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Efeitos agudos do consumo de bebidas energéticas nos parâmetros cardiovasculares em adultos saudáveis: uma revisão sistemática com metanálise de ensaios clínicos randomizados

Governador Valadares
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Dissertação apresentada ao Programa de Pós-Graduação em Ciências Aplicadas à Saúde, da Universidade Federal de Juiz de Fora, *campus* Governador Valadares, como requisito parcial à obtenção do título de Mestre em Ciências Aplicadas à Saúde, área de concentração Biociências.

Orientador: Prof. Dr. Luís Fernando Deresz
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"*I tried so hard and got so far*
But in the end, it doesn't even matter
I had to fall to lose it all
But in the end, it doesn't even matter."
(LINKIN PARK, **Hybrid Theory**, 2000)

RESUMO

O mercado de bebidas energéticas (BEs) tem crescido exponencialmente nos últimos anos entre a população jovem-adulta devido a sua capacidade de melhorar a sensação de fadiga, concentração e desempenho físico. Isso se deve ao alto teor de cafeína em sua composição. Evidências isoladas sugerem que o consumo de BE pode causar alterações agudas nos parâmetros cardiovasculares, mas não há concordância sobre a verdadeira magnitude desses efeitos. O objetivo desta revisão sistemática com metanálise de ensaios clínicos randomizados (ECRs) foi avaliar os efeitos agudos e subagudos do consumo de BEs em diferentes períodos de tempo na pressão arterial sistólica (PAS) e diastólica (PAD), frequência cardíaca de repouso (FCrep), débito cardíaco (DC), função endotelial, intervalo QT (QT) e QT corrigido (QTc) em adultos saudáveis. Um artigo protocolo foi previamente elaborado. As buscas incluíram as bases PubMed, EMBASE, Cochrane, LILACS, Web of Science e SportDiscus e a literatura cinzenta. Os resultados estão apresentados em diferença de médias entre o grupo intervenção (BE) comparado a condição controle (BC) e intervalo de confiança de 95% (IC 95%). Para estimar efeitos em estudos futuros foi incluído intervalo de predição de 95% (IP 95%; ≥ 3 estudos). A heterogeneidade foi avaliada pelo teste de Higgins (I^2). Outliers foram avaliados pela falta de sobreposição dos IC 95%. As análises foram realizadas no RStudio no pacote “meta”. Foram incluídos 17 estudos (n= 475), desses, 14 eram ECRs cruzado. Os dados de PAS e PAD foram avaliados em 16 estudos, a FC em 15, o DC em três, o QT e o QTc em cinco. Após o consumo da BE, a PAS aumentou 3,23 mmHg (IC 95% 1,19 a 5,28, p < 0,01) após 30 a 40 minutos, 4,61 mmHg (IC 95% 2,80 a 6,42, p < 0,01) após 60 a 80 minutos, 4,10 mmHg (IC 95% 1,63 a 6,56, p < 0,01) após 90 a 100 minutos e 3,64 mmHg (IC 95% 1,66 a 5,63, p < 0,01) após 120 minutos. A PAD aumentou 2,92 mmHg (IC 95% 0,91 a 4,94, p < 0,01) antes de 20 minutos, 2,22 mmHg (IC 95% 0,84 a 3,59, p < 0,01) entre 30 e 40 minutos, 2,73 mmHg (IC 95% 1,46 a 4,01, p < 0,01) entre 60 e 80 minutos, 3,77 mmHg (IC 95% 2,02 a 5,52, p < 0,01) entre 90 e 100 minutos e 4,58 mmHg (IC 95% 2,73 a 6,43, p < 0,01) após 120 minutos. O DC aumentou 0,43 L/min (IC 95% 0,08 a 0,77, p= 0,016) somente no período de 30 a 40 minutos após a intervenção. A FCrep, o QT e o QTc não apresentaram alterações significativas. Não foram encontrados estudos que avaliaram a função endotelial. Em conclusão, o consumo agudo de BEs aumenta a PAS e PAD por até duas horas após sua ingestão.

Além disso, houve pequena modificação no DC e nenhuma influência na FC e no QT/QTc em adultos saudáveis. No entanto, pelo reduzido número de estudos envolvidos, os resultados devem ser interpretados com cautela.

Palavras-chave: Cafeína. Pressão arterial. Frequência cardíaca.

ABSTRACT

The market for energy drinks (EDs) has grown exponentially among the young adult population in recent years due to their ability to improve feelings of fatigue, concentration and physical performance. This is due to the high caffeine content in their composition. Anecdotal evidence suggests that BE consumption may cause acute changes in cardiovascular parameters, but there is no agreement on the true magnitude of these effects. The objective of this systematic review and meta-analysis of randomized clinical trials (RCTs) was to evaluate the acute and subacute effects of different durations of EDs consumption on systolic (SBP) and diastolic (DBP) blood pressure, resting heart rate (HRrp), cardiac output (CO), endothelial function, QT interval (QT), and corrected QT interval (QTc) in healthy adults. A protocol article was previously developed. Searches included PubMed, EMBASE, Cochrane, LILACS, Web of Science and SportDiscus databases and grey literature. Results are presented as mean difference between the intervention group (EDs) and the control condition (BC) and 95% confidence interval (95% CI). To estimate effects in future studies, 95% prediction interval (95% PI; ≥ 3 studies) was included. Heterogeneity was assessed by the Higgins' test (I^2). Outliers were assessed by the lack of overlap of the 95% CIs. Analyses were performed in RStudio using the "meta" package. Seventeen studies (n= 475) were included, of which 14 were crossover RCTs. SBP and DBP data were evaluated in 16 studies, HR in 15, CO in three, QT and QTc in five. After BE consumption, SBP increased 3.23 mmHg (95% CI 1.19 to 5.28, $p < 0.01$) after 30 to 40 minutes, 4.61 mmHg (95% CI 2.80 to 6.42, $p < 0.01$) after 60 to 80 minutes, 4.10 mmHg (95% CI 1.63 to 6.56, $p < 0.01$) after 90 to 100 minutes, and 3.64 mmHg (95% CI 1.66 to 5.63, $p < 0.01$) after 120 minutes. DBP increased 2.92 mmHg (95% CI 0.91 to 4.94, $p < 0.01$) before 20 minutes, 2.22 mmHg (95% CI 0.84 to 3.59, $p < 0.01$) between 30 and 40 minutes, 2.73 mmHg (95% CI 1.46 to 4, 01, $p < 0.01$) between 60 and 80 minutes, 3.77 mmHg (95% CI 2.02 to 5.52, $p < 0.01$) between 90 and 100 minutes, and 4.58 mmHg (95% CI 2.73 to 6.43, $p < 0.01$) after 120 minutes. The CO increased by 0.43 L/min (95% CI 0.08 to 0.77, $p= 0.016$) only in the 30 to 40 minutes period after the intervention. HRrep, QT and QTc showed no significant changes. No studies were found that evaluated endothelial function. In conclusion, acute consumption of BEs increases SBP and DBP for up to two hours after ingestion. Furthermore, there was little change in CO and no effect on HR and QT/QTc in healthy

adults. However, due to the small number of studies involved, the results should be interpreted with caution.

Keywords: Caffeine. Blood pressure. Heart Rate.

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LISTA DE ABREVIATURAS E SIGLAS

AMPc	Adenosina 3,5-monofosfato cíclico
AVE	Acidente vascular encefálico
BE	Bebida energética
BEs	Bebidas energéticas
DAC	Doença arterial coronariana
DC	Débito cardíaco
DRC	Doença renal crônica
DCV	Doenças cardiovasculares
EFSA	*European Food Safety Authority* (Autoridade Europeia para a Segurança dos Alimentos)
FC	Frequência cardíaca
FCrep	Frequência cardíaca de repouso
HAS	Hipertensão arterial sistêmica
LDL	*Low-density lipoprotein* (Lipoproteína de baixa densidade)
NO	*Nitric oxide* (Óxido nítrico)
PA	Pressão arterial
PAS	Pressão arterial sistólica
PAD	Pressão arterial diastólica
PET	Polietileno tereftalato
QT	Intervalo QT
QTc	Intervalo QT corrigido
SNC	Sistema nervoso central
VHL	Virtual Health Library
VS	Volume sistólico

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1 INTRODUÇÃO GERAL

O mercado de bebida energética (BE) é o mais crescente desde a criação da água engarrafada (HECKMAN; SHERRY e DE MEJIA, 2010). Com a promessa de promover aumento de energia e concentração, e redução da fadiga física e mental (LIVERTOX, 2020), estas bebidas rapidamente assumiram um papel de relevância na rotina de crianças, adolescentes e adultos, devido aos seus estilos de vida pautados por intensas cargas horárias de estudos e/ou de trabalho (COSTA; HAYLEY e MILLER, 2014; LAL, 2007; SEIFERT *et al*., 2011).

Em 2013, um estudo desenvolvido pela *European Food Safety Authority* (EFSA) em 16 países da união europeia observou que a maior prevalência de consumo de BE foi entre os adolescentes (68%), seguido pelos adultos (30%) e as crianças (18%) (ZUCCONI *et al*., 2013). O aumento exponencial do consumo das bebidas energéticas (BEs) resultou na elevação do número de casos de efeitos adversos relacionados aos ingredientes de sua composição, em especial, a cafeína. Dentre os efeitos adversos, os eventos cardiovasculares possuem a maior prevalência, seguido pelos eventos neurológicos e gastrointestinais (NADEEM *et al*., 2021; ALI *et al*., 2015). De forma geral, os principais eventos cardiovasculares associados ao consumo das BEs são os relacionados às alterações na frequência cardíaca (FC), como palpitações, arritmias e taquicardia, além da elevação da pressão arterial (PA) (ALI *et al*., 2015; LASHERAS *et al*., 2021; NADEEM *et al*., 2021; SHAH *et al*., 2016a).

Entretanto, tais alterações ainda carecem de confirmação, uma vez que Shah *et al.* (2016a), por meio de uma revisão sistemática, observaram que o consumo agudo de BE pode elevar valores de PA sem modificar os valores de frequência cardíaca em repouso (FCrep). Da mesma forma, não há um consenso sobre os efeitos agudos das BEs em outros parâmetros cardiovasculares, como o débito cardíaco (DC) e função endotelial. Além disso, também não está claro como estes parâmetros respondem a diferentes volumes de bebida e dosagens de diferentes ingredientes. Diante disso, a proposta deste trabalho é sumarizar, por meio de uma revisão sistemática com metanálise de ensaios clínicos randomizados, os dados da literatura sobre os efeitos agudos das bebidas energéticas nos parâmetros cardiovasculares em adultos saudáveis.

1.1 BEBIDAS ENERGÉTICAS

As BEs surgiram por volta da década de 1960, porém, foi somente em 1987 na Áustria e, posteriormente, em 1997 nos Estados Unidos com a implementação da marca “Red Bull” que essas bebidas se popularizaram (REISSIG; STRAIN; GRIFFITHS, 2009). Caracterizadas como bebidas não alcoólicas, elas são compostas por uma variação de ingredientes que prometem reduzir a sensação de cansaço, aumentar a concentração, agilidade mental e desempenho físico. Isso porque além de seu principal ingrediente, a cafeína, possuem outros componentes que agem de forma sinérgica, como a taurina, açúcares, guaraná, vitaminas do complexo B, entre outros (Tabela 1). (DE CARVALHO *et al.*, 2006; ZUCCONII *et al.*, 2013).

Essas bebidas são encontradas comercialmente em vários tamanhos, desde recipientes menores de 60 mililitros, chamados “*shots*”, até recipientes maiores podendo conter de 250 a 710 mililitros (LIVERTOX, 2020). Entretanto, no Brasil, devido a expansão do mercado regional e a alta competitividade entre as marcas é possível encontrar garrafas PET contendo de 1 a 2 litros a um preço inferior às BEs tradicionais (SLONIAK, 2014). As marcas mais populares internacionalmente são a Red Bull®, Monster Energy®, Rockstar Energy®, NOS Energy®, Xyience®, Bang®, entre outras (LIVERTOX, 2020).

No ano de 2018 o mercado global de BE foi avaliado em aproximadamente US$ 53 bilhões, sendo que apenas os Estados Unidos são responsáveis por movimentar cerca de US$ 11,7 bilhões (MEYERSOHN, 2018). Nos dias atuais, a avaliação ultrapassa a marca de US$ 45,8 bilhões e está projetado para atingir US$ 108,4 bilhões até o ano de 2031 (KADAM; DESHMUKH, 2019), sendo o produto com maior taxa de crescimento na indústria de bebidas desde a criação da água engarrafada (HECKMAN; SHERRY e DE MEJIA, 2010). No Brasil, as BEs tiveram crescimento de 236% na produção em litros anuais nos últimos dez anos (ABIR, 2020).

Esse crescimento exponencial pode estar relacionado com as estratégias de marketing adotadas pelas empresas. Líder mundial no mercado de bebidas energéticas, a Red Bull® abandonou as estratégias de marketing convencionais e criou sua própria identidade atingindo seu público-alvo por meio da divulgação de conteúdos únicos relacionados ao esporte, cultura, estilo de vida e entretenimento utilizando suas próprias mídias sociais ou por meio de formadores de opinião, atletas,

equipes esportivas e eventos diversos (HILDEBRAND, 2014), criando assim um sentimento de identificação e pertencimento ao estilo de vida atrelada à marca.

Tabela 1 - Doses dos principais ingredientes* de três marcas populares de bebidas energéticas para uma porção de 250 ml.

Ingredientes	Red Bull® (250 ml)†	Monster® (250 ml)†‡	Rockstar® (250 ml)†
Cafeína (mg)	80	81,2	85
Taurina (mg)	1000	1000	0#
Açúcares (g)	27	28,7	33
Sódio (mg)	103	193,7	40
Glucoronolactona (mg)	0	5,2	0#
Inositol (mg)	0	5,2	0#
Riboflavina (Vitamina B2, mg)	1,3	1,6	0,69
Niacina (Vitamina B3, mg)	16	20	8,5
Ácido pantotênico (Vitamina B5, mg)	5	0	0
Piridoxina (Vitamina B6, mg)	1,3	1,6	0,9
Cianocobalamina (Vitamina B12, µg)	1,0	3	1,3

* Outros ingredientes como: água gaseificada, extrato de guaraná, maltodextrina, ácido cítrico, Panax ginseng, corante de caramelo, bicarbonato de sódio e magnésio, aromatizantes naturais e artificiais e conservantes (ácido sórbico e ácido benzóico) também podem ser encontrados nas composições das marcas citadas;
† Valores extraídos da ficha nutricional disponível nos rótulos das bebidas em sua versão tradicional;
# Dosagens não divulgadas, porém a empresa atesta a presença na composição de seu produto;
‡ Dosagens de ingredientes ajustadas de uma porção de 200 ml para 250 ml.

Outro fator que pode ter sido determinante para a rápida expansão dessas bebidas, principalmente entre o público do sexo masculino (52,1%) com idade média de 15,2 anos (variação, 11-63 anos), (NAADEM *et al*., 2021), se deve ao fato das marcas, em geral, afirmarem que seu produto pode reduzir a sensação de cansaço, melhorar a concentração, tempo de reação, estado de vigília, memória e desempenho

físico. Com isso, muitos consumidores ignoram até mesmo uma das principais características da bebida, o sabor, na expectativa de conquistarem maior desempenho físico e mental durante suas jornadas de trabalho, estudos, prática esportiva e festas noturnas (BALLISTRERI; CORRADI-WEBSTER, 2008; MCDONALD, 2011).

Mohammed *et al*. (2022) ao avaliarem o padrão de consumo de BEs por 515 indivíduos asiáticos observaram que as principais razões para o consumo foram: aumentar o estado de alerta e se manterem acordados (42,7%), reduzir a sensação de fadiga (21,7%) e aumentar a concentração durante os estudos (15,5%). Apenas 57 indivíduos (11,1%) relataram consumir por apreciarem o sabor. Entretanto, ao tratar das razões pelas quais os indivíduos escolhem uma marca preferida, o sabor foi o fator mais determinante para 43,7% dos participantes.

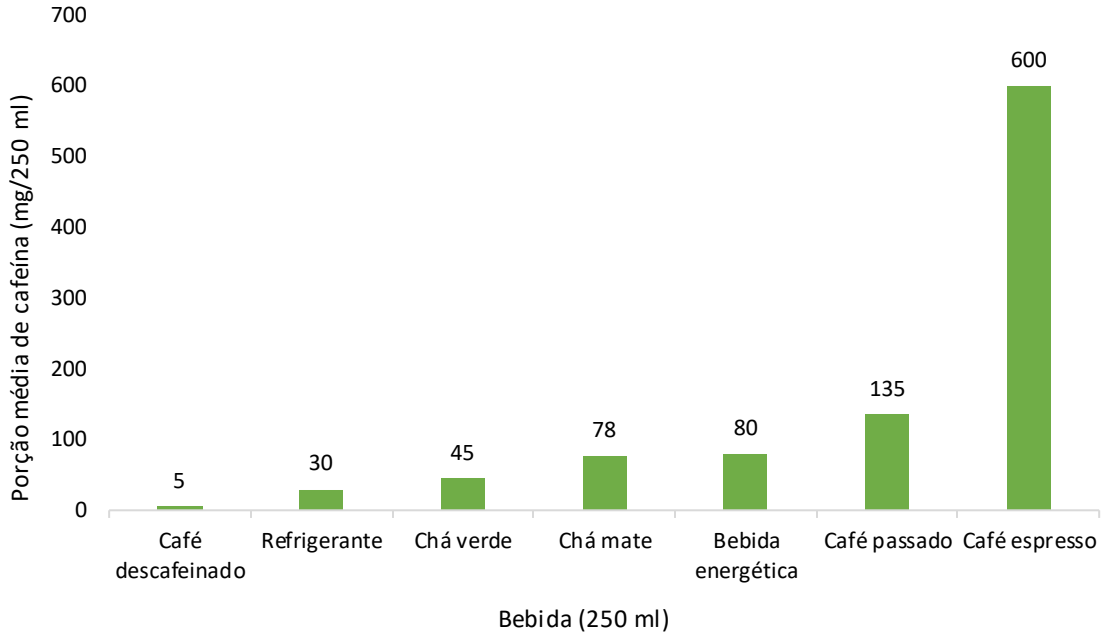
Visto o avanço do mercado e do consumo das BEs nos últimos anos, é crucial compreender o seu comportamento fisiológico, uma vez que a maioria dos consumidores não possuem conhecimento dos ingredientes que compõem essas bebidas (MOHAMMED *et al.*, 2022; RAHAMATHULLA, 2017), quem dirá possíveis riscos que o consumo, particularmente em excesso, dessas bebidas pode causar. Desse modo, veremos a seguir, os efeitos fisiológicos dos principais ingredientes presentes nas BEs e como o consumo em excesso podem causar efeitos adversos à saúde de seus consumidores.

1.2 COMPONENTES DAS BEBIDAS ENERGÉTICAS

1.2.1 Cafeína

A cafeína é o psicoestimulante mais consumido em todo o mundo, sendo encontrada não só no café, mas como componente de diferentes produtos, como alguns tipos de chás, cacau, guaraná, chocolates, refrigerantes e, principalmente, como aditivo das BEs (DIOGO *et al*., 2013; FREDHOLM *et al.*, 1999). Em geral, uma lata de 250 ml de BE contém, aproximadamente, 80 mg de cafeína (HLADUN *et al.*, 2021), quantidade semelhante à de uma xícara de café de 150 ml. Entretanto, a depender do seu tipo, uma xícara de café com o mesmo volume de uma BE convencional pode conter até sete vezes mais cafeína (Figura 1) (HECKMAN; WEIL; DE MEJIA, 2010).

Gráfico 1 - Comparação da concentração de cafeína em diferentes bebidas



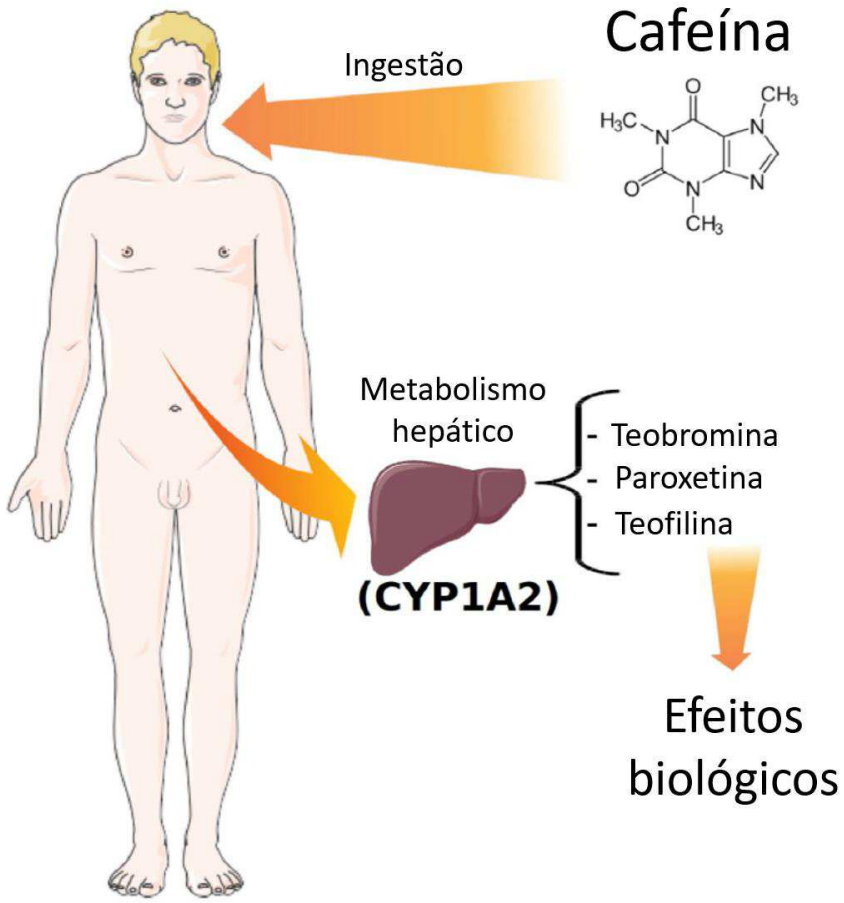
Fonte: Adaptação baseada no estudo de Heckman, Weil e de Mejia (2010).

1.2.1.1 Ações da cafeína no organismo

Bioquimicamente, a cafeína é considerada um alcalóide de metilxantina, ou seja, refere-se a um estimulante natural do sistema nervoso central (SNC), promovendo diferentes alterações comportamentais no estado de vigília, atenção, humor e excitação (FISONE; BORGKVIST; USIELLO, 2004). Após o consumo oral, a cafeína é rapidamente absorvida pelo trato gastrointestinal devido ao seu efeito lipofílico e é transportada pela corrente sanguínea para o fígado onde irá sofrer metabolização por meio da isoenzima hepática CYP1A2 (BARCELOS *et al*., 2020) (Figura 2). Seus principais efeitos agudos ocorrem em aproximadamente 30 a 60 minutos após o consumo e estão relacionados diretamente com a inibição dos quatro subtipos de receptores de adenosina acoplados à proteína G (A1, A2a, A2b e A3), seja no cérebro, músculo cardíaco e ou no endotélio vascular (SAWYNOK, 2011a). Em especial, a cafeína inibe principalmente os receptores A1 e A2a, que são responsáveis pela redução da excitabilidade neural, analgesia, regulação do sono e regulação de glutamato e dopamina (BALLESTEROS-YÁÑEZ *et al*., 2018; EHLERS *et al*., 2019).

Ademais, o antagonismo aos receptores de adenosina realizado pela cafeína concede a ela uma característica diurética, devido ao aumento da diurese e a natriurese por meio da inibição da reabsorção tubular de sódio causado por ela (SHIRLEY *et al*., 2002). O estudo de Riesenhuber *et al.* (2006) demonstrou que o consumo da cafeína, seja ela isolada ou presente em uma BE, aumentou de forma significativa a diurese (243 ml) e a natriurese (27 mmol).

Figura 1 - Metabolização hepática da cafeína



Fonte: Adaptação baseada no estudo Barcelos *et al.* (2020).

No entanto, Zhang *et al*. (2015) demonstraram por meio de metanálise que a diurese induzida pela ingestão de cafeína (mediana de 300 mg) é muito pequena (tamanho de efeito de 0,29; IC 95% 0,11 a 0,48). Ainda, quando realizado análises de subgrupos os autores demonstraram que o efeito do consumo de cafeína na diurese durante o exercício é ainda menor (tamanho de efeito de 0,1; IC 95% −0.07 to 0.27). Esse fenômeno foi justificado pelos autores por meio da ativação simpatoadrenal induzida pelo exercício, estimulando a liberação de catecolaminas, nas quais irão

realizar vasoconstrição das arteríolas renais reduzindo, portanto, a filtração glomerular.

Contudo, é possível que o consumo regular de bebidas cafeinadas, em especial as BEs, desenvolvam tolerância aos seus efeitos diuréticos, sugerindo um risco reduzido de desidratação a consumidores habituais e a atletas (MAUGHAN; GRIFFIN, 2003).

De forma geral, esses efeitos causados pela cafeína possuem meia-vida que varia entre 3 a 7 horas, podendo ser prolongados em indivíduos em uso de contraceptivos orais ou medicamentos (carbamazepina e rifampicina), recém-nascidos, gestantes e portadores de doenças hepáticas ou reduzido em indivíduos tabagistas e em uso de medicamentos (cimetidina ou ciprofloxacina) (MEJIA; RAMIREZ-MARES, 2014).

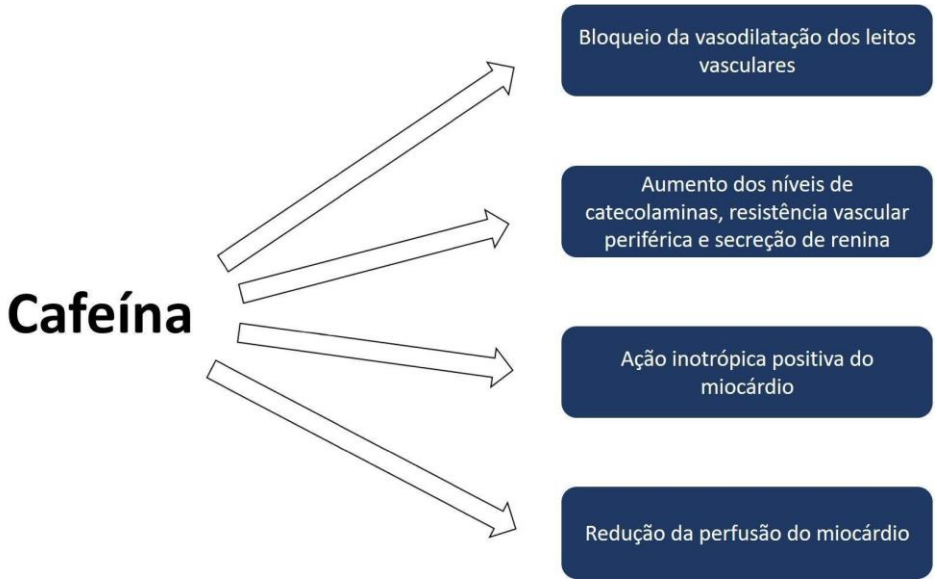
Vale ressaltar que as ações, bem como os efeitos da cafeína, podem variar amplamente dependendo da sensibilidade e tolerância do indivíduo, da quantidade e do momento do consumo (EVANS; GRIFFITHS, 1992). Em geral, a ingestão diária máxima recomendada de cafeína para a maioria dos adultos saudáveis é de cerca de 400 mg, o que é aproximadamente equivalente a três latas de 250 mL de uma bebida energética. Ademais, a Diretriz Brasileira de Hipertensão (2020) sugere que o consumo diário de cafeína/café não exceda doses a ≥ 200 mg (BARROSO *et al*., 2020). Ultrapassar os limites diários pode resultar em efeitos colaterais, incluindo ansiedade, irritação, dores de cabeça, insônia e alterações cardiovasculares (FOOD & DRUG ADMINISTRATION, 2018). Em razão disso, é importante que seu consumo diário não exceda doses consideradas de baixa a moderada (dose diária ≤ 200 mg) e que eventuais preocupações e ou efeitos colaterais sejam debatidos com um profissional de saúde.

