■ epidemiology ■ mortality ■ socioeconomic factors

There has been a significant reduction in stroke mortality rates in the United States and many other developed countries during the 20th century. Data from so-called "developing" countries are less plentiful, but decreasing mortality rates have also been detected in a number of countries.[1,2] In eastern Europe, an increase in stroke mortality between the 1970s and the 1990s was followed by a more recent decrease between 1990 and 2000.[3] The slope of decline may be less marked in Latin America than in the United States or Canada.[4]

In Brazil, declining mortality rates were found in analyses restricted to specific regions.[5,6] A decrease in cardiovascular mortality has been difficult to document during the 1960s and 1970s in Brazil, but a more recent decline may have occurred.[7] Inequalities in stroke and cardiovascular mortality distribution in Brazil can be expected to exist, considering the marked discrepancies in general health and socioeconomic conditions throughout the country. Regional disparities in stroke mortality in Brazil have not been previously studied.

We studied the evolution of Brazilian stroke mortality rates during the initial periods of the last 3 decades and explored the possible differences according to age and sex and among diverse geopolitical regions that exhibit marked socioeconomic disparities.

Methods

The number of deaths related to stroke was obtained from the Brazilian Mortality Information System made available by the National Health Ministry.[8] For the years 1980 through 1993, causes of death were classified according to the International Classification of Diseases (ICD)-9 code system. From 1994 onward, the ICD-10 system was used. The following codes for stroke were included: 430 to 438 (ICD-9) and I60-I69 (ICD-10). The number of deaths related to any cardiovascular cause was also obtained from the same system, as classified by the ICD-9 (codes 390 to 459) and ICD-10 (I00 to I99).

The mortality rate estimates, expressed as the number of deaths per 100 000 inhabitants, were calculated for the population estimates derived from the Brazilian censes held in 1980, 1991, and 2000 (Brazilian Institute of Geography and Statistics [IBGE]) and also made available by the National Health Ministry.[8] To place the evolution of stroke mortality rates in a larger perspective, total cardiovascular mortality rates during the same periods were also calculated. All rates were standardized by age according to the direct

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method, with the whole Brazilian population from the 1980 census as the standard.

In summary, the procedure consisted of a number of sequential steps.[9] Specific mortality rates for each period were calculated for the 6 prespecified age groups; these rates were then applied to the standard population, resulting in an "expected mortality" for each age group. The ratio between the sum of the expected mortality of all age groups and the total population in the same period resulted in the age-standardized mortality rate.

Standardized mortality rates for each decade correspond herein to the mean values of the first 3 years of that period, eg, 1980, 1981, and 1982 for the 1980 decade. This analysis of data for 3 consecutive years was thought necessary to attenuate the eventual and unexpected abnormal oscillations in the number of registered deaths in any particular year. The intercensus population figures (1981, 1982, 1990, 1992, 2001, and 2002) used in these calculations were estimated from the linear projections made by IBGE of the census population figures, classified according to sex and age stratum. The age distribution is presented according to the Pan American Health Organization system, with the 0- to 34-year and ≥75-year individuals gathered in composite groups.

We also explored the evolution of stroke mortality rates in the 5 Brazilian geopolitical regions, 2 of which (southeastern and southern regions) have a distinctly higher gross internal product and mean income per capita. Correction for undefined causes of death was routinely made, as a high, though declining, proportion of death certificates in Brazil still present this label (eg, 21.5% of deaths in 1980 versus 15.1% in 1999).[10]

To verify the changes for stroke mortality that occurred during the analyzed years from 1980 to 2002, we used a Poisson regression model, with the event rate under concern as the outcome variable.[11] The number of deaths, the corresponding population stratified by year, region, age, and sex were all entered into the Poisson model. The regression equation was estimated according to the following formula: logarithm (event rate)$=\alpha+(\beta^{*}\text{decade})+\varepsilon$; where α indicates intercept; β, angular coefficient; and ε, random error.

The Poisson regression was calculated for Brazil and separately for each sex, age group (6 categories), and geopolitical region (5 categories). Changes in time trends of the age-standardized mortality rate were additionally tested for possible interactions with sex, age group, and region. The results of the Poisson regression ($\hat{\beta}$) and the respective CIs are presented to analyze the mortality trends in the initial periods of the 1990 and 2000 decades compared with the 1980 decade. For all statistical analyses, a value of $P<0.05$ was considered statistically significant. All analyses were performed with the statistical software package SAS for Windows 9.[12]

Results

The number of deaths and corresponding population figures, stratified by age and sex, in the 3 periods studied are presented in Table 1. The stroke standardized mortality rates consistently decreased between 1980 to 1982 and 2000 to 2002: from 68.2 to 40.9 per 100 000 habitants (Figure 1). During the same period, total cardiovascular mortality rates also declined markedly, from 208.2 to 126.1 per 100 000 habitants. The decline in the stroke standardized mortality rate was evident in both decades, with the strongest decrease observed between 1990 to 1992 and 2000 to 2002. With the

TABLE 1. Number of Stroke Deaths and Average Population Size According to Sex and Age Strata in the Study Periods

	1980–1982		1990–1992		2000–2002	
Age Category/Sex	Deaths	Population Size, n	Deaths	Population Size, n	Deaths	Population Size, n
All						
0–34 y	3104	49 092 085	2956	59 127 329	2115	112 892 828
35–44 y	4859	12 539 255	5536	17 375 376	4787	23 143 499
45–54 y	9206	8 993 141	10 296	11 390 393	10 368	16 004 892
55–64 y	13 537	5 797 115	16 414	7 885 851	15 513	10 175 949
65–74 y	2081	3 469 916	23 244	4 701 906	24 337	6 401 288
75+ y	28 501	1 519 565	37 515	2 433 360	44 846	3 654 169
All ages	80 188	81 411 077	95 961	102 914 215	101 966	172 272 625
Male						
0–34 y	1591	24 384 323	1488	29 315 218	1083	56 587 442
35–44 y	2536	6 200 997	2921	8 495 161	2352	11 235 671
45–54 y	5221	4 445 311	5904	5 569 967	5642	7 739 957
55–64 y	7922	2 840 508	9728	3 739 667	9062	4 800 496
65–74 y	11 455	1 663 556	13 035	2 196 475	13 645	2 903 899
75+ y	12 741	659 517	16 954	1 040 663	20 231	1 529 420
All ages	41 466	40 194 212	50 030	50 357 151	52 015	84 796 885
Female						
0–34 y	1521	44 534 595	1489	34 464 979	1041	37 815 445
35–44 y	2332	6 338 258	2625	8 880 215	2445	11 907 829
45–54 y	3972	457 830	4392	5 820 426	4721	8 264 935
55–64 y	5605	2 956 607	6673	4 146 185	6446	5 375 453
65–74 y	9513	1 806 360	10 184	2 505 431	10 685	3 497 389
75+ y	12 100	860 048	15 317	1 392 697	18 012	2 124 749
All ages	35 043	56 953 698	40 680	57 209 933	43 350	68 985 800

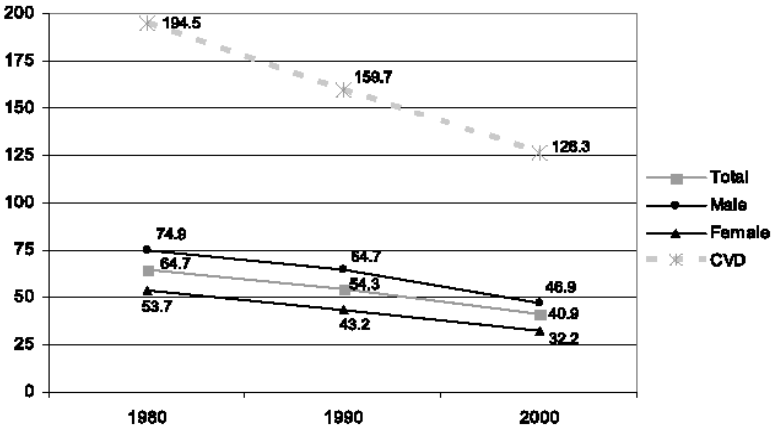


Figure 1. The evolution of age-standardized mortality rates attributable to stroke in Brazil, between the initial periods of the 1980 and 2000 decades. Data from the entire population and according to sex are presented. Total mortality attributable to all cardiovascular causes in the same periods is also shown.

1980 rate as a reference (Table 2), there was a 30% (95% CI, 30% to 31%) risk reduction (RR) in 1990 and a 55% (95% CI, 55% to 56%) RR in 2000 ($P<0.001$ for both measures).

The proportional reduction in stroke mortality was evident for both men and women, although it was more marked among men (Table 2 and Figure 1). Also, the decrease was observed in all age strata (Table 2). An interaction between sex and age was detected, with a more marked decline in standardized mortality rates evident in the young male population (up to 45 years) and a steeper decline for women of all other age strata ($P<0.001$ for all findings).

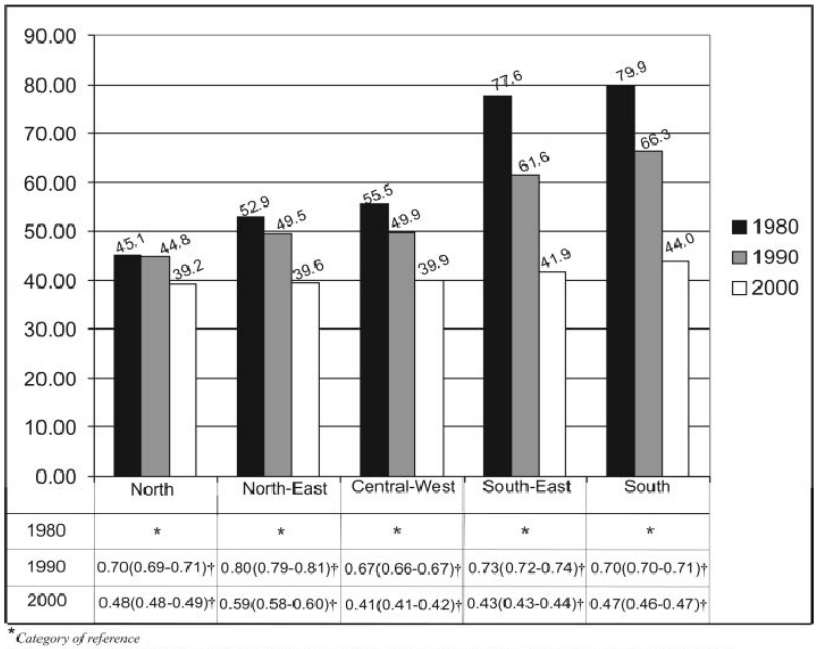
TABLE 2. Age-Standardized Stroke Mortality Rates According to Sex and Age Strata

	1980–1982* Standardized Mortality Rates	1990–1992		2000–2002	
		Standardized Mortality Rates	$\hat{\beta}$ (95% CI)†	Standardized Mortality Rates	$\hat{\beta}$ (95% CI)†
All					
0–34 y	8.22	6.29	0.70 (0.70–0.80)	1.87	0.40 (0.40–0.50)
35–44 y	38.76	31.87	0.80 (0.80–0.90)	20.70	0.70 (0.60–0.70)
45–54 y	102.37	90.47	1.00 (0.90–1.00)	64.79	0.80 (0.80–0.90)
55–64 y	233.63	208.28	0.90 (0.90–1.00)	152.49	0.80 (0.80–0.90)
65–74 y	604.94	494.75	0.80 (0.80–0.90)	380.18	0.80 (0.70–0.80)
75+ y	1878.21	1543.52	0.70 (0.70–0.80)	1227.04	0.60 (0.60–0.70)
All ages	68.17	56.85	0.70 (0.69–0.70)	40.90	0.45 (0.44–0;45)
Male					
0–34 y	8.52	6.46	0.78 (0.72–0.83)	1.91	0.29 (0.27–0.32)
35–44 y	40.88	34.40	0.84 (0.80–0.89)	20.94	0.51 (0.48–0.54)
45–54 y	117.45	106.08	0.90 (0.87–0.94)	72.91	0.62 (0.60–0.64)
55–64 y	278.91	260.26	0.93 (0.91–0.96)	188.82	0.68 (0.66–0.70)
65–74 y	688.76	593.91	0.86 (0.84–0.88)	469.86	0.68 (0.67–0.70)
75+ y	1933.93	1630.81	0.84 (0.82–0.86)	1322.58	0.68 (0.67–0.70)
All ages	74.89	64.68	0.69 (0.68–0.70)	46.95	0.30 (0.29–0.30)
Female					
0–34 y	3.41	2.89	1.27 (1.18–1.36)	1.85	0.81 (0.74–0.87)
35–44 y	36.81	29.56	0.80 (0.76–0.85)	20.54	0.56 (0.53–0.59)
45–54 y	87.37	75.53	0.80 (0.76–0.85)	57.13	0.56 (0.53–0.59)
55–64 y	189.77	161.05	0.85 (0.82–0.88)	119.95	0.63 (0.61–0.66)
65–74 y	527.05	406.85	0.77 (0.75–0.79)	305.49	0.58 (0.56–0.60)
75+ y	1434.54	1119.97	0.78 (0.76–0.80)	850.99	0.60 (0.59–0.62)
All ages	53.74	43.22	0.80 (0.79–0.81)	32.15	0.49 (0.49–0.50)

The rate changes for the study period as calculated by Poisson regression are also presented.

*1980–1982 is the reference period.

†$\hat{\beta}$–Poisson regression exponential, with the respective CIs that reflect how the rates increased or decreased during the study period.



*Category of reference
†Exponential with the respective confidence intervals that reflects how the rates increase or decrease along the studied period

Figure 2. Age-standardized stroke mortality rates in the 5 geopolitical regions of Brazil. Also shown are the rate changes during the study period, as assessed by Poisson regression.

A reduction in stroke standardized mortality rates occurred in all geopolitical regions (Figure 2). An interaction between the studied region and the magnitude of reduction was detected. The wealthiest regions (southern and southeastern) exhibited higher initial rates and also more marked reductions during the study period. The findings were confirmed by the Poisson regression model, in which the least marked reduction in stroke standardized mortality rate was found in the northeastern region: 41% (95% CI, 40% to 42%). The corresponding values for the other regions were as follows: northern, 52% (95% CI, 51% to 52%); central-western, 53% (95% CI, 53% to 54%); southern, 57% (95% CI, 56% to 57%); and southeastern, 59% (95% CI, 58% to 59%).

The total number of deaths related to stroke in Brazil has, however, steadily increased in the last 3 decades. The mean annual number of deaths attributable to stroke increased from 79 862 in 1980 to 1982 to 101 625 in 2000 to 2002. A similar trend was evident for total cardiovascular mortality: 239 876 deaths in 1980 to 1982 and 311 138 in 2000 to 2002. This increase mainly reflects the progressive aging of the Brazilian population.

Discussion

We have demonstrated a consistent and progressive decrease in Brazilian stroke standardized mortality rates during the initial periods of the last 3 decades. A parallel reduction in death rates from all cardiovascular causes has also been demonstrated and suggests that factors influencing both phenomena are probably operative.

The slope of decline in Brazilian stroke standardized mortality rates, a 55% RR between 1980 to 1982 and 2000 to 2002, is at least comparable to that found in the United States and Canada and is greater than reductions found in other Latin American countries between 1970 and 2000.[4] The decline was consistent during the whole study period and was even more accentuated in the second half of the study period. This consistent decline during a long period reproduces the pattern seen in western European countries but differs from that seen in eastern European countries, where huge increases between 1970 and 1990 were followed by marked declines between 1990 and 2000 (except in Poland, where it continued to increase).[3]

The reduction in stroke mortality rate was evident in all age strata but differed in intensity throughout the country, being most noticeable in the 2 wealthiest regions (responsible for 75.4% of the crude internal product) and less so in the poorest regions, which can be considered nonestablished market economy regions.[13] The discrepancies probably can be partially explained by variable improvements in the control of classic risk factors[14–16] but may additionally reflect marked discrepancies in the still much-understudied social risk factors for stroke and cardiovascular diseases. It has been suggested that general health and economic conditions, even in early life, can be partially responsible for variable death rates attributable to cardiovascular diseases, including stroke.[17–20]

In the absence of definitive data on stroke incidence and hospital mortality, we can only suggest some reasons to explain the marked reduction in mortality rates from stroke in Brazil, but a decreasing incidence seems probably more important. Recent data from a comprehensive community stroke survey in Joinville, a medium-size city in the southern region with a high human development index (0.86, compared with 0.79 for Brazil

as a whole), suggest that stroke mortality has diminished between 1995 and 2005 in relation to both a decreasing (29%) stroke incidence and a lower (from 26.1% to 20%) hospital mortality (N.L. Cabral, oral presentation at the IV Brazilian Stroke Congress, Salvador da Bahia, October 21, 2005). In other countries, improved acute stroke care has also been implicated in the mortality reduction.[21] Between 1984 and 1997, however, there was no apparent decline in hospital mortality from acute stroke in the Brazilian official health system, which encompasses ≈65% of the population.[22] Also, despite the increasing number of hospitalizations attributable to acute stroke during this period,[22] there has been no significant increase in the availability of hospital beds in Brazil during the last 3 decades: 3.7 per 1000 individuals in 1980 versus 3.1 per 1000 in 2001,[23] and only a small minority of acute stroke patients are currently treated in specialized stroke units.

Despite the reduction in stroke mortality rate detected in the present study, the total number of deaths attributable to stroke has been steadily increasing during the last 3 decades. This is not surprising and can be attributed to a progressive increase in the mean population age in Brazil, which should continue in the next decades. For instance, the mean life expectancy has increased from 62.6 years for people born in 1980 to 71.7 years for those born in 2004.[24] This phenomenon is expected to continue during the next several decades (eg, the projected life expectancy for those born in 2020 is 76.1 years).

Similarly, we anticipate that the proportion of deaths related to stroke in the next few decades will increase in the poorest regions of the country, where the lower initial stroke standardized mortality rate in the study period may be partially explained by the younger mean age of the population. For instance, in the southeastern region, the proportion of the population 14 years or younger has decreased between 1980 and 2000, from 34.2% to 26.7%, whereas the older age stratum (≥65 years) has increased, from 4.2% to 6.4%. The corresponding figures for the northern region are 46.2% to 37.2% (0 to 14 years) and 2.8% to 3.6% (≥65 years).[25] An additional factor that may, in the future, lead to a relative increase in the proportion of deaths attributable to stroke in poorer regions would be more comprehensive death notification coverage in rural areas and an improvement in the quality of mortality data collection, traditionally worse in regions with lower socioeconomic indices.[26] This is especially important in the analysis of trends in mortality attributable to stroke and other cardiovascular diseases, because most of the so-called deaths of undetermined cause are actually caused by cardiovascular conditions.[7]

An inadequate control of the classic cardiovascular risk factors, if sustained in the next few decades, may contribute to an unnecessary increase in the number of deaths attributable to stroke. Limited data suggest a very low (≈20%) degree of control of hypertension in Rio de Janeiro, 1 of the richest Brazilian states, where antihypertensive drugs of the main classes (β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and diuretics) can be obtained at no expense through the public health system.[27] Also, there has been a progressive increase in the rates of overweight/obesity and diabetes in Brazil.[28,29] The detected less marked decrease in stroke mortality rates in the most underdeveloped areas of Brazil suggests that continuing progressive urbanization of these regions may in the near future be accompanied by disproportionate increases in cardiovascular deaths related to unsafe health habits (eg, increases in smoking, obesity, and diabetes). This phenomenon would also be expected as a result of the steeper increase in the mean age of its population. On the other hand, a progressive increase in the human development index of these regions and easier access to the health system in urban settings may lead to progressively better detection and treatment of classic cardiovascular risk factors.

Some recent advances with a probable future impact for the whole country may be cited, including the recent launching of a national program to guarantee free access to the treatment of hypertension and diabetes.[28] Also, the prevalence of smoking decreased in Brazil between 1989 and 2003.[28] If nothing else is done, however, the number of deaths attributable to stroke and cardiovascular diseases will continue to grow unnecessarily, as in the United States and other countries.[30] This possibility should summon immediate action to continuously improve the preventive strategies for stroke, which has just recently been declared a catastrophic disease in Latin America, and other vascular causes of death. Continuing efforts to improve the detection and control of hypertension are associated with further reductions in stroke mortality, even in communities with already less-than-average rates.[31] Primary preventive strategies may be particularly indicated in developing countries facing budget restrictions for effectively delivering treatment of hypertension and other risk factors for stroke.[32,33]

In conclusion, there has been a consistent reduction in stroke and cardiovascular standardized mortality rates between 1980 and 2000 in Brazil. The reduction in stroke mortality rate was most marked in the more developed regions. It does not seem to be entirely explained by control of classic risk factors in high-risk individuals, technological advances, or improvements in acute stroke care but may in part reflect improvement in the general health conditions in Brazil. The progressive aging of the population will, however, lead to a progressive increase in the total number of deaths attributable to stroke and cardiovascular diseases in the next few decades.

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5.2. Anexo II – The decline of mortality from circulatory diseases in Brazil

The decline of mortality from circulatory diseases in Brazil

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Short title: Cardiovascular Mortality in Brazil

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Abstract

Background: Cardiovascular diseases (CVD) are the leading cause of death in the world. Although mortality rates declined gradually in developed countries, the scenario is less clear in developing countries. We describe the trends in cardiovascular mortality in Brazil along 24 years and investigate differences according to groups of diseases, socio-political region, gender and age. **Methods**: Official data on mortality and population estimates were retrieved to calculate Standardized Mortality Rates (SMR) in six age strata and in the five political regions from 1980 through 2003. The Negative Binomial Distribution model was used to estimate trends for mortality separately for each gender, age group, and geopolitical region along this period. **Results:** Total cardiovascular SMR decreased consistently along 24 years from 287.3 to 161.9 per 100 000 habitants with a mean annual reduction of 3.9%. Reductions in cardiovascular SMR were detected in all strata and for all groups of diseases, with stroke exhibiting the largest average decline from 95.2 to 52.6 per 100 000 habitants (mean 4.0% per year), followed by coronary disease – 80.3 to 49.2 per 100 000 (3.6% per year); and was especially marked in the most developed regions. **Conclusions**: CVD SMR consistently decreased in Brazil during the study period. The reduction is in apparent relationship with indices of increasing social development. Despite these encouraging findings, a gradual increase in the total number of deaths from CVD is expected in the next decades, and additional efforts in prevention are needed.

Key Words: Cardiovascular diseases, epidemiology, mortality.

Cardiovascular disease has become the leading cause of death in many developing countries and will soon attain this status in several others. The high burden of mortality from cardiovascular causes in developing countries (estimated at 9 million in 1990 and expected to increase to 19 million by 2020) [1] is explained not only by their large populations, but also by the increase of the mean age for death and of prevalence rates of classical cardiovascular risk factors such as hypertension, smoking, dislipidemia, diabetes and obesity [2-6].

An important decline in cardiovascular mortality has been detected in developed countries from North America, West Europe and Australasia [7-10]. It has been suggested that this could already be starting in Brazil [11,12]. This Country seems to experience the phenomenon called epidemiologic transition, in which still high (though declining) mortality from health problems characteristic of underdeveloped countries such as infectious diarrhea and gravid-puerperal cycle complications coexist with increasing numbers of fatalities related to chronic degenerative diseases including those of cardiovascular origin.

On the other hand, a number of factors may concert to reduce the incidence and death rates from cardiovascular diseases including stroke and coronary heart disease. These may include general factors affecting the whole population or large parts of it – such as a gradual improvement in Economic conditions – and more widespread access to drugs used in the treatment of major risk factors such as systemic arterial hypertension and diabetes.

Earlier studies of trends in mortality from cardiovascular diseases in Brazil analyzed data from specific cities or regions or addressed specific diseases [13-15]. An extensive analysis of the mortality rates from cardiovascular causes exploring eventual discrepancies between diverse groups of diseases has not been undertaken. Also, possible regional disparities in cardiovascular mortality in Brazil have not been previously studied.

Inequalities in cardiovascular mortality distribution are highly probable, considering the marked discrepancies in general health and socioeconomic conditions throughout the Country. As a matter of fact, we have shown that between 1980-1982 and 2000-2002 Brazilian stroke mortality rates declined more steeply in its richest regions [16]. We now present the evolution of mortality rates from the main groups of cardiovascular diseases in Brazil from 1980 through 2003, exploring possible differences according to age and gender and among diverse geopolitical regions exhibiting marked socioeconomic disparities.

Methods

The number of deaths from cardiovascular causes was obtained from the Brazilian Mortality Information System made available by the National Health Ministry [17]. Data were obtained for all cardiovascular deaths and for 4 large groups of diseases – coronary heart disease, stroke, complications of hypertension (essentially cardiac and renal disease), and other causes. For the years 1980 through 1995, causes of death were classified according to the ICD-9 code system: coronary heart disease (410 to 414); stroke (430-438); complications of hypertension (401 to 405), and other causes (390 to 398; 415 to 429; 440 to 459). From 1996 on, the ICD-10 system was used: coronary heart disease (I20 to I25); stroke (I60-I69); complications of hypertension (I10 to I13), and other causes (I00 to I09; I26 to I51; I70 to I99).

The mortality rate estimates, expressed as the number of deaths for 100 000 inhabitants, were calculated for the population estimates derived from the Brazilian censes held in 1980, 1991, 1996 and 2000 (Brazilian Institute of Geography and Statistics: IBGE) and also made available by the National Health Ministry [17]. The intercensitary populations (1981-1990, 1992-1995, 1997-1999, 2001-2003) used in these calculations were estimated

from the Lagrange interpolation, classified according to region, gender and age strata. The age distribution is presented according to the Pan American Health Organization system.

All rates were standardized by age through the direct method, with the whole Brazilian population from the 2000 census as the standard. In summary, the procedure consisted of a number of sequential steps [18]. Specific mortality rates for each period were calculated for the 6 prespecified age groups; these rates were then applied to the standard population, resulting in an "expected mortality" for each age group. The ratio between the sum of the expected mortality of all age groups and the total population in the same period resulted in the age-standardized mortality rate (SMR).

We explored the evolution of cardiovascular mortality rates stratifying them by gender, age group and region. There are five geopolitical regions in Brazil, two of which (South-East and South regions) have a distinctly higher gross internal product and mean income *per capita*. Correction for undefined causes of death was routinely made as a high although declining proportion of death certificates in Brazil still presents this label (*e.g.*, 21.5% of deaths in 1980 *vs*. 15.1% in 1999) [19].

Trends for mortality from cardiovascular diseases – total and related to the 4 prespecified groups of diseases – during the entire 1980 to 2003 period in Brazil and separately for each gender, age group (6 categories), and geopolitical region (5 categories) were analyzed by the Negative Binomial Regression Model. This model was adopted due to overdispersion found in the analyzed data [20].

The model is represented as follows:

$$\textbf{Log (event rate)} = \alpha + \beta * \textbf{Year} + \varepsilon$$

Where α indicates intercept; β, angular coefficient; and ε, random error.

Models were done for each stratum of the variables considered, e.g., model for the

mortality in the female gender, for the mortality in the 20 to 34 year age group etc. The average annual percent change (AAPC) for disease rates were obtained using the following formula: 100 [exp(β) - 1]. For all statistical analyses, a p value < 0.05 was considered to be statistically significant. All analyses were performed with the statistical software package SAS for Windows 9 [21].

Results

The number of deaths from cardiovascular diseases in Brazil stratified by gender in 1980 and 2003 is presented in Table 1. The total number of deaths attributable to cardiovascular diseases in Brazil increased steadily during the entire period studied. The mean annual number of deaths increased 45% between 1980 and 2003; a similar trend was evident for all 4 groups of diseases. This increase mainly reflects the progressive aging and growth of the Brazilian population.

Despite this, the SMR consistently decreased in Brazil between 1980 and 2003 for all groups of diseases (Table 2 and Figure 1): total cardiovascular mortality rates exhibited a mean annual reduction of 3.9% per 100 000 habitants. Stroke exhibited the highest mortality rates among cardiovascular diseases; but also the largest average annual decline –4.0% per 100 000 habitants per year; rates related to coronary disease exhibited an average reduction of 3.6% per 100 000 habitants.

For both genders, there was a statistically significant declining trend for death rates from all cardiovascular diseases and from the 4 subgroups of diseases (P<0.0001 for all). The average annual percent decline was similar between men and women in all groups of diseases (Table 2). Stroke was the main cause of death in women in 1980 and still in 2003. Ischemic heart disease has since 1999 surpassed stroke as the leading cause of cardiovascular death in Brazilian men (Figure 2).

The decrease in mortality rates was observed in all age strata (Table 2 and Figure 3). A more marked decline was apparent in the youngest population (up to 45 years) but all strata experienced a steep decline in the last 24 years ($P<0.0001$ for all findings). The mortality related to hypertensive complications in the oldest population (≥ 75 years) constituted an isolated exception, with rates increasing slightly (mean 0.4% per year) along the period studied.

A reduction in mortality rates occurred in all geopolitical regions (Table 2 and Figure 1). The North region exhibited more marked reductions during the study period; this finding must however be interpreted with caution since a parallel increase in migratory inflow from other Brazilian regions occurred between 1980 and 1991, resulting in a much higher than average demographic expansion in that region [22]. Excluding the North Region, the wealthiest regions (South and Southeast) exhibited higher initial mortality rates from cardiovascular diseases and also more marked reductions along time than other less well-developed regions. The trends go in the same general direction for stroke and ischemic heart disease.

Discussion

Standardized mortality rates from cardiovascular diseases consistently decreased in Brazil during a period of 24 years. In the early 1980s cardiovascular diseases constituted the first cause of death in Brazil, followed by external causes, infectious diseases, cancer, and respiratory diseases. In 2003, the scenario was essentially similar, with a relative increase in mortality from cancer, now second to cardiovascular causes; and a decline in mortality from infectious diseases, now in the fifth position. Among these 5 groups of diseases, only cardiovascular and infectious diseases presented decreasing mortality rates along the study period. The process of epidemiological transition is however still underway in Brazil, where mortality from infectious diseases and undernutrition declined steadily along the

last 70 years (most markedly between 1930 and 1985), and cardiovascular mortality increased until the early 1970s and after a period of apparent stability between 1970 and 1985, now exhibits a gradual decline similar to what happened in developed countries in previous decades [23]. This is somewhat different from what happened in the USA and Western Europe, for instance, where marked declines in cardiovascular mortality were detected between 1970 and 2000 [24,25]. On the other hand, stability or even an increase in cardiovascular mortality was evident in Eastern Europe and in underdeveloped countries during the 1980 and 1990 decades [24,25].

A striking finding of the present study is the homogenous decline in cardiovascular mortality from all groups of causes in both genders and in all age strata (isolated exception – deaths related to hypertension in the oldest stratum). This finding strongly suggests the interplay of factors influencing the incidence of cardiovascular diseases in the whole population such as a reduction in mean salt consumption and/or blood pressure levels. Antihypertensive drugs of the main classes (β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and diuretics) can now be obtained at no expense through the public health system [26]. The importance of blood pressure control as a core determinant of the global reduction is also suggested by the steeper decline in stroke mortality detected and resulting in coronary artery disease becoming the leading cause of death in men from 1999 on. In clinical trials, the reduction in stroke incidence has been greater than that in myocardial infarct incidence – 35-40% vs. 20-25% [27]. Other factor of potentially large impact should also be mentioned. The National Program of Smoking Control resulted in 32% decrease in *per capita* annual cigarette consumption between 1989 and 2002, as well as a reduction in the prevalence of current smoking [28].

A reduction in hospital mortality along time is also probably a factor leading to the detected reduction in cardiovascular mortality. The availability of hospital beds in Brazil

has decreased along the study period, from 3.7 per 1000 individuals in 1980 to 3.1 per 1000 in 2001 [29]. It should be remembered however that this was also the period where intensive care units and coronary care units became widely available [30]. The appearance and/or increasing availability of procedures potentially resulting in greater diagnostic accuracy or therapeutic benefit such as computerized tomography, echocardiography, endovascular interventions, renal dialysis etc., should also be mentioned as contributing factors [31**].**

The reduction in cardiovascular mortality along the period studied is in apparent relationship with indices of increasing social development. Coronary heart disease is now (since 1999) the leading cause of death in the richest region of the Country (South-East). We found an inverse and strong correlation between the Human Development Index (HDI) – which increases in association with the amelioration of economic and social indicators (life expectancy, education attainment and income *per capita*) [32] – and cardiovascular mortality between 1980 and 2000 (data available from the authors): Spearman correlation coefficient = –1.0; $p<0.001$. The importance of socioeconomic determinants is highlighted by the fact that although the reduction in cardiovascular mortality rates occurred in all geopolitical regions, it was more marked in the South and Southeast regions – responsible for 75.4% of the crude internal product and with higher HDI [33] – and less so in other regions, which exhibit medium (but also increasing) HDI and can be seen as non-established market economy regions.

The inter-regional differences probably reflect the variable impact of a number of factors including life-style differences (physical activity, smoking, dietary habits), thoroughness of detection and control of classical risk factors such as hypertension and diabetes and differences in hospital care. The two richest regions, for example, concentrate three quarters of both magnetic resonance and computerized tomography machines, with

additional intrinsic access inequalities (equipment heavily concentrated in private facilities that only assists 17.4% of the whole Brazilian population). The corresponding figures for Health facilities with emergency departments, intensive care beds, and Coronary Care Units are 65%, 71% and 88% respectively [33].

Disparities in cardiovascular mortality according to social and economic factors have been observed in other countries. The odds of coronary heart disease in both genders are more than two times greater in low-income groups [34]. In the USA, cardiovascular mortality seems to vary according not only to racial origin (probably reflecting different life-style and dietary risk factors) but also to social disparities [35]. A recent Scottish study indicates that both area-based indicators of poverty and individual social class influence the prevalence of common risk factors and morbidity/mortality from cardiovascular diseases [36].

Despite the encouraging finding of a steadily declining cardiovascular SMR, the total number of deaths from CVD in Brazil progressively increased in the last decades. This reflects the total population growth and also a progressive increase in mean population age, which will continue in the future. Mean life expectancy increased from 62.6 years for people born in 1980 to 71.7 years for those born in 2004 [37]. The projected life expectancy for those born in 2020 is 76.1 years. Additional factors may, in the future, lead to a relative increase in the number of cardiovascular deaths such as the observed increase in the prevalence of diabetes and obesity [28,38]. A National program to guarantee free access to the treatment of hypertension and diabetes has been launched in 2002 and was conceived to revert the present picture of a very low degree of hypertension control in large cities [26]. Developing countries face problems of prohibitive costs of care and therefore huge emphasis should be put on primary preventive strategies to effectively deliver treatment of hypertension and other cardiovascular risk factors [39].

A potential limitation of the present study should be mentioned. Death certificates are the only data source currently available to assess population trends in CVD mortality, provided that the accuracy remains relatively constant over time. The reliance on death certificates may however introduce bias as it could be influenced by the quality of data recording, a worldwide problem [40]. In Brazil the quality of mortality data collection is traditionally worse in regions with lower socioeconomic indices [19]. However, a gradual improvement in data recording is being noted [19].

In conclusion, over the past 24 years, CVD mortality in Brazil decreased steadily in women and men of all age strata, but the magnitude of the decline varied according to regional socio-economic differences. Furthermore, with the progressive increase in total number of annual deaths from CVD expected in the next decades, additional prevention efforts should be encouraged. Considering the observed association between socioeconomic conditions and cardiovascular mortality, broad interventions may be more successful if planned according to social inequality and cultural differences.

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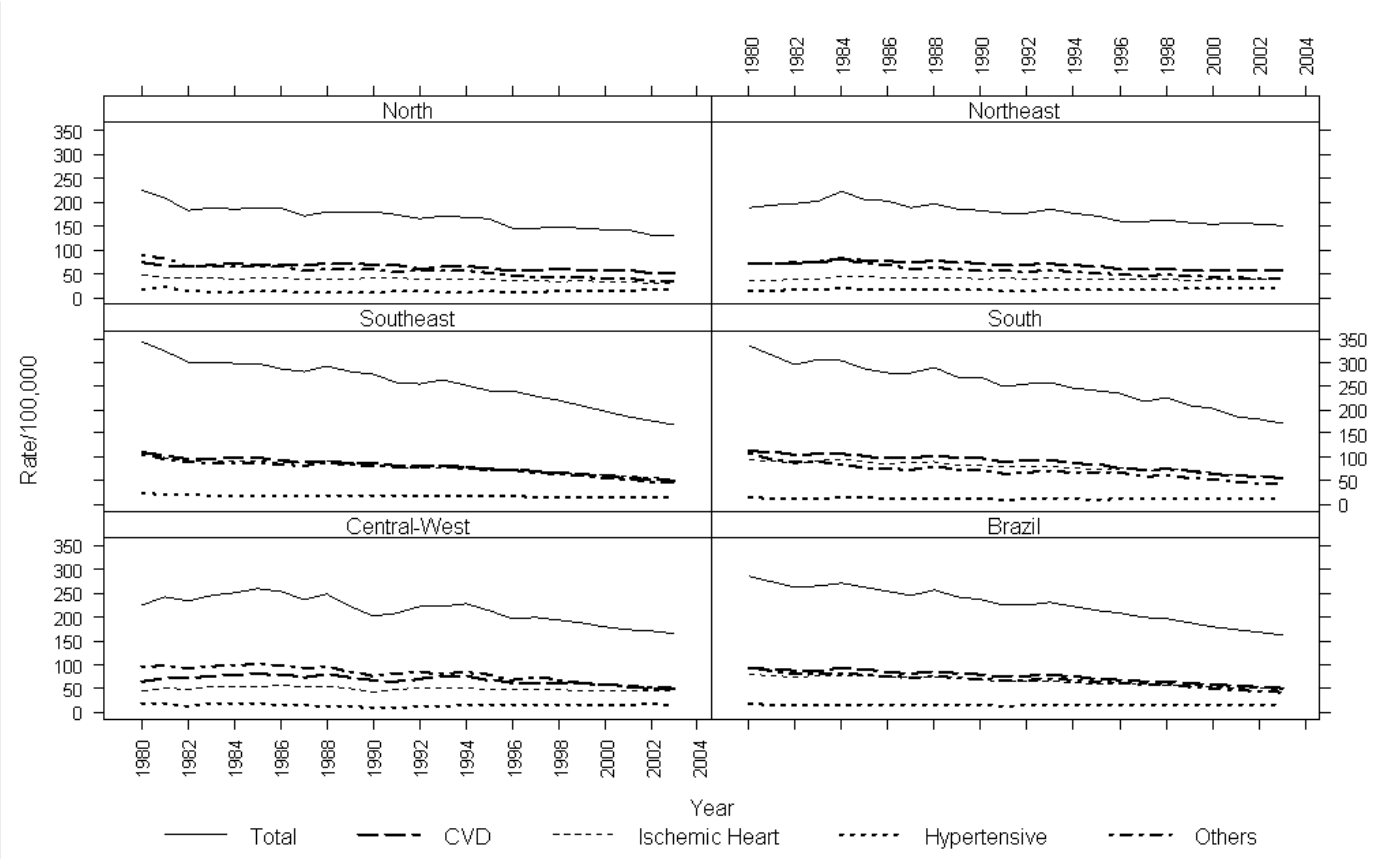

Figure 1 - The evolution of standardized mortality rates attributable to cardiovascular diseases in Brazil and its geopolitical regions between 1980 and 2003.

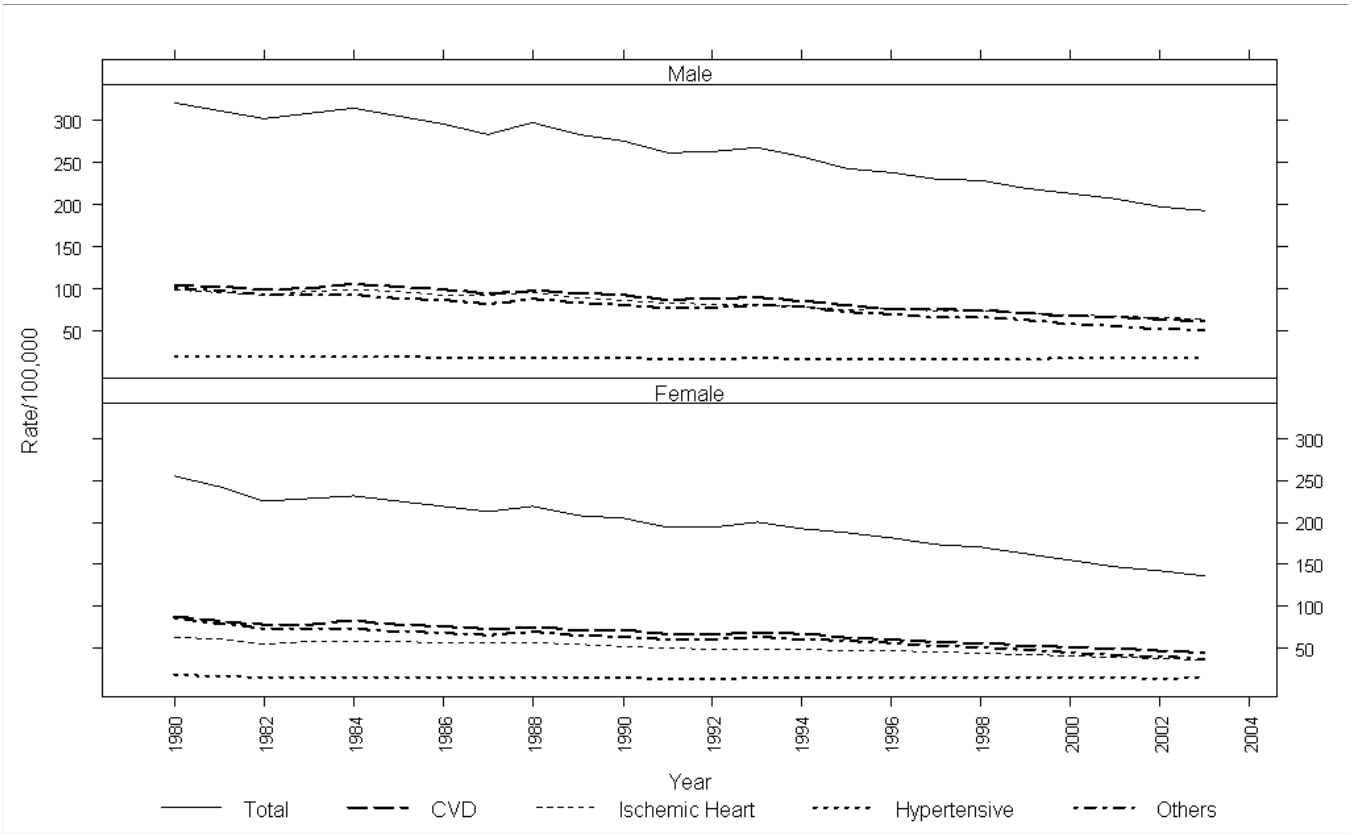

Figure 2 - The evolution of standardized mortality rates attributable to cardiovascular disease in Brazil according to gender between 1980 and 2003.

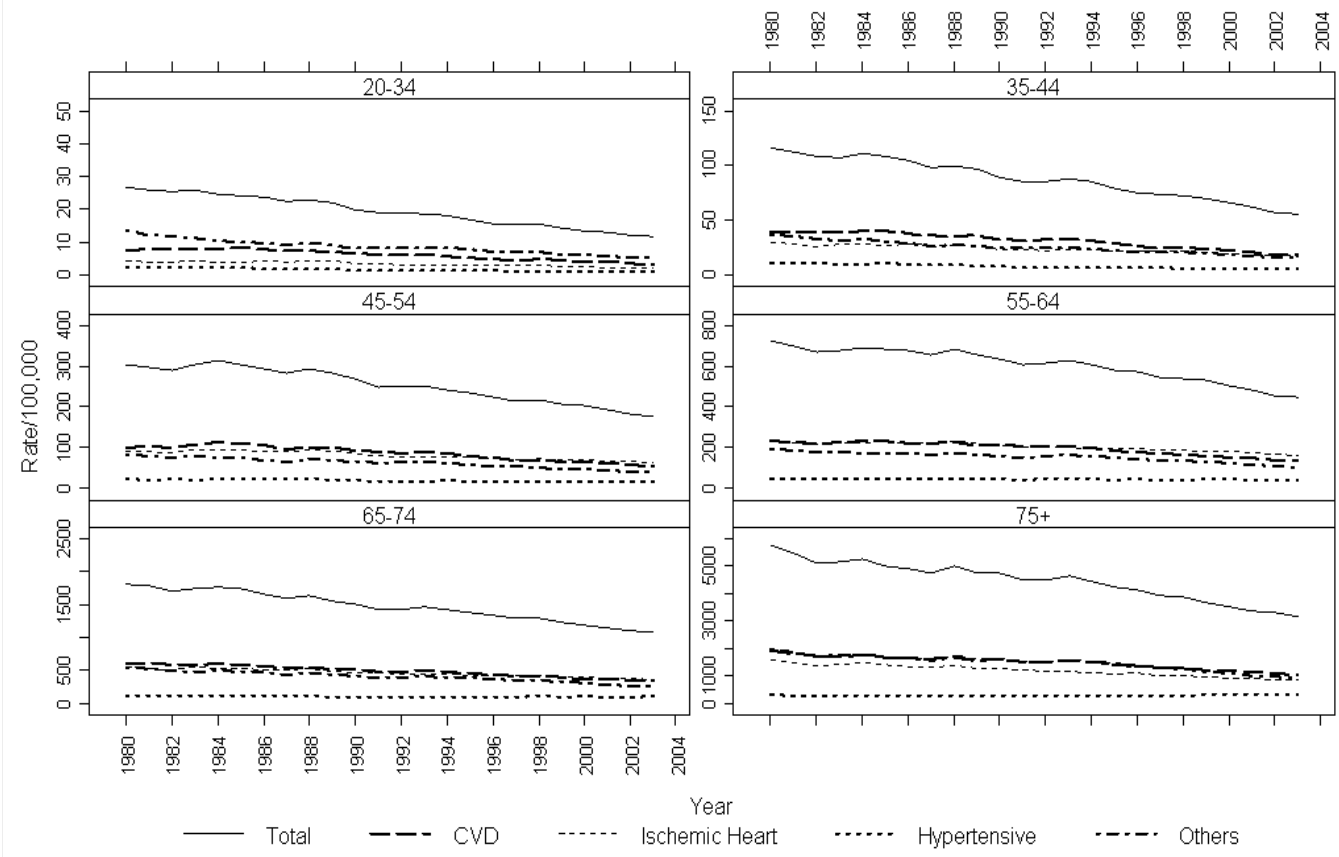

Figure 3 - The evolution of standardized mortality rates attributable to cardiovascular disease in Brazil according to age strata between 1980 and 2003.

Table 1. Total number of deaths from cardiovascular diseases in Brazil in 1980 and 2003.

	1980			**2003**		
	Total	Male	Female	Total	Male	Female
All Cardiovascular Diseases	189027	101148	87879	274029	144649	129380
Stroke	62305	32177	30128	83181	48237	34944
CHD	52784	31395	21389	89017	45553	43464
Hypertension	12693	6131	6562	27840	13038	14802
Other Causes	61245	31445	29800	73991	37821	36170
Total Population	118897614	59085593	59812019	185027366	90897174	94130191

CHD – Coronary Heart Disease

Table 2 - Standardized mortality rates from cardiovascular diseases according to regions, age strata and gender and the average annual percent change.