1.2.1.2 Ações da cafeína no sistema cardiovascular

No músculo cardíaco (Figura 3), a cafeína atua diretamente na inibição do receptor de adenosina A1, estimulando a hipófise a liberar acetilcolina que induzirá as glândulas suprarrenais a secretar adrenalina aumentando sua concentração plasmática e, consequentemente, aumentando a atividade do sistema nervoso simpático (ECHEVERRI *et al*., 2010). Ainda, ao atuar como antagonista do receptor A2a que está presente nos tecidos vasculares, a cafeína bloqueia seu efeito

vasodilatador, aumentando vasoconstrição periférica e coronariana (KAUR *et al*., 2022). Concomitantemente, a cafeína inibe a fosfodiesterase, aumentando o efeito e a duração da ação da adenosina 3,5-monofosfato cíclico (AMPc), potencializando os efeitos e a produção das catecolaminas o que, consequentemente, elevará a ação inotrópica positiva no miocárdio (CASTRO *et al*., 2005; SAWYNOK, 2011b; EVANS; RICHARDS; BATTISTI, 2022). A combinação destes mecanismos poderá resultar no aumento agudo da FC, DC, dos níveis pressóricos e do volume plasmático (ECHEVERRI *et al*., 2010; WASSEF; KOHANSEIH; MAKARYUS, 2017).

Figura 2 - Efeitos da cafeína no sistema cardiovasculares



Fonte: Adaptação baseada no estudo de Kaur *et al.* (2022).

No entanto, quando consumida em níveis inferiores ao limite diário de 400 mg a cafeína aparenta não modificar parâmetros cardiovasculares de indivíduos saudáveis de forma significativa. Salvo os níveis pressóricos que tendem a apresentar elevação, principalmente em indivíduos hipertensos e consumidores não habituais de cafeína (NAWROT *et al*., 2003; TURNBULL *et al*., 2017). Desta forma, o consumo moderado de cafeína pode não ser um risco para a saúde cardiovascular de indivíduos saudáveis.

1.2.1.3 Efeitos crônicos do consumo de cafeína

De acordo com Turnbull *et al*., 2017, o consumo regular de cafeína é capaz de gerar tolerância aos seus efeitos agudos, logo, consumidores habituais podem experimentar efeitos fisiológicos reduzidos em relação aos consumidores não habituais, que por sua vez experimentam efeitos mesmo em doses mais baixas de cafeína. Além da tolerância, há vários modificadores que podem influenciar as respostas da ingestão da cafeína, como os fatores farmacocinéticos que são responsáveis pela absorção, distribuição, metabolização e eliminação da cafeína, e fatores farmacodinâmicos, que são responsáveis pelos efeitos causados pela interação da cafeína com seus canais de ação. Por consequência, tirar conclusões em relação aos seus efeitos agudos e crônicos em níveis populacionais é um grande desafio.

1.2.2 Taurina

A taurina é caracterizada como um β-aminoácido, que diferentemente dos aminoácidos convencionais que possuem um ácido carboxílico, possui ácido sulfônico (CAINE; GERACIOTI, 2016). Encontrada naturalmente e em abundância em muitos tecidos excitáveis do corpo humano, particularmente no cérebro, coração e músculos ou por meio de alimentos e suplementos alimentares, a taurina desempenha papéis importantes no organismo como o de manutenção das membranas celulares, apoio às funções hepáticas, nervosas e musculares, incluindo os músculos cardíacos, além de promover atividade oxidante, protegendo as células contra danos causados por radicais livres (BOUCKENOOGHE; REMACLE; REUSENS, 2006; BALIOU *et al.*, 2021).

Frequentemente a taurina é incluída como um dos principais componentes das BEs e outros suplementos dietéticos, pois estudos demonstraram possíveis melhoras na performance, redução da fadiga e danos musculares (SOUZA *et al*., 2017; WARNOCK *et al*., 2017; WALDRON *et al*., 2018a; CHEN *et al*., 2021). Além do mais, acredita-se que a taurina possui benefícios no perfil cardiometabólico, atenuando a PA, índices glicêmicos e colesterol total, reduzindo o risco de desenvolvimento de doenças cardiovasculares (SUN *et al*., 2016; GUAN e MIAO, 2020; TAO *et al*., 2022).

Sun *et al.* (2016), avaliaram o efeito crônico do consumo de 1.600 mg/dia de taurina durante 12 semanas em 120 pacientes normotensos e pré-hipertensos. Os resultados demonstram que a suplementação de taurina foi capaz de reduzir

significativamente a PAS e PAD clínica (-7,2 e -4,6 mmHg, respectivamente) e ambulatorial (-3,8 e 3,5 mmHg, respectivamente). Pacientes classificados como pré-hipertensos obtiveram maiores benefícios na redução da PAS em relação a pacientes normotensos (-10,1 vs. -3,0 mmHg). Além disso, os autores também relataram melhoras na vasodilatação dependente e independente do endotélio (3,2 e 4,4%, respectivamente).

Adicionalmente, a metanálise realizada por Waldron *et al*. (2018b) demonstrou que a suplementação de taurina em doses de 1.000 a 6.000 mg/dia em intervalos de um dia à 12 semanas foi capaz de reduzir a PAS e PAD (-0,70 e -0,62 mmHg, respectivamente). No entanto, vale ressaltar que os autores incluíram diferentes tipos de populações na análise, inviabilizando a análise do comportamento da PA em populações específicas, porém esse mesmo fato nos permite sugerir que a taurina pode apresentar benefícios na saúde cardiovascular na população geral.

Apesar dos possíveis benefícios da suplementação de taurina, a eficácia e segurança de sua suplementação, seja ela isolada, ou em combinação com a cafeína e outros estimulantes encontrados em algumas BEs, ainda é motivo de debate no meio científico. Desta forma, não é possível estabelecer um consenso sobre recomendações de doses seguras e eficazes. Contudo, autores de diferentes estudos demonstraram que a suplementação de 1.000 a 10.000 mg/dia de taurina não apresentou efeitos adversos subagudos e crônicos (DURELLI; MUTANI; FASSIO, 1983; SHAO; HATHCOCK, 2008; WALDRON *et al.*, 2018b).

Por fim, embora a taurina seja considerada segura para a maioria das pessoas, é importante que mais pesquisas sejam realizadas para garantir e estabelecer parâmetros para sua segurança e eficácia em diferentes populações.

1.2.3 Açúcar

O açúcar é um tipo de carboidrato encontrado naturalmente em muitos alimentos, como frutas e vegetais, e também adicionado a muitos alimentos e bebidas processados. O tipo mais comum de açúcar é chamado de sacarose, que é composto de moléculas de glicose e frutose.

Estudos que avaliaram os efeitos agudos do consumo de bebidas açucaradas compostas por frutose e glicose em comparação com uma bebida controle em parâmetros cardiovasculares demonstraram que a bebida composta por frutose foi

capaz de promover elevação da PAS, PAD e FC. Já a glicose foi responsável por promover elevação do volume sistólico (VS) e DC, além da redução da resistência vascular periférica (BROWN, 2008; GRASSER; DULLOO; MONTANI, 2014a).

Desta forma, seria sugestivo crer que os açúcares presentes na composição das BEs também poderiam ter impacto sobre as modificações cardiovasculares apresentadas pela literatura. No entanto, de forma geral, as principais marcas de BEs utilizam a glicose em sua composição, portanto é provável que o aumento da PA promovido pelas BEs seja devido à ação da cafeína (SHAH *et al*., 2016a; TURNBULL *et al*., 2017; BASRAI *et al*., 2021). Além disso, quando avaliado os efeitos cardiovasculares do consumo de uma BE composta por glicose em comparação a uma BE livre de açúcares, identificou-se que ambas foram capazes de promover a elevação da PA. Enquanto apenas a BE composta por glicose promoveu elevação da FC, VS e, consequentemente, do DC (MILES-CHAN *et al*., 2014). Isso ocorre porque a glicose é rapidamente absorvida pela corrente sanguínea para então ser transportada para as células como energia. Quando os níveis de glicose no sangue aumentam rapidamente, o corpo pode responder liberando mais insulina, o que pode aumentar a contratilidade e a frequência cardíaca e, consequentemente, o DC (MUNIYAPPA *et al*., 2007; BARON; BRECHTEL, 1993.

Outro fator que poderia estar atrelado a inserção da glicose na composição destas bebidas, se dá ao fato de que a glicose é a principal fonte de energia para o funcionamento do corpo humano, em especial o cérebro, músculos esqueléticos e músculo cardíaco. Portanto, sua suplementação pode melhorar a curto prazo a performance física. Porém, quando comparado o efeito ergogênico da BE convencional com uma BE que carecia de açúcar em sua composição identificou-se que ambas foram capazes de melhorar a performance de corredores (REIS, 2017).

Diante do exposto, é provável que a presença dos açúcares entre os componentes das BEs esteja relacionada à irresistível sensação de prazer que é promovida ao se consumir produtos adoçados (LENOIR *et al*., 2007). No entanto, é preciso ter cuidado quanto ao consumo regular de bebidas açucaradas, pois ao longo prazo este comportamento pode contribuir para o desenvolvimento de doenças cardiovasculares como obesidade, hipertensão arterial e diabetes mellitus tipo 2, sendo estas as principais causas de morte em todo o mundo (PRÉCOMA *et al*., 2019).

1.3 BEBIDAS ENERGÉTICAS E OS EFEITOS ADVERSOS À SAÚDE

Evidências apontam que o consumo de BEs podem causar efeitos adversos à saúde acometendo, principalmente, o sistema cardiovascular, nervoso e gastrointestinal (Tabela 2) (ALI *et al.*, 2015; NADEEM *et al.*, 2021; VISRAM *et al.*, 2016). Um relatório da *Substance Abuse and Mental Health Services Administration* demonstrou que entre os anos de 2007 a 2011 o número de visitas ao departamento de emergência dos Estados Unidos devido a eventos adversos relacionados ao consumo de BE dobrou (de 10.068 para 20.783 visitas) (SEIFERT *et al*., 2011). Dados mais recentes da *American Association of Poison Control Center* apontam que aproximadamente mil casos de intoxicação por consumo de BE são relatados todos os anos (GUMMIN *et al.*, 2021).

Tabela 2 - Principais eventos adversos relacionados ao consumo de bebidas energéticas

Tipos de eventos	**Eventos adversos (%)**		
Cardiovasculares	Taquicardia (26,2%)	Palpitações (20,0%)	Dor torácica (10,3%)
Gastrointestinais	Dor abdominal (14,6%)	Náuseas, vômitos e diarreia (18,7%)	
Renais		Polaciúria (13,0%)	
Neurológicos	Cefaleia (18,4%)	Tontura (12,3%)	Tremores (11,4%)
Fisiológicos	Insônia (34,5%)	Nervosismo (25,1%)	Choque (22,6%)
Psicológicos	Estresse (35,4%)	Humor depressivo (23,0%)	Tentativa de suicídio (19,8%)

Fonte: Elaborado pelos autores (2022) com base no estudo de NADEEM *et al.*, 2021.

Sugere-se que estes efeitos adversos estejam relacionados à sobredosagem de cafeína, para qual a recomendação diária de consumo é entre 2,5 a 6 mg/kg/dia em crianças e ≤ 400 mg/dia em adultos (HECKMAN; WEIL; DE MEJIA, 2010) e do consumo associado com álcool, cigarro e outras substâncias (VISRAM *et al*., 2016). No entanto, apesar dos relatos da literatura (GOLDFARB; TELLIER;

THANASSOULIS, 2014; PICCIONI *et al*., 2021), os resultados relacionados aos efeitos adversos provocados pelo consumo de BEs ainda são inconsistentes. Somers e Svatikova (2020) sugerem que a ausência de padronização das marcas, volumes e períodos de monitoramento após o consumo por parte dos estudos seja uma das razões para tanta inconsistência entre os resultados. Desta forma, é necessário maior aprofundamento teórico, principalmente se tratando da saúde cardiovascular dos consumidores.

1.3.1 Efeitos adversos no sistema cardiovascular

A cafeína aparenta ser o principal agente causador de eventos cardiovasculares relacionados ao consumo de BEs, devido a sua ação inibitória aos receptores de adenosina presentes em todo organismo. Diante disso, seus efeitos poderão ser observados no miocárdio (aumento da força e velocidade de contração), endotélio vascular (redução do óxido nítrico e, consequentemente, aumento da vasoconstrição) e no sistema nervoso autônomo (aumento da ativação simpática) (ZULLI *et al*., 2016).

Evidências associando o consumo de BEs à eventos cardiovasculares, demonstraram que o consumo agudo, a depender do volume, é capaz de promover em adultos saudáveis palpitações cardíacas, arritmias e dor torácica, além de elevar a FC, DC, PA, prolongar o intervalo QT (QT)/QT corrigido (QTc) e prejudicar a função endotelial (ALI *et al*., 2015; GOLDFARB, TELLIER; THANASSOULIS, 2014; GRASSER *et al*., 2014b; LASHERAS *et al*., 2021; SHAH *et al*., 2016a; WORTHLEY *et al*., 2010).

Nadeem *et al*. (2021), ao avaliarem 32 estudos por meio de revisão sistemática evidenciaram que os eventos cardiovasculares mais relatados pela população adulta (18-63 anos) após o consumo de BEs foram a taquicardia (56,6%), palpitação cardíaca (20,7%) e dor torácica (4,9%). Além disso, o estudo de Goldfarb, Tellier e Thanassoulis (2014) revelou por meio da revisão de 17 estudos de caso que o consumo de BEs resultou em 4 casos de fibrilação atrial, 4 de fibrilação ventricular, 4 de elevação no segmento ST, 1 de prolongamento do QT, parada cardíaca, taquicardia supraventricular, taquicardia ventricular e supraventricular.

No entanto, quando os casos são observados de forma individual percebe-se que a maioria está relacionado com o consumo excessivo de BEs, combinação com

bebida alcoólica ou outras drogas e presença de anormalidades cardíacas. Sanchis-Gomar *et al*. (2015) atribuem as arritmias atriais e ventriculares e o prolongamento do segmento ST manifestados após o consumo de BEs ao uso excessivo dessas bebidas, combinação com drogas, estados de hipertireoidismo e anomalias cardíacas congênitas que causam dilatação atrial (estenose aórtica e mitral) ou defeitos auriculares envolvendo cirurgia.

Assim, os efeitos cardiovasculares causados pelas BEs parecem não estar associados ao seu consumo isolado em si, mas sim ao seu consumo excessivo ultrapassando os limites diários da cafeína presente em sua composição, além da combinação com o álcool ou outras drogas e da presença de anomalias cardíacas.

1.3.1.1 Pressão arterial

Quando o sangue é ejetado do ventrículo esquerdo para a aorta ao fim de um ciclo cardíaco ele exerce uma força sobre a parede dos vasos, sendo esta força denominada pressão arterial (STANFIELD, 2014).

De acordo com a Diretriz Brasileira de Hipertensão Arterial (BARROSO *et al*., 2020) é desejado que PA permaneça em valores inferiores a 120 e 80 mmHg de pressão arterial sistólica (PAS) e diastólica (PAD), respectivamente. Isso porque valores acima dos citados estão relacionados com aumento do dano vascular e, consequentemente, com o desenvolvimento de doenças cardiovasculares (DCV) como acidente vascular encefálico (AVE), doença renal crônica (DRC), doença arterial coronariana (DAC) e de morte. Doenças essas que foram responsáveis por cerca de 18 milhões (32%) das mortes em todo o mundo no ano de 2019 (WORLD HEALTH ORGANIZATION, 2021).

Lewington *et al*. (2002) demonstraram por meio de metanálise que o risco de desenvolvimento de DCV iniciam-se mesmo em valores de PA considerados baixos (115/75 mmHg), sendo esse risco dobrado quando há elevação de 20 mmHg na PAS e 10 mmHg na PAD.

Quando esses valores permanecem continuamente elevados, ou seja, PAS ≥ 140 mmHg e/ou PAD ≥ 90 mmHg, caracteriza-se a hipertensão arterial sistêmica (HAS) (BARROSO *et al*., 2020). Estima-se que 1,28 bilhões de adultos com idades entre 30 a 79 anos em todo o mundo possuam HAS. Destes, 54% sequer sabem que possuem a doença e menos da metade (42%) fazem qualquer tipo de tratamento.

Desta forma, a HAS é considerada uma das principais causas prematuras de morte no mundo (WORLD HEALTH ORGANIZATION, 2023).

Inúmeros são os estudos que associam o aumento da PA com o consumo de BEs (GRASSER *et al.*, 2014b; MILES-CHAN *et al*., 2015; SVATIKOVA *et al*., 2015; SHAH *et al*., 2016a; BASRAI *et al.*, 2019; STOPA *et al*., 2020). Em especial, a revisão sistemática de Shah *et al*. (2016a), ao analisar 15 estudos avaliando a PAS e 14 avaliando a PAD por meio de metanálise, demonstrou que a PAS aumentou em média 4,44 mmHg (n= 340) e a PAD 2,73 mmHg (n= 322) após o consumo BEs, sendo o aumento na PAS de forma mais acentuada (6,44 mmHg) quando consumido BEs com doses superiores a 200 mg de cafeína em sua composição. No entanto, como é desejável que a PAS se encontre ≤ 120 mmHg (PAS) e 80 mmHg (PA), é possível que o aumento temporário da PA provocado pelo consumo agudo de BEs compostas por doses inferiores à 200 mg de cafeína em sua composição não seja clinicamente relevante para a população adulta saudável (LA VIEILLE *et al*., 2021).

1.3.1.2 Frequência cardíaca

A frequência cardíaca (FC) refere-se à quantidade de vezes que o coração bate durante um minuto. É recomendado que seus valores se mantenham entre 60 a 100 batimentos por minuto entre a população adulta (AZEVEDO *et al*., 2016). No entanto, devido a sua regulação via sistema nervoso autônomo ela está sujeita a grande variabilidade advindo da ativação simpática (elevando a FC) ou parassimpática (reduzindo a FC) causada por estressores físicos, cognitivos e ambientais (PALATINI, 2009; VALENTINI e PARATI, 2009).

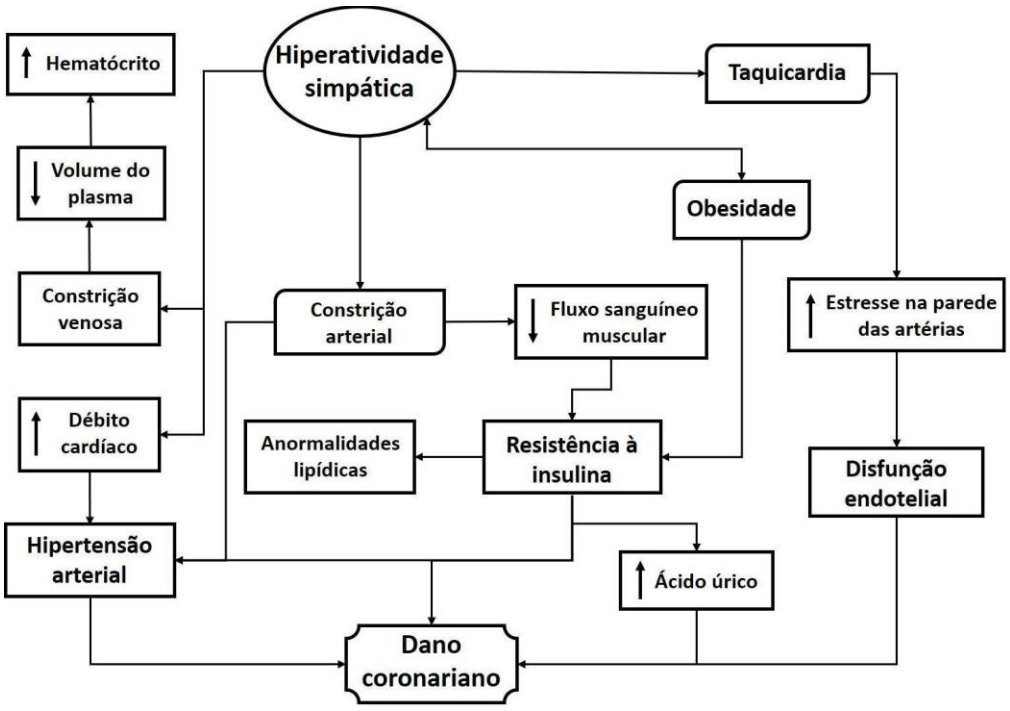
O aumento da ativação simpática e, consequentemente, o aumento dos valores de FC ao longo do tempo apresentam forte associação com o desenvolvimento de doenças cardiometabólicas (Figura 3), devido aos danos vasculares causados pelo aumento da expressão de genes pró-inflamatórios, pró-apoptóticos e pró-coagulantes, além da redução da produção de óxido nítrico (ARMSTRONG *et al*., 2021).

As BEs, devido à ação da cafeína, são conhecidas por aumentar a atividade simpática e, consequentemente, a FC (ALFORD; COX; WESCOTT, 2001; NOWAK *et al*., 2019). Desta forma, é sugestivo pensar que o consumo das mesmas pode desencadear a cadeia de eventos citada anteriormente, aumentando o risco de

desenvolvimento de doenças cardiometabólicas ao longo prazo. No entanto, a literatura atual não estabeleceu um consenso acerca deste comportamento.

A revisão sistemática com metanálise de Shah *et al*. (2016a) não encontrou modificações significativas na FC após o consumo de BEs. Além disso, ao modificarem suas análises para o modelo de eixo fixo, os autores relataram ter observado redução da FC, porém sem significância estatística. Adicionalmente, os resultados apresentados pela revisão sistemática de Lasheras *et al*. (2021) também foram conflitantes, onde 71,1% dos estudos incluídos relataram aumento da FC, porém apenas 38% com significância estatística. Paralelamente, os autores observaram redução na FC em 24,4% dos estudos, com 18,2% deles apresentando significância estatística.

Figura 3 - Frequência cardíaca como marcador de hiperatividade simpática e fator de risco para doenças cardiometabólicas



Fonte: Adaptação baseada no estudo de Palatini (2013).

Basrai *et al*. (2019) sugerem que a ausência da esperada elevação na FC após o consumo de BEs esteja relacionada à presença da taurina em sua composição. Esta que, como citado anteriormente, apresenta características cardioprotetoras, podendo atenuar o aumento da FC. Além disso, os mesmos autores em seu estudo

demonstraram que a ação sinérgica entre cafeína e taurina foi capaz de promover redução na FC.

Apesar de evidências isoladas sugerirem elevação da FC após o consumo de BEs, o que teoricamente é esperado devido a ação da cafeína no sistema simpático, ainda não é possível estabelecer conclusões devido às divergências existentes na literatura. Portanto, é necessário que novas pesquisas acerca do assunto sejam desenvolvidas, principalmente em torno da ação isolada e combinada da cafeína com a taurina.

1.3.1.3 Débito cardíaco

O débito cardíaco representa o volume de sangue ejetado pelo ventrículo esquerdo no período de um minuto, sendo este dependente de duas variáveis: frequência cardíaca e volume sistólico. A FC, como citado anteriormente, é o número de vezes que o coração bate em um minuto. Já o VS representa a quantidade de sangue ejetado pelo ventrículo esquerdo a cada batimento cardíaco (DAVORIC, 1995). Portanto, para determinar o DC é necessário multiplicar a FC pelo VS médio (DC = FC x VS). Em média o DC em repouso é de 5 litros de sangue por minuto (HATCHETT, 1998). Contudo, o DC pode ser afetado por uma variedade de fatores, incluindo exercícios, estresse, medicamentos e doenças cardíacas. Além disso, quando necessário, a FC pode aumentar em 250% em relação ao repouso e o VS pode praticamente dobrar (MARTINI *et al*., 2014), elevando de forma significativa o DC.

O DC muito reduzido pode resultar na redução do fluxo sanguíneo, comprometendo tecidos e órgãos do organismo, o que pode causar sintomas como fadiga, fraqueza e tontura. Por outro lado, um DC elevado pode resultar em sobrecarga cardíaca e desenvolver complicações como hipertensão arterial e insuficiência cardíaca ao longo do tempo (HALL, 2021).

Apesar de ser um importante marcador de desempenho cardíaco, poucos estudos que avaliaram os efeitos agudos do consumo das BEs sobre a saúde cardiovascular se preocuparam com este desfecho. No entanto, o grupo de pesquisa do professor Erik Grasser desenvolveu três importantes estudos avaliando o comportamento do DC em até duas horas após o consumo de uma BE de 355 mL (114 mg de cafeína), onde evidenciaram que o mesmo apresenta tendência de

elevação, porém por diferentes variáveis (FC/VS) a depender do momento de mensuração (GRASSER *et al*., 2014; MILES-CHAN *et al*., 2014; GRASSER; DULLO; MONTANI, 2015).

Nos estudos de Grasser *et al*. (2014) e Miles-Chan *et al*. (2014) o DC elevou até atingir um platô por volta de 30-50 minutos. Ainda que o DC seja dependente da FC e do VS, em ambos os estudos a FC apresentou redução durante o período de ascensão do DC, enquanto o VS apresentou elevação. Contudo, por volta de 80 minutos esse cenário apresentou comportamento oposto, onde a FC apresentou elevação e o VS redução. Este segundo cenário também foi observado no estudo de Grasser, Dullo e Montani (2015), porém vale destacar que este foi o único período de tempo de reavaliação por parte dos autores.

Desta forma, é possível que o aumento observado no DC durante a primeira hora após o consumo das BEs, seja influenciado pela elevação do VS e, posteriormente, pelo possível aumento da FC em consequência do aumento da contratilidade cardíaca promovido pela ação da cafeína ao sistema nervoso simpático. No entanto, como visto anteriormente, apesar de esperado, o comportamento da FC após o consumo das BEs ainda não está bem estabelecido pela literatura atual. Portanto, é necessário que mais estudos avaliando os desfechos responsáveis por modular o DC sejam realizados para que esta variável seja melhor compreendida.

1.3.1.4 Função endotelial

As células endoteliais são responsáveis pelo revestimento interno de todo o sistema circulatório, desde o coração até os capilares mais periféricos (RAJENDRAN *et al*., 2013). Elas desempenham papéis fundamentais na homeostase cardiovascular, regulação do tônus vascular (vasodilatação e vasoconstrição), angiogênese, adesão de monócitos/leucócitos e na fibrinólise, prevenindo a formação de coágulos, tromboses e placas ateroscleróticas, possibilitando maior fluidez do fluxo sanguíneo para conduzir seus constituintes celulares por todo o organismo (SUN *et al*., 2020).

Entre os agentes vasodilatadores e vasoconstritores sintetizados pelo endotélio, o óxido nítrico (*nitric oxide* – NO) possui destaque (VANHOUTTE, 1989), pois, além de sua função vasodilatadora, ele é capaz de regular o recrutamento de leucócitos em processos de inflamatórios agudos, auxiliando o processo de cicatrização de lesões produzidas no endotélio vascular (GARCIA; STEIN 2006;

MCMULLIN *et al*., 2005). Lesões estas que podem ser causadas por perturbações promovidas ao equilíbrio do NO proveniente ao déficit de antioxidantes capazes de neutralizar radicais livres presentes no organismo, caracterizando a disfunção endotelial. Uma vez danificado, o endotélio vascular se torna bastante permeável, permitindo que células e toxinas com potencial inflamatório, como a proteína C reativa, que deveriam permanecer na corrente sanguínea extravase para os demais tecidos (RAJENDRAN *et al*., 2013; RUBANYI e VANHOUTTE, 1986; DEVARAJ; SINGH e JIALAL, 2009).