	Cardiovascular Diseases (total)			Stroke			Ischemic Heart Disease			Complications of H		
Strata	**1980**	**2003**	**AAPC***	**1980**	**2003**	**AAPC***	**1980**	**2003**	**AAPC***	**1980**	**2003**	**A**
Regions												
North	223.6	131.1	-5.1 (-5.5,-4.7)	73.6	51.5	-4.4 (-4.8,-4.1)	47.0	31.2	-4.7 (-5,-4.3)	15.8	14.8	-3
Northeast	188.3	149.8	-2.8 (-3,-2.6)	70.1	54.6	-3.0 (-3.3,-2.7)	34.5	39.3	-1.5 (-1.7,-1.2)	13.1	18.5	-0
Southeast	343.9	169.3	-4.1 (-4.4,-3.8)	111.1	51.5	-4.4 (-4.7,-4.1)	104.7	54.1	-4 (-4.3,-3.8)	23.6	16.8	-2
South	335.0	171.3	-3.8 (-4.1,-3.5)	115.1	57.1	-4.1 (-4.5,-3.8)	95.0	56.7	-3.2 (-3.5,-2.9)	16.5	13.7	-1
Central-West	227.0	166.6	-3.8 (-4.1,-3.4)	64.4	51.0	-3.6 (-4.2,-3.1)	46.8	44.5	-2.8 (-3.1,-2.4)	19.6	18.1	-2
Brazil	287.3	161.9	-3.9 (-4.1,-3.6)	95.2	52.6	-4.0 (-4.3,-3.8)	80.3	49.2	-3.6 (-3.8,-3.4)	18.8	16.5	-2
Age Group												
20-34	26.8	11.6	-3.6 (-3.8,-3.4)	7.3	3.3	-3.9 (-4.3,-3.4)	4.2	2.2	-2.9 (-3.3,-2.5)	2.1	0.9	-4
35-44	115.6	55.8	-3.0 (-3.3,-2.8)	39.1	18.4	-3.4 (-3.8,-3.0)	29.6	16.6	-2.3 (-2.5,-2.0)	10.3	4.9	-3
45-54	301.9	175.9	-2.4 (-2.6,-2.1)	102.3	56.7	-2.8 (-3.2,-2.5)	91.8	61.3	-1.8 (-2,-1.5)	24.8	17.0	-1
55-64	720.9	449.2	-1.9 (-2.1,-1.6)	238.3	136.6	-2.3 (-2.6,-2.0)	231.8	162.8	-1.4 (-1.6,-1.2)	52.8	45.5	-0
65-74	1816.7	1080.2	-2.2 (-2.4,-2.1)	612.2	345.6	-2.5 (-2.7,-2.3)	538.7	360.4	-1.8 (-2,-1.7)	118.5	110.4	-0
75 or+	5810.5	3157.3	-2.3 (-2.5,-2.0)	1940.5	1072.6	-2.2 (-2.4,-2.0)	1546.4	827.0	-2.5 (-2.7,-2.3)	329.3	335.6	0.
Sex												
Male	320.8	193.2	-3.7 (-3.9,-3.5)	103.4	61.2	-3.9 (-4.1,-3.6)	98.3	64.0	-3.5 (-3.7,-3.3)	18.9	17.5	-2
Female	255.8	135.9	-4.0 (-4.2,-3.7)	87.7	45.7	-4.2 (-4.5,-3.9)	63.4	36.8	-3.7 (-3.9,-3.5)	18.7	15.5	-2

* p-value < 0.0001
AAPC - Average annual percent change

5.3. Anexo III - Weight reduction for primary prevention of stroke in adults with overweight or obesity

Weight reduction for primary prevention of stroke in adults with overweight or obesity

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Cover sheet

Reviewers

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Contribution of reviewers

Curioni, Cintia
Drafted the protocol and review, searched for trials, obtained copies of trials, selection of studies, data extraction, assistance with statistics, data analysis and data presentation.
André, Charles
Drafted the protocol and review, searched for trials, selection of studies, data extraction, data analysis and data presentation.
Veras, Renato
Draft the protocol and review, selection of studies, data presentation.

Synopsis

Rigorous scientific evidence linking overweight or obesity with increased risk for stroke is missing

Overweight and obesity are important public health problems and are associated with many serious health conditions including stroke which is a leading cause of death and severe long-term disability. It appears logical that weight reduction in overweight or obese people should have positive health consequences lowering the number and consequences of strokes. Overweight is defined as a "body mass index" (BMI) between 25.0 and 29.9 kg/m^2, if weight measured in kilogram is divided by height measured in meter, and obesity as a BMI equal or greater than 29.9 kg/m^2.
Despite a thorough search of the available literature we were not able to identify any study of good quality investigating the relationship between weight reduction and the occurrence of strokes. If overweight or obese people want to reduce their risk profile by losing weight they need sound evidence for doing so since every intervention might have negative consequences as well, for example losing and regaining weight ("weight cycling") is associated with health hazards like cardiovascular diseases. There is an urgent need for adequate research (good randomised controlled clinical trials) hopefully providing better advice in the future.

Abstract

Background
Obesity is seen as a worldwide chronic disease with high prevalence that has been associated with increased morbidity from many conditions including stroke, which is the third leading cause of death in developed countries and a leading cause of severe long-term disability. The causal association between overweight or obesity and stroke is unclear and there is no definite study clarifying the role of obesity treatment in the prevention of a first stroke (primary prevention). Given the prevalence of stroke and the enormous health and economic cost of the disease, it is important to establish the possible impact of weight reduction *per se* on stroke incidence.

Objectives
To assess the effects of weight reduction in people with overweight or obesity on stroke incidence.

Search strategy
MEDLINE, EMBASE, *The Cochrane Library*, LILACS, databases of ongoing trials and reference lists were used to identify relevant trials. The last search was conducted in April 2006.

Selection criteria
Randomised controlled trials comparing any intervention for weight reduction (single or combined) with placebo or no intervention in overweight or obese people.

Data collection & analysis
No trials were found in the literature for inclusion in this review.

Main results
There are currently no results to be reported.

Reviewers' conclusions
Obesity seems to be associated with an increased risk of stroke and it has been suggested that weight loss may lead to a reduction of stroke occurrence. However, this hypothesis is not based on strong scientific evidence resulting from randomised controlled clinical trials. This systematic review identified the urgent need for well-designed, adequately-powered, multicentre randomised controlled trials assessing the

effects of weight reduction in persons with overweight or obesity on stroke occurrence.

Background

Description of the condition

Obesity

According to the World Health Organization (WHO), obesity is a multifactorial chronic disease with increasing frequency in many countries that can be characterized as an epidemic of major public health concern (WHO 2000). Obesity is the condition of excessive fat in the body and might have significant health consequences. It is the result of weight gain caused when more energy is consumed than expended. In simple terms, people are getting fatter worldwide. The WHO defines overweight as a body mass index (BMI) between 25 to 29.9 kg/m² and obesity as a BMI equal or greater than 30 kg/m². Severe or morbid obesity is defined as a BMI equal or greater than 40 kg/m² or greater than 35 kg/m² in the presence of co morbidities (WHO 2000). BMI does not measure body fat directly but is a mathematical formula highly correlated with body fat. The basis for this BMI classification scheme stems from observational and epidemiologic studies which relate BMI to risk of morbidity and mortality (Clinical Gdlns 1998). Normal weight is classified as a BMI between 18.5 to 24.9 kg/m² and a BMI less than 18.5 kg/m² is considered underweight.

Others methods in addition to the measurement of BMI are valuable in identifying individuals at increased risk from obesity-related illness due to abdominal fat accumulation. Waist circumference and waist-to-hip circumference ratio (WHR) provide a useful estimation of the proportion of abdominal or upper-body fat (Björntorp 1984; Björntorp 1985; Kissebah 1985). A WHR greater than 1.0 in men and 0.85 in women indicates abdominal fat accumulation; a high-risk waist circumference is thought to be 88 cm or greater for women and 102 cm or greater for men (Clinical Gdlns 1998).

Overweight and obesity seems to be associated with higher morbidity from many conditions such as arterial hypertension, type 2 diabetes mellitus, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnoea and other respiratory problems and some types of cancer (for example, endometrium, breast, prostate, colon) (Clinical Gdlns 1998). The abdominal fat is assumed to better correlate with increased mortality and risk of disorders such as diabetes mellitus, hyperlipidaemia, hypertension and cardiovascular diseases (Donahue 1987; Ducimetiere 1986; Lapidus 1984; Larsson 1984; Ohlson 1985; Stokes 1985).

Obesity is seen as a condition, which requires treatment. Treatment means, first of all, weight reduction. The general goals of weight loss and management are: (1) to reduce body weight; and (2) to maintain a lower body weight over the long term; or (3) at a minimum, to prevent further weight gain. There is strong evidence that weight loss (5% to 15% of the body weight) in obese individuals reduces risk factors associated with obesity (Clinical Gdlns 1998).

Stroke

Stroke is the third leading cause of death in developed countries after heart disease and cancer and a leading cause of serious, long-term disability. Also, most of the developing countries show an increasing trend in mortality from stroke (Balaguer Vintro 2004). Worldwide, three million women and 2.5 million men die from stroke every year (WHO 2004).

Stroke comprises two major types, haemorrhagic and ischaemic. Approximately 15% to 20% of strokes are haemorrhagic, divided between subarachnoid haemorrhage and primary intracerebral haemorrhage. The majority of strokes (approximately 80%) are ischaemic. When the symptoms are rapidly reversed (that is, in less than 24 hours), this would be considered a transient ischaemic attack. Stroke, whether due to infarction or haemorrhage, is associated with a previous history of high blood pressure in 50% of patients (Britton 1986; Oppenheimer 1992).

The clinical diagnosis of stroke is relatively straightforward. The acute onset (along minutes to hours) of focal neurological deficits related to a specific vascular territory in the absence of another evident mechanism, such as trauma, should lead to the presumptive diagnosis. The clinical impression should usually be followed by a diagnostic workup including a reliable differentiation between cerebral infarction and haemorrhage using neuroimaging techniques and a search for specific causes, such as embolism or large artery atherothrombosis.
The most widely available diagnostic method for exclusion of alternative diagnoses and for discrimination between haemorrhagic and ischaemic lesions is computed tomography (CT). Its main advantages are widespread availability and good sensitivity for haemorrhage. However, CT is insensitive to very early ischaemic changes following acute cerebral infarction especially in cases with small or infratentorial lesions.
Magnetic resonance imaging (MRI) exhibits distinct advantages over CT. Its high sensitivity for the diagnosis of parenchymal and subarachnoid haemorrhage has also already been demonstrated. MRI is becoming increasingly available and its gradual substitution for CT can be anticipated along the next decades in many countries.
Because of the limited options for treating patients once a stroke has occurred, the recognition of risk factors and aggressive preventive efforts remain the best way to reduce the burden of stroke. Risk factors and risk markers for a first stroke are usually classified according to their potential for modification (non modifiable, modifiable, potentially modifiable) (Goldstein 2001). The non-modifiable risk factors include age, sex, race or ethnicity and family history. Although these factors are non-modifiable, they identify individuals at higher risk of stroke and those who may benefit from rigorous prevention or treatment of modifiable risk factors (Sacco 1997). The second group - modifiable risk factors - includes arterial hypertension, smoking, diabetes, hyperlipidaemia, asymptomatic carotid stenosis, atrial fibrillation, and other cardiac diseases. The third group includes conditions for which the evidence is still being mounted, such as obesity, alcohol and drug abuse, physical inactivity, hyperhomocysteinaemia, pro-thrombotic states, oral contraceptive use and hormone replacement therapy.

Stroke and obesity

Stroke incidence is higher in obese individuals, especially those with hypertension, diabetes or hypercholesterolaemia, all favoured by obesity. Adequate control of known risk factors reduces stroke incidence. Although recommended to improve the treatment of these cardiovascular risk factors (De Freitas 2001), the possible impact of weight reduction *per se* on stroke incidence and mortality has not been adequately explored.
Obesity is seen as a modifiable risk factor for cardiovascular diseases, especially ischaemic heart disease. The causal association between obesity and stroke is less clear. Obesity increases the risk for hypertension, diabetes and dyslipidaemia (Brown 2000; Dyer 1989; Ford 1997; Larsson 1981; Ohlson 1985). On the basis of these associations alone, obesity should be related to an increased risk of stroke. However, studies documenting the specific impact of obesity or overweight on stroke showed heterogeneous results. In women, an increasing body mass index correlated with an increased risk of ischaemic stroke (Goldstein 2001). Abdominal obesity in men and obesity and weight gain in women seem to be independent risk factors for stroke (Kurth 2002; Rexrode 1997). Weight gain after 18 years was also positively related to ischaemic stroke (Suk 2003).
In the Honolulu Heart Program, a high BMI was associated with an increased risk for thrombo-embolic strokes among nonsmoking middle-aged men (Abott 1994). In the Framingham Heart Study, an association between weight and incidence of atherothrombotic strokes was found only in women (Hubert 1983). The Nurses' Health Study showed that women with an increased BMI had a higher ischaemic stroke risk. The association disappeared, however, after adjustment for hypertension, diabetes mellitus and high cholesterol (Rexrode 1997).

A number of additional studies support the association between obesity and stroke (Benfante 1994; Jood 2004; Kurth 2002; Milionis 2003; Song 2004). Other authors, however, were unable to find any independent relationship (Folsom 1990; Lapidus 1984; Larsson 1984; Lindenstrom 1993; Njølstad 1996; Stokes 1987).

Stroke Prevention

Stroke is a life-changing event that affects not only the person who may be disabled, but the entire family and other caregivers as well. Effective prevention remains the best treatment for reducing the burden of stroke.

Primary prevention of stroke includes lifestyle modifications (increase of physical activity, smoking cessation, reduction of alcohol consumption in heavy drinkers) and measures to control blood pressure, cholesterol levels, diabetes mellitus and atrial fibrillation. Primary prevention is particularly important because more than 70% of strokes are first events (Goldstein 2006).

Secondary prevention should focus on reducing the risk of a new vascular event after stroke. Besides carotid surgery and antithrombotic drugs, when appropriate, an optimal management of modifiable risk factors for stroke decreases the risk of new vascular events (Leys 2002).

Because obesity is a contributing factor to other risk factors associated with stroke, promoting weight loss and the maintenance of a "healthy weight" is a high priority.

How the intervention might work

Weight reduction and weight maintenance, as part of a lifestyle modification program, remain the cornerstone of treatment in people with overweight or obesity. Weight reduction interventions include: dieting, exercise, psychological or behavioural interventions, pharmacotherapy to suppress appetite or to change metabolism, surgical or laparoscopic gastroplasty to reduce food consumption and alternative therapies (Clinical Gdlns 1998). A weight loss of 5% to 15% of baseline weight, may be associated with significant improvements in lipid levels, glycaemic control, and blood pressure control (Douketis 2005). These effects could have the potential to reduce for example the incidence of cardiovascular morbidity and mortality. In this manner, weight loss may help control diseases worsened by overweight or obesity and may also decrease the likelihood of developing these diseases.

Adverse effects of the intervention

Weight loss interventions in overweight or obese people could be associated with weight cycling. This condition could be dangerous because weight cycling may have a number of harmful consequences, including both physiological and psychological hazards (Nat Task Force 1994). Several large population-based studies have shown weight cycling to be associated with increased mortality (Blair 1993; Folsom 1996; Lissner 1991). An increased risk of morbidity, especially cardiovascular disease may be associated with fluctuations in body weight (Ernsberger 1996; Jeffery 1996). Therefore, additional studies are needed to investigate the long-term safety and effectiveness of approaches to weight loss.

Why it is important to do this review

There is no systematic review evaluating the role of obesity treatment in the prevention of a first stroke (primary prevention). It is unclear whether there is evidence scientifically rigorous enough to recommend weight reduction for preventing stroke.

Given the prevalence of stroke and the enormous health and economic costs of the disease, this systematic review tries to collate all available data from randomised controlled clinical trials of obesity or overweight treatment in the primary prevention of stroke.

Objectives

To assess the effects of weight reduction for primary prevention of stroke in adults with overweight and obesity.

Criteria for considering studies for this review

Types of studies

Randomised controlled clinical trials.

Types of participants

Studies including adults (at least 18 years) diagnosed as overweight (body mass index (BMI) 25 to 29.9 kg/m²) or obese (BMI equal to or more than 30 kg/m²). Studies with pregnant women as sole participants will be excluded. The diagnostic criteria for stroke will not be considered as an inclusion or exclusion criterion, but eventual differences will be explored in a sensitivity analysis.

Types of interventions

Randomised controlled clinical trials comparing any intervention for weight reduction with placebo or no intervention. Any concomitant interventions to control other cardiovascular risk factors, such as medication, should be identical in both groups. Trials will be included only if follow-up in the randomisation phase continued for at least one year.

Types of outcome measures

Primary outcomes

(1) incidence of first stroke;
(2) all -cause mortality;
(3) health-related quality of life (ideally measured by a validated instrument).

Secondary outcomes

(1) adverse effects (for example depressive symptoms);
(2) costs;
(3) sequelae of strokes (for example functioning);
(4) incidence of recurrent strokes;
(5) incidence of diverse stroke types (ischaemic, haemorrhagic and unknown cause);
(6) other vascular endpoints (for example fatal stroke, coronary heart disease, vascular death).

Specific patient covariates which may influence the weight reduction effect of the intervention as well as mortality and morbidity

(1) compliance with treatment;
(2) BMI categories;
(3) degree of weight reduction;
(4) co-morbidity at the time of inclusion in the trial (for example diabetes, hypertension);
(5) co-medication at the time of inclusion in the trial;
(6) smoking;
(7) weight regain, weight cycling;
(8) physical activity.

Timing of outcome assessment

Outcomes will be assessed in the long term (at least 12 months of follow-up).

Search strategy for identification of studies

Electronic searches

The following electronic databases were searched to identify relevant trials:

(1) *The Cochrane Library* (up to 2006, issue 2)
(2) MEDLINE (up to April 2006);
(3) EMBASE (up to April 2006);
(4) LILACS (up to April 2006).
The search strategy (for a detailed search strategy see under 'Additional tables' - Table 01) was used for MEDLINE and adapted to suit the other databases.

Databases of ongoing trials
The following databases of ongoing trials were searched:
(1) Current Controlled Trials (http://www.controlled-trials.com);
(2) National Research Register (http://www.update-software.com/National/nrr-frame.html);
(3) National Institutes of Health (http://clinicalstudies.info.nih.gov/).

Reference lists
We also searched the reference lists of reviews to try to identify relevant trials.

Methods of the review

Selection of studies
Two authors (CC and CA) will independently scan the titles, abstracts and keywords of trials identified through the respective search strategies. The full text of the articles will be evaluated for inclusion whenever there is a suggestion that they:
(1) included patients with overweight or obesity;
(2) addressed a weight-reducing intervention;
(3) assessed one or more relevant clinical outcome.

Articles will be rejected on initial screen if both authors can positively determine from the title and abstract that they do not meet the inclusion criteria. The full text of the article will also be reviewed if there is any persisting doubt about its inclusion. Agreement between the two authors will be expressed using the kappa statistic (Cohen 1960). Eventual disagreement will be resolved by discussion between the authors and if necessary with a third researcher. Excluded studies, after evaluation of full text articles, and the reasons for exclusion will be clearly reported in a specific table. An adapted QUOROM (quality of reporting of meta-analyses) flow-chart of study selection will be attached (Moher 1999).

Data extraction and management
Two authors (CC and CA) will independently extract data from each study using a data extraction form based on the one provided by the Cochrane Metabolic and Endocrine Disorders Review Group. Differences between authors' extraction results will be resolved by discussion, and where necessary, in consultation with a third author. The following information will be extracted:

(1) General information: published or unpublished, title, authors, source, contact address, country, language and year of publication, duplicate publications, sponsoring, and setting;
(2) Participants: sampling (random or convenience), exclusion criteria, total number and number in the compared groups, age, gender, initial body mass index (BMI), assessment of compliance, similarity of groups at baseline (including any co-morbidity), withdrawals or losses to follow-up (reasons or description), subgroups;
(3) Trial characteristics: design, duration, randomisation (and its method), allocation concealment (and its method), blinding (patients, people administering treatment, outcome assessors), and check of blinding;
(4) Interventions: types, duration, description (schedule, dose, route, timing);
(5) Outcomes: outcomes specified above, any other outcomes assessed, other events, length of follow-up, quality of reporting of outcomes;

(6) Results: For dichotomous outcomes (stroke and other morbidities), the number of participants experiencing the event and the total number of participants in each arm of the trial will be extracted. Data on the number of patients with each outcome event and allocated to each treatment group, irrespective of compliance or follow-up, will be sought to allow an intention-to-treat analysis.

Assessment of Methodological quality of included studies
We will explore the influence of individual quality criteria in a sensitivity analysis (for details see under 'Additional tables' - Table 03).

Additionally, we will assess the quality of reporting of each trial based largely on the quality criteria specified by Schulz and Jadad (Jadad 1996; Schulz 1995). In particular, the following factors will be studied:
(1) Minimisation of selection bias - a) was the randomisation procedure adequate? b) was the allocation concealment adequate?
(2) Minimisation of performance bias - were the patients and people administering the treatment blind to the intervention?
(3) Minimisation of attrition bias - a) were withdrawals and dropouts completely described? b) was analysis by intention-to-treat?
(4) Minimisation of detection bias - were outcome assessors blind to the intervention?

Based on these criteria, studies will be broadly subdivided into the following three categories (see: *Cochrane Handbook for Systematic Reviews of Interventions* - Higgins 2005):
A - all quality criteria met: low risk of bias.
B - one or more of the quality criteria only partly met: moderate risk of bias.
C - one or more criteria not met: high risk of bias.
This classification will also be used as a basis of a sensitivity analysis.

Each trial will be assessed independently by two authors (CC, CA). Interrater agreement will be calculated using the kappa statistic (Cohen 1960). In case of disagreement, a third researcher will be consulted and a judgement will be made based on consensus. Studies will not be excluded only on the basis of a low quality score.

Measures of treatment effect
Dichotomous data
For dichotomous outcomes (stroke incidence), results will be expressed as risk ratios (RR) or odds ratios (OR) together with 95% confidence intervals (CI).
Data will be analysed with a fixed effect model.

Time-to-event data
Time-to-event outcomes (for example time until death) will be expressed as hazard ratios (HR) with 95% CI.

Unit of analysis issues
Different units of analysis (for example OR and RR) will be subjected to a sensitivity analysis.

Dealing with missing data
When necessary, additional information will be sought by correspondence with the main authors of the studies. Evaluation of important numerical data such as screened, eligible and randomised patients as well as intention-to-treat and per-protocol population will be carefully performed. Drop-outs, misses to follow-up and withdrawn study participants will be investigated.

Dealing with duplicate publications
In the case of duplicate publications and companion papers of a primary study, we will try to maximise yield of information by simultaneous evaluation of all available data. In cases of doubt, the original publication (usually the oldest version) will obtain priority.

Assessment of heterogeneity
In the event of substantial clinical or methodological or statistical heterogeneity, study results will not be combined in meta-analysis. Heterogeneity will be identified by visual inspection of the forest plots, by using a standard ^{2} - test and a significance level of = 0.1, in view of the low power of such tests. Heterogeneity will also be examined with I^2, where I^2 values of 50% and more indicate a substantial level of heterogeneity (Higgins 2003). When heterogeneity is found, we will attempt to determine potential reasons for it by examining individual study characteristics and those of subgroups of the main body of evidence.

Assessment of reporting biases
Funnel plots will be used in exploratory data analysis to assess for the potential existence of small study bias. There are a number of explanations for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to study size, poor methodological design of small studies (Sterne 2001) and publication bias. Thus, this exploratory data tool may be misleading (Tang 2000, Thornton 2000) and we will not place undue emphasis on this tool.

Data synthesis (meta-analysis)
Data will be summarised statistically if they are available, sufficiently similar and of sufficient quality. Statistical analysis will be performed according to the statistical guidelines referenced in the newest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2005). Pooled results will be analysed using primarily a random effects model. Meta-regression will be performed using Stata/SE (version 7, Stata Corporation, Texas U.S.A.) to determine whether various study-level characteristics (for example follow-up interval, duration of the intervention, total attrition, year of publication) affect the between-group change in primary outcomes. We will examine interaction terms for all models.

Subgroup analyses and investigation of heterogeneity
We will perform the following subgroup analyses in order to explore effect size differences, if there is a significant result for one of the main outcome measures:
(1) population characteristics: age, gender and co-morbidity (presence of other risk factors);
(2) intervention characteristics: type of intervention, length of follow-up and degree of weight reduction.

Sensitivity analyses
We will perform sensitivity analyses in order to explore the influence of the following factors on effect size:
(1) repeating the analysis taking account of study quality, as specified above;
(2) repeating the analysis excluding unpublished studies;
(3) repeating the analysis excluding very long or very large studies to establish how much they dominate the results;
(4) repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

The robustness of the results will also be tested by repeating the analysis using different measures of effects size (risk difference, odds ratio etc.) and different statistical models

(fixed and random effects models).