Além disso, o aumento da permeabilidade da íntima também marca o início do processo aterosclerótico, pois permite que lipoproteínas de baixa densidade (LDL) sejam retidas no espaço subendotelial. A presença de LDL oxidado faz com que moléculas de adesão leucocitária se manifestem na superfície endotelial atraindo monócitos e linfócitos para o interior dos vasos. Posteriormente, os monócitos se diferenciarão em macrófagos, que captarão ainda mais moléculas de LDL oxidadas, resultando nas chamadas células espumosas que são o principal responsável pela formação das placas ateroscleróticas devido sua capacidade de secretar citocinas que amplificam o processo inflamatório e enzimas proteolíticas responsáveis por degradar colágeno e outros componentes teciduais (FALUDI *et al*., 2017).

Nos últimos anos, tem-se observado um crescente número de estudos interessados em identificar os possíveis efeitos do consumo das BEs sobre a função endotelial. Apesar de escassos e inconclusivos, estudos sugerem que o consumo desta classe de bebidas pode promover efeitos negativos (WORTHLEY *et al*., 2010; HIGGINS *et al*., 2017; HIGGINS *et al*., 2021). Worthley *et al*. (2010) ao avaliarem 34 homens adultos saudáveis demonstraram que após uma hora do consumo de 250 mL de uma BE sem açúcar foi capaz de aumentar significativamente a agregação plaquetária e reduzir a função endotelial após uma hora em relação ao grupo controle.

Higgins *et al*. (2017) também observaram redução (5,9 ± 4,6% *vs.*1,9 ± 2,1%; p=0,03) na função endotelial por meio da dilatação mediada por fluxo após 90 minutos do consumo de uma BE (Monster Energy®) de 710 mL por 11 jovens saudáveis. Ao ampliarem seu número amostral (n= 44), Higgins *et al*. (2021) encontraram resultados semelhantes ao seu estudo anterior, onde a função endotelial novamente apresentou redução (5,1 ± 4,4% *vs.* 2,8 ± 3,8%; p= 0,004) após o consumo da BE.

Contrariamente aos achados anteriores, Akhundova, Kaya e Uludağ (2021) não observaram modificações na função endotelial avaliada pela dilatação mediada por

fluxo em 30 indivíduos saudáveis uma hora após ingerirem 355 mL de uma BE (Red Bull®) de baixo teor de cafeína. Em discussão, os autores relatam que as bebidas utilizadas nos estudos anteriores (HIGGINS *et al.*, 2017; HIGGINS *et al.*, 2021) possuíam quatro vezes mais cafeína em sua composição, podendo esta ser a razão para a ausência de modificações de seu estudo. Diante dessa argumentação, era esperado que os autores apresentassem resultados aproximados ao estudo de Worthley *et al*. (2008) que também utilizaram uma BE com baixo teor de cafeína. No entanto, os autores atribuíram essas divergências à técnica de mensuração utilizada, sendo a dilatação mediada por fluxo, técnica adotada em seu estudo, a mais adequada para avaliar o referido desfecho.

Apesar dos sugestivos efeitos negativos sobre a função endotelial, ainda não é possível estabelecer uma significância clínica dada a literatura atual. No entanto, se tratando da integridade da camada interna dos vasos e de sua função regulatória, qualquer possível efeito deletério deve ser considerado como um potencial risco cardiovascular.

1.3.1.5 Intervalo QT e QT corrigido

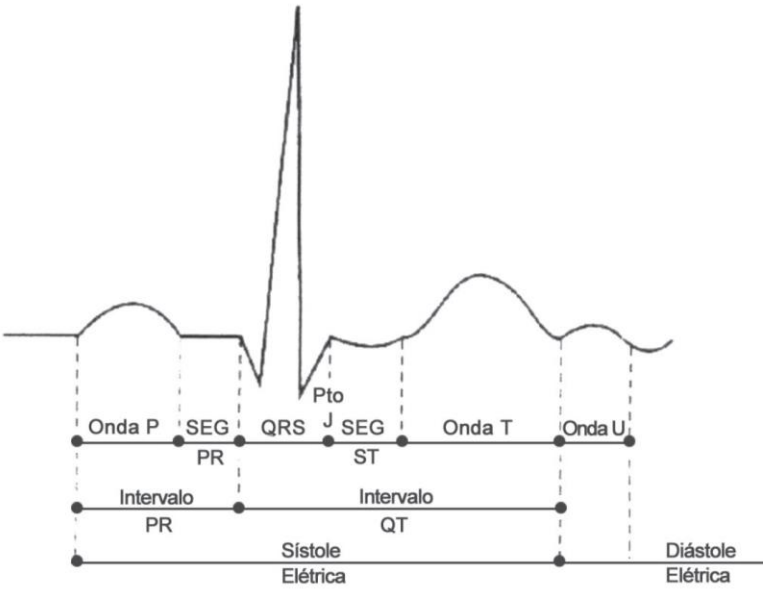
O intervalo QT é uma medida eletrocardiográfica que marca o início do complexo QRS e o final da onda T durante um único ciclo de despolarização e repolarização ventricular, ou seja, o período de sístole elétrica ventricular (Figura 4) (PASTORE *et al.*, 2016). Contudo, como o QT varia inversamente em relação a FC, é comum que o mesmo seja corrigido por meio de fórmulas matemáticas. Comumente adota-se a fórmula de Bazett ($QTc = QT / \sqrt{RR}$), principalmente em pacientes com FC entre 60 a 100 bpm (POSTEMA; WILDE, 2014) para fazer essa correção.

O intervalo QT é utilizado como um marcador de risco de mortalidade na população em geral (OKIN *et al.*, 2000), uma vez que o prolongamento (Figura 5) de seus valores de referência (≤ 450 ms para homens, ≤ 470 ms para mulheres e ≤ 460 ms para crianças em geral) (FELDMAN e GOLDWASSER, 2004) estão associados a maior risco de desenvolvimento de arritmias ventriculares e, consequentemente morte súbita, principalmente em intervalos ≥ 500 ms (PASTORE *et al.,* 2016; TRINKLEY *et al*., 2013).

Eventos como taquicardia, arritmias e até mesmo, morte súbita, têm sido relatados e associados ao possível prolongamento do QT/QTc provocado pelo

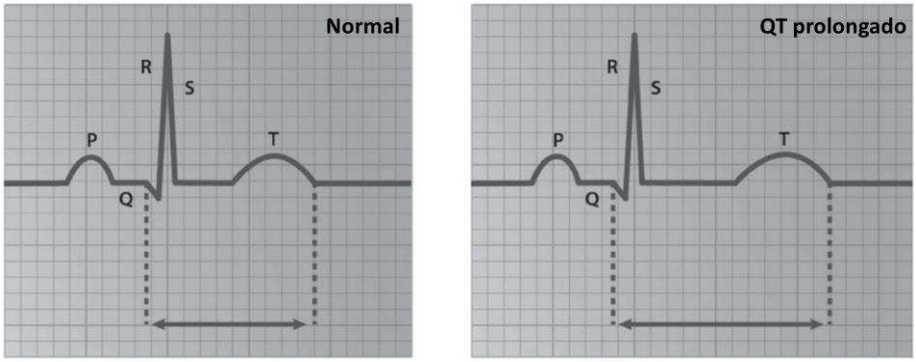
consumo de BEs (GOLDFARB; TELLIER; THANASSOULIS, 2014). Lasheras *et al*. (2021) relataram por meio de revisão sistemática que o QTc aumentou cerca de 14,7 ms após o consumo de BEs com volume médio de 444,4 mL (162,6 mg de cafeína). Corroborando estes achados, Shah *et al*. (2019) demonstram que o consumo de duas BEs distintas de 947,2 mL (304-320 mg de cafeína), foram capazes de elevar o QTc pela fórmula de Bazett em 17,9 ms e 19,6 ms, respectivamente. Curiosamente, o estudo de Kozik *et al*. (2016) relatou que o QTc aumentou em média 80 ms após o consumo de duas latas de uma BE de 473,6 mL (154 mg de cafeína). Além disso, 8 dos 14 participantes (57%) do estudo apresentaram valores de QTc > 500 ms, sugerindo, portanto, maior risco pró-arritmogênico às BEs.

Figura 4 - Eletrocardiograma normal



Fonte: Feldman e Goldwasser (2004).

Figura 5 - Eletrocardiograma normal e com QT prolongado



Fonte: Adaptação baseada no estudo de Trinkley *et al.* (2013).

No entanto, tais resultados devem ser analisados com cautela. A revisão sistemática de Lasheras *et al*. (2021) carece de homogeneidade entre os estudos incluídos, o que inviabiliza a possibilidade de generalização dos resultados devido às inerentes fragilidades. Além disso, inúmeros são os estudos que não relataram resultados semelhantes aos anteriormente citados (BROTHERS *et al.,* 2016; SHAH *et al*., 2016b; SHAH *et al*., 2016c; FLETCHER *et al*., 2017; HIGGINS *et al*., 2021). Exemplo disso é o próprio estudo de Shah *et al*. (2016b), que ao avaliarem os efeitos do consumo de uma BE de 59,2 ml (200 mg de cafeína) no QT/QTc durante o período de cinco horas não observaram diferenças significativas. Em um terceiro estudo realizado pelo mesmo autor (SHAH *et al*., 2016c), que avaliou o efeito do consumo de uma BE de 947,2 mL (320 mg de cafeína) sobre o QT/QTc durante o período de cinco horas e meia, demonstrou que apenas após duas horas o QTc apresentou aumento significativo de 3,37 ms.

Diante do exposto, é sugestivo inferir que o consumo das BEs possa causar riscos à saúde cardiovascular de seus consumidores devido a série de estudos e relatos de caso disponíveis na literatura, no entanto quando estes são analisados de forma crítica e aprofundada é possível perceber que os eventos adversos, em especial os cardiovasculares, estão associados sobredosagem de cafeína causada pelo alto volume de bebida consumido, a anomalias cardíacas previamente existentes e a combinação com outras substâncias como o álcool e outras drogas. Desta forma, diferentemente da ideia radical que se perpetua em relação aos riscos do consumo das BEs, estas parecem não apresentar riscos iminentes à saúde de indivíduos adultos saudáveis. Ainda assim, é extremamente necessário que novos estudos sejam desenvolvidos, contemplando principalmente as limitações metodológicas apresentadas pela literatura atual, pois só assim será possível esclarecer as dúvidas que ainda pairam em relação ao real risco do consumo destas bebidas.

2 ARTIGO I – Protocolo de revisão sistemática com metanálise

A ser submetido para avaliação.

TÍTULO: Effects of energy drink consumption on cardiovascular parameters in healthy adults: Protocol for a systematic review.

Systematic Review and Meta-analysis Protocol Article

Effects of energy drink consumption on cardiovascular parameters in healthy adults: Protocol for a systematic review

Abstract

Context: Isolated evidence indicates that the consumption of energy drinks can acutely alter cardiovascular parameters, however, there is still no consensus on the real magnitude of these effects.

Objective: This systematic review aims to examine the acute effects of energy drinks on blood pressure, heart rate, cardiac output, endothelial function, and QT interval and/or corrected QT in healthy adults.

Review methods: Only randomized clinical trials will be included. Searches will be performed in the following sources: PubMed, EMBASE, Cochrane, Web of Science, LILACS and SPORTDiscus. We will also search the gray literature and assess the quality of individual studies (RoB2) and strength of evidence (GRADE). We will follow the PRISMA guidelines and the PICOS framework. Statistical analyzes will be performed in RStudio via the R meta package.

Conclusion: The results of the meta-analyses described by this protocol will contribute to previous findings in the literature and will improve recommendations on its consumption in this population.

Registration: The study protocol for this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO - CRD42022295335).

Keywords: caffeine; central nervous system stimulants; blood pressure; heart hate; cardiac output; electrocardiography.

Introduction

Evidence shows that the consumption of energy drinks improves physical performance and concentration (Chtourou et al., 2019). People in need for a boost of energy to attenuate exercise-induced and/or everyday fatigue or even improve physical and mental performance have been resorting to energy drinks (Kopacz et al., 2012; Kumar et al., 2015) especially adolescents and young adults (Heckman et al., 2010). Unlike traditional drinks, such as coffee, tea and isotonic sports beverages, energy drinks contain high caffeine levels and large amounts of vitamins, minerals, taurine, amino acids and phytochemicals (Kumar et al., 2015). The consumption of these products has been a topic of research in different study areas over the last 10 years.

Caffeine consumption blocks the adenosine receptors in blood vessels and inhibits vasodilator effects resulting from sympathetic hyperactivity (Dunwiddie & Masino, 2001; Higgins & Babu, 2013). Exacerbated sympathetic activity stimulates the release of acetylcholine from the pituitary gland, which in turn stimulates the adrenal glands to secrete adrenaline. In parallel, caffeine increases cyclic adenosine 3,5-monophosphate (AMP) and has a positive inotropic action on myocardial tissue (Evans et al., 2021), resulting in increased heart rate (HR), blood pressure (BP) and blood volume (Wassef et al., 2017). Sugar is also an active ingredient in energy drinks that is potentially associated with cardiovascular responses. Grasser et al., (2016) suggested that sugar-sweetened energy drinks may produce cardiovascular changes by increasing cardiac output and reducing total peripheral resistance.

In contrast to caffeine and sugar, taurine is an ingredient commonly found energy drinks that appears to exert a protective effect on cardiovascular parameters. It acts on intracellular calcium regulation, increases cardiac contractility and attenuates angiotensin II effects producing vasodilation and BP reduction and thus protecting against arrhythmias and cardiomyopathy (Qaradakhi et al., 2020; Sun et al., 2016).

Shah et al., (2016) reported in a meta-analysis that energy drinks potentially increase systolic and diastolic blood pressure (SBP/DBP) without affecting resting HR. On the other hand, Lasheras et al., (2021) reviewed data from 43 prospective studies and found increased HR in response to the acute consumption of energy drinks compared to resting controls. Therefore, there is no consensus on the acute effects of energy drinks consumption on HR and other cardiovascular parameters, such as cardiac output and endothelial function. It is also unclear the magnitude of response of these parameters to different beverage volumes and ingredient amounts. We strongly believe that Shah et al. meta-analysis made a major contribution to the understanding of this subject matter. It is a starting point for further investigation into the acute cardiovascular effects of energy drink consumption and more studies to support these findings. As for the review by Lasheras et al. (2021), it has many knowledge gaps that need to be filled

by new research (i.e., no pooled results and no inconsistency and quality analysis of individual studies available) which limit the assessment of the methodological quality of their findings.
Considering that the acute consumption of energy drinks is likely to produce changes in cardiovascular parameters in healthy adults, regular energy drink consumption may pose increased cardiovascular health risk to consumers (Lasheras et al., 2021; Shah et al., 2016). For that reason, we designed a systematic review of randomized clinical trials (RCTs) to examine the acute effects of energy drink consumption on cardiovascular parameters, including BP, resting HR, cardiac output, endothelial function and QT/ QTc interval, in healthy adults.

Systematic review method

Study design

This study will consist of a systematic review and meta-analysis, so we will follow the Preferred Report Items for Systematic Reviews and Meta-Analysis (PRISMA) (Moher et al., 2015; Page, McKenzie, et al., 2021). Any amendments to this protocol will be documented in the main study. The protocol for this systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022295335). The database used for this meta-analysis will be available in the Mendeley Data repository as open access.

Eligibility criteria

We used Population, Intervention, Comparison, Outcomes and Study (PICOS) design as a framework to formulate the research question and assist database searches, as follows: a) Population (healthy adults aged ≥18 years); b) Intervention (energy drinks available); c) Comparator (water or placebo beverages that do not have an effect on the outcomes); d) Outcomes (mean BP, SBP/DBP, resting HR, cardiac output, endothelial function and QT/QTc interval); e) Study (RCTs).
There will be included in the systematic review studies whose titles and/or abstracts contain the text words "energy drinks" and "cardiovascular effects, including mean BP, SBP/DBP, resting HR, cardiac output, endothelial function and QT/QTc interval." The study population (healthy adults) should be mentioned in the main text. The “intervention” needs to include the use of energy drinks available and water or other beverages that do not have an effect on the outcomes should be used as "comparison". For subgroup analyses, whenever possible, all volumes, ingredient amounts, brands and effects times will be included.

Inclusion and exclusion criteria

This systematic review will include RCTs involving healthy adults aged 18 years or more with information available on cardiovascular parameters measured by the following methods/techniques:

a) Blood pressure: auscultatory or oscillometric methods;

b) Heart rate: portable cardiotachometer or electrocardiography;

c) Cardiac output: invasive and non-invasive methods;

d) Endothelial function: flow-mediated dilation (FMD); measurement of reactive hyperemia by venous occlusion plethysmography; or plethysmography using intra-arterial infusion of vasoactive agents; and

e) QT/QTc interval: electrocardiogram.

Studies involving additional interventions such as other non-energy drink beverages (fruit juice, tea, alcohol or coffee), drugs, energy bars, sports supplements, physical activity and psychological/emotional stimuli will be excluded. Similar studies published in different journals will be reviewed and excluded if deemed to be duplicates.

Search strategy

One investigator of our group (PIBG) did a preliminary search in Medline database via PubMed to determine whether the research question met all of the FINER criteria (feasible, interesting, novel, ethical and relevant) (Brian, 2006). The results were discussed by our group (PIBG, LFD and GW) and we agreed to go ahead and develop a protocol for this systematic review. We used the 2015 Peer Review of Electronic Search Strategies (PRESS) Guideline Evidence Based Checklist (McGowan et al., 2016) to develop and review the search strategy for the databases as recommended by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019) (Medline via PubMed; EMBASE and Cochrane Library). To expand our results, we will conduct searches in the following databases: Latin America and Caribbean Health Sciences Literature (LILACS)/Virtual Health Library (VHL); Web of Science and SPORTDiscus. To minimize any publication bias, we will also search for gray literature, including OpenGrey and the Brazilian Coordination for the Improvement of Higher Education Personnel (CAPES) Bank of Theses and Dissertations. For unpublished ongoing studies, we will conduct searches in the following clinical trial registries: ClinicalTrial.gov; Brazilian Clinical Trials Registry (REBEC) and the WHO International Clinical Trials Registry Platform (ICTRP). All database searches will be run during the first two weeks of July 2022 with a complete selection of eligible studies by the end of September 2022. The process of tabulation and data analysis will be finalized by the end of March 2022.

There will be no limitations to language and publication date. An additional search will be carried out in all databases and platforms to ensure that studies published since our initial searches could be included.

The main medical subject headings (MeSH) terms are: energy drinks, cardiovascular system, heart rate, blood pressure, arterial pressure, vascular endothelium, myocardial infarction, heart arrest, heart failure, cardiac arrhythmias and long QT syndrome. To increase the precision and sensitivity of our searches, the indexing terms for the studydesign (RCT) will be added to the search terms in MEDLINE (Robinson & Dickersin, 2002) and EMBASE (Glanville et al., 2019) databases. An example of one of the search strategies that will be used is detailed in Table 1. The detailed description of the search strategy of all databases is expressed in tables S2 and S3 of the supplementary material.

Table 1

*Example of the search strategy that will be applied in the databases**

Database	Search strategy
MEDLINE (PubMed)	***Energy Drink:*** *(Drink, Energy OR Drinks, Energy OR Energy Drink) AND* ***Cardiovascular parameters:*** *(Hemodynamics OR Atrial Pressure OR Baroreflex OR Blood Pressure OR Arterial Pressure OR Pulmonary Wedge Pressure OR Venous Pressure + Blood Volume OR Cerebral Blood Volume OR Erythrocyte Volume OR Plasma Volume OR Cardiac Output OR Stroke Volume OR Cardiac Volume OR Heart Rate OR Heart Rate, Fetal OR Respiratory Sinus Arrhythmia OR Heart Sounds OR Hemorheology OR Blood Flow Velocity OR Blood Viscosity OR Pulsatile Flow OR Kallikrein-Kinin System OR Pulse OR Renin-Angiotensin System OR Valsalva Maneuver OR Vascular Capacitance OR Vascular Resistance OR Capillary Resistance OR Vasoconstriction OR Vasodilation OR Ventricular Pressure) AND* ***Type of study:*** *(Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw])*

* The search strategies of the other databases followed the same model, however they were adjusted according to the specificities of each database. The same was adopted for gray literature.

Data extraction and management

All articles retrieved from our searches will be saved and exported as .ris or .txt files and imported into Rayyan Reference Manager. Duplicate studies will be removed using a

deduplication function. Two blinded reviewers (PIBG and VVB) will manually check for remaining duplicates by reviewing titles, authors, year of publication and abstracts.
Two blinded reviewers (PIBG and VVB) will independently screen eligible articles based on their titles and abstracts. They will use Rayyan application "to include" articles that meet the eligibility criteria. Those that do not meet the inclusion criteria will
be marked as "excluded" and categorized by reason for exclusion (i.e., ineligible outcome(s) or population and other non-RCT study design). If it is not clear whether a study should be included, it will be marked as "undecided". In the last step, both reviewers will compare the articles screened for any discrepancies. If the abstract of a study does not contain enough information, the full-text article will be retrieved and read. Discrepancies will be resolved by consensus and disagreements on inclusion criteria will be resolved by a third reviewer (LFD or GW).
Two blinded reviewers (PIBG and VVB) will independently conduct data extraction. If a study is relevant for inclusion in the review, they will extract and compile the main data in a pre-structured Excel 2010 for Windows data entry form, including: study (authors, journal, year of publication, intervention, characteristics of energy drink consumption); participants (age, gender, body mass index [BMI] and health status); methods (randomization, blinding); and outcomes (sample size and mean and standard deviation at baseline and post-intervention). For the extraction of data from eligible studies with results presented in graphs, we will contact the authors by email to obtain these data or use GetDate Graph Digitizer 2.26 to extract the data. For studies assessing the outcomes of interest at different time points, we will independently compare baseline measurements with the results at each time point. Our database will be formatted and imported into RStudio for data analysis.

Risk of bias of individual studies

The risk of bias of individual studies will be assessed using Cochrane Risk of Bias (RoB) 2 tool as discussed in the handbook (Sterne et al., 2019). The assessment is based on a set of six domains of bias: random sequence generation; allocation sequence concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; and selective outcome reporting. The studies will be classified as low risk of bias, some concerns of bias or high risk of bias. No study will be excluded based on the risk of bias. We will assess the risk of bias of primary outcomes of interest.
The strength of the body of evidence will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool (Brasil et al., 2014). This tool rates the quality of evidence from the assessment of confidence in specific pairwise effect estimates as well as treatment effect estimates from network meta-analysis in the following domains:

study design; methodological limitations (risk of bias); inconsistency; indirectness of evidence; imprecision; publication bias; magnitude of effect; dose-response gradient; and residual confounding (Brasil et al., 2014).

Statistical analysis

Statistical analyses will be carried out to estimate the effect of energy drink consumption on cardiovascular parameters compared to a control beverage. For outcomes with the same unit, summary effect estimates will be expressed as mean differences (MD) and related 95% confidence interval (95% CI). For outcomes with different units, summary effect estimates will be expressed as standardized mean differences (SMD) and related 95% CI. The SMD expresses the size of the intervention effect in each study relative to the variability in outcome measurements observed in that study. Given that the SMD provides an overall interpretation of the results (absolute unit), we will consider transforming SDM into units of the most common measurement instrument or into proportions (%) so that the data are presented in a language more adequate to the outcome analyzed. To summarize the data, the MD or SMD from individual studies will be pooled using a fixed- or random-effects model as appropriate. A fixed-effects model will be the method of choice if all factors determining the effect estimate are equal across eligible studies, with low inconsistencies across studies. If inconsistencies across studies are due to different participant characteristics (clinical heterogeneity) or methods (methodological heterogeneity), with different effect sizes across studies, we will use a random-effects model to incorporate the variability in the meta-analysis. Since the 95% CI from random effects refer to uncertainty in the location of the mean effects across studies, we will consider the calculated values for a 95% prediction interval (95% PI) as they reflect the interval of uncertainty of the effects to be expected in future RCTs (InHout J et al., 2016). To assess the consistency of energy drink effects across studies, the degree of heterogeneity (relative variability in effect estimates attributed to heterogeneity) will be tested using the inconsistency test by Higgins (I2) for every pairwise comparison (Dias et al., 2013; Higgins et al., 2019) (Box S1 shows the interpretation of heterogeneity results; see the supplementary material). To explore heterogeneity ($p<0.05$), we will conduct subgroup analyses and meta-regression analyses for effect modifiers with normal distribution in a quartile-quartile plot (qq-plot) and confirm it using the Shapiro-Wilk test ($p>0.05$) (Liberati et al., 2009). To identify discrepant data from the meta-analysis, forest plots will be constructed to display the effect estimates across studies and detect potential outliers based on non-CI overlapping that is due to heterogeneity (Dias et al., 2013). Potential effect modifiers (e.g., age, BMI, sex, amount of energy drinks consumed, geographic location and randomization) will be analyzed separately. When heterogeneity is significant and we do not have data to explain it, the meta-analysis will not be

performed, but we will present individual intervention effect estimates of the studies. Considering that selective publication and/or the suppression of specific results cause bias and consequently affect the validity of the results (Deeks et al., 2005), if applicable (≥10 studies; more than one study with significant statistical data; studies with different sample sizes), we will perform the Egger's test using a funnel plot to assess potential publication bias in the meta-analysis (Page, Higgins, et al., 2021; Simmonds, 2015). If publication bias is detected (Egger's test, $p<0.1$) the trim-and-fill method will be used to identify and correct for funnel plot asymmetry with an addition of information on the bias-corrected data to the original data (prior to the trim and imputation of data by the trim-and-fill method) (Duval & Tweedie, 2000; Mavridis & Salanti, 2014). Alternative analyses to the primary analysis of data including sensitivity analysis will be performed to assess the robustness of our decisions (e.g., imputation method used to impute the missing values; inclusion of studies with a high risk of bias, data from conference abstracts etc.) (Boutron et al., 2021). In multi-arm trials, we will determine the intervention groups that are relevant to be included in the systematic review. If there are multiple intervention groups with similar categories, these groups will be pooled for a single pairwise comparison using the equations suggested by Cochrane (Higgins et al., 2019) as follows:

- Sample size (N): Ngroup A + Ngroup B;
- Mean (M): Ngroup A * Mgroup A + Ngroup B * Mgroup B/Ngroup A + Ngroup B;
- Standard Standard deviation (SD): SD = √ (Ngroup A – 1) * SD2 group A + (Ngroup B – 1) * SD2 group B + (Ngroup A * Ngroup B/Ngroup A + Ngroup B) * (Mgroup A + Mgroup B – 2 * Mgroup A * Mgroup B)/Ngroup A + Ngroup B – 1.

To avoid errors due to diferent data units in RCTs with multiple intervention arms and a single control group, the sample size for the control group will be weighted by the number of groups and participants included. For crossover RCTs, we will use a more conservative approach to determine the smallest unit error as proposed by Cochrane (#section-23-2-6) (Higgins et al., 2019). Tus, we will collect all measurement data for energy drinks (pre- and post-intervention) and control drinks (pre- and post-control) and analyze them as parallel groups and individual SDs for each intervention. In case of missing SDs for changes from baseline in any eligible study, they will be imputed from SDs for each time period (intervention and control) and we will calculate a correlation coefficient using the equations as follows (Higgins et al., 2019):

- Correlation coefficient (CC) = SD2 baseline + SD2 final − ∆ SD2/2 * SD2 baseline * SD2 final
- ∆ SD = √ SD2 baseline + SD2 final – (2 * CC * SD baseline * SD final.

The measures of dispersion expressed as CIs or standard errors were converted into standard deviations (SDs = SE * √n) prior to the analysis. Two-tailed tests will be used at a significance level of $p<0.05$. Data modelizations will be performed with RStudio (version 1.3.959) using the

R package meta (version 3.6.1) for Windows. The main RStudio script for conducting the meta-analysis is presented in Box S2 (see supplementary material).

Discussion

Changes in BP and QT interval have been reported in response to acute consumption of energy drinks in some studies. However, we found two meta-analyses in our literature search (Lasheras et al., 2021; Shah et al., 2016) with conflicting results on the effects of energy drinks on HR. The fact that these analyses were not limited to RCTs only (Table S1 shows a description of cardiovascular parameters in response to acute consumption of energy drinks included in previews published systematic reviews; see supplementary material) may have affected the quality of their results. In addition, given the potential effects of energy drinks on other cardiovascular parameters, including cardiac output and endothelial function, a summary analysis of these results may provide input for better understanding cardiovascular effects of energy drinks consumption.