Description of studies

No studies were found.

Methodological quality of included studies

Not applicable.

Results

In order to find all possible studies, a search strategy was developed with a balance between comprehensiveness and precision. After checking the results of the search, no trials were eligible for inclusion. In the attempt to find studies, the search strategy was adapted. Again, no trials were found. Two additional searches were done, however, no studies could be included (for a detailed search strategy see under 'Additional tables' - Table 01).

As described in the protocol, we attempted to find high level information evidence, looking for randomised controlled clinical trials. Thereafter, we tried to identify prospective cohort studies. A search strategy was developed to identify this type of observational study (for details see under 'Additional tables' - Table 02). Unfortunately, we could not detect any prospective cohort study investigating the effects of weight loss or reduction on strokes in adults.

Discussion

We were not able to find suitable trials to assess the effects of weight reduction in people with overweight or obesity on stroke incidence. Therefore, at present we do not have reliable evidence to comment on the observed association between body weight and risk for stroke. Weight loss interventions, such as long-term pharmacotherapy, have to be justified by rigorous scientific evidence. Pathophysiological reasoning alone does not seem to be sufficient to draw inferences from association studies like cohort or case-control studies. Adequate long-term randomised trials are urgently needed to provide a better basis for rational decision making in this important public health area.

Reviewers' conclusions

Implications for practice

There are insufficient data to make recommendations for practice about the effects of weight reduction in people with overweight or obesity on stroke incidence.

Implications for research

Overweight and obesity seem to be associated with an increased risk of stroke and it has been suggested that weight loss may lead to a reduction of stroke occurrence. However, this hypothesis is not based on strong scientific evidence from randomised controlled clinical trials. Research is urgently needed using a structured approach in the assessment of the long-term effect of weight loss on stroke incidence, taking into account both demographic and clinical variables. Well-designed, adequately-powered trials should incorporate long-term interventions, including a weight-loss and maintenance program, which ensure a sustainable weight loss, allowing the assessment of the effect of weigh loss on stroke occurrence. These studies should control for any concomitant risk factor, such as hypertension, diabetes or dyslipidaemia in order to establish the true effect of weight-loss. Due to the high drop-out and withdrawal rates in studies involving obese or overweight people, a great number of participants is necessary. For this purpose, multicentre collaboration, perhaps on an international scale, may be needed. A systematic review will hopefully be able to pool appropriate data in the future.

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Potential conflict of interest
None known.

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Additional tables

01 Search strategy for randomised or controlled clinical trials

Electronic searches
Unless otherwise stated, search terms are free text terms; MesH = Medical subject heading (Medline medical index term); exp = exploded MeSH; the dollar sign ($) stands for any character(s); the question mark (?) = substitutes one or no character; tw = text word; pt = publication type; sh = MeSH; adj = adjacent. FIRST SEARCH STRATEGY [1] search terms for stroke: 1) exp carotid artery thrombosis/ (2) exp cerebrovascular accident/ (3) exp Ischemic attack, transient/ (4) exp cerebral infarction/ (5) exp intracranial aneurysm/ (6) exp "Intracranial Embolism and THrombosis"/ (7) exp cerebral hemorrhage/ or exp basal ganglia hemorrhage/ or exp putaminal hemorrhage/ or exp intracranial hemorrhage, hypertensive/ (8) exp subarachnoid hemorrhage/ (9) (stroke$ or apoplex$ or post-stroke or poststroke).tw. (10) lateral medullary syndrom$.tw. (11) or/1-10 (12) (cereb$ or brain$).tw. (13) exp Brain/ (14) 12 or 13 (15) exp Thrombosis/ (16) exp Embolism/ (17) exp Hemorrhage/ (18) (infarct$ or ischemi$ or ischaemi$ or thrombo$ or embol$ or haemorrhag$ or hemorrhag$ or bleeding).tw. (19) or/15-18 (20) 14 and 19 (21) 11 or 20 [2] search terms for obesity or overweight: (22) exp Obesity/ (23) exp Weight Loss/ (24) exp weight gain/ (25) exp body mass index/ (26) (weight adj2 (cyc$ or reduc$ or los$ or decreas$)).tw. (27) over?weight$.tw. (28) fat overload syndrom$.tw. (29) (over?eat or over?feed).tw. (30) (adipos$ or obes$).tw. (31) body mass ind$.tw. (32) or/22-31 [3] stroke and (obesity or overweight): (33) 21 and 32 [4] search terms for randomised controlled clinical trials (RCT) or controlled clinical trials (CCT): (34) randomized controlled trial.pt. (35) controlled clinical trial.pt. (36) randomized controlled trials.sh. (37) random allocation.sh. (38) double-blind method.sh. (39) single-blind method.sh. (40) or/34-39 (41) limit 40 to animal (42) limit 40 to human (43) 41 not 42

(44) 40 not 43
(45) clinical trial.pt.
(46) exp clinical trials/
(47) (clinic$ adj25 trial$).tw.
(48) ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
(49) placebos.sh.
(50) placebo$.tw.
(51) random$.tw.
(52) research design.sh.
(53) (latin adj square).tw.
(54) or/45-53
(55) limit 54 to animal
(56) limit 54 to human
(57) 55 not 56
(58) 54 not 57
(59) comparative study.sh.
(60) exp evaluation studies/
(61) follow-up studies.sh.
(62) prospective studies.sh.
(63) (control$ or prospectiv$ or volunteer$).tw.
(64) cross-over studies.sh.
(65) or/59-64
(66) limit 65 to animal
(67) limit 65 to human
(68) 66 not 67
(69) 65 not 68
(70) 44 or 58 or 69
[5] stroke and (obesity or overweight) and (RCT or CCT):
(71) 33 and 70

SECOND SEARCH STRATEGY
[1] search terms for obesity or overweight:
(1) exp Obesity/
(2) exp body mass index/
(3) body mass ind$.tw.
(4) (adipos$ or obes$).tw.
(5) (over?eat or over?feed).tw.
(6) over?weight$.tw.
(7) exp Overweight/
(8) or/1-7
[2] search term for weight-loss interventions:
(9) exp Weight Loss/
(10) (weight adj6 (cyc$ or reduc$ or los$ or decreas$)).tw.
(11) exp Exercise/
(12) exp Diet/
(13) exp Drug Therapy/
(14) exercis$.tw.
(15) diet$.tw.
(16) surger$.tw.
(17) exp surgery/
(18) ((drug$ or agent$) adj6 (therap$ or treatment$ combination$)).tw.
(19) exp acupuncture therapy/
(20) exp psychotherapy/
(21) exp life style/
(22) ((pharmacological or pharmaceutical) adj6 (therap$ or treatment$ or drug$ or agent$)).tw.
(23) leisure activit$.tw.
(24) counselling.tw.
(25) (psychological adj6 (therap$ or treatment$ or advic$ or counsel$)).tw.
(26) or/9-25
[3] (Obesity or overweight) and weight-loss interventions:

(27) 8 and 26
[4] search terms for stroke - see FIRST SEARCH STRATEGY above
[5] (Obesity or overweight) and weight-loss interventions and stroke:
(49) 27 and 48
[6] RCT and CCT - see FIRST SEARCH STRATEGY above
[7] (Obesity or overweight) and weight-loss interventions and stroke and (RCT or CCT):
(87) 49 and 86

THIRD SEARCH STRATEGY
[1] search terms for obesity or overweight - see SECOND SEARCH STRATEGY above

[2] search terms for stroke:
(9) exp Cerebrovascular Accident/
(10) exp Carotid Artery Thrombosis/
(11) exp Ischemic Attack, Transient/
(12) exp Cerebral Infarction/
(13) exp Intracranial Aneurysm/
(14) exp "Intracranial Embolism and Thrombosis"/
(15) exp cerebral hemorrhage/ or exp basal ganglia hemorrhage/ or exp putaminal hemorrhage/ or exp intracranial hemorrhage, hypertensive/
(16) exp Subarachnoid Hemorrhage/
(17) exp Cardiovascular diseases/
(18) (stroke$ or apoplex$ or post?stroke).tw.
(19) lateral medullary syndrom$.tw.
(20) cardiovascular diseas$.tw.
(21) vascular diseas$.tw.
(22) isch?emic event$.tw.
(23) or/9-22
(24) (cereb$ or brain$).tw.
(25) exp brain/
(26) 24 or 25
(27) exp Thrombosis/
(28) exp Embolism/
(29) exp Hemorrhage/
(30) (infarct$ or isch?emi$ or thrombo$ or embol$ or h?emorrag$ or bleeding$).tw.
(31) or/27-30
(32) 26 and 31
(33) 23 or 32

[3] search terms for RCT:
(34) randomized controlled trial.pt.
(35) controlled clinical trial.pt.
(36) randomized controlled trials.sh.
(37) random allocation.sh.
(38) double-blind method.sh.
(39) single-blind method.sh.
(40) or/34-39
(41) limit 40 to animal
(42) limit 40 to human
(43) 41 not 42
(44) 40 not 43
[4] (Obesity or overweight) and stroke and RCT:
(45) 8 and 33 and 44

FOURTH SEARCH STRATEGY
[1] search terms for obesity or overweight - see SECOND SEARCH STRATEGY above

[2] search terms for weight-loss Interventions:
(9) exp Weight Loss/
(10) (exercis$ or physic$ activ$ or exert$ or physic$ fit$ or sports).tw.

(11) (weight adj6 (cyc$ or reduc$ or los$ or decreas$)).tw.
(12) (weight lift$ or strength train$ or resistance train$ or circuit weight train$).tw.
(13) exp exertion/
(14) exp "Physical Education and Training"/
(15) exp Physical Fitness/
(16) exp Sports/
(17) or/9-16
(18) exp Diet/
(19) exp Diet Therapy/
(20) diet$.tw.
(21) ad lib.tw.
(22) or/18-21
(23) exp Bariatric Surgery/
(24) exp Gastric Balloon/
(25) (gastroplasty or gastric band$ or gastric bypass or lap band or roux$ or gastro?gastrostomy or restrictive surgery or malabsorptive surgery or bariatric surgery or stomach bubble).tw.
(26) (gastric balloon$ or gastric bubble$ or stomach bubble).tw.
(27) jejuno?ileal bypass.tw.
(28) or/23-27
(29) exp Anti-Obesity Agents/
(30) exp appetite depressants/ or exp diethylpropion/ or exp phenmetrazine/ or exp phentermine/ or exp phenylpropanolamine/
(31) exp diethylpropion/ or exp phenmetrazine/ or exp phentermine/ or exp phenylpropanolamine/
(32) exp Mazindol/
(33) exp amphetamines/ or exp amphetamine/
(34) (appetite adj2 (reduc$ or inhibitor$ or depressant$ or suppressant$)).tw.
(35) (anorectic adj2 (agent$ or drug$ or compound$ or treatment$)).tw.
(36) (anti-obesity adj2 (agent$ or drug$)).tw.
(37) ((pharmacological or pharmaceutical) adj6 (therap$ or treatment$ or drug$ or agent$)).tw.
(38) (mazindol$ or benzocain$ or phentermin$ or phenmetrazin$ or phendimetrazin$ or fenfluramin$ or dexfenfluramin$ or diethylpropion$ or diethyl propion$ or benzphetamin$).tw.
(39) ((drug$ or agent$) adj2 (therap$ or treatment$ combination$)).tw.
(40) or/29-39
(41) exp acupuncture therapy/
(42) exp psychotherapy/
(43) exp life style/
(44) (behavio?r adj2 (therap$ or modific$)).tw.
(45) (cognitiv$ adj2 therap$).tw.
(46) (psychological adj6 (therap$ or treatment$ or advic$ or counsel$)).tw.
(47) ((pharmacological or pharmaceutical) adj6 (therap$ or treatment$ or drug$ or agent$)).tw.
(48) leisure activit$.tw.
(49) or/41-48
(50) 17 or 22 or 28 or 40 or 49

[3] search terms for stroke - see FIRST SEARCH STRATEGY above

[4] search terms for RCT or CCT - see FIRST SEARCH STRATEGY above

[5] search terms for cardiovascular disease:
(109) (cardiovascular adj2 disorder$).tw.
(110) (cardiovascular adj2 diseas$).tw.
(111) exp Cardiovascular Diseases/

[6] stroke or cardiovascular disease

[7] (stroke or cardiovascular disease) and (obesity or overweight) and RCT

02 Search strategy for observational studies (prospective cohort studies)

Unless otherwise stated, search terms are free text terms; MesH = Medical subject heading (Medline medical index term); exp = exploded MeSH; the dollar sign ($) stands for any character(s); the question mark (?) = substitutes one or no character; tw = text word; pt = publication type; sh = MeSH; adj = adjacent.

(1) exp Obesity/
(2) exp Weight Gain/
(3) exp Weight Loss/
(4) exp body mass index/
(5) exp Skinfold thickness/
(6) exp Waist-hip ratio/
(7) exp Abdominal fat/
(8) Quetelet inde$.tw.

(9) 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

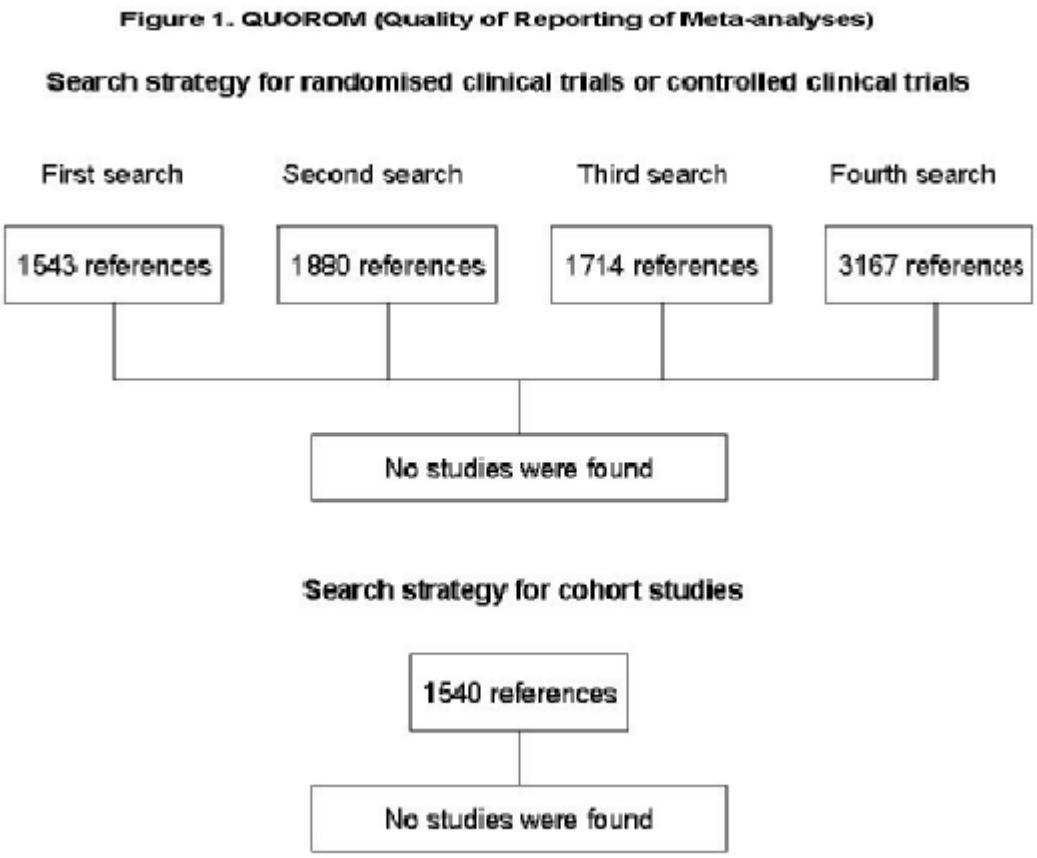
(10) *MORTALITY/
(11) *MORBIDITY/
(12) *EPIDEMIOLOGY/
(13) *PREVALENCE/
(14) *Primary Prevention/
(15) *Risk Factors/
(16) ((risk or mortality or morbidity or longevity or cohort or life expectancy or illness or incidence or predictor$ or death$ or disease$ or health outcome$) and (body size or BMI or body mass inde$ or overweight or over weight or obes$ or adipos$ or fat or hip circumference or waist)).ti.

(17) 10 or 11 or 12 or 13 or 14 or 15 or 16
(18) 9 and 17

Additional figures

Figure 01

QUOROM (quality of reporting of meta-analyses) flow chart of study selection



5.4. Anexo IV – Rimonabant for Obesity and Overweight

Rimonabant for overweight or obesity

Cochrane Database Syst Rev. 2006 Oct 18;(4):CD006162. Review.

Cover sheet

Reviewers

Curioni C, André C

Dates

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Synopsis

Rimonabant 20 mg produces modest weight loss among adults with overweight or obesity

Rimonabant is the first drug in a new class of selective cannabinoid type 1 receptor antagonists that seems to reduce body weight and improve cardiometabolic risk factors in patients who are overweight or obese. This review assessed the efficacy and safety of rimonbant interventions in clinical trials with overweight or obesity adults. Four studies met inclusion criteria and the primary outcome measures evaluated were weight loss change, morbidity occurrence and adverse effects of treatment. The four studies involved 6625 patients comparing rimonabant 20 mg with rimonabant 5 mg and placebo, associated to a hypocaloric diet in one or two years of treatment. Greater weight loss and cardiometabolic risk factors improvement are seen in the rimonabant 20 mg. Interpretation of results is limited due to high study attrition rates and the quality generally poor of the included studies. We conclude that: 1. average weight loss with rimonabant appears modest, and 2. more methodologically rigorous studies that are powered to examine efficacy and safety are required to fully evaluate any potential benefit of such drug.

Abstract

Background
Worldwide, the prevalence of obesity and overweight in industrialized countries and in a substantial number of developing countries is increasing at an alarming rate. Rimonabant is a selective cannabinoid-1 receptor antagonist that has been investigated for its efficacy in reducing body weight and associated risk factors in obese patients. Phase III trials are now under way to test the use of rimonabant for long-term weight-loss. Given the prevalence of overweight and obesity, it is important to establish the possible efficacy and safety of rimonabant in people suffering from these conditions.

Objectives
To assess the effects of rimonabant in overweight and obese people.

Search strategy
MEDLINE, EMBASE, The Cochrane Library, LILACS, databases of ongoing trials and reference lists were used to identify relevant trials. The last search was conducted in June 2006.

Selection criteria
Randomised controlled trials comparing rimonabant associated or not with other intervention with placebo or other weight loss intervention in overweight or obese adults.

Data collection & analysis
Two reviewers independently assessed all potentially relevant citations for inclusion and methodological quality. The primary outcome measures were weight loss change, morbidity and adverse effects occurrence.

Main results
Four studies evaluating rimonabant 20 mg versus rimonabant 5 mg versus placebo associated with hypocaloric diet with results at least in one year were included. Compared with placebo, rimonabant 20 mg produced a 4.9 kg greater reduction in body weight in trials with one-year results. Improvements in waist circumference, high-density lipoprotein cholesterol, triglyceride levels and systolic and diastolic blood pressure also were seen. However, the results with rimonabant 5 mg were not the same, and even being statistically significant the weight reduction was only 1.3 kg greater when compared with

placebo. No clinically relevant effects on plasma lipids and blood pressure were found. Comparing the two interventions groups the results were similar to the rimonabant 20 mg versus placebo comparison, favouring the first group. Rimonabant 20 mg caused significant more adverse effects both general and serious, especially of nervous system, psychiatric or gastro-intestinal origin. Attrition rates were approximately 50% at the end of one year.

Reviewers' conclusions

This review suggests that the use of rimonabant after one year could produce modest weight loss of approximately 5%. Even modest amounts of weight loss may be potentially beneficial. Some caution with the observed results should be take account since the studies presented some deficiencies in the methodological quality. Studies with follow-up after the end of treatment and more rigorous in the quality of methodology of this new drug should be done before definitive recommendations can be made regarding the role of this medication in the management of obese patients.

Background

Description of the condition

Worldwide, the prevalence of obesity and overweight in industrialized countries and in a substantial number of developing countries is increasing at an alarming rate (WHO 2000). This problem is associated with a large variety of health consequences representing an enormous burden on health care systems and, most importantly, the quality of life of the affected individuals might be substantially lowered.

Obesity refers to an excess of body fat or adiposity. Body mass index (BMI; in kg/m^2) is widely recognized as a weight-for-height index that has a high correlation with adiposity. In clinical terms, a BMI of 25-29 kg/m^2 is classified as overweight and a higher BMI (greater than 30 kg/m^2) reflects obesity (WHO 2000).

Overweight and obesity are associated with a large variety of health consequences, including hypertension (Brown 2000; Dyer 1989), type 2 diabetes mellitus (Medalie 1974; Ohlson 1985), heart diseases (NIHCD 1985; Willett 1995), stroke (Rexrode 1997; Walker 1996), osteoarthritis (Cicuttini 1996; Hart 1993), sleep apnea and respiratory difficulties (Chua 1994) and also several common cancers (Bergstrom 2001; Chu 1991; Schottenfeld 1996).

The presence of excess fat in the abdomen out of proportion to total body fat is an independent predictor of type 2 diabetes, dyslipidemia, hypertension, and cardiovascular disease (NHLBI 1998). Waist circumference and waist-to-hip circumference ratios (WHR) are simple and convenient for epidemiological studies and provide a useful estimation of the proportion of abdominal or upper-body fat (Kissebah 1985; Björntorp 1984; Björntorp 1985). Several studies have shown the correlation of abdominal fat and increased mortality and risk for disorders such as diabetes, hyperlipidemia, hypertension, and cardiovascular diseases (Donahue 1987; Ducimetiere 1986; Lapidus 1984; Larsson 1984; Ohlson 1985; Stokes 1985;).

Description of the intervention

Obesity is seen as a disease, which requires treatment. Treatment means, first of all, weight reduction. The general goals of weight loss and management are:
(1) to reduce body weight; and
(2) to maintain a lower body weight over the long term; or
(3) at a minimum, to prevent further weight gain.
There is strong evidence that weight loss (5% to 15% of the body weight) in obese

individuals reduces risk factors associated with obesity (NHLBI 1998).

Traditional methods to promote weight loss focus on reducing energy intake through low-calorie or low-fat diets, increasing energy expenditure by increase in physical activity, and behavioural modification. The inclusion of exercise in a weight reduction program is supposed to make the weight loss easier, compared with food restriction alone. However, the effectiveness of these weight reduction methods is limited, with an overall pattern of moderate weight loss followed by gradual weight regain (Curioni 2005).

Numerous other weight loss interventions are available including pharmacotherapy, surgery to reduce food consumption and alternative therapies. Surgical procedures have greater long-term success rates but are currently indicated for the very obese only (BMI greater than 40 kg/m^2 or BMI 35-40 kg/m^2 together with an obesity-related disorder). Operative mortality rates are reported to average below one percent, but long-term complications such as malabsorption syndromes may occur (Greenway 1996).

Pharmacotherapy should be considered in overweight and obese patients with a BMI greater than 27 kg/m^2, particularly in the presence of comorbidities or an increased waist circumference, when conservative measures such as behaviour therapy, diet and exercise have not resulted in the desired weight loss (NHLBI 1998). Drugs should always be used in conjunction with non-pharmacological therapy, though.

Approved anti-obesity medications can be divided into two broad categories:
(1) Inhibitors of intestinal fat absorption, on which the only agent currently available in this class is orlistat, a drug that inhibits pancreatic and other lipases. Side effects are related to malabsorption of fat within the gastrointestinal tract and include steatorrhea, bloating, and oily discharge. Fecal incontinence and malabsorption of fat-soluble vitamins, such as vitamin A, D, E, and K, have also been reported (McNeely 1998).
(2) Drugs that act to suppress appetite. An example of this category includes sibutramine, which inhibits re-uptake of serotonin and norepinephrine. The most common adverse effects are related to increased adrenergic activity and include dry mouth, headache, insomnia, and constipation. Sibutramine may also cause increases in blood pressure and heart rate (Luque 1999).
Orlistat and sibutramine are the only medications approved for long-term use.