We also deem it important to examine cardiovascular responses to different amounts of energy drinks consumed and how different ingredient combinations (amounts and types) may affect the outcomes of interest.

Previous studies have made a major contribution to the understanding of this subject matter, but we believe that a fresh investigation of these ingredients and variables using a more rigorous methodological approach including an analysis of inconsistency and quality of individual studies may help enhance our scientific knowledge.

Conclusions

In conclusion, a systematic review involving only RCTs assessing the acute effects of energy drink consumption on cardiovascular parameters in healthy adults can be helpful for understanding the effects of energy drinks and improving recommendations on their consumption in this population.

References

Boutron, I., Page, M. J., Higgins, J. P., Altman, D. G., Lundh, A., & Hróbjartsson, A. (2021). Chapter 7: Considering bias and conflicts of interest among the included studies. In Cochrane Handbook for Systematic Reviews of Interventions version 6.0. Retrieved from https://training.cochrane.org/handbook/current/chapter-07

Brasil, Saúde, M. d., Secretaria de Ciências, T. e. I. E., & Tecnologia, D. d. C. e. (2014). Diretrizes metodológicas: Sistema GRADE manual de graduação da qualidade da evidência e força de recomendação para tomada de decisão em saúde. In (pp. 74). Retrieved from https://bvsms.saude.gov.br/bvs/publicacoes/diretrizes_metodologicas_sistema_grade.pdf

Brian, H. R. (2006). Forming research questions. Journal of Clinical Epidemiology, 59(9), 881-886. https://doi.org/10.1016/j.jclinepi.2006.06.006

Chtourou, H., Trabelsi, K., Ammar, A., Shephard, R. J., & Bragazzi, N. L. (2019). Acute Effects of an "Energy Drink" on Short-Term Maximal Performance, Reaction Times, Psychological and Physiological Parameters: Insights from a Randomized Double-Blind, Placebo-Controlled, Counterbalanced Crossover Trial. Nutrients, 11(5), 992. https://doi.org/10.3390/nu11050992

Deeks, J. J., Macaskill, P., & Irwig, L. (2005). The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. Journal of Clinical Epidemiology, 58(9), 882-893. https://doi.org/10.1016/j.jclinepi.2005.01.016

Dias, S., Sutton, A. J., Welton, N. J., & Ades, A. E. (2013). Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. Medical Decision Making : an International Journal of the Society for Medical Decision Making, 33(5), 618-640. https://doi.org/10.1177/0272989X13485157

Dunwiddie, T. V., & Masino, S. A. (2001). The role and regulation of adenosine in the central nervous system. Annual Review of Neuroscience, 24. https://doi.org/10.1146/annurev.neuro.24.1.31

Duval, S., & Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics, 56(2), 455-463. https://doi.org/10.1111/j.0006-341x.2000.00455.x

Evans, J., Richards, J. R., & Battisti, A. S. (2021). Caffeine. In StatPearls. StatPearls Publishing. Retrieved from www.ncbi.nlm.nih.gov/books/NBK430685/

Glanville, J., Foxlee, R., Wisniewski, S., Noel-Storr, A., Edwards, M., & Dooley, G. (2019). Translating the Cochrane EMBASE RCT filter from the Ovid interface to Embase.com: a case study. Health Information and Libraries Journal, 36(3), 264-277. https://doi.org/10.1111/hir.12269

Grasser, E. K., Miles-Chan, J. L., Charrière, N., Loonam, C. R., Dulloo, A. G., & Montani, J.-P. (2016). Energy drinks and their impact on the cardiovascular system: potential mechanisms. Advances in Nutrition, 7(5), 950-960. https://doi.org/10.3945/an.116.012526

Heckman, M., Sherry, K., & De Mejia, E. G. (2010). Energy drinks: an assessment of their market size, consumer demographics, ingredient profile, functionality, and regulations in the United States. Comprehensive Reviews in Food Science and Food Safety, 9(3), 303-317. https://doi.org/10.1111/j.1541-4337.2010.00111.x

Higgins, J. P., & Babu, K. M. (2013). Caffeine reduces myocardial blood flow during exercise. The American Journal of Medicine, 126(8). https://doi.org/10.1016/j.amjmed.2012.12.023

Higgins, J. P., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., & Welch, V. A. (2019). Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons. Retrieved from https://training.cochrane.org/handbook

InHout J, Loannidis JP, Rovers MM, & JJ, G. (2016). Plea for routinely presenting prediction intervals in meta-analysis. BMJ Open, 6(7). https://doi.org/10.1136/bmjopen-2015-010247

Kopacz, A., Wawrzyniak, A., Hamulka, J., & Górnicka, M. (2012). Studies on the determinants of energy drinks intake by students. Roczniki Panstwowego Zakladu Higieny, 63(4), 491-497.

Kumar, G., Park, S., & Onufrak, S. (2015). Perceptions about energy drinks are associated with energy drink intake among U.S. youth. American Journal of Health Promotion: AJHP, 29(4). https://doi.org/10.4278/ajhp.130820-QUAN-435

Lasheras, I., Seral, P., Alonso-Ventura, V., & Santabárbara, J. (2021). The impact of acute energy drink consumption on electrical heart disease: A systematic review and meta-analysis. Journal of Electrocardiology, 65. https://doi.org/10.1016/j.jelectrocard.2021.01.020

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P. A., . . . Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. Annals of Internal Medicine, 6(7), 1-28. https://doi.org/10.1136/bmj.b2700

Mavridis, D., & Salanti, G. (2014). How to assess publication bias: funnel plot, trim-and-fill method and selection models. Evidence-based Mental Health, 17(1). https://doi.org/10.1136/eb-2013-101699

McGowan, J., Sampson, M., Salzwedel, D. M., Cogo, E., Foerster, V., & Lefebvre, C. (2016). PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. Journal of Clinical Epidemiology, 75, 40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., . . . Group, P.-P. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews, 4(1), 1-9. https://doi.org/10.1186/2046-4053-4-1

Page, M. J., Higgins, J. P., & Sterne, J. A. (2021). Chapter 13: Assessing risk of bias due to missing results in a synthesis. Retrieved from https://training.cochrane.org/handbook/current/chapter-13

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., . . . Brennan, S. E. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ, 372. https://doi.org/10.1136/bmj.n71

Qaradakhi, T., Gadanec, L. K., McSweeney, K. R., Abraham, J. R., Apostolopoulos, V., & Zulli, A. (2020). The Anti-Inflammatory Effect of Taurine on Cardiovascular Disease. Nutrients, 12(9), 2847. https://doi.org/10.3390/nu12092847

Robinson, K. A., & Dickersin, K. (2002). Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. International Journal of Epidemiology, 31(1), 150-153. https://doi.org/10.1093/ije/31.1.150

Shah, S., Chu, B., Lacey, C., Riddock, I., Lee, M., & Dargush, A. (2016). Impact of acute energy drink consumption on blood pressure parameters: a meta-analysis. Annals of Pharmacotherapy, 50(10), 808-815. https://doi.org/10.1177/1060028016656433

Simmonds, M. (2015). Quantifying the risk of error when interpreting funnel plots [OriginalPaper]. Systematic Reviews, 4(1), 1-7. https://doi.org/doi:10.1186/s13643-015-0004-8

Sun, Q., Wang, B., Li, Y., Sun, F., Li, P., Xia, W., . . . Zhu, Z. (2016). Taurine Supplementation Lowers Blood Pressure and Improves Vascular Function in Prehypertension: Randomized, Double-Blind, Placebo-Controlled Study. Hypertension, 67(3), 541-549. https://doi.org/10.1161/HYPERTENSIONAHA.115.06624

Sterne, J. A., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., . . . Higgins, J. P. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ, 366. https://doi.org/10.1136/bmj.l4898

3 ARTIGO II – Revisão sistemática com metanálise

PERIÓDICO: Nutrition Reviews - IF 7,11; Qualis A1 (Interdisciplinar)

OBJETIVOS E ESCOPO DA REVISTA: Nutrition Reviews is a highly cited, monthly, international, peer-reviewed journal that specializes in the publication of authoritative and critical literature reviews on current and emerging topics in nutrition science, food science, clinical nutrition, and nutrition policy. Readers of Nutrition Reviews include nutrition scientists, biomedical researchers, clinical and dietetic practitioners, and advanced students of nutrition.

NORMAS: https://academic.oup.com/nutritionreviews/pages/General_Instructions

SITUAÇÃO ATUAL: Submetido.

TÍTULO: Acute effects of energy drink consumption on cardiovascular parameters in healthy adults: a systematic review and meta-analysis of randomized clinical trials.

Systematic Review and Meta-analysis Article

ACUTE EFFECTS OF ENERGY DRINK CONSUMPTION ON CARDIOVASCULAR PARAMETERS IN HEALTHY ADULTS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CLINICAL TRIALS

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Abstract

Background: Energy drinks (ED) are beverages that contain ingredients which may pose a risk to consumers' cardiovascular health. But current evidence is conflicting and warrants further investigation.

Objective: We conducted a systematic review and meta-analysis of studies investigating the acute effects of ED consumption on systolic blood pressure (SBP), diastolic blood pressure (DBP), resting heart rate (HR), cardiac output (CO), endothelial function and QT/corrected QT interval (QT/QTc) in healthy adults.

Data source: We searched the databases PubMed, EMBASE, Cochrane, LILACS, Web of Science, SportDiscus and the gray literature to identify randomized controlled trials (RCTs).

Data extraction: Two independent evaluators screened 2,014 studies and extracted relevant data from those selected for the analysis. We also performed a risk of bias assessment using the RoB2 tool and a strength of evidence assessment using GRADE.

Data analysis: A total of 17 RCTs were included in the meta-analysis. As for the risk of bias, 11 studies were rated as having "some concerns" and six as "high risk of bias". The consumption of ED increased SBP, DBP and CO in different time frames. More pronounced effects were seen on SBP at 60-80 minutes (4.71 mmHg [95% CI 2.97–6.45], GRADE: moderate), DBP at 120 minutes (4.51 mmHg [95% CI 2.60–6.42], GRADE: low) and CO at 30-40 minutes after consumption (0.43 L [95% CI 0.08–0.77], GRADE: very low). The effects of ED consumption on resting HR and QT/QTc interval were not significant ($p \leq 0.05$). The effects on endothelial function were not assessed as we did not find any RCT meeting the inclusion criteria.

Conclusions: Acute consumption of ED increases SBP, DBP and CO in healthy adults. Yet, we found no changes in other cardiovascular parameters. Our results should be interpreted with caution due to the small number of studies included in the analysis.

Keywords: Caffeine; Central Nervous System Stimulants; Hemodynamics; Electrocardiography; Blood Pressure

INTRODUCTION

The consumption of energy drinks are popularly known to improve energy, mental concentration, memory and performance and attenuate physical and mental fatigue.[1] Energy drinks have become the fastest-growing drink markets since the creation of bottled water,[2] with currently nearly $45.8 billion in sales and a projected growth to $108.4 billion in sales by 2031.[3] However, the exponential growth of energy drink consumption especially among young and adult consumers[4] is concerning because of increasing numbers of reports of side effects associated with its ingredients especially caffeine.[5,6]

Energy drinks usually contain high levels of caffeine and the risk of toxic caffeine overdose is concerning.[7,8] Caffeine acts by inhibiting adenosine receptors that leads to exacerbated sympathetic activity,[9] increased resting heart rate (HR),[10] blood pressure (BP),[11] and plasma volume and[12] consequently increased risk of developing tachycardia, angina, arrhythmias from QT/corrected QT (QT/QTc) changes,[6,10,13] vascular endothelium damage [12,14] and even death.[15,16]

Shah et al.[11] conducted a meta-analysis and found that energy drinks acutely increased systolic blood pressure (SBP) and diastolic blood pressure (DBP) without affecting resting HR. Lasheras et al.[10] systematically reviewed data from 43 prospective clinical trials and found that only 38% of the studies reported changes in resting HR while 41.7% reported significant QTc prolongation when compared to baseline values and the control group.

We recognize that both review studies have made major contributions to the understanding of this subject. However, they included not only randomized clinical trials (RCTs) but also prospective clinical trials and their analyses of summary data may have been limited due to methodological weaknesses in these studies. Furthermore, we believe that assessing the risk of bias of individual studies and strength of evidence could provide more robust results.

Considering all these aspects, we understand that the acute effects of energy drink consumption on cardiovascular parameters in healthy adults warrant further investigation. Thus, we conducted a systematic review and meta-analysis of RCTs investigating any acute and subacute effects of consumption of commercially available energy drinks on SBP and DBP (as primary outcome) in healthy adults. Changes in resting HR, cardiac output (CO), endothelial function and QT/QTc interval were evaluated as secondary outcomes. In addition, we examined the potential effects on these same variables by caffeine content of energy drinks.

METHODS

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[17] and the Cochrane Handbook for Systematic Reviews of Intervention recommendations.[18] The protocol of this systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42022295335). All research data used in this study are available in the open-access Mendeley Data repository.[dataset][19]

Search strategy and study selection

We defined the study inclusion and exclusion criteria using the PICOS framework (Table 1). We conducted searches for eligible RCTs on the databases Medline (PubMed), EMBASE, Cochrane Library, Web of Science, SPORTDiscus and Latin America and Caribbean Health Sciences Literature (LILACS). To minimize any publication bias, we also searched the gray literature, including OpenGrey, the Brazilian Coordination for the Improvement of Higher Education Personnel (CAPES) Bank of Theses and Dissertations, ClinicalTrial.gov, the

Brazilian Clinical Trials Registry (REBEC) and the WHO International Clinical Trials Registry Platform (ICTRP).

We first searched these databases in June 2021 and then again in August 2022. Our search strategy did not include any restrictions of language or date of publication.

The search strategy contained main medical subject headings (MeSH) terms, including energy drinks, cardiovascular system, heart rate, blood pressure, arterial pressure, vascular endothelium, myocardial infarction, heart arrest, heart failure, cardiac arrhythmias and long QT syndrome. To increase the precision and sensitivity of our searches, the indexing terms for the study design of choice (RCT) were added to the search terms in MEDLINE[20] and EMBASE[21] databases. Our search strategy is detailed in the supplementary material (Table S3 and Table S4).

Data selection and management

All articles identified in our searches were saved and exported as .ris or .txt files and imported into Rayyan Reference Manager. Duplicate studies were removed using a deduplication function. Two blinded reviewers (PIBG and VVB) manually checked for remaining duplicates by reviewing titles, authors, year of publication and abstracts.

Two blinded reviewers (PIBG and VVB) screened articles independently by title and abstract to determine their eligibility. They used the Rayyan application "to include" articles that met the eligibility criteria. Those that did not meet the inclusion criteria were marked as "excluded" and categorized by reason for exclusion (i.e., ineligible outcome(s) or population and other non-RCT study design). When it was not clear whether a study should be included, it was marked as "undecided" and the full article was read. Disagreements between reviewers were resolved by consensus or *by the decision of a third independent reviewer* (LFD or GW).

Data extraction

Two blinded reviewers (PIBG and VVB) conducted data extraction independently. If a study was deemed relevant for inclusion in the review, they extracted and compiled the main data in a pre-structured Excel 2010 for Windows data entry form, including detailed information on **study** (authors, year of publication, journal, intervention and comparator groups and characteristics); **participants** (age, gender, body mass index); **methods** (randomization, blinding, crossover); and **outcomes** (sample size and mean and standard deviation at baseline and over time). For eligible studies with missing data or results in graphs, we contacted their authors by email or through ResearchGate on three separate occasions, five days apart. When there was no reply, studies with potentially relevant data were excluded from the meta-analysis. For studies with results in graphs, we used GetData Graph Digitizer 2.26 to extract the data when appropriate. For the amounts of ingredients in drinks that were not reported or verified by the authors, we visited manufacturer websites to obtain amount information for subgroup analyses. For studies reporting results in different time frames, we extracted individual data in each time frame for separate analyses (section 6.2.4, Cochrane Handbook) stratified into five categories: (A) ≤20 minutes; (B) 30-40 minutes; (C) 60-80 minutes; (D) 90-100 minutes; and (E) ≥120 minutes. For studies reporting results at different time frames in the same category, we excluded data from the longest period to avoid unit errors in the meta-analysis. For example, when the acute effects of energy drink consumption were evaluated at 60 and 80 minutes (category C), we included data obtained at 60 minutes but excluded that obtained at 80 minutes. The measures of dispersion expressed as confidence intervals (CIs) or standard errors (SEs) were converted into standard deviations (SDs = EP * $\sqrt{n}$) prior to the analysis.

Risk of bias of individual studies and strength of evidence

The risk of bias in individual studies was assessed using the Cochrane Risk of Bias (RoB) 2 tool.[18,22] The studies were rated as having low risk of bias, some concerns of bias, or high risk of bias for each of the five domains: D1) randomization process; D2) deviations from intended interventions; D3) missing outcome data; D4) measurement of the outcome; D5) selection of the reported result. The overall risk of bias is the combined assessment across the domains of bias. No study was excluded based on the risk of bias. When a single study reported multiple outcomes of interest, we assessed the overall risk of bias rather than the risk of bias for each outcome.

The strength of the body of evidence was assessed using the GRADE tool.[18,23] This tool rates the quality of evidence from the assessment of confidence in specific pairwise effect estimates as well as treatment effect estimates from network meta-analysis in the following domains: study design; methodological limitations (risk of bias); inconsistency; indirectness of evidence; imprecision; publication bias; magnitude of effect; dose-response gradient; and residual confounding. We assessed the overall level of certainty (or quality) of the body of evidence for each outcome in all time frames.

Data analysis

Statistical analyses were carried out to estimate the acute effects of energy drink consumption on cardiovascular parameters compared to a control drink. The results are presented as mean difference (MD) and related 95% confidence interval (95% CI). To summarize the data, MDs of individual studies were pooled using a random-effects model. Since 95% CIs for random effects depict the uncertainty in the location of the estimated mean effects across studies, to improve the interpretation of uncertainties we calculated 95% prediction interval (95% PI) values as they express the uncertainty of the effects in RCTs.[24] To assess the consistency of energy drink effects across studies, the degree of heterogeneity (relative variability in effect

estimates attributed to heterogeneity) was tested using the inconsistency test by Higgins (I^2) for every pairwise comparison (interpretation of heterogeneity results in Box S1 of the supplementary material).[18,24] We performed meta-regression analyses on the summary data that showed the effects of ED (SBP, DBP, and CO), even though these showed low inconsistency, to examine possible changes in outcomes for each mg of caffeine added in the ED. Since the EDs in the studies had different volumes and mg, we corrected the caffeine described for the same volume of 250 mL. The same procedure was performed for the taurine component (mg) for subsequent calculation of the taurine/caffeine ratio (mg). To estimate the effect of caffeine in energy drinks for each outcome of interest we performed subgroup analyses divided in two groups based on median caffeine content (196 mg) obtained from the interquartile range of the amounts reported in the studies: (a) low caffeine (LC) (<196 mg) and high caffeine (HC) (>196 mg). We also performed subgroup analyses to estimate the effect of studies rated as having "some concerns" and "high risk of bias" using RoB 2 assessment. To identify discrepant data from the meta-analysis, forest plots were constructed to display the effect estimates across studies and to detect potential outliers based on non-CI overlapping.[25] To avoid errors due to different data units in RCTs with multiple intervention arms and a single control group, the sample size for the control group was weighted by the number of groups and participants included. For crossover RCTs, we used a more conservative approach to determine the smallest unit error as proposed by Cochrane (Section 23.2.6, Cochrane Handbook).[26] We collected all measurement data for energy drinks (pre- and post-intervention) and the control drink (pre- and post-control) and analyzed them as parallel groups and individual SDs for each intervention. For all studies analyzed, we estimated the SD of the differences using an imputed correlation coefficient (CC) of 0.5 in the following equation (Section 6.5.2.8, Cochrane Handbook)[27]:

· $CC\ \Delta\ SD = \sqrt{SD^2\ baseline + SD^2\ final - (2 * CC * SD\ baseline * SD\ final)}$

Sensitivity analyses were also conducted to verify the robustness of our decisions.[28] Two-tailed tests were used at a significance level of $p< 0.05$. Data modelizations were performed with RStudio (version 1.3.959) using the R package meta (version 3.6.1) for Windows. The main RStudio script for conducting the meta-analysis is presented in Box S2 (supplementary material).

RESULTS

Selection of studies

We identified 1,314 articles by searching electronic databases. After an initial screening, 394 were excluded due to duplicates. We read the titles and/or abstracts of 920 studies and excluded 754. Due to insufficient information in the titles and/or abstracts, we retrieved 166 full-text studies. Of these, 34 studies were selected for full-text reading and then 17 were excluded. Table S5 shows the reasons for excluding individual studies (supplementary material). In addition, we searched the gray literature and identified 700 studies, abstracts, and/or protocols. Of these, 684 were excluded after reading the titles and/or abstracts. Eight studies were retrieved for full-text reading, but none of them was included in the review as they did not meet the inclusion criteria.

We contacted the authors of 19 studies via email and/or through the ResearchGate website to obtain unpublished or missing data and/or ask questions about their studies (Supplementary Table S6).[8,12,29,30,33,36,38-41,43-52] The authors of six studies responded to our inquiries[12,29,30,38,47,51] but only one of these studies met the inclusion criteria for this review.[28] Yet, we also included the other five[8,38-41] as the clarifications requested would not affect the quantitative analysis. In addition, we were also able to include two other studies[30,33] as we managed to extract the quantitative data from graphs using a software program. Three other studies were excluded[12,47,51] as the data made available by the authors and/or their

clarifications were either not sufficient or did not meet the inclusion criteria. Finally, we excluded eight studies[43-46,48-50,52] due to missing data for the quantitative analysis. A total of 17 studies were included in this review (Figure 1).[1,8,29-42]

Characteristics of the included studies

Table 2 presents the main characteristics of the included studies. They were mostly published from 2001 to 2020, but the study by Alford[1] consisted of a 1997 preliminary study that met the inclusion criteria and was thus included in this analysis. Fifteen studies were published in English, one in Portuguese and one in Korean language. Fourteen (82.3%) were crossover RCTs[1,30-38,41,42] and nine (52.9%) double-blind.[1,8,11,29,34,36,38,42] The overall sample involved 475 individuals (222 men and 253 women; 350 in the intervention groups and 346 in the control groups) with mean age of 23.7 ± 2.3 years. The number of participants per study ranged from 8 to 88, median of 24. Baseline SBP/DBP and resting HR values for the intervention and control groups were 117/74.3 mmHg and 117/74.8 mmHg, and 68.9 and 69.0 bpm respectively. A detailed description of cardiovascular variables evaluated is shown in Supplementary Table S1.

Energy drinks most commonly investigated were Red Bull® (8 studies; 47.1%),[1,8,29-31,33,37] followed by Rockstar® (2; 11.8%),[34,42] 5-hour ENERGY® (2; 11.8%)[35,37], Monster® (1; 5.9%)[37] and Harvard YA® (1; 5.9%)[32]. The energy drink brand was not available in five (29,4%) studies.[36,38-41] Fifteen studies (88.2%) evaluated regular energy drinks[1,8,30-32,34-42] and two (11.8%) also examined a sugar-free energy drink in addition to regular ones.[29,33] The most common control drinks were flavored water (8 studies; 47.1%),[1,29,34-36,38,41] followed by plain drinking water (5; 29.4%),[30,31,33,39,40] soft drink (2, 11.8%),[37,42] vitamin water (1; 5.9%)[32] and isotonic drink (1; 5.9%).[9]

The mean volume consumed of regular energy drinks was 471 ± 283 mL and the median volume consumed of sugar-free energy drinks was 303 mL (range 250-355 mL). The mean caffeine concentration was 196 ± 90.5 mg for regular energy drinks and the median caffeine concentration of sugar-free energy drinks was 97 mg (range 80-114 mg). The mean volume consumed of control drinks was 479 mL ± 262 mL.

As for primary outcomes, 16 (94.1%) studies evaluated the acute effects of energy drink consumption on SBP and DBP.[1,8,29-37,39-42] Of these, 14 (87.5%) used oscillometric methods[1,8,29-31,33,35-37,39-42] and two (12.5%) auscultatory methods for measuring blood pressure.[32,34] As for secondary outcomes, 16 (94.1%) studies evaluated resting HR,[1,8,29-31,33-42] measured by an electrocardiogram (ECG) in 15 (88.2%)[1,8,29-31,33-37,39-42] and a cardiotachometer in one study (6.7%).[38] Three studies (17.6%) evaluated CO by multiplying resting HR by stroke volume (SV), i.e., CO = HR x SV.[30,31,33] Five (29.4%) studies evaluated QT interval[29,35,36,41,42] and corrected QT interval by Bazett's formula (QTc = QT / √RR) using ECG.[8,35,36,41,42]

Risk of bias assessment and strength of evidence of studies

Only one study reported concealed allocation of participants before they were assigned to the intervention group (item 1.2);[30] seven studies were unblinded or did not report methods of blinding of participants and/or raters (items 2.1 and 2.2);[30-33,37,39,40] and two studies made their study protocols available (item 5.1).[34,41] Ten studies were rated as having some concerns of bias[1,8,29,34-36,38,41,42] because these items were missing and/or not reported. Seven studies were unblinded or did not report methods of blinding of raters (item 4.3) which may have affected their results (items 4.4 and 4.5), and thus were rated as having high risk of bias (Figure 3).[30-33,37,39,40]

The strength of evidence was assessed using GRADE for each outcome in different time frames. SBP at 60-80 minutes and 90-100 minutes (Supplementary Table S7) and DBP at 30-40 minutes and 60-80 minutes (Supplementary Table S8) were rated as moderate-certainty and SBP at ≥120 minutes (Supplementary Table S7) was rated as high-certainty evidence. All other outcomes were rated as very low or low-certainty. The main reasons for reducing certainty of the evidence were: a) greater weight and/or statistical significance across studies rated as high risk of bias; b) non-overlapping of point estimates in the "inconsistency" item; and c) insufficient total sample size and/or lack of statistical significance in the "imprecision" item. It should be noted that we decided not to downgrade the evidence for "indirect evidence" when external validity was potentially weak; although mean age of 23.7 ± 2.3 years is not representative of the entire adult population, this age group is consistent with that reported for energy drink consumers in the literature. In addition, for "imprecision," we considered a minimum of 400 participants for the overall analysis and if the summary estimate favored the intervention and the confidence interval did not cross the null line. A detailed analysis for each outcome and time frame evaluated can be found in the supplementary material (Tables S7-S12).

Systolic blood pressure

The summarization of data in the meta-analysis of 16 studies[1,8,29-37,39-42] evaluating SBP (total n = 384) did not show any significant changes within the first 20 minutes (n = 43) after the consumption of energy drinks (Figure 2A). However, SBP increased by 3.23 mmHg (95% CI 1.19-5.28, $p<0.01$; 95% PI 0.91-5.55; $I^2 = 0\%$; GRADE: low) after 30-40 minutes (n = 198, Figure 2B), 4.71 mmHg (CI 95% 2.97-6.45, $p<0.01$; 95% PI 2.79-6.63; $I^2 = 0\%$; GRADE: moderate) after 60-80 minutes (n = 278, Figure 2C), 4.10 mmHg (95% CI 1.63-6.56, $p<0.01$; 95% PI 0.61-7.59; $I^2 = 0\%$; GRADE: moderate) after 90-100 minutes (n = 113, Figure 2D)

and 3.64 mmHg (95% CI 1.66-5.63, p<0.01; 95% PI 1.31-5.98; I^2 = 0%; GRADE: high) after 120 minutes (n = 215, Figure 2E).