A number of anti-obesity drugs are currently undergoing clinical development. These include:
(1) Centrally-acting drugs, such as the noradrenergic and dopaminergic re-uptake inhibitor rodafaxine, the endocannabinoid antagonist rimonabant, the selective serotonin 5-HT$_{2C}$ agonist APD-356, and oleoyl-estrone;
(2) Drugs that target peripheral episodic satiety signals, such as glucagon-like peptide-1, peptide YY and amylin;
(3) Drugs that block fat absorption, such as the novel lipase inhibitors cetilistat and GT-389255; and
(4) A human growth hormone fragment (AOD-9604) that increases adipose tissue breakdown (Halford 2006).
Most of these investigational drugs are in the early or mid-stages of development. Rimonabant is the only drug in the late-stage of results.

How the intervention might work
Rimonabant is a selective cannabinoid-1 receptor antagonist that has been investigated for its efficacy in reducing body weight and associated risk factors in obese patients (Bonner 2005). The cannabinoid-1 receptor plays a role in the regulation of appetite and body weight. The endocannabinoid system (EC) consists of cannabinoids receptors (CB$_1$

receptors) and endocannabinoids, as well as enzymes catalyzing their biosynthesis and degradation (Di Marzo 2005). CB_1 receptors are expressed predominantly in several areas of the brain and in peripheral organs, including the autonomic nervous system, liver, muscle, gastrointestinal tract, and adipose tissue (Di Marzo 2004). Pharmacological stimulation of CB_1 receptors by systemic administration of plant or endogenous cannabinoids stimulates eating, even in satiated animals (Colombo 1998; Rowland 2001; Simiand 1998).

The administration of the first selective CB_1 antagonist (rimonabant) attenuated agonists' stimulatory effects on food intake and strongly reduced both the consumption of palatable food (such as sweet food) and the intake of normal food by animals deprived of food (Rinaldi-Carmona 2004; Werner 2003).

The EC system may regulate food intake by modulating actions or expressions of many anorectic and orexigenic mediators in the brain, particularly hypothalamic peptides such as corticotrophin-releasing hormone (CRH) and melanin-concentrating hormone (MCH). Of particular importance are the effects of endocannabinoids on the mesolimbic system that modulates reward behaviours (such as food intake as a reward after managing stressful situations). Endocannabinoids enhance dopamine release in the nucleus accumbens, thus increase the drive to eat (Di Marzo 2005). Rimonabant has been shown to reduce food intake, hunger and body weight in overweight /obese men after seven days of treatment (Vickers 2005).

Phase III trials are now under way to test the use of rimonabant for long-term weight-loss. Four clinical trials (RIO (rimonabant in obesity) US, RIO Europe, RIO-Diabetes and RIO-Lipid) involving 6000 patients suggest that rimonabant 20 mg produces a placebo-subtracted weight loss of approximately five kg. No major side effects were reported; however, given the wide distribution of CB_1 receptors within the body, it is possible that the drug could affect a number of systems unrelated to eating (Halford 2006).

A Cochrane systematic review is being developed to analyse the efficacy of cannabinoid type 1 receptor antagonists for smoking cessation (Hey 2005)

Why it is important to do this review
There is no systematic review evaluating the efficacy and also the possible adverse effects of rimonabant in overweight or obese people. Given the prevalence of overweight and obesity, it is important to establish the possible impact of rimonabant in people suffering from these conditions.

Objectives
To assess the effects of rimonabant in overweight and obese people.

Criteria for considering studies for this review

Types of studies
Only randomised controlled trials were considered for inclusion.

Types of participants
Individuals aged 18 years and older defined as overweight or obese at baseline. Criteria for defining overweight or obesity include BMI cut-off points (WHO 2000). Ideally, diagnostic criteria should have been described. If necessary, authors' definition of overweight or obesity were used and eventually subjected to sensitivity analysis. Studies including children, pregnant women, or patients with serious medical conditions would have been excluded.

Types of interventions

Interventions eligible for inclusion in the review include:

- Rimonabant versus placebo;
- Rimonabant plus other intervention such as diet or exercise versus placebo plus the same intervention;
- Rimonabant versus any other pharmacological intervention;
- Rimonabant versus a non-pharmacological intervention.

Types of outcome measures

To be eligible for inclusion in the review, trials had to report one or more of the following outcomes:

Primary outcomes

- Change in weight measures (for example body weight, body mass index (BMI), waist circumference or hip/waist circumference, other anthropometric measures);
- Morbidity (such as cardiovascular disorders, gastrointestinal disorders, nervous system disorders, psychiatric disorders, renal and urinary disorders);
- Adverse effects of treatment (such as headache, nausea, anxiety, insomnia, gastrointestinal syntoms)

Secondary outcomes

- All-cause mortality;
- Change in risk factors (such as blood pressure, lipid profile and HbA_{1c});
- Health-related quality of life (ideally using a validated instrument);
- Costs.

Specific patient covariates thought to be effect modifiers

- Compliance with the treatment;
- Initial overweight or obesity;
- Duration of intervention.

Timing of outcome assessment (duration of the intervention)

- Short-term (four weeks to 24 weeks of treatment);
- Medium-term (more than 24 weeks to 12 monts of treatment);
- Long-term (more than 12 months of treatment).

Search strategy for identification of studies

Electronic searches

The following electronic databases were searched to identify relevant trials, reviews, meta-analyses, and economic analyses:

- *The Cochrane Library* (up to ...);
- MEDLINE (up to June 2006);
- EMBASE (up to June 2006);
- LILACS (up to June 2006);

There were no language restrictions for either searching or trial inclusion. The search strategy using a combination of MeSH terms and text words was used for MEDLINE and was adapted to suit the other databases. For a detailed search strategy, please see under 'Additional tables' - Table 01.

Handsearching

Efforts were made to identify additional studies by searching the references lists of relevant trials and reviews identified.

Other search strategies
Authors of relevant identified studies and other experts were contacted to obtain additional references, unpublished trials, ongoing trials and missing data not reported in the published trials.

Databases of ongoing trials
- Current Controlled Trials (http://www.controlled-trials.com);
- National Research Register (http://www.update-software.com/National/nrr-frame.html);
- National Institutes of Health (http://clinicalstudies.info.nih.gov/).

Methods of the review

Selection of studies
Two reviewers (CC and CA) independently scanned the titles, abstracts and keywords of trials identified through the respective search strategies. The articles were evaluated for inclusion whenever there was a suggestion that they:
- Included patients with overweight or obesity;
- Compared rimonabant with placebo or other active intervention;

Articles were rejected on initial screen if both reviewers could positively determine from the title and abstract that they did not meet the inclusion criteria. All potentially relevant articles were investigated as full text. Agreement between the two reviewers was expressed using the kappa statistic (Cohen 1960). Eventual disagreement was resolved by discussion between the reviewers. Excluded studies and the reasons for exclusion were clearly reported in a specific table.

Data extraction and management
Two reviewers (CC and CA) independently extracted data from each study using standard data extraction forms (for details see 'Characteristics of included studies' and under 'Additional tables' - Table 02; Table 03; Table 04; Table 05; Table 06). Differences between reviewers' extraction results were resolved by discussion. The standard data extraction forms included the following items:
- General information: published or unpublished, title, authors, source, contact address, country, language and year of publication, duplicate publications, sponsoring, and setting;
- Participants: sampling (random or convenience), exclusion criteria, total number and number in the compared groups; age; gender; initial BMI, assessment of compliance, similarity of groups at baseline (including any co-morbidity), withdrawals or losses to follow-up (reasons or description), subgroups;
- Trial characteristics: design, duration, randomisation (and its method), allocation concealment (and its method), blinding (patients, people administering treatment, outcome assessors), and check of blinding;
- Interventions: types, duration, description (schedule, dose, route, timing, etc.);
- Outcomes: outcomes specified above, any other outcomes assessed, other events, length of follow-up, quality of reporting of outcomes;
- Results: measures of effect specified above, use of intention-to-treat analysis;

Assessment of methodological quality of included studies
Two reviewers evaluated independently methodological quality of trials by means of individual quality component analysis (CC and CA). Inter-rater agreement was planned to be calculated using the kappa statistic (Cohen 1960). Studies were not excluded only on the basis of low quality.

Measures of treatment effect

Continuous data
Continuous outcomes (for example weight loss measure by weight) were expressed, if possible, as weighted mean differences with 95% confidence intervals (CI). If results for continuous outcomes are presented on different scales, we will use the standardised mean differences (SMD).

Dichotomous data
Dichotomous outcomes (for example stroke yes/no) were expressed as odds ratios (OR) or relative risks (RR) with 95% CI.

Time-to-event data
Time-to-event outcomes (for example time until death) were expressed as hazard ratios (HR) with 95% CI.

Unit of analysis issues
Different units of analysis (for example OR and RR) were planned to be subjected to a sensitivity analysis.

Dealing with missing data
When necessary, relevant missing data were sought by correspondence with the main authors of the studies. Evaluation of important numerical data such as screened, eligible and randomised patients as well as intention-to-treat and per-protocol population were carefully performed. Drop-outs, misses to follow-up and withdrawn study participants were investigated.

Dealing with duplicate publications
Multiple publications were planned to be collated and assessed as one study to try maximise yield of information by simultaneous evaluation of all available data.

Assessment of heterogeneity
Heterogeneity between trial results were tested for using a standard chi-squared test. Tests of heterogeneity are used for examining whether the observed variation in study results is compatible with the variation expected by chance alone. A significance level of alpha set at 0.1 was used for the test of heterogeneity in view of the low power of such tests. Heterogeneity was also examined with I^2, where I^2 values of 50% and more indicate a substantial level of heterogeneity (Higgins 2003). When found, we attempted to determine potential reasons for it by examining individual study characteristics and those of subgroups of the main body of evidence.

Assessment of reporting biases
Funnel plot asymmetry were planned to be assessed statistically to explore publication bias if sufficient randomised clinical trials are identified (Egger 1997).

Data synthesis (meta-analysis)
Data were be summarised statistically if they are available, sufficiently similar and of sufficient quality. Statistical analysis were be performed according to the statistical guidelines referenced in the newest version of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005). Pooled results were analysed using primarily a fixed effect model.

Subgroup analyses
We planned to perform subgroup analyses to explore whether there are any systematic

differences between groups of patients. If the results of at least one of the main outcomes are significant in order to explore effect size differences and if the amount of data permits, subgroup analyses will be conducted according to the following:

- Weight level (BMI) at baseline;
- Age;
- Gender;
- Different comparison interventions;
- Duration of intervention.

Sensitivity analyses

We performed sensitivity analyses to explore the influence of the following factors on effect size:

- Repeating the analysis excluding unpublished studies;
- Repeating the analysis taking study quality, as specified above, into account;
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results.
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

The robustness of the results was also be tested by repeating the analysis using different measures of effects size (risk difference, odds ratio etc) and different statistic models (fixed and random effects models).

Description of studies

From the initial search, 326 records were identified, and from these, 75 full papers were identified for further examination. The other studies were excluded on the basis of their abstracts because they were not relevant to the question under study. See Figure 01 for details of the amended Quorom statement.

After screening the full text of the selected papers, six studies finally met the inclusion criteria. Two studies were only presented as abstract of congress. One of these was a subgroup analysis of the RIO-studies and it was not included in the results. This study is included in the 'Characteristics of excluded studies' table. One of the six studies in an one ongoing trial, with expected end on Agust, 2007. See 'Characteristics of ongoing studies' table for details. One additional title was selected, but it was not retrieved because the reference was wrong. The other three articles were published in peer review journals.

Assessment of publication bias inter-rater agreement

Two authors (CC and CA) reviewed the studies. There was agreement on the studies to be extracted for closer inspection from the searches. The full papers were obtained, and from these, the studies eligible for the review were selected. The authors agreed on the final papers chosen for the review.

Missing data

Some authors were contacted for further information. The authors of the RIO-North America (Dr. Pi-Sunyer and Dr. Aronne) were contacted by e-mail to ask whether they could send details about the results, only published as placebo subtracted changes from baseline or changes from baseline only presented in figures, but unfortunately we had no answer. Professor Hollander, who presented the results of RIO-Diabetes in the '1st International Congress on "Prediabetes" and the Metabolic Syndrome, 2005', was contacted by e-mail for particulars about the methodology and results of the study, but also we did not obtain any answer. Dr Jensen was contact by e-mail to ask about more information about the study entitled "The selective CB1-receptor antagonist rimonabant reduces body weight and waist circumference in obese subjects" which was presented only as an abstract. He was quick to answer, and stated that the presented study

constituted a subgroup analysis of the results of three RIO-studies (RIO-Europe, RIO-Lipids and RIO-North America); the abstract publication therefore was not included in the present analysis. About the selected title which the reference was wrong entitled "SR141716, a selective cannabinoid CB1 receptor antagonist, reduces hunger, caloric intake and body weight in over weight or obese men" , we got answer from Dr Belisse, one of authors, informing that the study was part of a series of trials done by the Sanofi company on this product, and the methods and results are the property of Sanofi. Unfortunately we got no answer of Sanofi when we asked for unpublished data.

Excluded studies
Excluded studies and the reasons for exclusion are given in the Table: 'Characteristics of excluded studies'.

Included studies
Details of the characteristics of the included studies are given in the Table: 'Characteristics of included studies'. The following gives a brief overview.

Characteristics of included studies

Methods
All four studies finally selected for the review were randomised controlled trials published in English. The duration of the intervention was 24 months for the RIO-North America and12 months for the RIO-Diabetes, RIO-Lipids and RIO-Europe. Although the last two described a period of 24 months during which they were conducted, only the 12-months results are provided. All trials had a run-in, single blind period before the randomisation.

Participants
The included studies involved 6625 participants. The main inclusion criteria involved adults (18 years or older), with body mass index greater than 27 kg/m² and less than 5 kg variation in body weight within the three months before study entry.

Intervention
All trials are multicentric. The RIO-North America was conducted in USA and Canada, RIO-Europe in Europe and USA, RIO-Diabetes in USA and 10 other different countries not specified, and RIO-Lipids in 8 different countries not specified.
The intervention received was placebo, 5mg of rimonabant or 20 mg of rimonabant once daily in addition to a mild hypocaloric diet (600 kcal/day deficit).

Outcomes
Primary: In all studies the primary outcome assessed was weight change from baseline after 1 year of treatment and the RIO-North America study also evaluated the prevention of weight regain between the first and second years. All studies evaluated adverse effects, including those of any kind and serious events. Quality of life was measured in only one study, but the results are not described (RIO-Europe).

Secondary and additional outcomes included prevalence of metabolic syndrome after one year and change in cardiometabolic risk factors such as blood pressure, lipid profile, etc. No study included mortality and costs as outcome.
The timing of outcome measures was variable and could include monthly, evaluations every three months or a single final evaluation after one year.

Methodological quality of included studies

The methodological characteristics of the included studies are summarised in Table 02 in the Additional Tables. There was complete agreement between the two authors regarding

quality assessment; therefore a kappa-statistic was not calculated.

Overview
All 4 studies had some methodological weaknesses according to the methodological quality criteria evaluated. None fulfilled all quality criteria.

Randomisation and allocation concealment
All selected trials were described as randomised. However, only two studies reported an appropriate method of randomisation (RIO-Europe and RIO-North America). Most studies did not mention any procedure for allocation concealment, with only one reporting adequate allocation concealment (RIO-Europe). The main characteristics of the participants in the three groups were similar at baseline in all selected studies.

Blinding
The selected trials were described as double-blind. However, no details of the methods employed or of which stage of the process was blinded were reported. No trial reported blinding of outcome assessors (those taking samples or carrying out laboratory tests). None of the included studies specifically reported blinding of either the study participants or the providers of treatment.

Power calculation
Power calculations were reported as incorporated in the design of one of the four studies included in this review. The sample size of the RIO-North America study was based on 99% power to detect a 3-kg difference between one dose of rimonabant and placebo after one year with $p < 0.025$. No other included study reported power calculations.

Descriptions of losses to follow-up
Three of the selected trials described the losses of follow-up (RIO-Europe, RIO-Lipids and RIO-North America). Only one, RIO-Diabetes, described the number of patients who discontinued treatment because of adverse events.

Intent-to-treat (ITT) population analyses
All studies reported an intention-to-treat analysis. The method used for missing data was mainly last-observation-carried-forward. No study described the ITT population in detail.

Results
Changes from the published protocol are detailed under 'Additional tables' - Table 07. Results of the meta-analyses are reported below. Data from the studies were pooled for meta-analysis at one year.

Primary outcomes

Weight (kg) change
Comparing rimonabant 20 mg with placebo, meta-analysis of all included studies showed evidence of heterogeneity with a reduction in mean weight of 4.6 kg for the rimonabant group but this result could not be considered ($I^2 = 60.6\%$). When we performed the analysis excluding the RIO-Diabetes study which was only published as abstract of congress we observed that the heterogeneity was eliminated and the pooled data showed a reduction in mean weight of 4.9 kg (-4.9 weighted mean difference [WMD], 95% confidence interval [CI] -5.3 to -4.5). In the comparison between rimonabant 5 mg and placebo, the pooled effect was a weight reduction of 1.3 kg for the rimonabant group excluding the RIO-North America study due to lack of data (-1.3 WMD, 95% CI -1.6 to -0.9). Comparing the two intervention groups, there was a pooled effect of weight reduction of 3.3 kg for the rimonabant 20 mg group, also excluding the RIO-North

America study (-3.3 WMD, 95% CI -3.7 to -2.9). All results were statistically significant ($p < 0.0001$).

Waist circumference (cm) change
The pooled meta-analysis of all included studies showed evidence of a reduction in waist circumference of 3.8 cm for the rimonabant 20 mg group when compared with placebo (-3.8 WMD, 95% CI -4.3 to -3.4). In the rimonabant 5 mg versus placebo comparison, the pooled effect was a reduction of 1.2 cm for the rimonabant group excluding the RIO-North America study due to lack of data (-1.2 WMD, 95% CI -1.7 to -0.7). Comparing the two intervention groups, the pooled data showed heterogeneity ($I^2 = 53.5\%$). We performed sensitivity analysis, but even excluding the RIO-Diabetes study which was only published as abstract of congress, we could not explain the observed heterogeneity. For this reason the pooled data are not shown. All results were statistically significant ($p < 0.0001$).

Adverse effects (general)
The combined results of the 3 trials (excluding RIO-Lipids study) indicated that compared to placebo, patients treated with rimonabant 20 mg reported significantly more general adverse effects: RR = 1.05, 95% CI 1.01 to 1.08 ($p = 0.005$). There were no statistically significant differences for adverse effects in the meta-analysis comparing the results of rimonabant 5 mg with placebo (also excluding the RIO-Lipids study). Comparing the two intervention groups, patients treated with rimonabant 20 mg reported significantly more adverse effects than the rimonabant 5 mg group: RR = 1.04, 95% CI 1.01 to 1.06 ($p = 0.008$). The RIO-Lipids study was not included because it did not provide overall numbers for adverse effects but for single events only (multiple episodes were possible for each patient).

Adverse effects (serious)
The pooled meta-analysis of all included studies showed that compared to placebo, patients treated with rimonabant 20 mg reported significantly more serious adverse effects: RR = 1.37, 95% CI 1.04 to 1.80 ($p = 0.03$). There were no statistically significant differences for serious adverse effects in the meta-analysis comparing the results of rimonabant 5 mg with placebo and also for the comparison between the two intervention groups.

Discontinuation due to adverse effects
The pooled meta-analysis of all included studies showed that compared to placebo, patients treated with rimonabant 20 mg reported significantly greater rate of discontinuation due to adverse effects: RR = 1.92, 95% CI 1.57 to 2.34 ($p < 0.00001$). There were no statistically significant differences comparing the results of rimonabant 5 mg with placebo. For the comparison between the two intervention groups patients treated with rimonabant 20 mg also reported significantly greater rate of discontinuation due to adverse effects: RR = 1.58, 95% CI 1.34 to 1.85 ($p < 0.00001$).

Secondary outcomes

Blood pressure change
Comparing rimonabant 20 mg with placebo, the meta-analysis of the included studies, excluding RIO-North America study due to lack of data, showed evidence of an average reduction in systolic and diastolic blood pressure of 1.6 mm Hg (-1.6 WMD, 95% CI -2.6 to -0.6) and 1.2 (-1.2 WMD, 95% CI -1.9 to -0.5) respectively in the rimonabant group. There were no statistically significant differences for the rimonabant 5 mg versus placebo comparison in the same three studies, considering both systolic and diastolic blood pressures.
Comparing the two intervention groups, the pooled data showed heterogeneity ($I^2 = 55.6\%$). We performed sensitivity analysis, but even excluding the RIO-Diabetes study

which was only published as abstract of congress, we could not explain the observed heterogeneity. For this reason the pooled data are not shown.

Lipid Profile change
Serum triglyceride levels were reported in all studies as well as the high density lipoprotein cholesterol and a meta-analysis of these data was carried out.
The pooled data of the all studies showed a significant lowering of plasma triglycerides in the rimonabant 20 mg group compared with placebo of 19.8 mg/dl (-19.8 WMD, 95% CI -24.1 to -15.6; $p < 0.00001$). There was no statistically significant reduction of plasma triglycerides in the rimonabant 5 mg and placebo comparison in three studies (excluding RIO-North America due to lack of data). In the rimonabant 20 mg versus 5 mg comparison the meta-analysis of same three studies showed a statistically significant average reduction of 19.9 mg/dl (-19.9 WMD, 95% CI -25.4 to -14.4; $p < 0.00001$) for the 20 mg group.
For the high density lipoprotein cholesterol analysis, the pooled data of all studies of the rimonabant 20 mg versus placebo comparison showed an increase of 3.5 mg/dl in the rimonabant group (3.5 WMD, 95% CI 3.0 to 4.0). For the rimonabant 5 mg versus placebo comparison, excluding the RIO-North America study, there was an increase of 1.3 mg/dl in the rimonabant group (1.3 WMD, 95% CI 0.3 to 1.9). Comparing the two intervention groups, an average increase of 2.3 mg/dl (2.3 WMD, 95% CI 1.7 to 3.0) was found favouring the rimonabant group. All analyses were statistically significant ($p < 0.00001$).

Health-related quality of life
This was measured in only one study, but the results are not described (RIO-Europe).

Mortality and Costs
No study evaluated mortality or costs as outcome. Even mortality was not described as outcome, the RIO-Lipids study described in the the results session that there were no deaths in any of the three groups. The RIO-Europe mentioned in the results session that two deaths ocurred, one in the placebo group (haemorragic cerebrovascular accident, about 2.5 months after randomisation) and one in the rimonabant 20 mg group (uterine adenocarcinoma 2 months after randomisation). The other two studies did not describe about mortality.

Heterogeneity
Statistical tests for heterogeneity yielded statistically significant results in weight change in the rimonabant 20 mg with placebo comparison, waist circumference change in the rimonabant 20 mg with rimonabant 5 mg comparison and in diastolic blood pressure comparing the two intervention groups. In general the studies seem to be homogeneous, but one of them (RIO-Diabetes) was only published in abstract of congress. This possible source for heterogeneity was investigated in the sensitivity analyses and is described below.

Subgroup analyses
We did not have sufficient data to perform subgroup analyses for weight initial level, age, sex or duration of treatment.

Sensitivity analyses
Since we had statistical heterogeneity for some pooled estimates, we performed sensitivity analyses. Excluding the RIO-Diabetes study, the only which was not published in peer review journal, appeared to eliminate the observed heterogeneity in the weight change outcome for the rimonabant 20 mg versus rimonabant 5 mg comparison. In the other two results with heterogeneity (waist and diastolic blood pressure change in the rimonabant 20 mg versus rimonabant 5 mg comparison), even excluding the same study

we could not explain the found heterogeneity. The studies showed to be similar, and explore the influence of other factors on effect size do not seem appropriate. For this reason, we did not present the pooled data of these analyses.

Assessment of publication bias
Funnel plots were not carried out due to the small number of included studies.