Diastolic blood pressure

We conducted a second analysis involving the same 16 studies mentioned before[1,8,29-37,39-42] to examine the acute effects of energy drink consumption on DBP (total n = 334). We found no changes 20 minutes after the consumption of energy drinks (n = 43) (Figure 3-A). However, DBP increased by 2.37 mmHg (95% CI 0.99-3.74, p < 0.01; 95% PI 0.81-3.93; I^2 = 0%; GRADE: moderate) after 30-40 minutes (n = 198, Figure 3-B), 3.07 mmHg (95% CI 1.86-4.28, p < 0.01; 95% PI 1.74-4.40; I^2 = 0%; GRADE: moderate) after 60-80 minutes (n = 278, Figure 3-C), 3.60 mmHg (95% CI 1.86-5.35, p < 0.01; 95% PI 1.13-6.08; I^2 = 0%; GRADE: low) after 90-100 minutes (n = 113, Figure 3-D) and 4.51 mmHg (95% CI 2.60-6.42, p < 0.01; 95% PI –0.52-9.54; I^2 = 43.5%; GRADE: low) after 120 minutes (n = 215, Figure 3-E).

Subgroup analysis (systolic and diastolic blood pressure)

The subgroup analysis for the effect modifier "caffeine amount" did not find any differences between LC vs. HC groups in the time frames evaluated [at 30-40 minutes, SBP: 2.58 mmHg (95% CI –0.20-5.36) vs. 4.00 mmHg (95% CI 1.00-7.01), p = 0.495 (Supplementary Figure S1-A); DBP: 1.47 mmHg (95% CI –0.30-3.23) vs. 3.75 (95% CI 1.56-5.93), p = 0.112 (Supplementary Figure S2-A)]; [60-80 minutes, SBP: 5.55 mmHg (95% CI 2.84-8.25) vs. 4.11 (95% CI 1.83-6.40), p = 0.427 (Supplementary Figure S1-B); DBP: 2.65 mmHg (95% CI 0.93-4.36) vs. 3.48 mmHg (95% CI 1.78-5.18), p = 0.499 (Supplementary Figure S2-B)]; [90-100 minutes, SBP 3.48 mmHg (95% CI –0.55-7.51) vs. 4.47 (95% CI 1.35-7.59), p = 0.705 (Supplementary Figure S1-C); DBP: 4.10 mmHg (95% CI 1.52-6.67) vs. 3.00 mmHg (0.45-5.54), p = 0.551 (Supplementary Figure S2-C]; [≥120 minutes, SBP: 3.02 mmHg (95% CI –

0.61-6.66) vs. 3.91 mmHg (95% CI 1.54-6.27) p = 0.688 (Supplementary Figure S1-D); DBP: 3.44 mmHg (95% CI 1.20-5.67) vs. 5.14 mmHg (95% CI 2.48-7.80), p = 0.336) (Supplementary Figure S2-D)].

Heart rate

The analysis of 16 studies[1,8,29-31,33-42] did not show any changes in resting HR (total n = 309) in the time frames evaluated (Supplementary Figure S5). The subgroup analysis for "caffeine amount" showed a difference in resting HR at 90-100 minutes after energy drink consumption: LC = 3.93 bpm ([95% CI 0.83-7.03, p = 0.541; I^2 = 0%] vs. HC = –1.47 bpm [95% CI –4.65 to 1.96, p = 0.845; I^2 = 0%], p = 0.017 – Supplementary Figure S6 D). In addition, the subgroup analysis for the effect modifier "risk of bias" showed a difference in resting HR at 90-100 minutes: some concerns of bias: –1.48 bpm ([95% CI –4.65-1.69, p = 0.845; I^2 = 0%] vs. high risk of bias: 3.93 bpm [95% CI 0.83-7.02, p = 0.541; I^2 = 0%], p = 0.017 – Supplementary Figure S7-D).

Cardiac output

Only three studies included in the analysis evaluated CO (total n = 53).[30,31,33] We found an increase of CO by 0.43 L/min (95% CI 0.08-0.77, p = 0.016; I^2 = 27.4%; GRADE: very low) after 30-40 minutes (n = 33, Figure 4B) and 0.41 L/min (95% CI 0.10-0.71, p = 0.286, I^2 = 20.2%; GRADE: very low) after 60-80 minutes (n = 33, Figure 4C). Figure 4 shows the results for other time frames evaluated. A subgroup analysis was not performed given the small number of studies included in this analysis.

QT/QTc interval and endothelial function

Five studies[29,35,36,41,42] evaluated QT interval (total n = 105) and QTc interval (total n = 107).[8,34,35,40,41] We found no differences for both outcomes in the different time frames evaluated (Supplementary Figures S8 and S9). A subgroup analysis was not performed given the small number of studies included in this analysis. Furthermore, we found no studies evaluating endothelial function that met the eligibility criteria of this review.

Meta-regression analyses

Meta-regression was performed by adjusting the results of the SBP, DBP, and CO variables for caffeine and taurine. When caffeine was adjusted for the 250 mL volume of the ED, it was estimated that for every 1 mg of caffeine added to the ED, there was an increase of 0.0012 mmHg in SBP, 0.0004 mmHg in DBP, and 0.0565 L/min in CO over 2 hours post-ingestion. However, when the values of taurine (1 mg) combined with 1 mg of caffeine were adjusted for the same volume (250 mL) of ED, a decrease of 0.3241 mmHg in SBP and an increase of 0.0970 mmHg in DBP and 0.0565 L/min in CO were observed over 2 hours post-ingestion.

DISCUSSION

Our analysis involving 17 studies showed that acute consumption of commercially available energy drinks—regardless of their caffeine content—increased SBP, DBP and CO compared to a control drink in different time frames in healthy volunteers aged ≥18 years. The other variables evaluated, including resting HR and QT/QTc interval, did not show any significant changes. Furthermore, we were not able to examine these effects on endothelial function as we did not identify any studies that met the inclusion criteria of this review. To the best of our knowledge this is the first systematic review that: a) the study protocol was registered in the PROSPERO database; b) included a search of six databases and the gray literature; c) examined two new cardiovascular outcomes; d) excluded studies with interventions other than

the consumption of energy drinks and/or control drinks that could affect cardiovascular parameters; e) included RCTs only; f) used stratified meta-analysis to assess for the effects over time; and g) assessed the risk of bias using RoB 2 and the strength of evidence using GRADE.

Systolic and diastolic blood pressure

Our findings of increased SBP and DBP after the consumption of energy drinks corroborate that reported in a meta-analysis by Shah et al.[11] These authors reported mean SBP increase by 4.44 mmHg (95% CI 2.71–6.17; p = 0.001) and mean DBP increase by 2.73 mmHg (95% CI 1.52-3.95; p = 0.05) after acute consumption of energy drinks. In addition, in a subgroup analysis of caffeine amount (<200 mg; ≥200 mg), they found significantly greater SBP increase in the ≥200 mg caffeine group (6.44 vs. 3.72 mmHg). In contrast, we performed a subgroup analysis to examine the effect modifier "caffeine amount," but did not find any statistical differences between high vs. low caffeine content in the time frames evaluated. We further explored this effect in a subgroup analysis of the effect modifier "risk of bias." We found that most studies pointing to greater increase of SBP and DBP in the LC group were rated as having "high risk of bias," which may suggest that the risk of bias potentially affected their results.

In addition to subgroup analyses of the effect modifier "caffeine amount," Noordzij et al.[53] reported that regular consumption of coffee (average of 410 mg of caffeine/day) or caffeine alone (295-750 mg of caffeine/day) increased SBP/DBP by 2.04/0.73 mmHg. However, these authors found that regular consumption of caffeine alone primarily increased SBP (3.64 vs. 1.64 mmHg) and this increase was even greater with caffeine amounts ≥410 mg/day (2.68 vs. 0.76 mmHg). Similarly, Basrai et al.[8] evaluated the acute effects of the consumption of energy drinks and their compounds—caffeine, taurine, caffeine + taurine and glucuronolactone—on

BP in healthy adults. They found there was an increase in SBP (4.7 ± 9.8 and 7.0 ± 7.6 mmHg) and DBP (1.6 ± 9.0 and 3.8 ± 8.0 mmHg) within one hour of consumption only in the energy drink group and "control drink + caffeine" group. All other compounds did not promote any changes or reductions in BP, though these results were not significantly different. Thus, we can infer that energy drink volume and caffeine amount consumed have a dose-response association with BP increase. The time frame appears to have an important role in BP change after energy drink consumption. The main effects of caffeine, a major component of energy drinks, are experienced within 30 to 60 minutes of consumption as caffeine acts by inhibiting adenosine receptors in the brain, heart muscle and vascular endothelium.[54] These effects usually last 3 to 7 hours,[55] but may vary based on individual caffeine sensitivity and tolerance.[56] Bearing this in mind, we accurately chose to conduct stratified analyses in different time frames. They allowed to evidence that the consumption of energy drinks effectively increase BP within 30 minutes of consumption, which may last up to two hours. However, these changes are likely to have no clinical relevance for cardiovascular health in the population studied. Despite there was an increase in BP values, they remained within the normal range.[57]

Finally, the effect sizes for the meta-analyses were small and similar to PIs, which suggests accuracy of our results, even for future similar interventions. In addition, the analyses of data in specific time frames showed moderate strength of evidence for 60-80 minutes and 90-100 minutes and high strength of evidence for ≥120 minutes, pointing to greater confidence in our results. There was also an increase in BP within 30-40 minutes of consumption, but the strength of evidence was low and thus it should be interpreted with caution.

Resting heart rate

Evidence suggests that acute consumption of energy drinks induces an increase in resting HR.[1,40,47] However, we did not find any changes in resting HR in our meta-analysis. This finding is consistent with that reported by Shah et al.[11] of no changes in resting HR after the consumption of energy drinks. They also analyzed this same data using a fixed-effects model and found a significant reduction in resting HR, but without clinical relevance.

In their systematic review, Lasheras et al.[10] found that 71.1% of the included studies reported an increase in resting HR after the consumption of energy drinks, of which 38% were significantly different (mean increase of 11.2 bpm). In turn, 24.4% of the studies reported a reduction in resting HR, of which 18.2% were significant different (mean reduction of 6.71 bpm). In a study published by Grasser et al.,[30] these authors suggested that the change evidenced in the opposite direction is related to the measurement time frame of resting HR since it tends to reduce within 40 minutes of consumption and then increase steadily up to 90 minutes after the consumption of energy drinks. However, when this data was analyzed in the meta-analysis, we did not find any significant differences of resting HR in either direction for these time frames. The findings are further supported by subgroup analyses of the effect modifier "caffeine amount" that showed LC energy drinks increased resting HR in 90-100 minutes when compared to HC energy drinks (3.93 bpm [95% CI 0.83-7.02] vs. –1.48 bpm [95% CI –4.65-1.69], between groups p = 0.017). However, when subgroup analyses of the effect modifier "risk of bias" were performed for the same time frame, we found an increase in resting HR more likely to be reported in studies rated as "high risk of bias" when compared to studies rated as "some concerns" (3.93 bpm [95% CI 0.83-7.02] vs. –1.48 bpm [95% CI –4.65-1.69], between groups p = 0.017). Interestingly, studies rated as having "high risk of bias" are those categorized as "LC," which suggests that the high risk of bias of the included studies may have affected the statistical significance in the previous analysis.

Although the strength of evidence was rated as very low in the GRADE assessment in all analyses of time frames mostly because of the small number of participants and non-significant results, resting HR in response to the acute consumption of energy drinks is likely to remain unchanged or even decrease. This is probably due to a potential cardioprotective effect of taurine found abundantly in energy drinks that acts together with taurine found in heart tissue increasing the inotropic action of the heart by reducing resting HR and thus attenuating the expected dose-response of caffeine and BP increase as well.[8,58,59] The combined action of taurine and caffeine has been reported as a potential mechanism for producing a significant reduction in resting HR.[8,60]

Furthermore, an increase in BP produced by caffeine contained in energy drinks induces the activation of arterial pressoric receptors that, to reduce BP, inhibits the sympathetic nervous system and consequently reduces HR.[61,62] Therefore, the consumption of energy drinks is likely to induce a reduction in resting HR or to maintain it unchanged. But as no studies rated as low risk of bias were included in the analysis, we do not have any corroborating evidence to support this hypothesis and draw conclusions on this outcome.

Cardiac output

In this review, we aimed to evaluate new cardiovascular outcomes such as CO. However, we identified only very few studies evaluating the effects of energy drink consumption on CO in healthy adults and therefore we were not able to conduct a more reliable in-depth analysis of this variable. In their study, Grasser et al.[30] and Miles-Chan et al.[33] reported an acute increase in CO after the consumption of energy drinks compared to a control drink that peaked within 30-50 minutes, which was similar to BP response to caffeine. CO is the product of HR by SV and both studies reported a decrease in HR as CO increased. But in the study by Miles-Chan et al,[33] SV and thus heart contractility increased suggesting that SV is a major modifier of this

outcome. This effect is probably due to an increase in heart contractility produced by the action of caffeine on the sympathetic nervous system.[63]

On the other hand, Grasser[31] evidenced an increase in CO within 80 minutes of energy drink consumption based on resting HR as resting HR increased while SV decreased. These contrasting results may be explained by different measurement time frames as the studies mentioned before demonstrated that resting HR tends to decrease up to 30-40 minutes of consumpiton[30,33] while SV increases up to 30-50 minutes.[33] These variables then move in the opposite direction; i.e., resting HR increases[30,33] while SV decreases.[31]

The finding of an increase in CO in 30-40 and 60-80 minutes in our meta-analysis should be interpreted with caution as only three studies rated as having low strength of evidence were included in the analyses.

QT and QTc interval

Shortened (≤340 ms) and/or prolonged (≥460 ms) QT/QTc interval durations compared to reference values (men: ≤450 ms; women: ≤470 ms) are associated with increased risk of developing ventricular arrhythmias and sudden death, especially when ≥500 ms.[64]

Considering that there is no sufficient supportive evidence, the US Food and Drug Administration (FDA)[64] advices that drugs that prolong QT/QTc interval from 5 to 20 ms are potentially proarrhythmogenic and that this risk increases substantially with prolongations ≥20 ms.

Our study did not find any changes in QT/QTc interval in the different time frames evaluated. This finding contrasts with single pieces of evidence[8,36,41,66] and the results of a systematic review by Lasheras et al.[10] reporting QTc prolongation of 14.7 ms after the consumption of energy drinks and thus increased proarrhythmogenic risk associated with energy drink consumption. These conflicting results can be explained by low volume of energy drinks

consumed and short follow-up in the studies.[66] A review study that evaluated 17 case reports of adverse effects of acute energy drink consumption on cardiovascular parameters evidenced a dose-response relationship. Major cardiovascular events included 4 cases of atrial fibrillation, 4 cases of ventricular fibrillation, 4 cases of ST segment elevation, 1 case of QT prolongation, cardiac arrest, supraventricular tachycardia, and ventricular and supraventricular tachycardia.[13] Yet, it should be noted that most cases were reported after excessive acute consumption of energy drinks (>3 cans of 473 mL), which is up to 4 times the daily caffeine limit of 400 mg, and were associated with alcohol intake or use of other drugs and cardiac channelopathy. Thus, cardiovascular changes and events after the acute consumption of energy drinks may be associated with excessive intake, probably due to caffeine dose-response effects combined with drug intake and/or cardiac anomalies.

Strengths and limitations

This review study has some strengths such as the inclusion of RTCs only as a way to minimize the risk of bias and potential confounding factors. Establishing strict inclusion criteria ensured low levels of statistical heterogeneity (I^2) among studies. Prediction intervals and GRADE assessments allowed to suggest target outcomes for future studies, especially for BP. The use of RoB2 tool to assess risk of bias allowed more robust analyses and pointed to limitations of RCTs to be addressed in future studies. Finally, stratified analyses in different time frames outlined the acute effects of energy drink consumption on cardiovascular parameters in healthy adults over time.

However, this study has some limitations. First, the small number of studies included in the analyses especially those evaluating CO and QT/QTc interval, and we did not identify any study evaluating endothelial function. Some studies examined the effects within short time frames and did not allow to establish the actual effects of energy drink consumption because

they are mostly experienced within 30 to 60 minutes. Although this review included RCTs only to reduce the risk of bias, all studies were rated as having either some concerns or high risk of bias especially due to missing data or unavailable relevant data, which may have affected the results of the analyses as well as the risk of bias and GRADE assessments. Similarly, wide prediction intervals for resting HR and QT/QTc intervals require further studies for more consistent summarization of results. Lastly, missing data regarding frequency of caffeine intake may also have influenced our results because the effects produced by caffeine contained in energy drinks differ between habitual/sensitive and non-habitual/non-sensitive consumers.

CONCLUSIONS

The acute consumption of commercially available energy drinks—regardless of their caffeine content—increases SBP and DBP for up to two hours. The small change evidenced in CO and no effect on resting HR and QT/QTc interval may indicate that the acute consumption of energy drinks poses low cardiovascular risk in healthy adults. However, given the small number of studies included in this analysis, our results must be interpreted with caution. We also recommend carrying out further RCTs taking into consideration the limitations highlighted here to obtain more robust data.

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Supporting Information

PRISMA Check-list

Supplementary Material

Supplementary Table S1. Cardiovascular outcomes mean baseline values of the studies included in the meta-analysis (n= 17).

Supplementary Table S2. Description of studies that evaluated the effects of energy drinks on cardiovascular parameters and were included in previously published systematic reviews.

Supplementary Table S3. Main database search strategies.

Supplementary Table S4. Search strategies used in grey literature and unpublished studies.

Supplementary Table S5. Excluded references and the reasons for their exclusion

Supplementary Table S6. List of authors contacted, data requested, means of communication used, authors' responses and decisions made.

Supplementary Table S7. Summary of Findings Table (SoFT) for changes in systolic blood pressure after consumption of energy drinks compared to a control drink in healthy adults.

Supplementary Table S8. Summary of Findings Table (SoFT) for changes in diastolic blood pressure after consumption of energy drinks compared to a control drink in healthy adults.

Supplementary Table S9. Summary of Findings Table (SoFT) for changes in heart hate after consumption of energy drinks compared to a control drink in healthy adults.

Supplementary Table S10. Summary of Findings Table (SoFT) for changes in cardiac output after consumption of energy drinks compared to a control drink in healthy adults.

Supplementary Table S11. Summary of Findings Table (SoFT) for changes in QT interval after consumption of energy drinks compared to a control drink in healthy adults.

Supplementary Table S12. Summary of Findings Table (SoFT) for changes in corrected QT interval after consumption of energy drinks compared to a control drink in healthy adults.

Supplementary Figure S1. Subgroup analysis comparing low-caffeine and high-caffeine energy drinks on systolic blood pressure [SBP]. Time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (D) ≥120 minutes. * Preliminary study conducted in 1997 and published in 2001 along with another study.

Supplementary Figure S2. Subgroup analysis comparing low-caffeine and high-caffeine energy drinks on diastolic blood pressure [DBP]. Time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (C) ≥120 minutes. * Preliminary study conducted in 1997 and published in 2001 along with another study.

Supplementary Figure S3. Subgroup analysis comparing studies classified by RoB2 with some concerns and high risk of bias on systolic blood pressure [SBP]. Time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (D) ≥120 minutes. * Preliminary study conducted in 1997 and published in 2001 along with another study.

Supplementary Figure S4. Subgroup analysis comparing studies classified by RoB2 with some concerns and high risk of bias on diastolic blood pressure [DBP]. Time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (D) ≥120 minutes. * Preliminary study conducted in 1997 and published in 2001 along with another study.

Supplementary Figure S5. Meta-analysis of the acute effects of energy drink consumption compared to a control drink on heart rate [HR] in healthy adults. Time frames: (A) ≤20

minutes, (B) 30-40 minutes, (C) 60-80 minutes, (D) 90-100 minutes and (E) ≥120 minutes. * Preliminary study conducted in 1997 and published in 2001 along with another study.

Supplementary Figure S6. Subgroup analysis comparing low-caffeine and high-caffeine energy drinks on heart rate [HR]. Time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (D) ≥120 minutes. * Preliminary study conducted in 1997 and published in 2001 along with another study.

Supplementary Figure S7. Subgroup analysis comparing studies classified by RoB2 with some concerns and high risk of bias on heart rate [HR]. Time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (D) ≥120 minutes. * Preliminary study conducted in 1997 and published in 2001 along with another study.

Supplementary Figure S8. Meta-analysis of the acute effects of energy drink consumption compared to a control drink on QT interval [QT] in healthy adults. Time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (D) ≥120 minutes.

Supplementary Figure S9. Meta-analysis of the acute effects of energy drink consumption compared to a control drink on corrected QT interval [QTc] in healthy adults. Time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (D) ≥120 minutes.

Supplementary Box S1. Interpretation of heterogeneity results.

Supplementary Box S2. Example of a script used to perform the meta-analysis using RStudio.

REFERENCES

1. Alford C, Cox HR, Wescott RA. The effects of red bull energy drink on human performance and mood. *Amino acids*. 2001;21(2). doi: 10.1007/s007260170021

2. Heckman MA, Sherry K, De Mejia EG. Energy Drinks: An Assessment of Their Market Size, Consumer Demographics, Ingredient Profile, Functionality, and Regulations in the United States. *Compr Rev Food Sci Food Saf*. 2010;9(3):303-317. doi: 10.1111/j.1541-4337.2010.00111.x

3. Kadam A, Deshmukh R. Energy Drinks Market by Type (Alcoholic, Nonalcoholic), by End User (Kids, Adults, Teenagers): Global Opportunity Analysis and Industry Forecast,

2020-2031. Allied Market Research. https://www.alliedmarketresearch.com/energy-drink-market. Accessed April 15, 2023.
4. Zucconi S, Volpato C, Adinolfi F, et al. Gathering consumption data on specific consumer groups of energy drinks. *EFSA J*. 2013;10(3):394. doi: doi.org/10.2903/sp.efsa.2013.EN-394
5. Nadeem IM, Shanmugaraj A, Sakha S, Horner NS, Ayeni OR, Khan M. Energy Drinks and Their Adverse Health Effects: A Systematic Review and Meta-analysis. *Sports Health*. 2021;13(3):265-277. doi:10.1177/1941738120949181
6. Ali F, Rehman H, Babayan Z, Stapleton D, Joshi D-D. Energy drinks and their adverse health effects: A systematic review of the current evidence. *Postgrad Med*. 2015;127(3):308-322. doi: 10.1080/00325481.2015.1001712
7. Phan JK, Shah SA. Effect of caffeinated versus noncaffeinated energy drinks on central blood pressures. *Pharmacotherapy*. 2014;34(6):555-560. doi: 10.1002/phar.1419
8. Basrai M, Schweinlin A, Menzel J, et al. Energy Drinks Induce Acute Cardiovascular and Metabolic Changes Pointing to Potential Risks for Young Adults: A Randomized Controlled Trial. *J Nutr*. 2019;149(3):441-450. doi: 10.1093/jn/nxy303
9. Echeverri D, Montes FR, Cabrera M, Galán A, Prieto A. Caffeine's Vascular Mechanisms of Action. *Int J Vasc Med*. 2010;2010:834060. doi: 10.1155/2010/834060
10. Lasheras I, Seral P, Alonso-Ventura V, Santabárbara J. The impact of acute energy drink consumption on electrical heart disease: A systematic review and meta-analysis. *Journal of electrocardiology*. 2021;65:128-135. doi: 10.1016/j.jelectrocard.2021.01.020
11. Shah S, Chu B, Lacey C, Riddock I, Lee M, Dargush A. Impact of acute energy drink consumption on blood pressure parameters: a meta-analysis. *Ann Pharmacother*. 2016;50(10):808-815. doi: 10.1177/1060028016656433
12. Worthley M, Prabhu A, Sciscio P, Schultz C, Sanders P, Willoughby S. Detrimental effects of energy drink consumption on platelet and endothelial function. *Am J Med*. 2010;123(2):184-187. doi: 10.1016/j.amjmed.2009.09.013
13. Goldfarb M, Tellier C, Thanassoulis G. Review of published cases of adverse cardiovascular events after ingestion of energy drinks. *Am J Cardiol*. 2014;113(1):168-172. doi: 10.1016/j.amjcard.2013.08.058
14. Higgins JP, Yang B, Herrin NE, et al. Consumption of energy beverage is associated with attenuation of arterial endothelial flow-mediated dilatation. *World J Cardiol*. 2017;9(2):162-166. doi: 10.4330/wjc.v9.i2.162
15. Cao DX, Maiton K, Nasir JM, Estes N, Shah SA. Energy Drink-Associated Electrophysiological and Ischemic Abnormalities: A Narrative Review. *Front Cardiovasc Med*. 2021;8:679105. doi: 10.3389/fcvm.2021.679105
16. Lévy S, Santini L, Capucci A, et al. European Cardiac Arrhythmia Society Statement on the cardiovascular events associated with the use or abuse of energy drinks. *J Interv Card Electrophysiol*. 2019;56(1):99-115. doi: 10.1007/s10840-019-00610-2
17. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372. doi: 10.1136/bmj.n71
18. Higgins JP, Thomas J, Chandler J, et al. *Cochrane handbook for systematic reviews of intervention* version 6.3 (updated February 2022). Cochrane, 2022. https://training.cochrane.org/handbook. Accessed 15 April, 2023.
19. [dataset]Barbalho PIG, Vieira VB, Waclawovsky G, Deresz LF (2023). Acute effects of energy drinks consumption on cardiovascular parameters in healthy adults: a systematic review with meta-analysis of randomized clinical trials. Mendeley Data, V1. https://doi.org/10.17632/c2gydp65cp.2
20. Robinson KA, Dickersin K. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. *Int J Epidemiol*. 2002;31(1):150-153.

doi: 10.1093/ije/31.1.150
21. Glanville J, Foxlee R, Wisniewski S, Noel-Storr A, Edwards M, Dooley G. Translating the Cochrane EMBASE RCT filter from the Ovid interface to Embase.com: a case study. *Health Info Libr J*. 2019;36(3):264-277. doi: 10.1111/hir.12269
22. Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366. doi: 10.1136/bmj.l4898
23. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-394. doi: 10.1016/j.jclinepi.2010.04.026
24. InHout J, Loannidis JP, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open*. 2016;6(7). doi: 10.1136/bmjopen-2015-010247
25. Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. *Med Decis Making*. 2013;33(5):618-640. doi: 10.1177/0272989X13485157
26. Higgins J, Eldridge S, Li T. Chapter 23: Including variants on randomized trials. In*:* Higgins JP, Thomas J, Chandler J, et al. *Cochrane handbook for systematic reviews of intervention version* 6.3 (updated February 2022). https://training.cochrane.org/handbook/current/chapter-23. Accessed 15 April, 2023.
27. Higgins J, Li T, Deeks J. Chapter 6: Choosing effect measures and computing estimates of effect. In*:* Higgins JP, Thomas J, Chandler J, et al. *Cochrane handbook for systematic reviews of intervention version* 6.3 (updated February 2022). https://training.cochrane.org/handbook/current/chapter-06. Accessed 15 April, 2023.
28. Boutron I, Page MJ, Higgins JP, Altman DG, Lundh A, Hróbjartsson A. Chapter 7: Considering bias and conflicts of interest among the included studies. In*:* Higgins JP, Thomas J, Chandler J, et al. *Cochrane handbook for systematic reviews of intervention version* 6.3 (updated February 2022). https://training.cochrane.org/handbook/current/chapter-07. Accessed 15 April, 2023.
29. Ragsdale F, Gronli T, Batool N, et al. Effect of Red Bull energy drink on cardiovascular and renal function. *Amino Acids*. 2010;38(4):1193-1200. doi: 10.1007/s00726-009-0330-z
30. Grasser E, Yepuri G, Dulloo A, Montani J. Cardio- and cerebrovascular responses to the energy drink Red Bull in young adults: a randomized cross-over study. *Eur J Nutr*. 2014;53(7):1561-1571. doi: 10.1007/s00394-014-0661-8
31. Grasser E, Dulloo A, Montani J. Cardiovascular and cerebrovascular effects in response to red bull consumption combined with mental stress. *Am J Cardiol*. 2015;115(2):183-189. doi: 10.1016/j.amjcard.2014.10.017
32. Jo S, Lee C. The Effect of Caffeinated Energy Drink Consumption on Intraocular Pressure in Young Adults. *Journal of the Korean Ophthalmological Society*. 2015:1096-1103.
33. Miles-Chan J, Charrière N, Grasser E, Montani J, Dulloo A. The blood pressure-elevating effect of Red Bull energy drink is mimicked by caffeine but through different hemodynamic pathways. *Physiol Rep*. 2015;3(2):e12290. doi: 10.14814/phy2.12290
34. Svatikova A, Covassin N, Somers K, et al. A Randomized Trial of Cardiovascular Responses to Energy Drink Consumption in Healthy Adults. *JAMA*. 2015;314(19):2079-2082. doi: 10.1001/jama.2015.13744
35. Shah S, Dargush A, Potts V, et al. Effects of Single and Multiple Energy Shots on Blood Pressure and Electrocardiographic Parameters. *Am J Cardiol*. 2016;117(3):465-468. doi: 10.1016/j.amjcard.2015.11.017