Discussion

Summary
In this systematic review, we found a statistically significant effect of rimonabant on body weight, blood pressure and plasma lipids. Compared with placebo, rimonabant 20 mg produced a 4.9 kg greater reduction in body weight in trials with one-year results. Improvements in waist circumference, high-density lipoprotein cholesterol, triglyceride levels and systolic and diastolic blood pressure also were seen with rimonabant 20 mg. However, the results with rimonabant 5 mg were not the same, and even being statistically significant the weight reduction was only 1.3 kg greater when compared with placebo. No clinically relevant effects on plasma lipids and blood pressure were found with 5 mg. Comparing the two interventions groups the results were similar to the rimonabant 20 mg versus placebo comparison, favouring the first group. Rimonabant 20 mg caused significant more adverse effects both general and serious, especially of nervous system, psychiatric or gastro-intestinal origin.
Although the studies are large trials, we detected deficiencies in the methodological quality of all included studies in this review. Methods for concealing allocation were described in only one study, and the randomisation method was described in only two. Most studies were described as double-blind, but it was unclear which two parties were blinded (patient, treatment administrator or outcome assessor). In spite of the studies reported some deficiencies in the methodological quality, the data were too homogeneous to explore the effects of allocation concealment and blinding on outcomes. Only one study described power calculation analyses, and in the intention-to-treat (ITT) analysis no study described the ITT population. The quality of descriptive information on study population and the intervention were generally adequate.

Comparison with existing literature
Although this is the first systematic review concerning rimonabant in overweight and obesity, some reviews have been published recently (Boyd 2005, Cox 2005, Gelfand 2006, Tonstad 2006). They only focused on describing the clinical results in the published studies. The quality of these reviews is limited: selection criteria for the studies were insufficiently specified and there was no mention to the criteria used to assess the validity of individual trials. Further, these reviews did not present explicit methods on data extraction, assessment of quality or heterogeneity analyses.
Presently the approved anti-obesity pharmacotherapy options are limited to orlistat and sibutramine. Padwal (Padwall 2003) carried out a systematic review and meta-analysis of long term pharmacotherapy for overweight and obesity. Compared with placebo, those receiving orlistat had a 2.7 kg decrease in body weight, and the treatment with sibutramine produced a weight loss of 4.3 kg. Orlistat-treated patients displayed improvements in total cholesterol, low-density lipoprotein cholesterol, blood pressure, and glycemic control but had increased rates of gastrointestinal side effects and slightly lower high-density lipoprotein levels. Sibutramine produced small improvements in high-density lipoprotein cholesterol and triglyceride levels, but was associated with a net increase in blood pressure.
Comparing the results obtained in this review with results of the review evaluating the other two cited drugs it seems that the weight loss associated with Rimonabant use was slightly greater to that related to sibutramine use, with more positive impact on cardiometabolic risk factors. The effects compared with orlistat seem to be greater weight

loss and less frequent adverse effects. However in the rimonabant studies the number of discontinuation due to adverse effects it seems to be greater when compared with orlistat studies. The authors of the rimonabant studies cited that the adverse effects were transient, based on the occurrence in the first months of the study. Although the number of patients discontinuing therapy due to adverse effects is approximately 10% in all studies, high study attrition rates raise the possibility that some of these events remained uncaptured.
Considering the figures presented in all studies related to weight loss change during the entire period, the pattern of weight loss observed seems that approximately after the 36th week, the level of weight loss decrease and the body weight is maintained practically until the end of the studies. The RIO-North America evaluated the data in two years, and the patients who remained on rimonabant 20 mg seem maintained their weight loss, while those who were re-randomised to placebo gained significant weight. Since only RIO-North America has results of two years where the patients were re-randomised after the end of the first year, and the results were only presented as placebo subtracted changes from baseline, we did not include the data of the second year.
Both the American Food and Drugs Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA) demand that any anti-obesity drug should produce significantly greater weight loss compared to placebo. The FDA specifically demands that placebo-subtracted weight loss is at least 5%. Moreover, significantly more individuals in the drug treated group should lose 5% or more of their initial body weight compared to placebo. On the other hand, the EMEA demands a weight loss of at least 10% from baseline, and which is also greater than placebo. The secondary outcome of anti-obesity drug trials is to ensure that this weight loss is sustained and able to induce a significant reduction in risk factors for a number of obesity related co-morbidities. And also, drug induced weight loss should have a positive impact on health related quality of life.
Rimonabant is a not approved drug and more research is necessary for a real evaluation if its efficacy is sustained and if there is any improvement in the heath related quality of life of the evaluated patients.

Strengths of the review
This is the first high-quality systematic review and meta-analysis on the topic of rimonabant related to overweight and obesity. It offers an up-to-date and complete overview of all randomised trials concerning the topic as it is based in an extensive search, including unpublished studies. In addition, maximum efforts have been done to minimise missing or incomplete data by attempting to contact all authors.
Even if this review presents a possibly confusing amount of data and figures, completeness is one of the strengths of a Cochrane systematic review. The way we presented these data, subdivided in subheadings in different tables, makes it possible for the reader to find every specific piece of information obtained from the individuals trials. This review will be regularly updated, allowing eventual addition of information or correction of possible errors.

Limitations of the review
The major methodological limitation of this review could be in all attributed to the quality of the included studies. We observed a high attrition rates in both treatment and placebo groups (almost 50% in all studies). Their authors tried to address this by carrying forward the last observation on record to the end of the study. When the data are analysed in this way, bias results can occur in either direction, depending on the reasons for withdrawal and the differential dropout rates in treatment and placebo groups. If we consider, for example, that patients in the placebo group may drop out of the study early because of weight gain due to lack of efficacy, measuring their weight at the point of withdrawal will likely underestimate their weight at the end of the study period supposing that they should slowly gain weight during the rest of the intervention period. This would underestimate the

degree of weight gain in the placebo group and suggest a falsely lower overall treatment effect. On the other hand, if non-responders in the treatment arm drop out early leaving only responders to complete the trial, the treatment effect may be overestimated. Such high attrition rates are difficult to compensate by any form of analysis. Considerable bias may be introduced into the results of these studies, and should be kept in mind when interpreting the results of this review.
The RIO-North America reported outcomes in a way that could not contribute to meta-analyses. This problem was not solved by asking authors for additional data, because unfortunately we got no answer.
Research funded by pharmaceutical companies could be more likely to produce results favouring the tested drug. Consistent evidence also demonstrated that industry ties are associated with both publication delays and data withholding. These restrictions serve to compound bias in biomedical research. Rather, such behaviour appears to arise when investigators are involved in the process of bringing their research results to market. (Bakelmen 2003). In this review all studies were sponsored by the pharmaceutical company, in which the sponsor was the producer of the evaluated drug. The results should be interpreted with caution since conflict of interests could have influence in the results.
The health related quality of life is an important question that was not considered in the included studies. The effect of treatment on patient-reported outcomes, including any report coming directly from affected persons concerning their life, health conditions and treatment should be considered in clinical trials.
Despite a thorough search, including requests to manufacturers, we still cannot rule out publication bias. The included studies are phase III clinical trials evaluating the effects, tolerability and safety of the rimonabant. Others studies have probably been done primarily to evaluate the effects of the drug in short-time, as cited by one of the authors contacted. We tried to obtain unpublished studies from the manufacturer, but unfortunately we got no answer. Still, we welcome unpublished data for future updates.

Reviewers' conclusions

Implications for practice

This review suggests that the use of rimonabant after one year could produce modest weight loss of approximately 5%. Even modest amounts of weight loss may be potentially beneficial. Some caution with the observed results should be take account since the studies presented some deficiencies in the methodological quality. Studies with follow-up after the end of treatment and more rigorous in the quality of methodology of this new drug should be done before definitive recommendations can be made regarding the role of this medication in the management of obese patients.
Drug therapy should be considered, always associated with non-pharmacological interventions, on an individual basis, with stronger consideration given to those individuals with greater degrees of obesity and associated comorbidities. Efforts focusing on the prevention of obesity in non-obese people and non-pharmacological management in obese people should remain the cornerstone of obesity therapy.

Implications for research

Further high quality research is needed to assess the efficacy and safety of rimonabant over longer follow-up periods. Future adequately-powered trials should incorporate appropriate design principles including methods of allocation concealment, randomization, blinding, minimization of attrition and follow-up of dropouts. Whilst drop-outs and withdrawals can not always be controlled, every effort should be made to ascertain the reasons for withdrawals so that factors affecting adherence can be further elucidated. Future studies should evaluate the use of medication associated with exercise and behavioural modification, identify subgroups of patients that may derive greater benefit from drug therapy, incorporate health-related quality outcome and also assess the

economic cost of treatment.

Acknowledgements
We are grateful to Bernd Richter for his valuable contribution and suggestions for this review

Potential conflict of interest
None Known

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation conceal-ment
RIO-Diabetes	DURATION OF INTERVENTION: 12 months DURATION OF FOLLOW-UP: 0 months RUN-IN PERIOD: 1- ? LANGUAGE OF PUBLICATION: English	WHO PARTCIPATED: INCLUSION CRITERIA: Age: 18-70 years old; BMI of 27 - 40 kg/m2; type 2 diabetes that had been treated with metformin or various sulfonylurea monotherapy for at least 6 months. hemoglobin A1C between 6.5% and 10%, fasting plasma glucose between 100 mg/dL and 271 mg/dL, variation in body weight within the previous three months < 5kg EXCLUSION CRITERIA: ?	NUMBER OF STUDY CENTRES: 151 COUNTRY/LOCATION: USA and 10 other countries (?) SETTING: ? INTERVENTION (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Placebo or Rimonabant 20 mg or Rimonabant 5 mg - daily in addition to a hipocaloric diet	PRIMARY: weight change in 1 year SECONDARY: change in hemoglobin A1C, waist circumference, fasting lipid levels with emphasis on HDL and triglycerides, and change in metabolic syndrome prevalence as defined by the ATP III criteria. TIMING OF OUTCOME MEASURES: body weigh, BP, waist circumference - monthly, the other measures every 3 months ALL-CAUSE MORTALITY: 0 DISEASE SPECIFIC MORTALITY: 0 MORBIDITY/COMPLICATIONS: QUALITY OF LIFE: ADVERSE EFFECTS: 1 COSTS: 0		B
RIO-Europe	DURATION OF INTERVENTION: 12 months DURATION OF FOLLOW-UP: 0 RUN-IN PERIOD: 1 - 4 weeks LANGUAGE OF PUBLICATION: English	WHO PARTCIPATED: INCLUSION CRITERIA: BMI > 30 or 27 with HAS or dyslipidemia patients had less than 5 Kg variation within 3 months before EXCLUSION CRITERIA: clinical disorders (endocrine disease,	NUMBER OF STUDY CENTRES: 60 (40 - Europe and 20 - USA) COUNTRY/LOCATION: Europe and USA SETTING: ? INTERVENTION (ROUTE, TOTAL DOSE/DAY,	PRIMARY: weight change SECONDARY: waist circumference, glucose and insuline in serum when fasting, HDL and TG and the prevalence of metabolic syndrom ADDICIONAL changes in total cholesterol and LDL, changes in insulin resistence		A

		DM, CV, pulmonary, hepatic, renal, neurological, psychological, severe depression); previous history of surgical procedures for weight loss; concomitant use of medications known to alter body weight or appetite was not allowed; marijuana or hashish use. DIAGNOSTIC CRITERIA:	FREQUENCY): Placebo or Rimonabant 20 mg or Rimonabant 5 mg - once/day in addition to a hipocaloric diet and stimulus for exercising	TIMING OF OUTCOME MEASURES: body weight, waist circumference, BP - monthly fasting glucose and insulin - every 3 months other measures - 12 months ALL-CAUSE MORTALITY: 0 DISEASE SPECIFIC MORTALITY: 0 MORBIDITY/COMPLICATIONS: QUALITY OF LIFE: 1, but not analysed ADVERSE EFFECTS: 1 COSTS: 0		
RIO-Lipids	DURATION OF INTERVENTION: 12 months DURATION OF FOLLOW-UP: 0 months RUN-IN PERIOD: 1 LANGUAGE OF PUBLICATION: English	WHO PARTCIPATED: INCLUSION CRITERIA: Age: 18 to 70 years old; BMI of 27 to 40 kg/m2; TG of 1,7 to 7,9 mmol/l Col/HDL >5 (men) and >4,5 (women) variation in body weight within the previous three months < 5kg EXCLUSION CRITERIA: * DIAGNOSTIC CRITERIA:	NUMBER OF STUDY CENTRES: 67 COUNTRY/LOCATION: 8 countries - ? SETTING: ? INTERVENTION (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Placebo or Rimonabant 20 mg or Rimonabant 5 mg - daily in addition to a hipocaloric diet	PRIMARY: weight change SECONDARY: changes in HDL, TG, Glucose and insulin during an oral glucose-tolerance test and the prevalence of metabolic syndrom ADDITIONAL: waist circumference, leptin and adiponectin levels and relevant biochemical CV markers TIMING OF OUTCOME MEASURES: body weigh, BP, waist circumference - monthly, the other measures only 12 months ALL-CAUSE MORTALITY: 0 DISEASE SPECIFIC MORTALITY: 0 MORBIDITY/COMPLICATIONS: QUALITY OF LIFE: ADVERSE EFFECTS: 1 COSTS: 0		B
* history of pharmacologic treatment for dyslipidemia 6 weeks before or treatment with VLCD 6 months before; DM (1 and 2); clinically significant findings indicating CV, endocrine, pulmonary, neurologic, psychiatric, gastrointestinal, hepatic, hematologic, renal or dermatologic disease; + test for hepatitis B surface antigen or hepatitis C antibody, abnormal thyrotropin level; levels of alanine aminotransferase or aspartate aminotransferase > 2,5 timesthe upper limit; hemoglobin levels < 11g/dl; neutrophil levels < 1500 ml3; platelet levels < 100,000 ml3; creatinine levels > 150mmol/l; a history of marijuana or hashish use; severe depression; treatment for epilepsy, an eating disorder; malignant disease; BP > than 165 or 105 mm Hg; pregnancy; or lactation; < 80% compliance with a hypocaloric diet and placebo during the post-screening four week single blind run in period.						
RIO-North America	DURATION OF INTERVENTION: 24 months DURATION OF FOLLOW-UP: 0 RUN-IN PERIOD:	WHO PARTCIPATED: INCLUSION CRITERIA: 18 years or older; BMI of 30 or 27 with treated or untreated dyslipidemia or hypertension	NUMBER OF STUDY CENTRES: 72 (64 - USA and 8 - Canada) COUNTRY/LOCATION: USA and Canada	PRIMARY: weight change in 1 year prevention of weight regain between the first and second years SECONDARY: changes in HDL in 1 year and the prevalence of metabolic syndrom		B

	1 - 4 weeks LANGUAGE OF PUBLICATION: English	EXCLUSION CRITERIA: weight fluctuation of more than 5 Kg in the previous 3 months; clinically significant cardiac, renal, hepatic, gastrointestinal tract, neuropsychiatric or endocrine disorders, drug-treated or diagnosed type 1 or 2 DM, use of medications that alter body weight or appetite, a history of current substance abuse; changes in smoking habits or smoking cessation within the past 6 months DIAGNOSTIC CRITERIA:	SETTING: INTERVENTION (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Placebo or Rimonabant 20 mg or Rimonabant 5 mg - once/day in addition to a hipocaloric diet and stimulus for exercising	ADDITIONAL: changes in BP, levels of glucose and insulin, lipids, and insulin resistence TIMING OF OUTCOME MEASURES: in the end of year 1 and 2 ALL-CAUSE MORTALITY. 0 DISEASE SPECIFIC MORTALITY: 0 MORBIDITY/COMPLICATIONS: QUALITY OF LIFE: 0 ADVERSE EFFECTS: 1 COSTS: 0		

Characteristics of ongoing studies

Study	Trial name or title	Participants	Interventions	Outcomes	Starting date	Contact information	Notes
STRADIVARIUS	STRADIVARIUS (Strategy To Reduce Atherosclerosis Development InVolving Administration of Rimonabant - the Intravascular Ultrasound Study)	Ages Eligible for Study: 18 Years and above, Genders Eligible for Study: Both Criteria Inclusion **	Study Type: Interventional Study Design: Treatment, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Safety/Efficacy Study	Inhibition of Atherosclerosis Progression Assessed by IVUS (IntraVascular UltraSounds)	Study start: January 2005; Study completion: August 2007	Sponsored by: Sanofi-Aventis Information provided by: Sanofi-Aventis ClinicalTrials.gov Identifier: NCT00124332	Data from "www.clinicaltrials.gov" The purpose of this study is to determine if rimonabant 20 mg administered during 18-20 months will reduce progression of coronary atherosclerosis as assessed by (IVUS) when administered on top of standard behavioral and pharmacological therapy, in patients with abdominal obesity associated with current smoking and/or metabolic syndrome. Study ID Numbers: EFC5827; SR141716 Location Information - Ohio: The Cleveland Clinic Foundation, Cleveland, Ohio, 44195, United States This study is no longer recruiting patients.

** Inclusion Criteria:
Written and signed informed consent
Indication for coronary angiography
Abdominal obesity defined by waist circumference > 88 cm in women or > 102 cm in men
At least one of the two following conditions: *a) Metabolic syndrome as defined by the presence of at least two of the following additional risk factors: 1. Triglyceride level >= 150 mg/dL (1.69 mmol/L); 2. HDL cholesterol < 40 mg/dL (1.03 mmol/L) [men] or 50 mg/dL (1.28 mmol/L) [women]; 3. Fasting glucose >= 110 mg/dL (6.1 mmol/L); 4. High blood pressure (>= 140 mmHg systolic and/or >= 90 mmHg diastolic) at Screening visit, or current treatment by anti-hypertensive medication; *b) Currently smoking (> 10 cigarettes /day) and willing to stop
Angiographic evidence of coronary heart disease as defined by at least 1 lesion in a native coronary artery that has >= 20% reduction in lumen diameter by angiographic visual estimation
Presence of at least one coronary artery complying with the definition of “target vessel” for IVUS assessment
Acceptation of the Baseline IVUS tape by the IVUS Core Laboratory
Exclusion Criteria:
Age < 18 years
Pregnant or breast-feeding women
History of very low-calorie diet or surgical procedures for weight loss (eg, stomach stapling, bypass) within 6 months prior to screening visit
Obesity of known endocrine origin
Uncontrolled diabetes with HBA1c >10%
Presence of any severe medical or psychological condition, that in the opinion of the Investigator would compromise the subject’s safety or successful participation in the study
Severe congestive heart failure (New York Heart Association [NYHA] Class III or IV)
Clinically significant heart disease which in the opinion of the Investigator is likely to require coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), cardiac transplantation, surgical repair and/or replacement during the course of the study
Angioplasty of a non-qualifying artery which is considered at high risk of acute complication or restenosis, during baseline catheterization
>50% reduction in lumen diameter of the left main coronary artery by visual angiographic estimation
Recent ST-elevation myocardial infarction (MI) <= 72 hours prior to randomization

References to studies

References to included studies

RIO-Diabetes {unpublished data only}

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RIO-North America {published data only}

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References to ongoing studies

STRADIVARIUS {published data only}

** indicates the primary reference for the study*

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Other references

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Additional tables

01 Search Strategy in MEDLINE

Obesity 1. exp Obesity/ 2. exp Weight Gain/ 3. exp Weight Loss/ 4. body mass index/ 5. (overweight or over weight).tw. 6. fat overload syndrom$.tw. 7. (overeat or over eat).tw. 8. (overfeed or over feed).tw. 9. (adipos$ or obes$).tw. 10. (weight adj (cyc$ or reduc$ or los$ or maint$ or decreas$ or watch$ or control$ or gain or chang$)).tw. 11. body mass inde$.tw. 12. or/1-11 Rimonabant 13. rimonabant.tw. 14. SR141716A.ti,ab. 15. acomplia.tw. 16. 13 or 14 or 15 Obesity and Rimonabant 17. 12 and 16 Controlled Clinical Trials 18. limit 17 to humans [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained] 19. randomized controlled trial.pt. 20. controlled clinical trial.pt. 21. randomized controlled trials.sh. 22. random allocation.sh. 23. double-blind method.sh. 24. single-blind method.sh. 25. or/19-24 26. limit 25 to animal 27. limit 25 to human [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained] 28. 26 not 27 29. 25 not 28 30. clinical trial.pt.

31. exp clinical trials/
32. (clinic$ adj25 trial$).tw.
33. ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
34. placebos.sh.
35. placebo$.tw.
36. random$.tw.
37. research design.sh.
38. (latin adj square).tw.
39. or/30-38
40. limit 39 to animal
41. limit 39 to human [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]
42. 40 not 41
43. 39 not 42
44. comparative study.sh.
45. exp evaluation studies/
46. follow-up studies.sh.
47. prospective studies.sh.
48. (control$ or prospectiv$ or volunteer$).tw.
49. cross-over studies.sh.
50. or/ 44-49
51. limit 50 to animal
52. limit 50 to human [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]
53. 51 not 52
54. 50 not 53
55. 29 or 43 or 54

Obesity and Rimonabant and Controlled Clinical Trials
56.18 and 55

02 Study quality (included studies)

Characteristic	**RIO-Lipids**	**RIO-Europe**	**RIO-North America**	**RIO-Diabetes**
Randomised controlled clinical trial	Y	Y	Y	Y
Non-inferiority / equivalence trial	N	N	N	N
Controlled clinical trial	NA	NA	NA	NA
Design: Parallel study	Y	Y	Y	Y
Design: Crossover study	NA	NA	NA	NA
Design: Factorial study	N	N	N	N
Crossover study: Wash-out phase	NA	NA	NA	NA
Crossover study: Carryover effect tested	NA	NA	NA	NA
Crossover study: Period effect tested	NA	NA	NA	NA
Method of randomisation	?	Y	Y	?
Unit of randomisation (individuals,	?	individuals	individuals	?

cluster - specify)				
Randomisation stratified for centres	?	?	Y	?
Concealment of allocation	double	double	double	double
Stated blinding (open; single, double, triple blind)	?	?	?	?
Actual blinding: Patient	?	?	?	?
Actual blinding: Carer / treatment administrator	?	?	?	?
Actual blinding: Outcome assessor	?	?	?	?
Actual blinding: Others	?	?	?	?
Blinding checked: Patient	?	?	?	?
Blinding checked: Carer / treatment administrator	?	?	?	?
Primary endpoint defined (power calculation)	?	?	Y	?
Total number of outcomes	22	12	10	6
Prior publication on design of study	N	N	N	N
Outcomes of prior / current publication identical	N	N	N	N
Power calculation	?	?	Y	?
[n] patients per group calculated	?	?	Y	?
Non-inferiority trial: Interval for equivalence specified	NA	NA	NA	NA
Intention-to-treat analysis	Y	Y	Y	Y
Per-protocol-analysis	?	?	?	?
Analysis stratified for centres	N	N	N	N
Missing data: Last-observation-carried-forward (LOCF)	Y	Y	Y	Y
Missing data: Other methods	N	N	Y: baseline imputed	N
Treatment Y (T1) / treatment 2 (T2) / control Y (C1)				
[n] of screened patients (T1/ T2 / C1 / total)	?	2168	4604	?
[n] of eligible patients (T1/ T2 / C1 / total)	?	1676	3500	?
[n] of randomised patients (T1/ T2 / C1 / total)	346 / 345 / 342 / 1033	599 / 603 / 305 / 1507	1222 / 1216 / 607 / 3045	339 / 358 / 348 / 1045
[n] of patients finishing the study (T1/ T2 / C1 / total)	221 / 208 / 214 / 643	363 / 379 / 178 / 920	673 / 620 / 309 / 1602	?
[n] of ITT patients (T1/ T2 / C1 / total)	344 / 340 / 334 / 1018	599 / 603 / 305 / 1507	1189 / 1191 / 590 / 2970	339 / 358 / 348 / 1045
[n] of patients analysed (T1/ T2 / C1 / total)	344 / 340 / 334 / 1018	599 / 603 / 305 / 1507	1189 / 1191 / 590 / 2970	339 / 358 / 348 / 1045