36. Shah SA, Occiano A, Nguyen TA, et al. Electrocardiographic and blood pressure effects of energy drinks and Panax ginseng in healthy volunteers: A randomized clinical trial. *Int J Cardiol*. 2016;218:318-323. doi: 10.1016/j.ijcard.2016.05.007
37. Peveler W, Sanders G, Marczinski C, Holmer B. Effects of Energy Drinks on Economy and Cardiovascular Measures. *J Strength Cond Res* 2017;31(4):882-887. doi: 10.1519/JSC.0000000000001553
38. Polito M, Souza D, França D. The acute energy drink intake improve performance in resistance exercises. *R Bras Cie e Mov*. 2017;25(3):61-66.
39. Nowak D, Gośliński M, Nowatkowska K. The Effect of Acute Consumption of Energy Drinks on Blood Pressure, Heart Rate and Blood Glucose in the Group of Young Adults. *Int J Environ Res Public Health*. 2018;15(3):544. doi: 10.3390/ijerph15030544
40. Nowak D, Golinski M, Wesolowska A, Berenda K, Poplawski C. Effects of Acute Consumption of Noni and Chokeberry Juices vs. Energy Drinks on Blood Pressure, Heart Rate, and Blood Glucose in Young Adults. *Evid Based Complement Alternat Med*. 2019:1-9. doi: 10.1155/2019/6076751
41. Shah S, Szeto A, Farewell R, et al. Impact of High Volume Energy Drink Consumption on Electrocardiographic and Blood Pressure Parameters: A Randomized Trial. *J Am Heart Assoc*. 2019;8(11):e011318. doi: 10.1161/JAHA.118.011318
42. Stopa M, Łobacz M, Niemczyk M, et al. Influence of energy drinks on acute hemodynamic parameters in young healthy adults: a randomized double-blind placebo-controlled crossover pilot study. *Kardiol Pol* 2020;78(4):335-337. doi: 10.33963/KP.15231
43. Szotowska M, Bartmanska M, Wyskida K, et al. The influence of so called „energy drinks" on the blood pressure and the pulse rate in young, healthy adults. *Arterial Hypertension*. 2013;17(2):169-174.
44. Nelson MT, Biltz GR, Dengel DR. Cardiovascular and ride time-to-exhaustion effects of an energy drink. *J Int Soc Sports Nutr*. 2014;11(2):1-7. doi: 10.1186/1550-2783-11-2
45. Brothers RM, Christmas KM, Patik JC, Bhella PS. Heart rate, blood pressure and repolarization effects of an energy drink as compared to coffee. *Clin Physiol Funct Imaging*. 2017;37(6):675-681. doi: 10.1111/cpf.12357
46. Del Coso J, Salinero J, González-MC, Abián-Vicén J, Pérez-González B. Dose response effects of a caffeine-containing energy drink on muscle performance: a repeated measures design. *J Int Soc Sports Nutr*. 2012;5(1):7. doi: 10.1186/1550-2783-9-21
47. Rashti SL, Ratamess NA, Kang J, Faigenbaum AD, Chilakos A, Hoffman JR. Thermogenic effect of meltdown RTD™ energy drink in young healthy women: a double blind, cross-over design study. *Lipides Health Dis*. 2009;8(1):57. doi: 10.1186/1476-511X-8-57
48. Sillivent J, Blevins J, Peak K. Energy Drinks: Ergolytic or Ergogenic? *Int J Exerc Sci*. 2012;5(3):214-222.
49. García A, Romero C, Arroyave C, Giraldo F, Sánchez L. Acute effects of energy drinks in medical students. *Eur J Nutr*. 2017;56(6):2081-2091. doi: 10.1007/s00394-016-1246-5
50. Sheehan KM, Hartzler LK. Effects of XS® energy drink on aerobic exercise capacity of athletes. *Int J Exerc Sci*. 2011;4(2):152.
51. Bloomer R, Majaj R, Moran R, MacDonnchadh J. Comparison of 5-Hour ENERGY and Caffeine on Cognitive Performance and Subjective Feelings in Young Men and Women. *J Caffeine Res*. 2015;5(3):130-139. doi: 10.1089/jcr.2015.0005
52. AdibSaber F, Ansari S, Elmieh A, Rajabzadeh H. Effect of an Energy Drink On Muscle and Liver Damage Enzymes, And Cardiovascular Indices in Soccer Players. *Sci Med Footb*. 2022:7(1):8-14. doi: 10.1080/24733938.2022.2051728

53. Noordzij M, Uiterwaal CS, Arends LR, Kok FJ, Grobbee DE, Geleijnse JM. Blood pressure response to chronic intake of coffee and caffeine: a meta-analysis of randomized controlled trials. *J Hypertens*. 2005;23(5):921-928. doi: 10.1097/01.hjh.0000166828.94699.1d
54. Sawynok J. Methylxanthines and pain. *Handb Exp Pharmacol*. 2011;(200):311-329. doi: 10.1007/978-3-642-13443-2_11
55. Mejia EGD, Ramirez-Mares MV. Impact of caffeine and coffee on our health. *Trends Endocrinol Metab*. 2014;25(10):489-492.
56. Turnbull D, Rodricks JV, Mariano GF, Chowdhury F. Caffeine and cardiovascular health. *Regul Toxicol Pharmacol*. 2017;89:165-185. doi: 10.1016/j.yrtph.2017.07.025
57. Barroso WKS, Rodrigues CIS, Bortolotto LA, et al. Diretrizes brasileiras de hipertensão arterial–2020. *Arq Bras Cardiol*. 2021;116(3):516-658. doi: 10.36660/abc.20201238
58. Xu YJ, Arneja AS, Tappia PS, Dhalla NS. The potential health benefits of taurine in cardiovascular disease. *Exp Clin Cardiol*. 2008;13(2):57-65.
59. Bousquet P, Feldman J, Bloch R, Schwartz J. Central cardiovascular effects of taurine: comparison with homotaurine and muscimol. *J Pharmacol Exp Ther*. 1981;219(1):213-218.
60. Bichler A, Swenson A, Harris MA. A combination of caffeine and taurine has no effect on short term memory but induces changes in heart rate and mean arterial blood pressure. *Amino Acids*. 2006;31(4):471-476. doi: 10.1007/s00726-005-0302-x
61. Campagnole-Santos MJ, Haibara AS. Reflexos cardiovasculares e hipertensão arterial. *Rev Bras Hipertens*. 2001;8(1):30-40.
62. Irigoyen MC, Consolim-Colombo FM, Krieger EM. Controle cardiovascular: regulação reflexa e papel do sistema nervoso simpático. *Rev Bras Hipertens*. 2001;8(1):55-62.
63. Evans J, Richards JR, Battisti AS. Caffeine. In: *StatPearls*. StatPearls Publishing; 2021. https://www.ncbi.nlm.nih.gov/books/NBK519490/. Accessed 15 April, 2023.
64. Pastore C, Pinho J, Pinho C, et al. III Diretrizes da Sociedade Brasileira de Cardiologia sobre análise e emissão de laudos eletrocardiográficos. *Arq Bras Cardiol*. 2016;106:1-23.
65. Guidance for industry. E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Food and drug administration; 2005. https://www.fda.gov/files/drugs/published/E14-Clinical-Evaluation-of-QT-QTc-Interval-Prolongation-and-Proarrhythmic-Potential-for-Non-Antiarrhythmic-Drugs.pdf. Accessed April 15, 2023.
66. Fletcher EA, Lacey CS, Aaron M, Kolasa M, Occiano A, Shah SA. Randomized Controlled Trial of High-Volume Energy Drink Versus Caffeine Consumption on ECG and Hemodynamic Parameters. *J Am Heart Assoc*. 2017;6(5):e004448. doi: 10.1161/JAHA.116.004448

Table Legends

Table 1. PICOS criteria for inclusion and exclusion of studies.

Table 2. Characteristics of the studies included in the quantitative analysis.

Legend for Table 2. In the column "Outcome" values are mean ± standard deviation, or median (min-max).

Abbreviations: C, crossover; DB, double-blind; DBP, diastolic blood pressure; F, females; HR, heart rate; M_e, mean; QT, QT interval; QTc, corrected QT interval; M, males; NS, not significant; R, randomized; SBP, systolic blood pressure.

[a] Preliminary study conducted in 1997 and published in 2001 along with another study.

[†] Statistical significance in the comparison between the energy drink and the control drink, taking into account the greatest difference presented in the variable throughout the period evaluated in the study.

Figure Legends

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection.

Figure 2. Meta-analysis of the acute effects of energy drink consumption compared to a control drink on systolic blood pressure [SBP] in healthy adults.

Legend for Figure 2. Time frames: (A) ≤20 minutes, (B) 30-40 minutes, (C) 60-80 minutes, (D) 90-100 minutes and (E) ≥120 minutes. * Preliminary study conducted in 1997 and published in 2001 along with another study.

Figure 3. Meta-analysis of the acute effects of energy drink consumption compared to a control drink on diastolic blood pressure [DBP] in healthy adults.

Legend for Figure 3. Time frames: (A) ≤20 minutes, (B) 30-40 minutes, (C) 60-80 minutes, (D) 90-100 minutes and (E) ≥120 minutes. * Preliminary study conducted in 1997 and published in 2001 along with another study.

Figure 4. Meta-analysis of the acute effects of energy drink consumption compared to a control drink on cardiac output [CO] in healthy adults.

Legend for Figure 4. Time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (D) ≥120 minutes.

Figure 5. Risk of bias assessment of individual studies.

Table 1 **PICOS criteria for inclusion and exclusion of studies.**

Criteria	Inclusion criteria	Exclusion criteria
P (population)	Studies with healthy adults aged ≥18 years	
I (intervention)	Studies involving commercially available energy drinks	Studies involving additional interventions such as non-energy drinks (fruit juice, tea, alcohol or coffee), drugs, energy bars, sports supplements, physical activity and painful, psychological and/or emotional stimuli
C (comparison)	Studies involving a control drink or water	Control drink containing caffeine or any compound that can potentially modify cardiovascular outcomes
O (outcomes)	Studies reporting means and standard deviations of one or more outcomes using the following measurement methods: A. Systolic and diastolic blood pressure: auscultatory or oscillometric methods B. Resting heart rate: portable cardiotachometer or electrocardiography C. Cardiac output: invasive and non-invasive methods D. Endothelial function: flow-mediated dilation (FMD) measurement of reactive hyperemia by venous occlusion plethysmography; or plethysmography using intra-arterial infusion of vasoactive agents E. QT/QTc interval: electrocardiogram	Studies not reporting means and standard deviations of outcomes pre- and/or post-intervention (after contacting the authors or failing to obtain data from graphs using GetDate Graph Digitizer)
S (study design)	Randomized controlled trial	Similar studies published in different journals

Table 2 **Characteristics of the studies included in the quantitative analysis.**

Author, year	Mean age ± SD or min.-max.	Study design	n	Energy drink (volume) [caffeine concentration]	Control drink (volume)	Outcome
Alford 1997, (2001[a])[1]	23, 18-30	R, C, DB	10	Red Bull® (250 mL) [80 mg]	Flavored water (250 mL)	SBP: 116.30 ± 8.54 vs. 114.10 ± 11.38 (1.93%, NS) DBP: 72.20 ± 9.96 vs. 68.00 ± 6.64 (6.18%, NS) HR: 77.80 ± 9.17 vs. 74.60 ± 8.54 (4.30%, NS)
Alford (2001[b])[1]	24, 18-35	R, C, DB	14	Red Bull® (250 mL) [80 mg]	Flavored water (250 mL)	SBP: 118.30 ± 11.97 vs. 118.30 ± 12.72 (0.00%, NS) DBP: 74.30 ± 11.22 vs. 69.10 ± 11.22 (7.52%, NS) HR: 83.30 ± 10.85 vs. 75.40 ± 7.11 (10.48%, $p < 0.05$)
Ragsdale et al (2010)[29]	19.8 ± 1.6	R, DB	68	Regular Red Bull® (250 mL) [80 mg]	Flavored water (250 mL)	SBP: 124.50 ± 10.10 vs. 119.70 ± 14.70 (4.01%, NS)† DBP: 77.90 ± 9.40 vs. 73.60 ± 11.20 (5.84%, NS)† HR: 72.80 ± 16.00 vs. 72.50 ± 10.90 (0.41%, NS)† QT: 379.30 ± 4.80 vs. 385.20 ± 8.10 (1.55%, NS)†
				Sugar-free Red Bull® (250 mL) [80 mg]		SBP: 120.40 ± 14.20 vs. 117.70 ± 10.40 (2.29%, NS)† DBP: 76.90 ± 8.30 vs. 78.10 ± 8.30 (1.56%, NS)† HR: 72.40 ± 11.60 vs. 74.60 ± 12.30 (3.03%, NS)† QT: 373.00 ± 6.10 vs. 373.50 ± 5.50 (0.13%, NS)†
Grasser et al (2014)[30]	22.5 ± 3	R, C	25	Red Bull® (355 mL) [114 mg]	Water (355 mL)	SBP: 117.27 ± 4.80 vs. 113.31 ± 3.30 (3.49%, $p < 0.01$) DBP: 77.07 ± 3.70 vs. 74.32 ± 2.25 (3.70%, $p < 0.01$) HR: 60.55 ± 2.80 vs. 59.11 ± 2.00 (2.43%, $p < 0.01$) CO: 5.02 ± 0.25 vs. 4.97 ± 0.15 (1.01%, $p < 0.05$)
Grasser (2015)[31]	22.1 ± 2.2	R, C	20	Red Bull® (355 mL) [114 mg]	Water (355 mL)	SBP: 124.00 ± 13.42 vs. 118.00 ± 8.94 (5.08%, NS) DBP: 80.00 ± 8.94 vs. 76.00 ± 8.94 (5.26%, NS) HR: 71.00 ± 8.94 vs. 64.00 ± 8.94 (10.94%, NS) CO: 5.90 ± 0.89 vs. 5.40 ± 0.89 (9.26%, NS)
Jo (2015)[32]	24.9 ± 3.8	R, C	40	Not available ® (200 mL) [350 mg]	Vitamin water (200 mL)	SBP: 117.15± 12.44 vs. 108.80 ± 13.79 (7.67%, $p = 0.07$)† DBP: 69.25 ± 8.80 vs. 67.55 ± 10.87 (2.52%, NS)†
Miles-Chan et al (2015)[33]	25.4 ± 6.5	R, C	8	Regular Red Bull® (355 mL) [114 mg]	Water (355 mL)	SBP: 130.00 ± 5.10 vs. 123.10 ± 5.40 (5.60%, $p < 0.01$)† DBP: 77.40 ± 1.70 vs. 71.90 ± 4.00 (7.65%, $p < 0.01$)† HR: 69.30 ± 9.10 vs. 60.50 ± 0.80 (14.50%, $p < 0.01$)† CO: 6.20 ± 1.10 vs. 5.10 ± 0.00 (21.57%, $p < 0.01$)†
						SBP: 125.20 ± 5.30 vs. 123.10 ± 5.40 (1.70%, $p < 0.01$)†

				Sugar-free Red Bull® (355 mL) [114 mg]		DBP: 77.40 ± 3.30 vs. 71.90 ± 4.00 (7.65%, $p < 0.01$)[†] HR: 62.70 ± 7.10 vs. 59.90 ± 2.50 (4.67%, $p < 0.05$)[†] CO: 5.20 ± 0.60 vs. 5.00 ± 0.00 (4.00%, $p < 0.05$)[†]
Svatikova et al (2015)[34]	29 ± 6.4	R, C, DB	24	Rockstar® (480 mL) [355 mg]	Flavored water (480 mL)	SBP: 115.0 ± 9.40 vs. 111.60 ± 9.50 (3.05%, $p = 0.01$) DBP: 68.50 ± 5.40 vs. 64.90 ± 5.50 (5.55%, $p < 0.01$) HR: 63.10 ± 10.60 vs. 64.10 ± 10.50 (1.58%, $p = 0.45$)
Shah et al (2016a)[35]	28 ± 6	R, C, DB	26	5-hour ENERGY® (59 mL) [200 mg]	Flavored water (59 mL)	SBP: 125.10 ± 10.00 vs. 119.00 ± 9.00 (5.13%, $p = 0.05$)[†] DBP: 81.00 ± 8.00 vs. 77.00 ± 6.00 (9.10%, $p = 0.02$)[†] HR: 66.00 ± 10.00 vs. 67.00 ± 8.00 (1.51%, NS)[†] QT: 408.00 ± 23.00 vs. 400.00 ± 20.00 (2.00%, NS)[†] QTc: 412.00 ± 20.00 vs. 416.00 ± 19.00 (0.97%, NS)[†]
Shah et al (2016b)[36]	21.6 ± 2.6	R, C, DB	27	Not available (473 mL) [320 mg]	Flavored water (500 mL)	SBP: 115.00 ± 6.40 vs. 110.33 ± 5.80 (4.23%, $p < 0.03$)[†] DBP: 76.54 ± 6.10 vs. 73.46 ± 4.10 (4.19%, NS)[†] HR: 72.16 ± 9.30 vs. 67.37 ± 7.40 (7.11%, NS)[†] QT: 387.26 ± 20.80 vs. 394.80 ± 16.80 (1.95%, NS)[†] QTc: 420.37± 10.70 vs. 413.81 ± 11.80 (1.58%, $p < 0.03$)[†]
Peveler et al (2017)[37]	M: 21.8 ± 2.2 F: 24.0 ± 4.4 M_e: 22.9 ± 3.3	R, C	15	Red Bull® (250 mL) [80mg]	Soda (355 mL)	SBP: 119.27 ± 8.26 vs. 117.13 ± 8.36 (1.83%, NS)[†] DBP: 75.73 ± 7.72 vs. 74.80 ± 5.97 (1.24%, NS)[†] HR: 68.33 ± 11.37 vs. 67.07 ± 10.17 (1.88%, NS)[†]
				Monster® (473 mL) [163 mg]		SBP: 123.07 ± 9.56 vs. 117.13 ± 8.36 (5.07%, NS)[†] DBP: 75.73 ± 6.88 vs. 74.80 ± 5.97 (1.24%, NS)[†] HR: 71.87 ± 10.74 vs. 68.27 ± 10.02 (5.27%, NS)[†]
				5-hour ENERGY® (27 mL) [207 mg]		SBP: 121.20 ± 9.16 vs. 117.13 ± 8.36 (3.47%, NS)[†] DBP: 75.87 ± 6.94 vs. 74.80 ± 5.97 (1.43%, NS)[†] HR: 69.40 ± 10.15 vs. 68.27 ± 10.02 (1.65%, NS)[†]
Polito (2017)[38]	21.6 ± 0.5	R, C, DB	15	Not available (620 mL) [200 mg]	Flavored water (450 mL)	HR: 82.80 ± 1.90 vs. 76.90 ± 2.80 (7.67%, $p = 0.04$)
Nowak et al (2018)[39]	25 ± 7.1	R	68	Not available (750 mL) [240 mg]	Water (750 mL)	SBP: 122.20 ± 14.00 vs. 121.70 ± 10.70 (0.41%, NS) DBP: 82.70 ± 9.30 vs. 76.90 ± 8.60 (7.54%, $p < 0.01$) HR: 78.70 ± 12.10 vs. 75.80 ± 10.90 (3.82%, NS)
Basrai et al (2019)[8]	22.3 ± 1.8	R, C, DB	19	Red Bull® (750 mL) [240mg]	Isotonic drink (1000 mL)	SBP: 120.60 ± 10.00 vs. 116.50 ± 7.60 (3.52%, $p < 0.05$) DBP: 76.20 ± 9.50 vs. 74.70 ± 6.70 (2.00%, $p < 0.05$) HR: 62.0 (59.5 – 67.5) vs. 63.0 (59.5 – 74.0) (1.61%, $p < 0.05$) QTc: 403.90 ± 25.10 vs. 401.10 ± 22.40 (0.70%, NS)

				Red Bull® (1000 mL) [320 mg]	Isotonic drink (1000 mL)	SBP: 120.90 ± 11.50 vs. 117.30 ± 10.60 (3.07%, p < 0.05) DBP: 77.60 ± 7.50 vs. 73.80 ± 8.10 (5.15%, p < 0.05) HR: 67.0 (57.5 – 70.5) vs. 61.0 (56.0 – 66.5) (9.84%, p < 0.05) QTc: 394.60 ± 23.20 vs. 401.10 ± 22.40 (1.65%, NS)
Nowak et al (2019)[40]	25 ± 6.5	R	88	Not available (600 mL) [192 mg]	Water (600 mL)	SBP: 124.80 ± 14.10 vs. 124.00 ± 11.40 (0.64%, NS) DBP: 84.80 ± 9.90 vs. 75.80 ± 8.00 (11.87%, NS) HR: 80.80 ± 11.40 vs. 69.10 ± 9.00 (16.93%, NS)
Shah et al (2019)[41]	22.1 ± 3	R, C	34	Not available (946 mL) [304 mg]	Flavored water (946 mL)	SBP: 127.60 ± 5.50 vs. 121.70 ± 5.00 (4.85%, p < 0.05)† DBP: 79.40 ± 4.30 vs. 75.10 ± 3.10 (5.72%, p < 0.05)† HR: 66.50 ± 7.90 vs. 67.70 ± 6.20 (1.80%, NS)† QT: 419.50 ± 18.30 vs. 412.40 ± 11.50 (1.72%, p < 0.05)† QTc: 423.10 ± 13.80 vs. 412.60 ± 12.90 (2.54%, p < 0.05)†
				Not available (946 mL) [320 mg]		SBP: 124.10 ± 4.00 vs. 119.70 ± 4.80 (3.67%, p < 0.05)† DBP: 78.90 ± 4.50 vs. 75.00 ± 4.00 (5.20%, p < 0.05)† HR: 65.50 ± 6.40 vs. 67.70 ± 6.20 (3.36%, NS)† QT: 397.50 ± 12.60 vs. 396.60 ± 12.90 (0.23%, NS)† QTc: 420.60 ± 15.10 vs. 412.60 ± 12.90 (1.94%, p < 0.05)†
Stopa et al (2020)[42]	23.7 ± 1.2	R, C, DB	18	Rockstar® (500 mL) [160 mg]	Soda drink (500 mL)	SBP: 125.11 ± 26.06 vs. 116.50 ± 13.72 (7.39%, p = 0.03)† DBP: 78.28 ± 9.10 vs. 72.50 ± 8.99 (7.97%, p = 0.03)† HR: 71.06 ± 8.95 vs. 70.50 ± 9.18 (0.79%, NS)† QT: 403.39 ± 29.76 vs. 406.89 ± 28.41 (0.87%, NS) QTc: 410.89 ± 20.54 vs. 416.22 ± 25.91 (1.30%, NS)

In the column "Outcome" values are mean ± standard deviation, or median (min-max).
Abbreviations: C, crossover; DB, double-blind; DBP, diastolic blood pressure; F, females; HR, heart rate; M_e, mean; QT, QT interval; QTc, corrected QT interval; M, males; NS, not significant; R, randomized; SBP, systolic blood pressure.
[a] Preliminary study conducted in 1997 and published in 2001 along with another study.
† Statistical significance in the comparison between the energy drink and the control drink, taking into account the greatest difference presented in the variable throughout the period evaluated in the study.