Drop-outs described	Y	Y	Y	N
Withdrawals described	Y	Y	Y	N
Losses-to-follow-up described	Y	Y	Y	N
[n] of drop-outs (T1/ T2 / C1 / total)	125 / 137 / 128 / 390	236 / 224 / 127 / 587	549 / 596 / 298 / 1443	?
[%] attrition rate (T1/ T2 / C1 / total)				
Differences to [n] / power calculation	?	?	?	?
[n] of subgroups				
Subgroups: Pre-defined				
Subgroups: Post-hoc				
Adjustment for multiple outcomes / repeated measurements	Y	Y	Y	
Baseline characteristics: Clinically relevant differences	N	N	N	N
Treatment identical (apart from intervention)	Y	Y	Y	Y
Timing of outcomes' measurement comparable between groups	Y	Y	Y	Y
Compliance measured	?	?	?	?
Other important covariates measured				
Co-morbidities measured				
Co-medications measured	Y	?	?	?
Specific doubts about study quality				
Funding: Commercial	Y	Y	Y	Y
Funding: Non-commercial	N	N	N	N
Publication status: Peer review journal	Y	Y	Y	N
Publication status: Journal supplement	N	N	N	N
Publication status: Abstract	N	N	N	N
Publication status: Other	N	N	N	Y: presentation in congress
Notes				
Symbols: yes=Y; no=N; unclear=?				
Abbreviations: T=treatment; C=control				

03 Baseline characteristics (included studies)

Characteristic	**RIO-Lipids**	**RIO-Europe**	**RIO-North America**	**RIO-Diabetes**
[n] (T1/ T2 / C1 / total)	346 / 345 / 342 / 1033	599 / 603 / 305 / 1507	1219 / 1214 / 607 / 3040	339 / 358 / 348 / 1045
Sex [n,%] (T1/ T2 / C1 / total)	T1 M - 133, 38.4%, F - 213, 61.6%	T1 M - 121, 20.2%, F - 478, 79.8%	T1 M - 230, 18.9%, F - 989, 81.1%	T1 M - 169, 50%, F - 170,

	T2 M - 130, 37.7%, F - 215, 62.3% C M - 144, 42.1%; F - 198, 57.9%	T2 M - 127, 21.1%, F - 476, 78.9% C M - 61, 20%; F - 244, 80%	T2 M - 245, 20.2%, F - 969, 79.8% C M - 113, 18.6%; F - 494, 81.4%	50% T2 M - 172, 48%, F - 186, 52% C M - 188, 54%; F - 160, 46%"
Age, years [mean,SD] (T1/ T2 / C1 / total)	T1 48,4 (10,0) T2 48,1 (10,2) C 47,0 (10,1)"	T1 44,6 (11,9) T2 45,4 (11,2) C 45,0 (11,6)	T1 45,6 (11,8) T2 44,4 (11,3) C 44,8 (11,6)	T1 56,0 (8,5) T2 55,9 (8,6) C 54,8 (8,6)
Ethnic groups (T1/ T2 / C1 / total)	?	T1 white 555 (92,7%) T2 white 565 (93,7%) C1 white 290 (95,1%)	T1 white 1027 (84.2%) black 132 (10,8%) T2 white 1010 (11,5%) black 140 (11,5%) C1 white 516 (85,0%) black 67 (11.0%)"	T1 caucasian 302 (89,1%) T2 caucasian 315 (88,0%) C1 caucasian 308 (88,5%)"
Duration of disease [mean,SD] (T1/ T2 / C1 / total)	?	?	?	?
Weigh [mean,SD] (T1/ T2 / C1 / total)	T1 - 95.3 (15.1) T2 - 96.0 (14.6) C - 97.0 (15.4)	T1 - 101.7 (19.5)T2 - 100.9 (19.8)C - 100.0 (20.3)	T1 - 103.0 (20.3) T2 - 105.5 (21.9) C - 105.0 (21.8)	?
Body mass index [mean,SD] (T1/ T2 / C1 / total)	T1 - 33.9 (3.3) T2 - 34.1 (3.5) C - 34.0 (3.5)	T1 - 36,0 (5,8) T2 - 36,0 (5,9) C - 35,7 (5,9)	T1 - 37.2 (6.2) T2 - 38.0 (6.7) C - 37.6 (6.4)	T1 - 34.1 (3.6) T2 - 34.4 (3.6) C - 34.2 (3.6)
Pharmaco-naive patients [n,%] (T1/ T2 / C1 / total)	NA	NA	NA	NA
Co-morbidity (T1/ T2 / C1 / total)	Metabolic syndrom T1 - 183 (52,9%) T2 - 193 (55,9%) C - 178 (51,9%)	Metabolic syndrom T1 - 251 (42,4%) T2 - 243 (40,8%) C - 121 (40,6%) Hypertension T1 - 237 (39,6%) T2 - 264 (43,8%) C - 116 (38,0%)	Metabolic syndrom T1 - 419 (34,6%) T2 - 438 (36,3%) C - 192 (31,8%) Hypertension T1 - 390 (32,0%) T2 - 367 (30,2%) C - 168 (63,9%)	Metabolic syndrom T1 - 269 (79,2%) T2 - 285 (79,5%) C - 276 (79,2%) Hypertension T1 - 216 (63,7%) T2 - 218 (60.9%) C - 206 (59,2%)
Co-medication (T1/ T2 / C1 / total)	?	?	?	Anti-diabetic treatment Metformin T1 - 218 (64,3%) T2 - 230 (64,2%) C - 230 (66,1%) Sulfonylureas T1 - 121 (35,7%) T2 - 128 (35.8%) C - 118 (33,9%)
HbA1c [mean,SD] (T1/ T2 / C1 / total)	NA	NA	NA	NA
Smoker status	T1 - 53 (15,3%) T2 - 58 (16,8%) C - 61 (17,8%)	T1 - 102 (17,0%) T2 - 136 (22,6%) C - 60 (19,7%)	T1 - 118 (9,7%) T2 - 102 (8,4%) C - 64 (10,5%)	?
Blood pressure systolic	T1 - 124.9 (12.7)	T1 - 127.0 (14.1)	T1 - 121.7 (12.7)	?

mm Hg [mean,SD] (T1/ T2 / C1 / total)	T2 - 123.8 (13.5) C - 124.0 (13.8)	T2 - 127.0 (14.8) C - 126.0 (13.7)	T2 - 121.9 (12.7) C - 121.7 (12.4)	
Blood pressure diastolic mm Hg [mean,SD] (T1/ T2 / C1 / total)	T1 - 78.2 (7.7) T2 - 78.1 (8.9)C - 78.2 (8.4)	T1 - 79.4 (8.8) T2 - 79.6 (9.1) C - 79.6 (8.5)	T1 - 77.7 (8.2) T2 - 78.2 (8.1) C - 78.1 (7.8)	?
Note				
Symbols: unclear=?				
Abbreviations: T=treatment; C=control; NA=not applied				

04 Adverse events (included studies)

Characteristic	RIO-Lipids	RIO-Europe	RIO-North America	RIO-Diabetes
[n] adverse events (T1/ T2 / C1 / total)	407 / 367 / 340 / 1114	522 / 498 / 257 / 1277	1042 / 1013 / 498 / 2553	288 / 293 / 276 / 857
[%] adverse events (T1/ T2 / C1 / total)	117.6 / 106.4 / 99.4 / 107.8	87.1 / 82.6 / 84.3 / 84.7	85.5 / 83.4 / 82.0 / 84.0	85 / 81.8 / 79.3 / 82
[n] nausea (T1/ T2 / C1 / total)	44/ 25 / 11 / 80	77 / 31 / 13 / 121	117 / 69 / 29 / 215	41 / 22 / 20 / 83
[%] nausea (T1/ T2 / C1 / total)	12.7 / 7.2 / 3.2 / 7.7	12.9 / 5.1 / 4.3 / 8.0	11.2 / 6.8 / 5.8 / 7.1	12.1 / 6.1 / 5.7 / 7.9
[n] dizziness (T1/ T2 / C1 / total)	36 / 29 / 23 / 88	52 / 42 / 15 / 109	58 / 46 / 20 / 114	31 / 11 / 17 / 59
[%] dizziness (T1/ T2 / C1 / total)	10.4 / 8.4 / 6.7 / 8.5	8.7 / 7.0 / 4.9 / 7.2	5.6 / 4.5 / 4.0 / 4.1	9.1 / 3.1 / 4.9 / 5.6
[n] serious adverse events (T1/ T2 / C1 / total)	15 / 19 / 10 / 44	52 / 45 / 23 / 120	55 / 46 / 21 / 122	27 / 27 / 15 / 69
[%] serious adverse events (T1/ T2 / C1 / total)	4.3 / 5.5 / 2.9 / 4.3	8.7 / 7.5 / 7.5 / 8.0	4.5 / 3.8 / 3.5 / 4.0	8.0 / 7.5 / 4.3 / 6.6
[n] psychiatric disorders (T1/ T2 / C1 / total)	1/ 1 / 1 / 3	9 / 2 / 1 / 12	76 / 44 / 14 / 134	?
[%] psychiatric disorders (T1/ T2 / C1 / total)	0.3 / 0.3 / 0.3 / 0.3	1.5 / 0.3 / 0.3 / 0.8	6.2 / 3.6 / 2.3 / 4.4	?
[n] nervous system disorders (T1/ T2 / C1 / total)	2 / 0 / 2 / 4	3 / 7 / 3 / 13	27 / 14 / 6 / 47	?
[%] nervous system disorders (T1/ T2 / C1 / total)	0.6 / 0 / 0.6 / 0.4	0.5 / 1.2 / 1.0 / 0.9	2.2 / 1.2 / 1.0 / 1.6	?
[n] neoplasms (T1/ T2 / C1 / total)	2 / 3 / 0 / 5	7 / 5 / 2 / 14	?	?
[%] neoplasms (T1/ T2 / C1 / total)	0.6 / 0.9 / 0 / 0.5	1.2 / 0.8 / 0.7 / 0.9	?	?
[n] discontinuation due to adverse events (T1/ T2 / C1 / total)	52 / 29 / 24 / 105	87 / 50 / 28 / 165	156 / 114 / 44 / 314	51 / 28 / 19 / 98
[%] discontinuation due to adverse events (T1/ T2 / C1 / total)	15.0 / 8.4 / 7.0 / 10.2	14.5 / 8.3 / 9.2 / 10.9	12.8 / 9.4 / 7.2 / 10.3	15.0 / 7.8 / 5.5 / 9.4
[n] hospitalisation (T1/ T2 / C1 / total)	?	?	?	?
[%] hospitalisation (T1/ T2 / C1 / total)	?	?	?	?
[n] out-patient treatment (T1/ T2 / C1 / total)	NA	NA	NA	NA

[%] out-patient treatment (T1/ T2 / C1 / total)	NA	NA	NA	NA
[n] hypoglycaemic episodes (T1/ T2 / C1 / total)	NA	NA	NA	NA
[%] hypoglycaemic episodes (T1/ T2 / C1 / total)	NA	NA	NA	NA
[n] severe hypoglycaemic episodes (T1/ T2 / C1 / total)	NA	NA	NA	NA
[%] severe hypoglycaemic episodes (T1/ T2 / C1 / total)	NA	NA	NA	NA
[n] nocturnal hypoglycaemic episodes (T1/ T2 / C1 / total)	NA	NA	NA	NA
[%] nocturnal hypoglycaemic episodes (T1/ T2 / C1 / total)	NA	NA	NA	NA
[n] with symptoms (T1/ T2 / C1 / total)	NA	NA	NA	NA
[%] with symptoms (T1/ T2 / C1 / total)	NA	NA	NA	NA
Notes				
Symbols: unclear=?				
Abbreviations: T=treatment, C=control				

05 Primary outcome data (included studies)

Characteristic	**RIO-Lipids**	**RIO-Europe**	**RIO-North America**	**RIO-Diabetes**
Weight change [mean,SD] (T1/ T2 / C1 / total)	T1 -6.9 (6.1) T2 -3.1 (4.8) C -1.5 (5.0)	T1 -6.6 (7.2) T2 -3.4 (5.7) C -1.8 (6.4)	T1 -6.3 (?) T2 -2.9 (?) C -1.6 (?)	T1 -5.3 (0.3) T2 -2.3 (0.2) C -1.4 (0.2)
Waist circumference change [mean,SD] (T1/ T2 / C1 / total)	T1 -7.1 (6.8) T2 -3.5 (6.0) C -2.4 (5.7)	T1 -6.5 (7.4) T2 -3.9 (6.3) C -2.4 (6.9)	T1 -6.1 (?) T2 -3.1 (?) C -2.5 (?)	T1 -5.2 (0.3) T2 -2.9 (0.3) C -1.9 (0.3)
Adverse effects - see under Additional table - Table xx				
Symbols: unclear=?				
Abbreviations: T=treatment; C=control				

06 Secondary outcome data (included studies)

Characteristic	**RIO-Lipids**	**RIO-Europe**	**RIO-North America**	**RIO-Diabetes**
Total cholesterol / HDL ratio change [mean,SD] (T1/ T2 / C1 / total)	T1 -0.72 (0.93) T2 -0.47 (0.82) C -0.40 (0.90)	T1 -0.71 (0.78) T2 -0.52 (0.80) C -0.42 (0.83)	?	?
Triglycerides change [mean,SD] (T1/ T2 / C1 / total)	T1 -12.6 (41.2) T2 +1.2 (39.4) C -0.2 (38.7)	T1 -0.20 (0.64) T2 -0.02 (0.77) C -0.20 (0.64)	T1 -5.3 (?) T2 -3.7 (?) C +7.9 (?)	T1 -31.0 (113.0) T2 -1.0 (70.0) C +4.0 (77.0)
HDL change [mean,SD] (T1/ T2 / C1 / total)	T1 +19.1 (20.9) T2 +14.2 (17.6) C +11.0 (15.8)	T1 +0.26 (0.26) T2 +0.19 (0.23) C +0.15 (0.23)	T1 +12.6 (?) T2 +7.6 (?) C +5.4 (?)	T1 +6.0 (8.0) T2 +4.0 (7.0) C +3.0 (6.0)
LDL change	T1 +7.2 (28.4)	T1 +0.08 (0.63)	?	?

[mean,SD] (T1/ T2 / C1 / total)	T2 +6.6 (21.4) C +7.0 (22.4)	T2 +0.13 (0.62) C +0.17 (0.70)		
Blood pressure systolic change [mean,SD] (T1/ T2 / C1 / total)	T1 -2.1 (12.3) T2 -0.4 (11.8) C -0.3 (10.1)	T1 -1.0 (12.5) T2 -0.9 (12.5) C -0.3 (12.3)	?	T1 -0.8 (12.8) T2 -0.4 (12.9) C +1.6 (13.2)
Blood pressure diastolic change [mean,SD] (T1/ T2 / C1 / total)	T1 -1.7 (8.5) T2 -0.1 (8.3) C -0.2 (7.4)	T1 -0.9 (8.7) T2 -0.8 (8.8) C -0.1 (8.5)	?	T1 -1.9 (8.2) T2 -0.4 (8.5) C -0.7 (8.4)
Notes	results by LOCF	results by LOCF	results published as placebo subtract changes frm baseline for 1 year, this results were obtained from results published in American Hearth Association 2004 Scientific Sessions - http://www.medscape.com/viewarticle/493901	
Symbols: unclear=?				
Abbreviations: T=treatment; C=control				

07 Changes from the published protocol

Important changes
1) In the protocol quality assessment according to the criteria by Schulz and Jadad were planned. We did not persue bias categorisation but preferred an individual component analysis approach instead.

Additional figures

Figure 01

QUOROM (quality of reporting of meta-analyses) flow chart for study selection

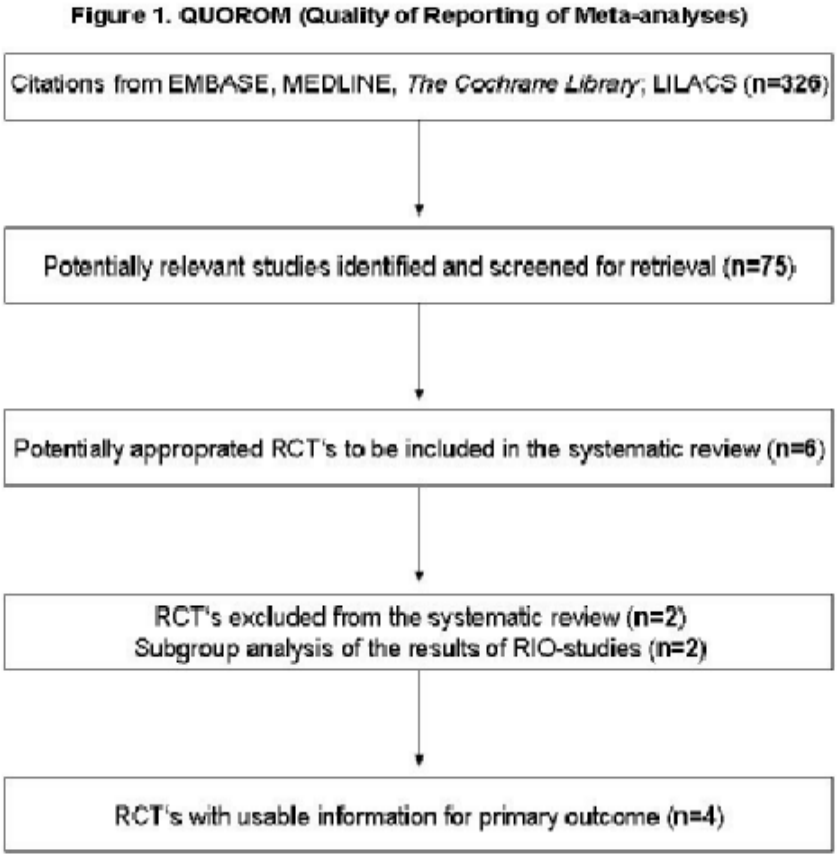


Table of comparisons

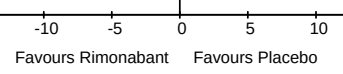
Comparision or outcome	Studies	Participants	Statistical method	Effect size
01 Rimonabant 20 mg vs placebo (after one year)				
01 Weight [kg] change	3	3418	WMD (fixed), 95% CI	-4.89 [-5.30, -4.48]
02 Waist circumference [cm] change	4	4105	WMD (fixed), 95% CI	-3.84 [-4.26, -3.42]
03 Adverse effects (general)	3	3417	RR (fixed), 95% CI	1.05 [1.01, 1.08]
04 Adverse effects (serious)	4	4105	RR (fixed), 95% CI	1.37 [1.04, 1.80]
05 Systolic blood pressure [mmHg] change	3	2279	WMD (fixed), 95% CI	-1.57 [-2.59, -0.55]
06 Diastolic blood pressure [mmHg] change	3	2279	WMD (fixed), 95% CI	-1.16 [-1.86, -0.47]
07 Triglycerides levels [mg/dl] change	4	4105	WMD (fixed), 95% CI	-19.82 [-24.10, -15.55]
08 High-density lipoprotein [mg/dl] change	4	4105	WMD (fixed), 95% CI	3.51 [2.99, 4.04]
09 discontinuation due to adverse events	4	4105	RR (fixed), 95% CI	1.92 [1.57, 2.34]
02 Rimonabant 5 mg vs Placebo (after one year)				
01 Weight [kg] change	3	2301	WMD (fixed), 95% CI	-1.25 [-1.64, -0.86]
02 Waist circumference [cm] change	3	2301	WMD (fixed), 95% CI	-1.18 [-1.69, -0.68]
03 Adverse effects (general)	3	3435	RR (fixed), 95% CI	1.01 [0.98, 1.04]
04 Adverse effects (serious)	4	4122	OR (fixed), 95% CI	1.29 [0.96, 1.73]
05 Systolic blood pressure [mmHg] change	3	2301	WMD (fixed), 95% CI	-0.79 [-1.80, 0.21]
06 Diastolic blood pressure [mmHg] change	3	2301	WMD (fixed), 95% CI	-0.11 [-0.81, 0.58]
07 Triglycerides levels [mg/dl] change	3	2301	WMD (fixed), 95% CI	-2.31 [-8.04, 3.42]
08 High-density lipoprotein [mg/dl] change	3	2301	WMD (fixed), 95% CI	1.26 [0.64, 1.88]
09 Discontinuation due to adverse events	4	4122	OR (fixed), 95% CI	1.21 [0.96, 1.53]
03 Rimonabant 20 mg vs Rimonabant 5 mg (after one year)				
01 Weight [kg] change	3	2590	WMD (fixed), 95% CI	-3.29 [-3.72, -2.86]
02 Waist circumference [kg] change			WMD (fixed), 95% CI	No total
03 Adverse effects (general)	3	4332	RR (fixed), 95% CI	1.04 [1.01, 1.06]
04 Adverse effects (serious)	4	5023	RR (fixed), 95% CI	1.10 [0.88, 1.38]
05 Systolic blood pressure [mmHg] change	3	2590	WMD (fixed), 95% CI	-0.63 [-1.59, 0.33]
06 Diastolic blood pressure [mmHg] change			WMD (fixed), 95% CI	No total
07 Triglycerides levels [mg/dl] change	3	2590	WMD (fixed), 95% CI	-19.89 [-25.37, -14.40]
08 High-density lipoprotein [mg/dl] change	3	2590	WMD (fixed), 95% CI	2.31 [1.65, 2.96]
09 Discontinuation due to adverse events	4	5023	RR (fixed), 95% CI	1.58 [1.34, 1.85]

Rimonabant 20 mg vs. Placebo

Review: Rimonabant for overweight or obesity
Comparison: 01 Rimonabant 20 mg vs placebo (after one year)
Outcome: 01 Weight [kg] change

Study or sub-category	Rimonabant 20 mg N	Rimonabant 20 mg Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
RIO-Europe	599	-6.60(7.20)	305	-1.80(6.40)		20.03	-4.80 [-5.72, -3.88]
RIO-Lipids	346	-6.90(6.10)	342	-1.50(5.00)		24.49	-5.40 [-6.23, -4.57]
RIO-North America	1219	-6.30(7.00)	607	-1.60(4.90)		55.47	-4.70 [-5.25, -4.15]
Total (95% CI)	2164		1254			100.00	-4.89 [-5.30, -4.48]

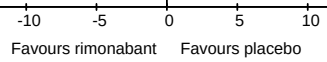
Test for heterogeneity: Chi² = 1.93, df = 2 (P = 0.38), I² = 0%
Test for overall effect: Z = 23.26 (P < 0.00001)



Review: Rimonabant for overweight or obesity
Comparison: 01 Rimonabant 20 mg vs placebo (after one year)
Outcome: 02 Waist circumference [cm] change

Study or sub-category	Rimonabant 20 mg N	Rimonabant 20 mg Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
RIO-Diabetes	339	-5.20(5.50)	348	-1.90(5.60)		25.75	-3.30 [-4.13, -2.47]
RIO-Europe	599	-6.50(7.40)	305	-2.40(6.90)		18.65	-4.10 [-5.08, -3.12]
RIO-Lipids	346	-7.10(6.80)	342	-2.40(5.70)		20.19	-4.70 [-5.64, -3.76]
RIO-North America	1219	-6.10(7.00)	607	-2.50(7.40)		35.41	-3.60 [-4.31, -2.89]
Total (95% CI)	2503		1602			100.00	-3.84 [-4.26, -3.42]

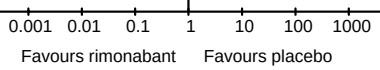
Test for heterogeneity: Chi² = 5.58, df = 3 (P = 0.13), I² = 46.2%
Test for overall effect: Z = 17.86 (P < 0.00001)



Review: Rimonabant for overweight or obesity
Comparison: 01 Rimonabant 20 mg vs placebo (after one year)
Outcome: 03 Adverse effects (general)

Study or sub-category	Rimonabant 20 mg n/N	Placebo n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
RIO-Diabetes	288/339	276/348		21.32	1.07 [1.00, 1.15]
RIO-Europe	522/599	257/305		26.65	1.03 [0.98, 1.10]
RIO-North America	1042/1219	498/607		52.03	1.04 [1.00, 1.09]
Total (95% CI)	2157	1260		100.00	1.05 [1.01, 1.08]

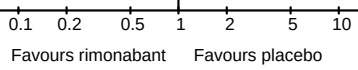
Total events: 1852 (Rimonabant 20 mg), 1031 (Placebo)
Test for heterogeneity: Chi² = 0.63, df = 2 (P = 0.73), I² = 0%
Test for overall effect: Z = 2.83 (P = 0.005)



Review: Rimonabant for overweight or obesity
Comparison: 01 Rimonabant 20 mg vs placebo (after one year)
Outcome: 04 Adverse effects (serious)

Study or sub-category	Rimonabant 20 mg n/N	Placebo n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
RIO-Diabetes	27/339	15/348		17.75	1.85 [1.00, 3.41]
RIO-Europe	52/599	23/305		36.56	1.15 [0.72, 1.84]
RIO-Lipids	15/346	10/342		12.06	1.48 [0.68, 3.25]
RIO-North America	55/1219	21/607		33.63	1.30 [0.80, 2.14]
Total (95% CI)	2503	1602		100.00	1.37 [1.04, 1.80]

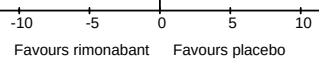
Total events: 149 (Rimonabant 20 mg), 69 (Placebo)
Test for heterogeneity: Chi² = 1.51, df = 3 (P = 0.68), I² = 0%
Test for overall effect: Z = 2.20 (P = 0.03)



Review: Rimonabant for overweight or obesity
Comparison: 01 Rimonabant 20 mg vs placebo (after one year)
Outcome: 05 Systolic blood pressure [mmHg] change

Study or sub-category	Rimonabant 20 mg N	Rimonabant 20 mg Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
RIO-Diabetes	339	-0.80(12.80)	348	1.60(13.20)		27.49	-2.40 [-4.34, -0.46]
RIO-Europe	599	-1.00(12.50)	305	-0.30(12.30)		35.74	-0.70 [-2.41, 1.01]
RIO-Lipids	346	-2.10(12.30)	342	-0.30(10.10)		36.77	-1.80 [-3.48, -0.12]
Total (95% CI)	1284		995			100.00	-1.57 [-2.59, -0.55]

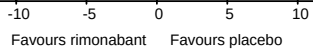
Test for heterogeneity: Chi² = 1.77, df = 2 (P = 0.41), I² = 0%
Test for overall effect: Z = 3.02 (P = 0.003)



Review: Rimonabant for overweight or obesity
Comparison: 01 Rimonabant 20 mg vs placebo (after one year)
Outcome: 06 Diastolic blood pressure [mmHg] change

Study or sub-category	Rimonabant 20 mg N	Rimonabant 20 mg Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
RIO-Diabetes	339	-1.90(8.20)	348	-0.70(8.40)		31.33	-1.20 [-2.44, 0.04]
RIO-Europe	599	-0.90(8.70)	305	-0.10(8.50)		34.60	-0.80 [-1.98, 0.38]
RIO-Lipids	346	-1.70(8.50)	342	-0.20(7.40)		34.07	-1.50 [-2.69, -0.31]
Total (95% CI)	1284		995			100.00	-1.16 [-1.86, -0.47]

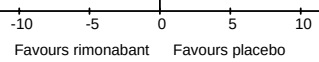
Test for heterogeneity: Chi² = 0.67, df = 2 (P = 0.71), I² = 0%
Test for overall effect: Z = 3.28 (P = 0.001)



Review: Rimonabant for overweight or obesity
Comparison: 01 Rimonabant 20 mg vs placebo (after one year)
Outcome: 07 Triglycerides levels [mg/dl] change

Study or sub-category	Rimonabant 20 mg N	Rimonabant 20 mg Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
RIO-Diabetes	339	-31.00(113.00)	348	4.00(77.00)		8.70	-35.00 [-49.50, -20.50]
RIO-Europe	599	-17.71(56.69)	305	-0.89(60.23)		27.57	-16.82 [-24.96, -8.68]
RIO-Lipids	346	-23.55(77.00)	342	-0.36(70.30)		15.07	-23.19 [-34.21, -12.17]
RIO-North America	1219	-7.26(57.39)	607	10.51(65.54)		48.66	-17.77 [-23.90, -11.64]
Total (95% CI)	2503		1602			100.00	-19.82 [-24.10, -15.55]

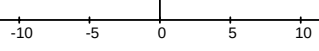
Test for heterogeneity: Chi² = 5.52, df = 3 (P = 0.14), I² = 45.7%
Test for overall effect: Z = 9.09 (P < 0.00001)



Review: Rimonabant for overweight or obesity
Comparison: 01 Rimonabant 20 mg vs placebo (after one year)
Outcome: 08 High-density lipoprotein [mg/dl] change

Study or sub-category	Rimonabant 20 mg N	Rimonabant 20 mg Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
RIO-Diabetes	339	6.00(8.00)	348	3.00(6.00)		24.21	3.00 [1.94, 4.06]
RIO-Europe	599	10.05(10.05)	305	5.80(8.89)		16.54	4.25 [2.97, 5.53]
RIO-Lipids	346	8.20(8.97)	342	4.68(6.72)		19.41	3.52 [2.34, 4.70]
RIO-North America	1219	6.17(8.55)	607	2.65(8.45)		39.84	3.52 [2.69, 4.35]
Total (95% CI)	2503		1602			100.00	3.51 [2.99, 4.04]

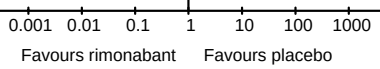
Test for heterogeneity: Chi² = 2.17, df = 3 (P = 0.54), I² = 0%
Test for overall effect: Z = 13.21 (P < 0.00001)



Review: Rimonabant for overweight or obesity
Comparison: 01 Rimonabant 20 mg vs placebo (after one year)
Outcome: 09 discontinuation due to adverse events

Study or sub-category	Rimonabant 20 mg n/N	Placebo n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
RIO-Diabetes	51/339	19/348		13.51	2.76 [1.66, 4.57]
RIO-Europe	87/599	28/305		26.74	1.58 [1.06, 2.37]
RIO-Lipids	52/346	24/342		17.40	2.14 [1.35, 3.39]
RIO-North America	156/1219	44/607		42.34	1.77 [1.28, 2.43]
Total (95% CI)	2503	1602		100.00	1.92 [1.57, 2.34]

Total events: 346 (Rimonabant 20 mg), 115 (Placebo)
Test for heterogeneity: Chi² = 3.33, df = 3 (P = 0.34), I² = 10.0%
Test for overall effect: Z = 6.34 (P < 0.00001)

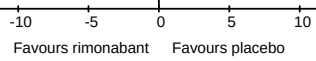


Rimonabant 5mg vs. Placebo

Review: Rimonabant for overweight or obesity
Comparison: 02 Rimonabant 5 mg vs Placebo (after one year)
Outcome: 01 Weight [kg] change

Study or sub-category	N	Rimonabant 5 mg Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
RIO-Diabetes	358	-2.30(3.80)	348	-1.40(3.70)		50.18	-0.90 [-1.45, -0.35]
RIO-Europe	603	-3.40(5.70)	305	-1.80(6.40)		21.24	-1.60 [-2.45, -0.75]
RIO-Lipids	345	-3.10(4.80)	342	-1.50(5.00)		28.58	-1.60 [-2.33, -0.87]
Total (95% CI)	1306		995			100.00	-1.25 [-1.64, -0.86]

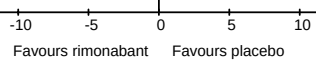
Test for heterogeneity: Chi² = 3.06, df = 2 (P = 0.22), I² = 34.7%
Test for overall effect: Z = 6.25 (P < 0.00001)



Review: Rimonabant for overweight or obesity
Comparison: 02 Rimonabant 5 mg vs Placebo (after one year)
Outcome: 02 Waist circumference [cm] change

Study or sub-category	N	Rimonabant 5 mg Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
RIO-Diabetes	358	-2.90(5.70)	348	-1.90(5.60)		36.73	-1.00 [-1.83, -0.17]
RIO-Europe	603	-3.90(6.30)	305	-2.40(6.90)		29.94	-1.50 [-2.42, -0.58]
RIO-Lipids	345	-3.50(6.00)	342	-2.40(5.70)		33.33	-1.10 [-1.98, -0.22]
Total (95% CI)	1306		995			100.00	-1.18 [-1.69, -0.68]

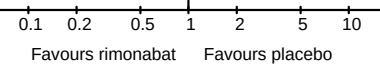
Test for heterogeneity: Chi² = 0.67, df = 2 (P = 0.71), I² = 0%
Test for overall effect: Z = 4.59 (P < 0.00001)



Review: Rimonabant for overweight or obesity
Comparison: 02 Rimonabant 5 mg vs Placebo (after one year)
Outcome: 03 Adverse effects (general)

Study or sub-category	Rimonabant 5 mg n/N	Placebo n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
RIO-Diabetes	293/358	276/348		21.78	1.03 [0.96, 1.11]
RIO-Europe	498/603	257/305		26.56	0.98 [0.92, 1.04]
RIO-North America	1013/1214	498/607		51.66	1.02 [0.97, 1.06]
Total (95% CI)	2175	1260		100.00	1.01 [0.98, 1.04]

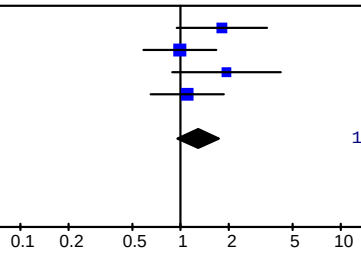
Total events: 1804 (Rimonabant 5 mg), 1031 (Placebo)
Test for heterogeneity: Chi² = 1.37, df = 2 (P = 0.50), I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)



Review: Rimonabant for overweight or obesity
Comparison: 02 Rimonabant 5 mg vs Placebo (after one year)
Outcome: 04 Adverse effects (serious)

Study or sub-category	Rimonabant 5 mg n/N	Placebo n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
RIO-Diabetes	27/358	15/348		17.86	1.81 [0.95, 3.47]
RIO-Europe	45/603	23/305		35.89	0.99 [0.59, 1.67]
RIO-Lipids	19/345	10/342		12.05	1.93 [0.89, 4.22]
RIO-North America	46/1214	21/607		34.20	1.10 [0.65, 1.86]
Total (95% CI)	2520	1602		100.00	1.29 [0.96, 1.73]

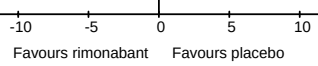
Total events: 137 (Rimonabant 5 mg), 69 (Placebo)
Test for heterogeneity: Chi² = 3.44, df = 3 (P = 0.33), I² = 12.7%
Test for overall effect: Z = 1.66 (P = 0.10)



Review: Rimonabant for overweight or obesity
Comparison: 02 Rimonabant 5 mg vs Placebo (after one year)
Outcome: 05 Systolic blood pressure [mmHg] change

Study or sub-category	N	Rimonabant 5 mg Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
RIO-Diabetes	358	-0.40(12.90)	348	1.60(13.20)		27.37	-2.00 [-3.93, -0.07]
RIO-Europe	603	-0.90(12.50)	305	-0.30(12.30)		34.99	-0.60 [-2.30, 1.10]
RIO-Lipids	345	-0.40(11.80)	342	-0.30(10.10)		37.65	-0.10 [-1.74, 1.54]
Total (95% CI)	1306		995			100.00	-0.79 [-1.80, 0.21]

Test for heterogeneity: Chi² = 2.24, df = 2 (P = 0.33), I² = 10.8%
Test for overall effect: Z = 1.55 (P = 0.12)



Review: Rimonabant for overweight or obesity
Comparison: 02 Rimonabant 5 mg vs Placebo (after one year)
Outcome: 06 Diastolic blood pressure [mmHg] change

Study or sub-category	N	Rimonabant 5 mg Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
RIO-Diabetes	358	-0.40(8.50)	348	-0.70(8.40)		30.94	0.30 [-0.95, 1.55]
RIO-Europe	603	-0.80(8.80)	305	-0.10(8.50)		34.27	-0.70 [-1.88, 0.48]
RIO-Lipids	345	-0.10(8.30)	342	-0.20(7.40)		34.79	0.10 [-1.08, 1.28]
Total (95% CI)	1306		995			100.00	-0.11 [-0.81, 0.58]

Test for heterogeneity: Chi² = 1.49, df = 2 (P = 0.47), I² = 0%
Test for overall effect: Z = 0.32 (P = 0.75)

Review: Rimonabant for overweight or obesity
Comparison: 02 Rimonabant 5 mg vs Placebo (after one year)
Outcome: 07 Triglycerides levels [mg/dl] change

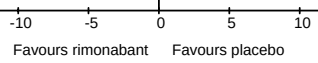
Study or sub-category	N	Rimonabant 5 mg Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
RIO-Diabetes	358	-1.00(70.00)	348	4.00(77.00)		27.85	-5.00 [-15.86, 5.86]
RIO-Europe	603	-1.77(68.20)	305	-0.89(60.23)		43.64	-0.88 [-9.56, 7.80]
RIO-Lipids	345	-2.23(73.30)	342	-0.36(70.30)		28.50	-1.87 [-12.61, 8.87]
Total (95% CI)	1306		995			100.00	-2.31 [-8.04, 3.42]

Test for heterogeneity: Chi² = 0.35, df = 2 (P = 0.84), I² = 0%
Test for overall effect: Z = 0.79 (P = 0.43)

Review: Rimonabant for overweight or obesity
Comparison: 02 Rimonabant 5 mg vs Placebo (after one year)
Outcome: 08 High-density lipoprotein [mg/dl] change

Study or sub-category	Rimonabant 5 mg N	Rimonabant 5 mg Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
RIO-Diabetes	358	4.00(7.00)	348	3.00(6.00)		41.13	1.00 [0.04, 1.96]
RIO-Europe	603	7.35(8.89)	305	5.80(8.89)		25.33	1.55 [0.33, 2.77]
RIO-Lipids	345	6.04(7.49)	342	4.68(6.72)		33.54	1.36 [0.30, 2.42]
Total (95% CI)	1306		995			100.00	1.26 [0.64, 1.88]

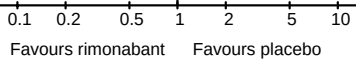
Test for heterogeneity: Chi² = 0.53, df = 2 (P = 0.77), I² = 0%
Test for overall effect: Z = 4.01 (P < 0.0001)



Review: Rimonabant for overweight or obesity
Comparison: 02 Rimonabant 5 mg vs Placebo (after one year)
Outcome: 09 Discontinuation due to adverse events

Study or sub-category	Rimonabant 5 mg n/N	Placebo n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
RIO-Diabetes	28/358	19/348		13.97	1.47 [0.80, 2.68]
RIO-Europe	50/603	28/305		26.83	0.89 [0.55, 1.45]
RIO-Lipids	29/345	24/342		17.37	1.22 [0.69, 2.13]
RIO-North America	114/1214	44/607		41.82	1.33 [0.92, 1.91]
Total (95% CI)	2520	1602		100.00	1.21 [0.96, 1.53]

Total events: 221 (Rimonabant 5 mg), 115 (Placebo)
Test for heterogeneity: Chi² = 2.14, df = 3 (P = 0.54), I² = 0%
Test for overall effect: Z = 1.59 (P = 0.11)

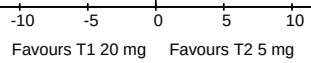


Rimonabant 20 mg vs. Rimonabant 5 mg

Review: Rimonabant for overweight or obesity
Comparison: 03 Rimonabant 20 mg vs Rimonabant 5 mg (after one year)
Outcome: 01 Weight [kg] change

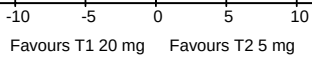
Study or sub-category	Rimonabant 20 mg N	Rimonabant 20 mg Mean (SD)	Rimonabant 5 mg N	Rimonabant 5 mg Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
RIO-Diabetes	339	-5.30(5.50)	358	-2.30(3.80)		37.51	-3.00 [-3.71, -2.29]
RIO-Europe	599	-6.60(7.20)	603	-3.40(5.70)		34.61	-3.20 [-3.93, -2.47]
RIO-Lipids	346	-6.90(6.10)	345	-3.10(4.80)		27.88	-3.80 [-4.62, -2.98]
Total (95% CI)	1284		1306			100.00	-3.29 [-3.72, -2.86]

Test for heterogeneity: Chi² = 2.20, df = 2 (P = 0.33), I² = 9.0%
Test for overall effect: Z = 14.93 (P < 0.00001)



Review: Rimonabant for overweight or obesity
Comparison: 03 Rimonabant 20 mg vs Rimonabant 5 mg (after one year)
Outcome: 02 Waist circumference [kg] change

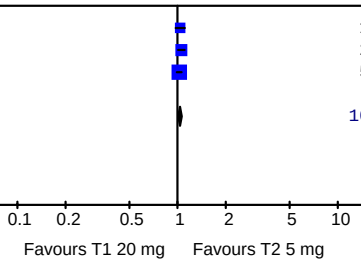
Study or sub-category	Rimonabant 20 mg N	Rimonabant 20 mg Mean (SD)	Rimonabant 5 mg N	Rimonabant 5 mg Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
RIO-Diabetes	339	-5.20(5.50)	358	-2.90(5.70)		34.47	-2.30 [-3.13, -1.47]
RIO-Europe	599	-6.50(7.40)	603	-3.90(6.30)		39.46	-2.60 [-3.38, -1.82]
RIO-Lipids	346	-7.10(6.80)	345	-3.50(6.00)		26.07	-3.60 [-4.56, -2.64]



Review: Rimonabant for overweight or obesity
Comparison: 03 Rimonabant 20 mg vs Rimonabant 5 mg (after one year)
Outcome: 03 Adverse effects (general)

Study or sub-category	Rimonabant 20 mg n/N	Rimonabant 5 mg n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
RIO-Diabetes	288/339	293/358		15.87	1.04 [0.97, 1.11]
RIO-Europe	522/599	498/603		27.63	1.06 [1.01, 1.11]
RIO-North America	1042/1219	1013/1214		56.51	1.02 [0.99, 1.06]
Total (95% CI)	2157	2175		100.00	1.04 [1.01, 1.06]

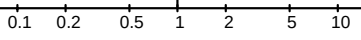
Total events: 1852 (Rimonabant 20 mg), 1804 (Rimonabant 5 mg)
Test for heterogeneity: Chi² = 0.98, df = 2 (P = 0.61), I² = 0%
Test for overall effect: Z = 2.64 (P = 0.008)



Review: Rimonabant for overweight or obesity
Comparison: 03 Rimonabant 20 mg vs Rimonabant 5 mg (after one year)
Outcome: 04 Adverse effects (serious)

Study or sub-category	Rimonabant 20 mg n/N	Rimonabant 5 mg n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
RIO-Diabetes	27/339	27/358		19.28	1.06 [0.63, 1.76]
RIO-Europe	52/599	45/603		32.92	1.16 [0.79, 1.71]
RIO-Lipids	15/346	19/345		13.97	0.79 [0.41, 1.52]
RIO-North America	55/1219	46/1214		33.83	1.19 [0.81, 1.75]
Total (95% CI)	2503	2520		100.00	1.10 [0.88, 1.38]

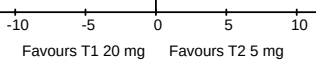
Total events: 149 (Rimonabant 20 mg), 137 (Rimonabant 5 mg)
Test for heterogeneity: Chi² = 1.26, df = 3 (P = 0.74), I² = 0%
Test for overall effect: Z = 0.83 (P = 0.41)



Review: Rimonabant for overweight or obesity
Comparison: 03 Rimonabant 20 mg vs Rimonabant 5 mg (after one year)
Outcome: 05 Systolic blood pressure [mmHg] change

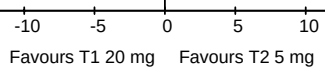
Study or sub-category	Rimonabant 20 mg N	Rimonabant 20 mg Mean (SD)	Rimonabant 5 mg N	Rimonabant 5 mg Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
RIO-Diabetes	339	-0.80(12.80)	358	-0.40(12.90)		25.31	-0.40 [-2.31, 1.51]
RIO-Europe	599	-1.00(12.50)	603	-0.90(12.50)		46.15	-0.10 [-1.51, 1.31]
RIO-Lipids	346	-2.10(12.30)	345	-0.40(11.80)		28.54	-1.70 [-3.50, 0.10]
Total (95% CI)	1284		1306			100.00	-0.63 [-1.59, 0.33]

Test for heterogeneity: Chi² = 1.96, df = 2 (P = 0.38), I² = 0%
Test for overall effect: Z = 1.29 (P = 0.20)



Review: Rimonabant for overweight or obesity
Comparison: 03 Rimonabant 20 mg vs Rimonabant 5 mg (after one year)
Outcome: 06 Diastolic blood pressure [mmHg] change

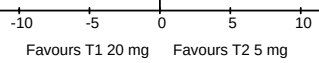
Study or sub-category	Rimonabant 20 mg N	Rimonabant 20 mg Mean (SD)	Rimonabant 5 mg N	Rimonabant 5 mg Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
RIO-Diabetes	339	-1.90(8.20)	358	-0.40(8.50)		28.17	-1.50 [-2.74, -0.26]
RIO-Europe	599	-0.90(8.70)	603	-0.80(8.80)		44.24	-0.10 [-1.09, 0.89]
RIO-Lipids	346	-1.70(8.50)	345	-0.10(8.30)		27.59	-1.60 [-2.85, -0.35]



Review: Rimonabant for overweight or obesity
Comparison: 03 Rimonabant 20 mg vs Rimonabant 5 mg (after one year)
Outcome: 07 Triglycerides levels [mg/dl] change

Study or sub-category	Rimonabant 20 mg N	Rimonabant 20 mg Mean (SD)	Rimonabant 5 mg N	Rimonabant 5 mg Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
RIO-Diabetes	339	-31.00(113.00)	358	-1.00(70.00)		15.25	-30.00 [-44.05, -15.95]
RIO-Europe	599	-17.71(56.69)	603	-1.77(68.20)		59.87	-15.94 [-23.03, -8.85]
RIO-Lipids	346	-23.55(77.00)	345	-0.36(70.30)		24.89	-23.19 [-34.18, -12.20]
Total (95% CI)	1284		1306			100.00	-19.89 [-25.37, -14.40]

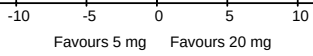
Test for heterogeneity: Chi² = 3.53, df = 2 (P = 0.17), I² = 43.3%
Test for overall effect: Z = 7.11 (P < 0.00001)



Review: Rimonabant for overweight or obesity
Comparison: 03 Rimonabant 20 mg vs Rimonabant 5 mg (after one year)
Outcome: 08 High-density lipoprotein [mg/dl] change

Study or sub-category	Rimonabant 5 mg N	Rimonabant 5 mg Mean (SD)	Rimonabant 20 mg N	Rimonabant 20 mg Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
RIO-Diabetes	339	6.00(8.00)	358	4.00(7.00)		34.35	2.00 [0.88, 3.12]
RIO-Europe	599	10.05(10.05)	603	7.35(8.89)		37.33	2.70 [1.63, 3.77]
RIO-Lipids	346	8.20(8.97)	345	6.04(7.49)		28.31	2.16 [0.93, 3.39]
Total (95% CI)	1284		1306			100.00	2.31 [1.65, 2.96]

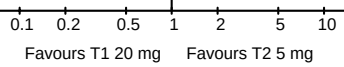
Test for heterogeneity: Chi² = 0.86, df = 2 (P = 0.65), I² = 0%
Test for overall effect: Z = 6.90 (P < 0.00001)



Review: Rimonabant for overweight or obesity
Comparison: 03 Rimonabant 20 mg vs Rimonabant 5 mg (after one year)
Outcome: 09 Discontinuation due to adverse events

Study or sub-category	Rimonabant 20 mg n/N	Rimonabant 5 mg n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
RIO-Diabetes	51/339	28/358		12.36	1.92 [1.24, 2.98]
RIO-Europe	87/599	50/603		22.62	1.75 [1.26, 2.43]
RIO-Lipids	52/346	29/345		13.18	1.79 [1.16, 2.75]
RIO-North America	156/1219	114/1214		51.84	1.36 [1.08, 1.71]
Total (95% CI)	2503	2520		100.00	1.58 [1.34, 1.85]

Total events: 346 (Rimonabant 20 mg), 221 (Rimonabant 5 mg)
Test for heterogeneity: Chi² = 3.09, df = 3 (P = 0.38), I² = 2.9%
Test for overall effect: Z = 5.59 (P < 0.00001)



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