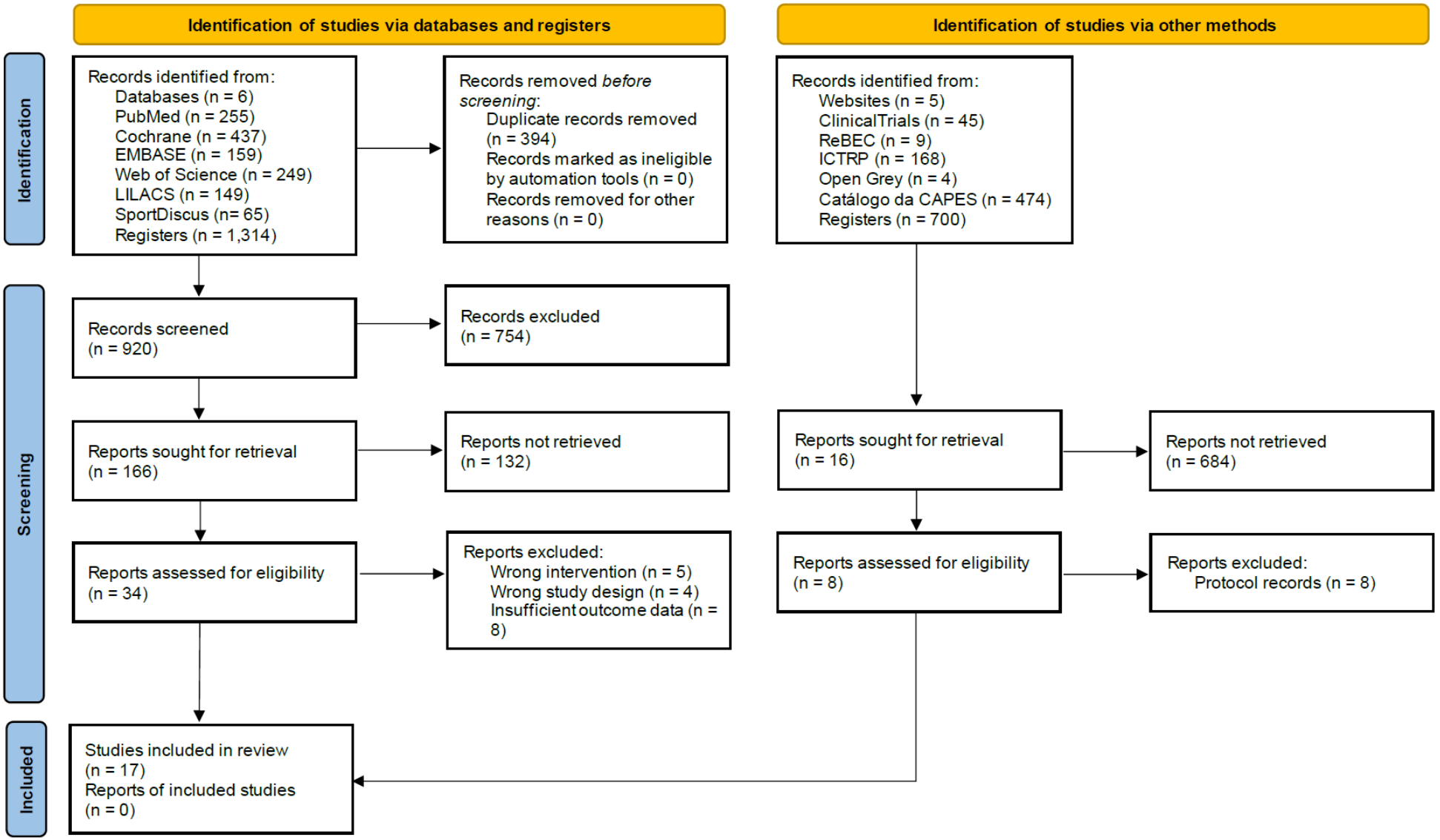

Figure 1 **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection.**

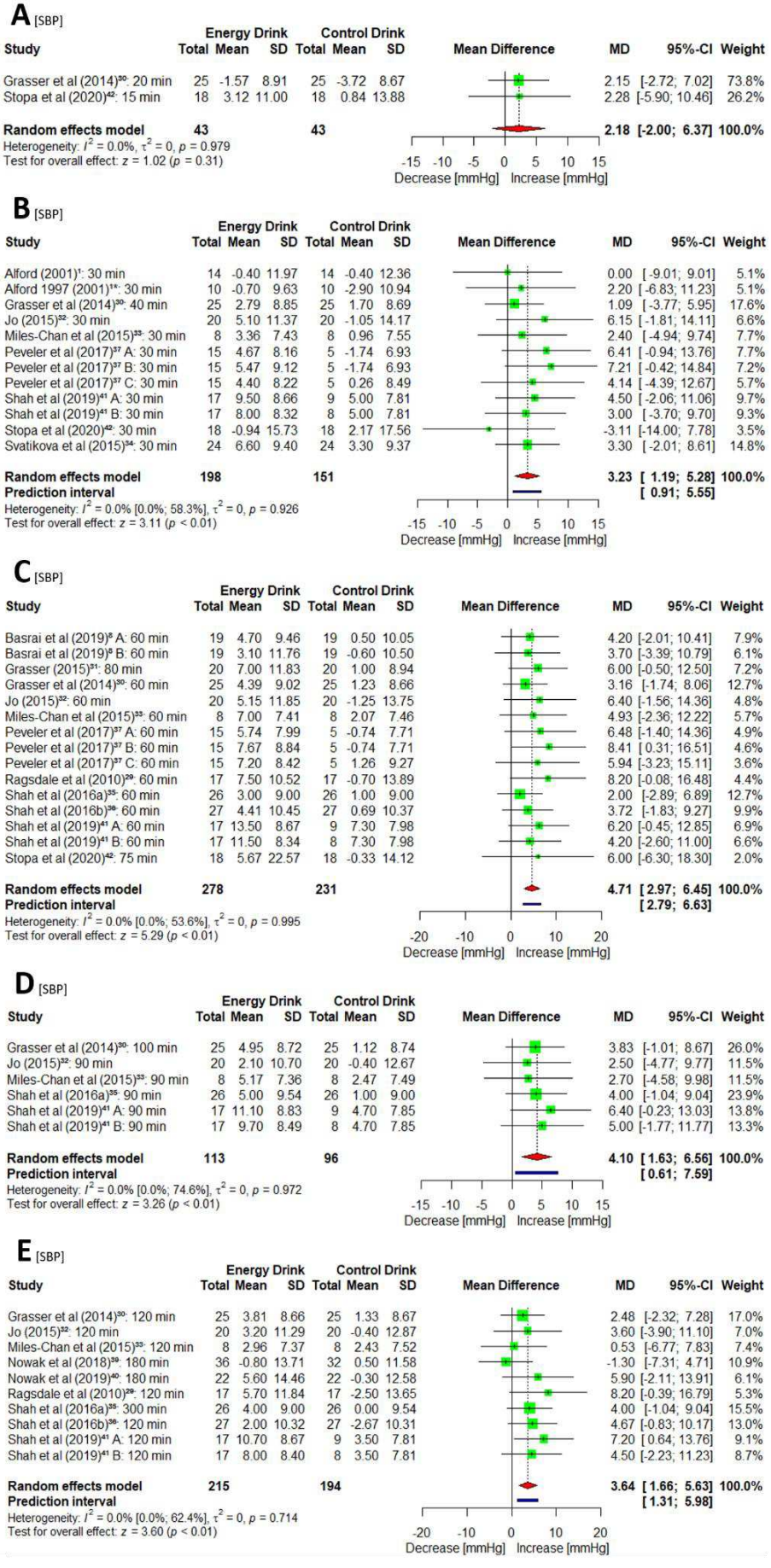

Figure 2 **Meta-analysis of the acute effects of energy drink consumption compared to a control drink on systolic blood pressure [SBP] in healthy adults.**

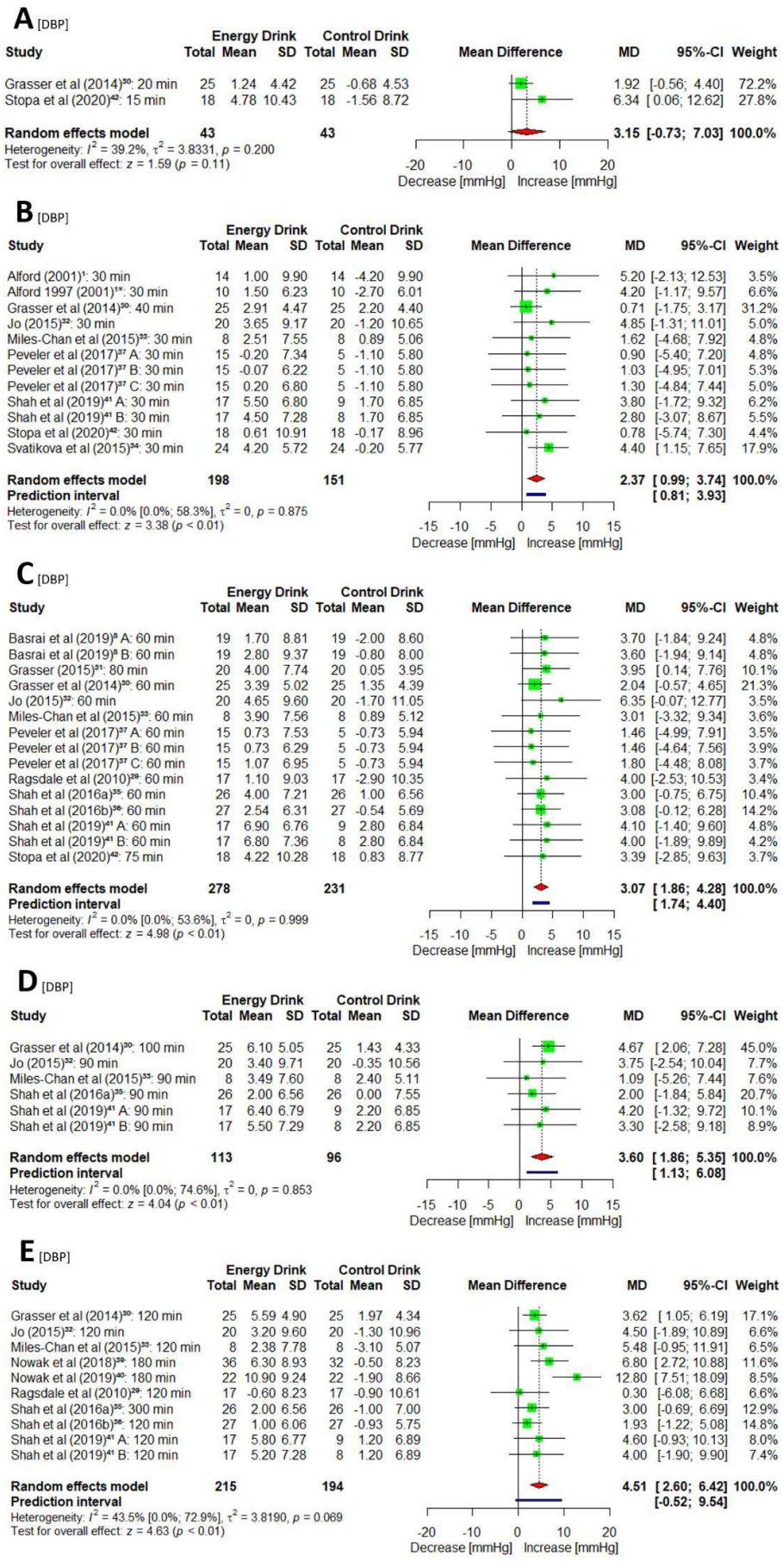

Figure 3 **Meta-analysis of the acute effects of energy drink consumption compared to a control drink on diastolic blood pressure [DBP] in healthy adults.**

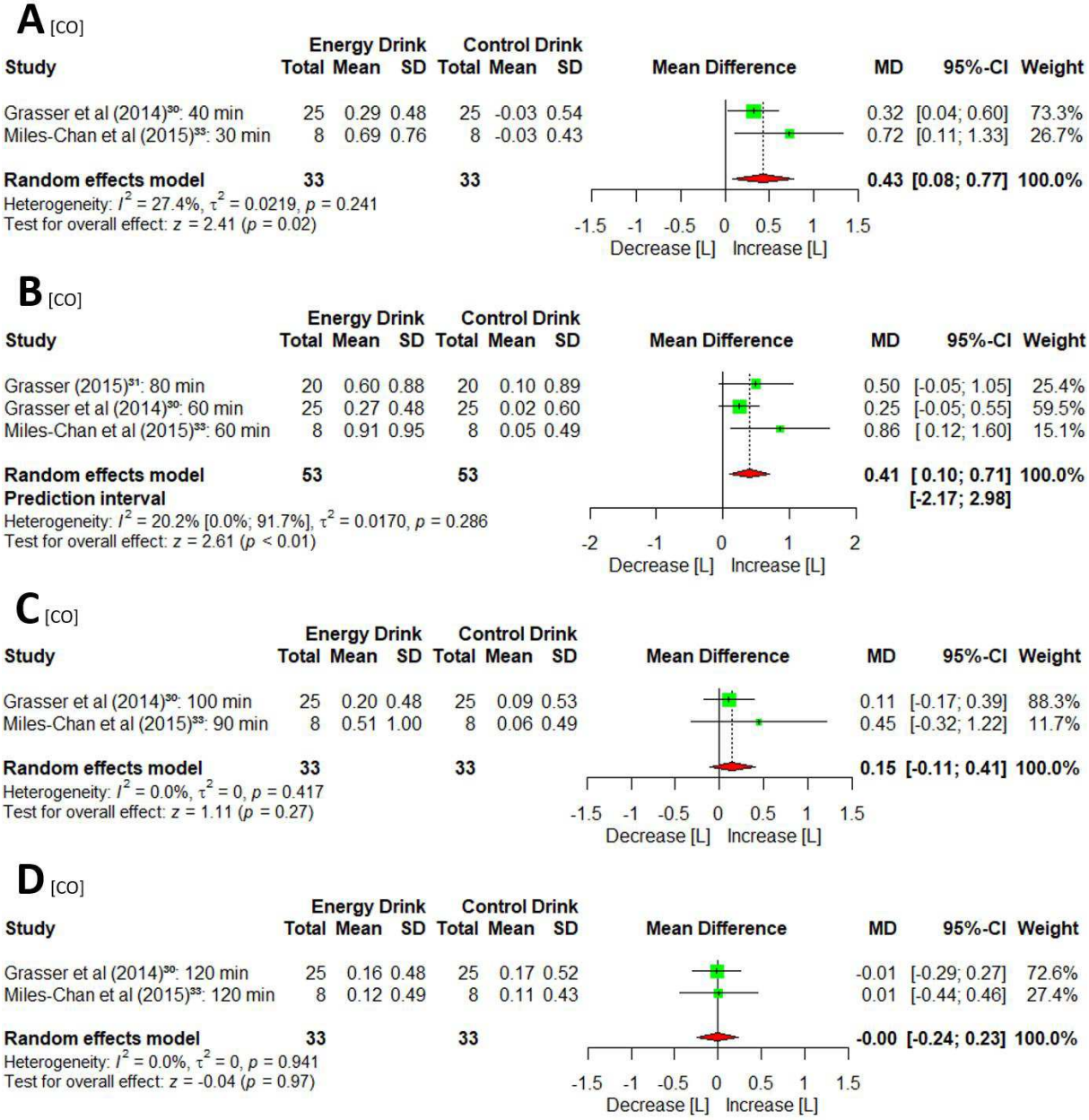

Figure 4 **Meta-analysis of the acute effects of energy drink consumption compared to a control drink on cardiac output [CO] in healthy adults.**

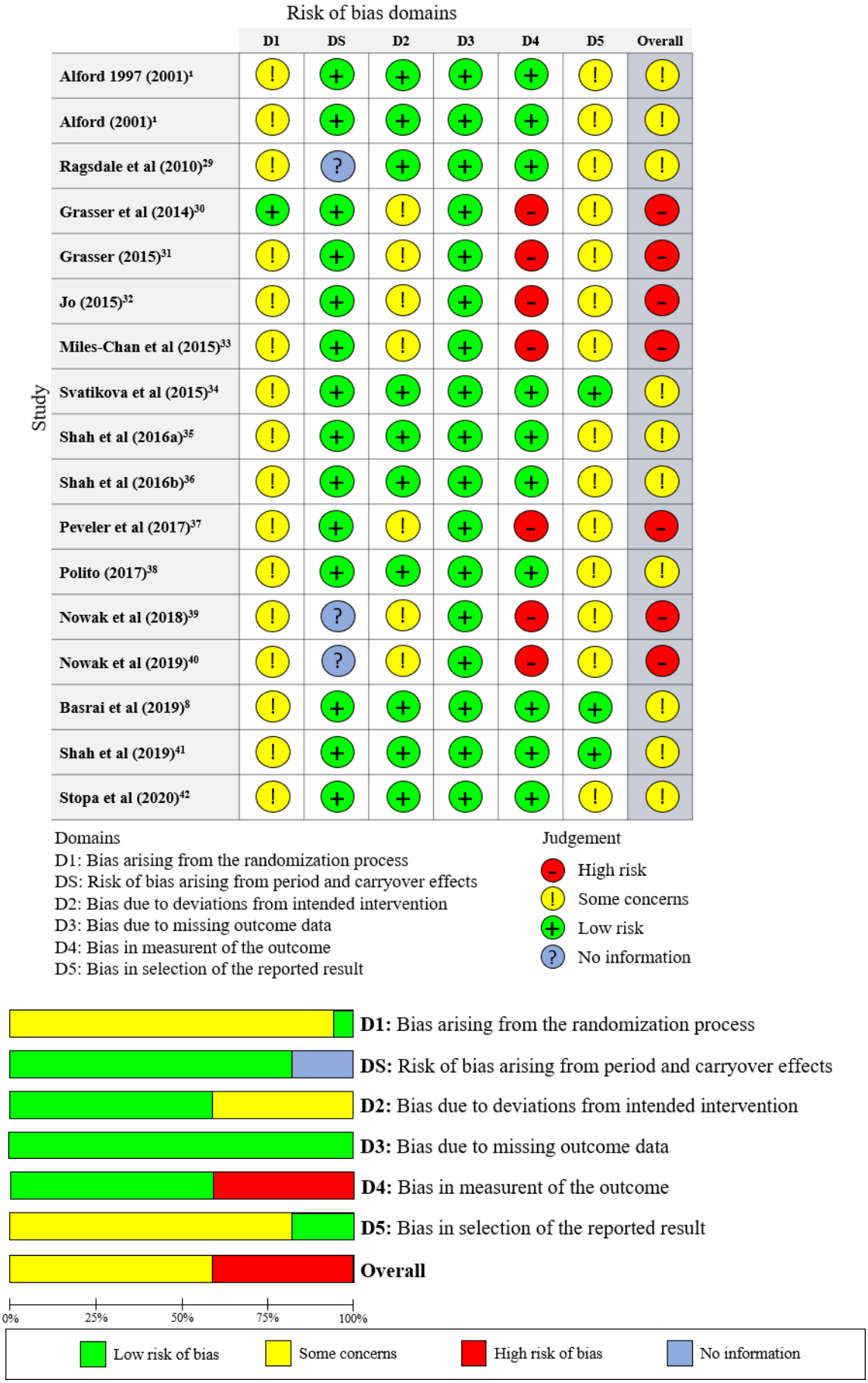

Figure 5 **Risk of bias assessment of individual studies**

4 CONCLUSÕES GERAIS

O presente estudo conclui que o consumo agudo de BEs disponíveis comercialmente, independentemente do seu teor de cafeína, foi capaz de elevar os valores de PAS e PAD de adultos saudáveis em níveis significantes por até duas horas após sua ingestão. Além disso, apesar de pequena, também se observou elevação do DC.

A não influência das BEs sobre a FC, QT/QTc e a pequena magnitude de efeito na elevação da PAS, PAD e DC indicam que o consumo de BEs possui risco baixo, ou não induz riscos à saúde cardiovascular em adultos saudáveis. Porém, deve-se atentar para casos onde há consumo excessivo de BEs, da combinação com álcool ou outras substâncias e/ou na existência de anomalias cardíacas, situações nas quais o risco ainda precisa ser melhor investigado.

Tais resultados são reforçados pela acertiva decisão de incluir apenas ECRs como forma de minimizar o risco de viés e possíveis fatores de confusão. Além disso, o alto rigor metodológico empregado nesta revisão garantiu baixos níveis de heterogeneidade estatística entre os estudos. Os curtos intervalos de predição e as avaliações da força da evidência geradas pelo GRADE permitiram sugerir possíveis resultados para estudos futuros, especialmente para a PA. A ferramenta RoB2 utilizada para avaliar o risco de viés permitiu a realização de análises mais robustas e apontou limitações dos estudos incluídos que devem ser contempladas em ECRs futuros. Por fim, as análises estratificadas em diferentes períodos de tempo evidenciaram os efeitos agudos do consumo de BEs nos parâmetros cardiovasculares em adultos saudáveis ao longo do tempo.

No entanto, destacamos que esta revisão sistemática com metanálise possui limitações a serem consideradas, como o baixo número de estudos incluídos nas análises, especialmente na avaliação do DC e intervalo QT/QTc. Desta forma, os resultados aqui evidenciados devem ser interpretados com cautela.

REFERÊNCIAS

ALFORD, C.; COX, H.; WESCOTT, R. The effects of red bull energy drink on human performance and mood. **Amino Acids**, v. 21, p. 139-150, 2001.

AKHUNDOVA, J.; KAYA, C. T.; ULUDAĞ, D. M. G. Acute effects of consumption of low-caffeine energy drinks on endothelial functions in healthy volunteers. **Anatolian Journal of Cardiology**, v. 25, n. 10, p. 678-683, 2021.

ALI, F. *et al.* Energy drinks and their adverse health effects: A systematic review of the current evidence. **Postgraduate Medicine**, v. 127, n. 3, p. 308-322, 2015.

ARMSTRONG, R. *et al*. Heart rate: control mechanisms, pathophysiology and assessment of the neurocardiac system in health and disease. **QJM: An International Journal of Medicine**, v. 115, n. 12, p. 806-812, 2022.

ASSOCIAÇÃO BRASILEIRA DAS INDÚSTRIAS DE REFRIGERANTES E DE BEBIDAS NÃO ALCOÓLICAS. Energéticos. 2020. Disponível em: https://abir.org.br/o-setor/dados/energeticos/. Acesso em: 06 maio 2023.

AZEVEDO, C. R.F. A. *et al*. Protocolos de Suporte Avançado de Vida. In: **Protocolos de Suporte Avançado de Vida.** 2016. p. 683-683.

BALIOU, S. *et al*. Protective role of taurine against oxidative stress. **Molecular Medicine Reports,** v. 24, n. 2, p. 1-19, 2021.

BALLESTEROS- YÁÑEZ , I. *et al*. The Role of Adenosine Receptors in Psychostimulant Addiction. **Frontiers in Pharmacology**, v. 8, p. 985, 2018.

BALLISTRERI, M. C.; CORRADI-WEBSTER, C. M. Consumption of energy drinks among physical education students. **Revista Latino-americana de Enfermagem**, v. 16, p. 558-564, 2008.

BARCELOS, R. P. *et al*. Caffeine effects on systemic metabolism, oxidative-inflammatory pathways, and exercise performance. **Nutrition Research**, v. 80, p. 1-17, 2020.

BARON, A. D.; BRECHTEL, G. Insulin differentially regulates systemic and skeletal muscle vascular resistance. **American Journal of Physiology-Endocrinology And Metabolism**, v. 265, n. 1, p. E61-E67, 1993.

BARROSO, W. K. S. *et al*. Diretrizes brasileiras de hipertensão arterial–2020. **Arquivos Brasileiros de Cardiologia**, v. 116, p. 516-658, 2021.

BASRAI, M. *et al*. Energy drinks induce acute cardiovascular and metabolic changes pointing to potential risks for young adults: A randomized controlled trial. **The Journal of Nutrition**, v. 149, n. 3, p. 441-450, 2019.

BOUCKENOOGHE, T.; REMACLE, C.; REUSENS, B. Is taurine a functional nutrient?. **Current Opinion in Clinical Nutrition & Metabolic Care**, v. 9, n. 6, p. 728-733, 2006.

BROTHERS, R. M. *et al.* Heart rate, blood pressure and repolarization effects of an energy drink as compared to coffee. **Clinical Physiology and Functional Imaging,** v. 37, n. 6, p. 675-681, 2017.

BROWN, C. M. *et al*. Fructose ingestion acutely elevates blood pressure in healthy young humans. American Journal of Physiology-Regulatory, **Integrative and Comparative Physiology**, v. 294, n. 3, p. R730-R737, 2008.

CAINE, J. J.; GERACIOTI, T. D. Taurine, energy drinks, and neuroendocrine effects. **Cleveland Clinic Journal of Medicine**, v. 83, n. 12, p. 895-904, 2016.

CASTRO, A. *et al*. Cyclic nucleotide phosphodiesterases and their role in immunomodulatory responses: advances in the development of specific phosphodiesterase inhibitors. **Medicinal Research Reviews**, v. 25, n. 2, p. 229-244, 2005.

CHEN, Q. *et al*. The dose response of taurine on aerobic and strength exercises: A systematic review. **Frontiers in Physiology**, v. 12, p. 700352, 2021.

COSTA, B.; HAYLEY, A.; MILLER, P. Young adolescents' perceptions, patterns, and contexts of energy drink use. A focus group study. **Appetite**, v. 80, p. 183-189, 2014.

DAROVIC, G. O. **Hemodynamic monitoring: invasive and noninvasive clinical application**. Saunders, 2002.

DE CARVALHO, J. M. *et al*. Perfil dos principais componentes em bebidas energéticas: cafeína, taurina, guaraná e glucoronolactona. **Revista do Instituto Adolfo Lutz**, v. 65, n. 2, p. 78-85, 2006.

DEVARAJ, S.; SINGH, U.; JIALAL, I. The evolving role of C-reactive protein in atherothrombosis. **Clinical Chemistry**, v. 55, n. 2, p. 229-238, 2009.

DIOGO, J. S. G. *et al*. Risk assessment of additives through soft drinks and nectars consumption on Portuguese population: a 2010 survey. **Food and Chemical Toxicology**, v. 62, p. 548-553, 2013.

DURELLI, L.; MUTANI, R.; FASSIO, F. The treatment of myotonia: evaluation of chronic oral taurine therapy. **Neurology**, v. 33, n. 5, p. 599-599-a, 1983.

ECHEVERRI, D. *et al.* Caffeine's Vascular Mechanisms of Action. **International Journal of Vascular Medicine**, v. 2010, 2010.

EHLERS, A. *et al*. Risk assessment of energy drinks with focus on cardiovascular parameters and energy drink consumption in Europe. **Food and Chemical Toxicology**, v. 130, p. 109-121, 2019.

EVANS, S. M.; GRIFFITHS, R. R. Caffeine tolerance and choice in humans. **Psychopharmacology**, v. 108, n. 1, p. 51-59, 1992.

EVANS, J.; RICHARDS, J. R.; BATTISTI, A. S. Caffeine. *In*: **StatPearls [Internet]**: Treasure Island (FL): StatPearls Publishing, 2022. Disponível em: https://www.ncbi.nlm.nih.gov/books/NBK519490/#_NBK519490_pubdet_. Acesso em: 06 maio 2023.

FALUDI, A. A. *et al*. Atualização da diretriz brasileira de dislipidemias e prevenção da aterosclerose–2017. **Arquivos Brasileiros de Cardiologia**, v. 109, p. 1-76, 2017.

FELDMAN, J.; GOLDWASSER, G. P. Eletrocardiograma: recomendações para a sua interpretação. **Revista da SOCERJ**, v. 14, n. 4, p. 256, 2004.

FISONE, G.; BORGKVIST, A.; USIELLO, A. Caffeine as a psychomotor stimulant: mechanism of action. **Cellular and Molecular Life Sciences CMLS**, v. 61, p. 857-872, 2004.

FLETCHER, E. A. *et al*. Randomized controlled trial of high-volume energy drink versus caffeine consumption on ECG and hemodynamic parameters. **Journal of the American Heart Association**, v. 6, n. 5, p. e004448, 2017.

FOOD & DRUG ADMINISTRATION. Spilling the Beans: How Much Caffeine is Too Much?. **Food & Drug Administration**, 12 dez. 2018. Disponível em: https://www.fda.gov/consumers/consumer-updates/spilling-beans-how-much-caffeine-too-much. Acesso em: 06 maio 2023.

FREDHOLM, B. B. *et al.* Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. **Pharmacological Reviews**, v. 51, n. 1, p. 83-133, 1999.

GARCIA, X.; STEIN, F. Nitric oxide. In: Seminars in pediatric infectious diseases. **WB Saunders**, 2006. p. 55-57.

GOLDFARB, M.; TELLIER, C.; THANASSOULIS, G. Review of published cases of adverse cardiovascular events after ingestion of energy drinks. **The American Journal of Cardiology**, v. 113, n. 1, p. 168-172, 2014.

GRASSER, E. K.; DULLOO, A.; MONTANI, J. Cardiovascular responses to the ingestion of sugary drinks using a randomised cross-over study design: does glucose attenuate the blood pressure-elevating effect of fructose? **British Journal of Nutrition**, v. 112, n. 2, p. 183-192, 2014a.

GRASSER, E. K. *et al*. Cardio-and cerebrovascular responses to the energy drink Red Bull in young adults: a randomized cross-over study. **European Journal of Nutrition**, v. 53, p. 1561-1571, 2014b.

GRASSER, E. K.; DULLOO, A. G.; MONTANI, J. Cardiovascular and cerebrovascular effects in response to red bull consumption combined with mental stress. **The American Journal of Cardiology**, v. 115, n. 2, p. 183-189, 2015.

GUAN, L.; MIAO, P. The effects of taurine supplementation on obesity, blood pressure and lipid profile: A meta-analysis of randomized controlled trials. **European Journal of Pharmacology**, v. 885, p. 173533, 2020.

GUMMIN, D. *et al.* 2020 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 38th Annual Report. **Clinical Toxicology**, 59, n. 12, p. 1282-1501, 2021.

HALL, J. E. G. **Tratado de fisiologia médica**. Elsevier Health Sciences, 2021.

HATCHETT, R. The principles of augmenting the cardiac output in adults. **Intensive and Critical Care Nursing**, v. 14, n. 5, p. 244-251, 1998.

HECKMAN, M.; SHERRY, K.; DE MEJIA, E. Energy Drinks: An Assessment of Their Market Size, Consumer Demographics, Ingredient Profile, Functionality, and Regulations in the United States. **Comprehensive reviews in Food Science and Food Safety**, v. 9, n. 3, p. 303-371, 2010.

HECKMAN, M.; WEIL, J.; DE MEJIA, E. G. Caffeine (1, 3, 7-trimethylxanthine) in foods: a comprehensive review on consumption, functionality, safety, and regulatory matters. **Journal of Food Science**, v. 75, n. 3, p. R77-R87, 2010.

HIGGINS, J. P. *et al*. Consumption of energy beverage is associated with attenuation of arterial endothelial flow-mediated dilatation. **World Journal of Cardiology**, v. 9, n. 2, p. 162-166, 2017.

HIGGINS, J. P. *et al*. Energy Drink Effects on Hemodynamics and Endothelial Function in Young Adults. **Cardiology**, v. 146, n. 2, p. 258-262, 2021.

HILDEBRAND, T. B. **Internacionalização e Estratégias de Marketing Internacional da Red Bull**. Orientador: Dr. Luiz Carlos de Carvalho Júnior. 2014. 71. TCC (Graduação). Curso de Relações Internacionais, Universidade Federal de Santa Catarina, Santa Catarina, 2014. Disponível em: https://repositorio.ufsc.br/bitstream/handle/123456789/124701/Monografia%20do%20Thomas%20Bolduan%20Hildebrand.pdf?sequence=1&isAllowed=y. Acesso em: 06 maio 2022.

HLADUN, O. *et al.* Interaction of Energy Drinks with Prescription Medication and Drugs of Abuse. **Pharmaceutics**, v. 13, n. 10, p. 1532, 2021.

KADAM, A.; DESHMUKH, R. Energy Drinks Market to Garner $ 86.01 Bn, Globally, by 2026 at 7.2% CAGR, Says Allied Market Research. **Allied Market Research**, mar. 2019. Disponível em: https://www.alliedmarketresearch.com/energy-drink-market. Acesso em: 06 maio 2023.

KAUR, A. *et al*. Energy drink consumption: a rising public health issue. **Reviews in Cardiovascular Medicine**, v. 23, n. 3, p. 83, 2022.

KOZIK, T. M. *et al*. Cardiovascular responses to energy drinks in a healthy population: the C-energy study. **The American Journal of Emergency Medicine**, v. 34, n. 7, p. 1205-1209, 2016.

LAL, G. G. Getting Specifie with Functional Beverages. **Food Technology (Chicago)**, v. 61, n. 12, 2007.

LASHERAS, I. *et al*. The impact of acute energy drink consumption on electrical heart disease: A systematic review and meta-analysis. **Journal of Electrocardiology**, v. 65, p. 128-135, 2021.

LA VIEILLE, S. *et al*. Caffeinated energy drinks in the Canadian context: health risk assessment with a focus on cardiovascular effects. **Applied Physiology, Nutrition, and Metabolism**, v. 46, n. 9, p. 1019-1028, 2021.

LENOIR, M. *et al*. Intense sweetness surpasses cocaine reward. **PloS One**, v. 2, n. 8, p. e698, 2007.

LEWINGTON S. *et al*. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. **Lancet**, v. 360, n. 9349, p. 1903-13, 2002.

LIVERTOX. **Clinical and Research Information on Drug-Induced Liver Injury [Internet]**. National Institute of Diabetes and Digestive and Kidney Diseases National Institute of Diabetes and Digestive and Kidney Diseases, 2020. 1-11 p. Disponível em: https://www.ncbi.nlm.nih.gov/books/NBK559836/?report=reader. Acesso em: 06 maio 2023.

MARTINI, F. H *et al*. **Anatomia e Fisiologia Humana: uma abordagem visual**. São Paulo: Pearson Universidades, 2014.

MAUGHAN, R. J.; GRIFFIN, J. Caffeine ingestion and fluid balance: a review. **Journal of Human Nutrition and Dietetics**, v. 16, n. 6, p. 411-420, 2003.

MCDONALD, D. Red Bulls billionaire maniac becomes media mogul. **NBC News**, 22 maio 2011. Disponível em: https://www.nbcnews.com/id/wbna43112711. Acesso em: 06 maio 2023.

MCMULLIN, B. B. et al. The antimicrobial effect of nitric oxide on the bacteria that cause nosocomial pneumonia in mechanically ventilated patients in the intensive care unit. **Respiratory Care**, v. 50, n. 11, p. 1451-1456, 2005.

MEJIA, E.; RAMIREZ-MARES, M. Impact of caffeine and coffee on our health. **Trends in Endocrinology and Metabolism**, v. 25, n. 10, p. 489-492, 2014.

MEYERSOHN, N. Look out Red Bull. Monster is flying. **CNNMoney**, 19 jan. 2018. Disponível em: https://money.cnn.com/2018/01/19/news/companies/monster-energy-red-bull/index.html. Acesso em: 06 maio 2023.

MILES-CHAN, J. L. *et al*. The blood pressure-elevating effect of Red Bull energy drink is mimicked by caffeine but through different hemodynamic pathways. **Physiological Reports**, v. 3, n. 2, p. e12290, 2015.

MOHAMMED, A. H. et al. Knowledge, Consumption Pattern, and Adverse Effects of Energy Drinks among Asian Population: A Cross-Sectional Analysis from Malaysia. **Journal of Nutrition and Metabolism**, v. 2022, 2022.

MUNIYAPPA, R. *et al*. Cardiovascular actions of insulin. **Endocrine Reviews**, v. 28, n. 5, p. 463-491, 2007.

NADEEM, I. *et al.* Energy Drinks and Their Adverse Health Effects: A Systematic Review and Meta-analysis. **Sports Health**, v. 13, n. 3, p. 265-277, 2021.

NAWROT, P. *et al*. Effects of caffeine on human health. **Food Additives & Contaminants,** v. 20, n. 1, p. 1-30, 2003.

NOWAK, D. *et al*. Effects of acute consumption of noni and chokeberry juices vs. energy drinks on blood pressure, heart rate, and blood glucose in young adults. **Evidence-Based Complementary and Alternative Medicine**, v. 2019, p. 1-9, 2019.

OKIN, P. M. *et al*. Assessment of QT interval and QT dispersion for prediction of all-cause and cardiovascular mortality in American Indians: The Strong Heart Study. **Circulation**, v. 101, n. 1, p. 61-66, 2000.

PALATINI, P. Elevated heart rate in cardiovascular diseases: a target for treatment?. **Progress in Cardiovascular Diseases**, v. 52, n. 1, p. 46-60, 2009.

PARK, LINKIN. [Chester Bennington]: Hybrid Theory. Califórnia: Warner Bros, 2000. Faixa 8. CD.

PASTORE, C. A. *et al*. III Diretrizes da Sociedade Brasileira de Cardiologia sobre análise e emissão de laudos eletrocardiográficos. **Arquivos Brasileiros de Cardiologia**, v. 106, p. 1-23, 2016.

PICCIONI, A. *et al*. Energy drinks: a narrative review of their physiological and pathological effects. **Internal Medicine Journal**, v. 51, n. 5, p. 636-646, 2021.

G POSTEMA, P.; AM WILDE, A. The measurement of the QT interval. **Current Cardiology Reviews**, v. 10, n. 3, p. 287-294, 2014.

PRÉCOMA, D. B. *et al*. Atualização da diretriz de prevenção cardiovascular da Sociedade Brasileira de Cardiologia-2019. **Arquivos Brasileiros de Cardiologia**, v. 113, p. 787-891, 2019.

RAHAMATHULLA, M. P. Prevalence, side effects and awareness about energy drinks among the female university students in Saudi Arabia. **Pakistan Journal of Medical Sciences**, v. 33, n. 2, p. 347, 2017.

RAJENDRAN, P. *et al*. The vascular endothelium and human diseases. **International Journal of Biological Sciences**, v. 9, n. 10, p. 1057, 2013.

REIS, H. H. T. **Efeitos da ingestão de diferentes tipos de bebidas energéticas no exercício de corrida**. Orientador: João Carlos Bouzas Marins. 2017. 101 f. (Dissertação) – Mestrado em Educação Física, Universidade Federal de Viçosa, Viçosa, 2017.

REISSIG, C.; STRAIN, E.; GRIFFITHS, R. Caffeinated Energy Drinks -- A Growing Problem. **Drug and Alcohol Dependence**, v. 99, n. 1-3, p. 1-10, 2009.

RIESENHUBER, A. *et al*. Diuretic potential of energy drinks. **Amino Acids**, v. 31, p. 81-83, 2006.

RUBANYI, G.M.; VANHOUTTE, P.M. Superoxide anions and hyperoxia inactivate endothelium-derived relaxing factor(s). **American Journal of Physiology**, v. 250, p. H822-827, 1986.

SANCHIS-GOMAR, F. *et al*. Energy drink overconsumption in adolescents: implications for arrhythmias and other cardiovascular events. **Canadian Journal of Cardiology**, v. 31, n. 5, p. 572-575, 2015.

SAWYNOK, J. Methylxanthines and pain. **Handbook of Experimental Pharmacology**, v. 200, p. 311-329, 2011a.

SAWYNOK, J. Caffeine and pain. **Pain**, 152, n. 4, p. 726-729, 2011b.

SEIFERT, S. *et al*. Health effects of energy drinks on children, adolescents, and young adults. **Pediatrics**, v. 127, n. 3, p. 511-528, 2011.

SHAH, S. *et al.* The Impact of Acute Energy Drink Consumption on Blood Pressure Parameters: A Meta-analysis. **Annals of Pharmacotherapy**, v. 50, n. 10, p. 808-815, 2016a.

SHAH, S. A. *et al*. Effects of single and multiple energy shots on blood pressure and electrocardiographic parameters. **The American Journal of Cardiology**, v. 117, n. 3, p. 465-468, 2016b.

SHAH, S. A. *et al*. Electrocardiographic and blood pressure effects of energy drinks and Panax ginseng in healthy volunteers: a randomized clinical trial. **International Journal of Cardiology**, v. 218, p. 318-323, 2016c.

SHAH, S. A. *et al*. Impact of high volume energy drink consumption on electrocardiographic and blood pressure parameters: a randomized trial. **Journal of the American Heart Association,** v. 8, n. 11, p. e011318, 2019.

SHAO, A.; HATHCOCK, J. N. Risk assessment for the amino acids taurine, L-glutamine and L-arginine. **Regulatory Toxicology and Pharmacology**, v. 50, n. 3, p. 376-399, 2008.

SHIRLEY, D. G.; WALTER, S. J.; NOORMOHAMED, F. H. Natriuretic effect of caffeine: assessment of segmental sodium reabsorption in humans. **Clinical Science**, v. 103, n. 5, p. 461-466, 2002.

SLONIAK, M. C. **Estudo do potencial desmineralizante de bebidas energéticas sobre a hidroxiapatita**. 2014. (Dissertação) – Mestrado em Odontologia.

SOMERS, K. R.; SVATIKOVA, A. Cardiovascular and autonomic responses to energy drinks—clinical implications. **Journal of Clinical Medicine**, v. 9, n. 2, p. 431, 2020.

SOUZA, D. B. *et al*. Acute effects of caffeine-containing energy drinks on physical performance: a systematic review and meta-analysis. **European Journal of Nutrition**, v. 56, p. 13-27, 2017.

STANFIELD, C. **Fisiologia Humana: Com MyHeathLab**. Editora: Editora Pearson. Edição 5ª. 2014.

STOPA, M. *et al*. Influence of energy drinks on acute hemodynamic parameters in young healthy adults: a randomized double-blind placebo-controlled crossover pilot study. **Kardiologia Polska** (Polish Heart Journal), v. 78, n. 4, p. 335-337, 2020.

SUN, H. *et al*. Role of endothelial dysfunction in cardiovascular diseases: the link between inflammation and hydrogen sulfide. **Frontiers in Pharmacology**, v. 10, p. 1568, 2020.

SUN, Q. *et al*. Taurine supplementation lowers blood pressure and improves vascular function in prehypertension: randomized, double-blind, placebo-controlled study. **Hypertension**, v. 67, n. 3, p. 541-549, 2016.

SVATIKOVA, A. *et al*. A randomized trial of cardiovascular responses to energy drink consumption in healthy adults. **JAMA**, v. 314, n. 19, p. 2079-2082, 2015.

TAO, X. *et al*. The effects of taurine supplementation on diabetes mellitus in humans: A systematic review and meta-analysis. **Food Chemistry: Molecular Sciences**, p. 100106, 2022.

TRINKLEY, K. E. *et al*. QT interval prolongation and the risk of torsades de pointes: essentials for clinicians. **Current Medical Research and Opinion**, v. 29, n. 12, p. 1719-1726, 2013.

TURNBULL, D. *et al*. Caffeine and cardiovascular health. **Regulatory Toxicology and Pharmacology**, v. 89, p. 165-185, 2017.

VALENTINI, M.; PARATI, G. Variables influencing heart rate. **Progress in Cardiovascular Diseases**, v. 52, n. 1, p. 11-19, 2009.

VANHOUTTE, P. M. Endothelium and control of vascular function. State of the Art lecture. **Hypertension**, v. 13, n. 6_pt_2, p. 658-667, 1989.

VISRAM, S. *et al*. Consumption of energy drinks by children and young people: a rapid review examining evidence of physical effects and consumer attitudes. **BMJ Open**, v. 6, n. 10, p. e010380, 2016.

WALDRON, M. *et al*. The effects of an oral taurine dose and supplementation period on endurance exercise performance in humans: a meta-analysis. **Sports Medicine**, v. 48, p. 1247-1253, 2018a.

WALDRON, M. et al. The effects of oral taurine on resting blood pressure in humans: a meta-analysis. **Current Hypertension Reports**, v. 20, p. 1-8, 2018b.

WARNOCK, R. *et al*. The effects of caffeine, taurine, or caffeine-taurine coingestion on repeat-sprint cycling performance and physiological responses. International **Journal of Sports Physiology and Performance**, v. 12, n. 10, p. 1341-1347, 2017.

WASSEF, B.; KOHANSEIH, M.; MAKARYUS, A. N. Effects of energy drinks on the cardiovascular system. **World Journal of Cardiology**, v. 9, n. 11, p. 796, 2017.

WORLD HEALTH ORGANIZATION. **Cardiovascular diseases (CVDs)**. World Health Organization, 11 jun. 2021a. Disponível em: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). Acesso em: 06 maio 2023.

WORLD HEALTH ORGANIZATION. **Hypertension**. World Health Organization, 16 mar. 2023. Disponível em: https://www.who.int/news-room/fact-sheets/detail/hypertension. Acesso em: 06 maio 2023.

WORTHLEY, M. I. et al. Detrimental effects of energy drink consumption on platelet and endothelial function. **The American Journal of Medicine**, v. 123, n. 2, p. 184-187, 2010.

ZHANG, Y. *et al*. Caffeine and diuresis during rest and exercise: A meta-analysis. **Journal of Science and Medicine in Sport**, v. 18, n. 5, p. 569-574, 2015.

ZUCCONI, S. *et al.* Gathering consumption data on specific consumer groups of energy drinks. **EFSA Supporting Publications**, v. 10, n. 3, p. 394E, 2013.

ZULLI, A. *et al.* Caffeine and cardiovascular diseases: critical review of current research. **European Journal of Nutrition**, 55, n. 4, p. 1331-1343, 2016.

APÊNDICE A – Material suplementar do Artigo I

Supplementary material of the protocol article

Effects of energy drink consumption on cardiovascular parameters in healthy adults: Protocol for a systematic review

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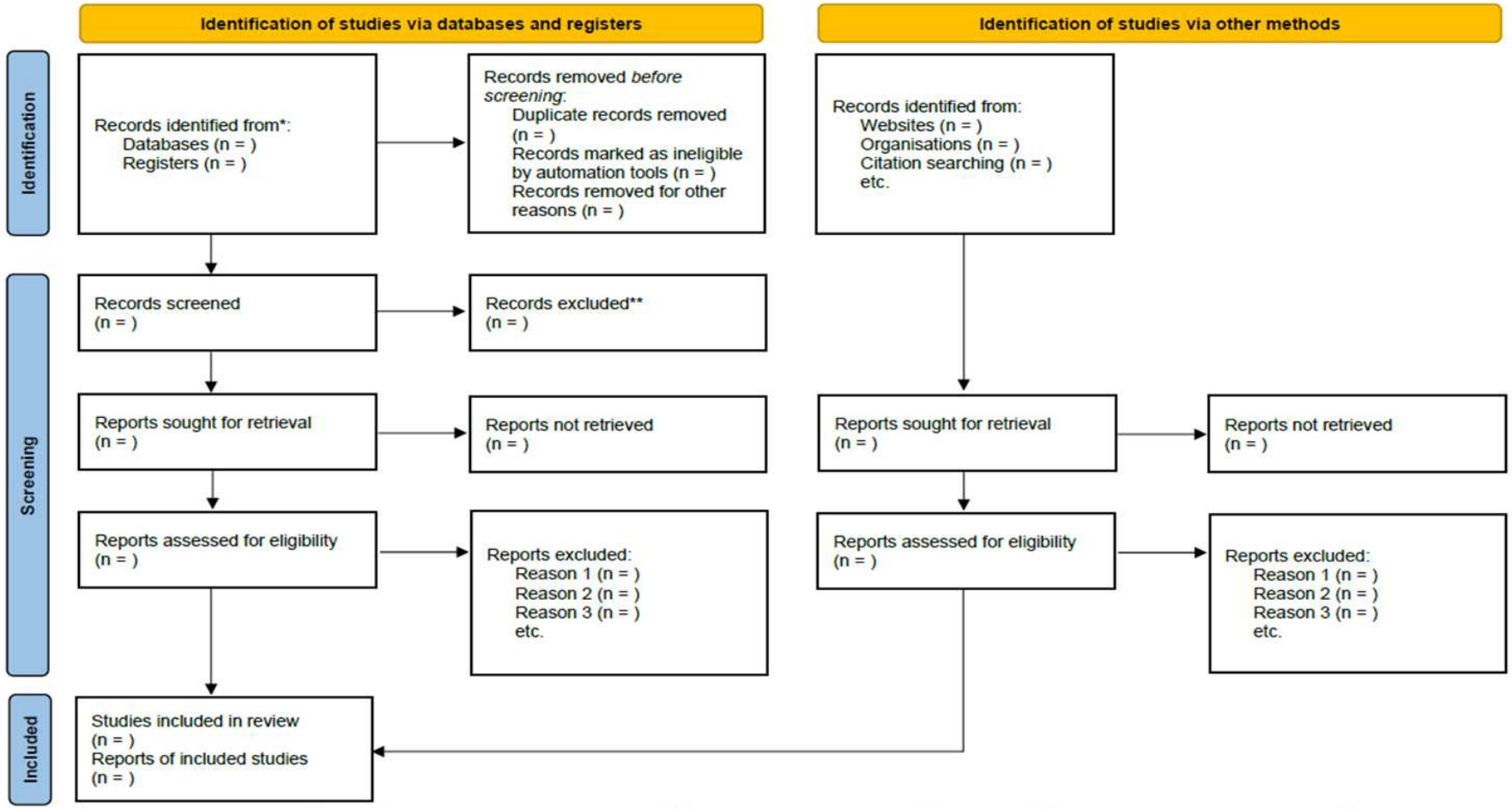
Figure 1

Online PRISMA flow chart for the systematic review (template)



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Table S1

Description of cardiovascular parameters in response to acute consumption of energy drinks included in previews published systematic reviews[1,2]

References	Sample	Outcomes	Authors (year)	Study design	Intervention group (caffeine concentration)	Control group (caffeine concentration)
Shah et al. (2016) #	Healthy adults	SBP, DBP, HR	Al-Fares et al. (2015)	R, SB, PC, C	Energy drink (unknown)	Placebo (none)
		SBP, DBP, HR	Doerner et al. (2015)	OL, AC, C	Energy drink (105 mg)	Caffeinated drink (105 mg)
		SBP, DBP, HR	Hajsadeghi et al. (2015)	OL, NC	Energy drink (80 mg)	None
		SBP, DBP, HR	Svatikova et al. (2014)	R, DB, PC, C	Energy drink (240 mg)	Placebo (none)
		SBP	Fletcher et al. (2014)	R, DB, AC, C	Energy drink (unknown)	Caffeinated drink (unknow)
		SBP, DBP, HR	Grasser et al. (2014)	OL, R, PC, C	Energy drink (114 mg)	Placebo (none)
		SBP, DBP, HR	Marczinski et al. (2014)	PC, C	Energy drink (200 mg)	Decaffeinated drink (6 mg)
		SBP, DBP, HR	Phan and Shah (2014)	R, DB, AC, C	Energy drink (200 mg)	Decaffeinated drink (6 mg)
		SBP, DBP, HR	Kurtz et al. (2013)	R, DB, AC, C	Energy drink (200 mg)	Decaffeinated drink (6 mg)
		SBP, DBP, HR	Menci et al. (2013)	OL, PC, C	Energy drink (unknown)	Placebo (none)
		SBP, DBP, HR	Ragsdale et al. (2010)	DB, P	Energy drink (80 mg)	Placebo (none)
		SBP, DBP, HR	Walker et al. (2010)	R, DB, PC, C	Caffeinated drink (5 mg/kg)	Placebo (none)
		SBP, DBP, HR	Rashti et al. (2009)	R, DB, PC C	Energy drink (230 mg)	Placebo (none)
		SBP, DBP, HR	Steinke et al. (209)	OL, NC	Energy drink (200 mg)	Placebo (none)
		SBP, DBP, HR	Alford 1997 (2001)	R, DB, C	Energy drink (80 mg)	Placebo (none)

To be continued…

Table S1

Continuation

References	Sample	Outcomes	Authors (year)	Study design	Intervention group (caffeine concentration)	Control group (caffeine concentration)
Lasheras et al. (2021) [#&]	Healthy adults	HR, QTc	Kozik et al. (2016)	OL, NC	Energy drink (320 mg)	None
		HR, QTc	Shah et al. (2019)	R, DB, PC, C	Energy drink (414 mg)	Placebo (none)
		HR, QTc	Shah et al. (2019)	R, DB, PC, C	Energy drink (320 mg)	Placebo (none)
		HR, QTc	Fletcher et al. (2017)	R, DB, AC, C	Energy drink (320 mg)	Caffeinated drink (320 mg)
		HR	Del Coso et al. (2012)	R, DB, PC, C	Energy drink (207 mg)	Placebo (none)
		HR	An (2014)	SB, PC, P	Energy drink (90 mg)	Placebo (none)
		HR	An (2014)	SB, PC, P	Energy drink (180 mg)	Placebo (none)
		HR	Peveler et al. (2018)	R, DB, PC, C	Energy drink (180 mg)	Placebo (none)
		HR	Peveler et al. (2018)	R, DB, PC, C	Energy drink (163 mg)	Placebo (none)
		HR	Peveler et al. (2018)	R, DB, PC, C	Energy drink (103 mg)	Placebo (none)
		HR	Petreli et al. (2018)	OL, NC	Energy drink (114 mg)	None
		HR	Alford (2001)	R, DB, PC, C	Energy drink (80 mg)	Placebo (none)
		HR	Alford (2001)	R, DB, PC, C	Energy drink (80 mg)	Placebo (none)
		QTc	Kozik et al. (2018)	R, OL, PC, C	Energy drink (320 mg)	None
		QTc	Shah et al. (2016)	R, DB, PC, C	Energy drink (414 mg)	Placebo (none)
		HR, QTc	Wiklund et al. (2009)	OL, NC	Energy drink (240 mg)	None

To be continued…

Table S1

Continuation

References	Sample	Outcomes	Authors (year)	Study design	Intervention group (caffeine concentration)	Control group (caffeine concentration)
Lasheras et al. (2021) [#&]	Healthy adults	HR	Rashti et al. (2009)	R, DB, PC, C	Energy drink (89 mg)	Placebo (none)
		HR	Steinke et al. (2009)	OL, NC	Energy drink (200 mg)	None
		HR	Sillivent (2012)	R, DB, PC, C	Energy drink (250 mg)	Placebo (none)
		HR	Franks et al. (2012)	R, OL, AC, C	Energy drink (80 mg)	Caffeinated drink (80 mg)
		HR	Kurtz et al. (2013)	R, DB, AC, C	Energy drink (207 mg)	Decaffeinated drink (6 mg)
		QTc	Alsunni et al. (2015)	OL, NC	Energy drink (1,6 mg/kg)	None
		HR	Grasser et al. (2014)	R, OL, PC, C	Energy drink (114 mg)	Placebo (none)
		HR	Elitok et al. (2015)	OL, NC	Energy drink (114 mg)	None
		HR	Doerner et al. (2015)	OL, AC, C	Energy drink (105 mg)	Caffeinated drink (105 mg)
		HR	Svatikova et al. (2015)	R, DB, PC, C	Energy drink (240 mg)	Placebo (none)
		HR	Miles-chan et al. (2015)	R, SB, PC, AC, C	Energy drink (114 mg)	Placebo (none)
		HR	Nowak et al. (2019)	SB, PC, AC, P	Energy drink (64 mg)	Placebo (none)
		HR, QTc	Hajsadeghi (2016)	OL, NC	Energy drink (80 mg)	None
		HR	Nowak (2018)	R, OL, PC, C	Energy drink (32 mg)	Placebo (none)
		HR	Quinlivan et al. (2015)	R, DB, PC, C	Energy drink (248 mg)	Placebo (none)
		HR	Gray et al. (2017) [$]	R, DB, PC, C	Energy drink (160 mg)	Placebo (none)

To be continued…

Table S1

Continuation

AC, active control; C, crossover; DB, double-blind; DBP, diastolic blood pressure; HR, heart rate; NC, noncontrolled; OL, open-label; P, parallel; PC, placebo-controlled; QTc, QTc interval; R, randomized; SB, single-blind; SBP, systolic blood pressure. [$] Participants had long QT syndrome. [#] For both meta-analyses there was no protocol article published, PROSPERO registration, analysis of the risk of bias of individual studies and analysis of quality of individual studies. [&] No assessment of the study quality is available. [1] Shah, S., Chu, B., Lacey, C., Riddock, I., Lee, M., & Dargush, A. (2016). Impact of acute energy drink consumption on blood pressure parameters: a meta-analysis. Annals of Pharmacotherapy, 50(10), 808-815. https://doi.org/10.1177/1060028016656433. [2] Lasheras, I., Seral, P., Alonso-Ventura, V., & Santabárbara, J. (2021). The impact of acute energy drink consumption on electrical heart disease: A systematic review and meta-analysis. Journal of Electrocardiology, 65. https://doi.org/10.1016/j.jelectrocard.2021.01.020.

Table S2

Search strategies that will be applied in the main databases

Databases	Search strategies
MEDLINE (PubMed)	***Energy Drink:*** *(Drink, Energy OR Drinks, Energy OR Energy Drink) AND* ***Cardiovascular parameters:*** *(Hemodynamics OR Atrial Pressure OR Baroreflex OR Blood Pressure OR Arterial Pressure OR Pulmonary Wedge Pressure OR Venous Pressure + Blood Volume OR Cerebral Blood Volume OR Erythrocyte Volume OR Plasma Volume OR Cardiac Output OR Stroke Volume OR Cardiac Volume OR Heart Rate OR Heart Rate, Fetal OR Respiratory Sinus Arrhythmia OR Heart Sounds OR Hemorheology OR Blood Flow Velocity OR Blood Viscosity OR Pulsatile Flow OR Kallikrein-Kinin System OR Pulse OR Renin-Angiotensin System OR Valsalva Maneuver OR Vascular Capacitance OR Vascular Resistance OR Capillary Resistance OR Vasoconstriction OR Vasodilation OR Ventricular Pressure) AND* ***Type of study:*** *(Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw])*
EMBASE	***Energy Drink:*** *('drink, energy':ab,ti OR 'drinks, energy':ab,ti OR 'energy drink':ab,ti) AND* ***Cardiovascular parameters:*** *(hemodynamics:ab,ti OR 'atrial pressure':ab,ti OR baroreflex:ab,ti OR 'blood pressure':ab,ti OR 'arterial pressure':ab,ti OR 'pulmonary wedge pressure':ab,ti OR 'venous pressure + blood volume':ab,ti OR 'cerebral blood volume':ab,ti OR 'erythrocyte volume':ab,ti OR 'plasma volume':ab,ti OR 'cardiac output':ab,ti OR 'stroke volume':ab,ti OR 'cardiac volume':ab,ti OR 'heart rate':ab,ti OR 'heart rate, fetal':ab,ti OR 'respiratory sinus arrhythmia':ab,ti OR 'heart sounds':ab,ti OR hemorheology:ab,ti OR 'blood flow velocity':ab,ti OR 'blood viscosity':ab,ti OR 'pulsatile flow':ab,ti OR 'kallikrein-kinin system':ab,ti OR pulse:ab,ti OR 'renin-angiotensin system':ab,ti OR 'valsalva maneuver':ab,ti OR 'vascular capacitance':ab,ti OR 'vascular resistance':ab,ti OR 'capillary resistance':ab,ti OR vasoconstriction:ab,ti OR vasodilation:ab,ti OR 'ventricular pressure':ab,ti)*
COCHRANE	***Energy Drink:*** *(Energy Drinks OR Drinks, Energy OR Drink, Energy OR Energy Drink) AND* ***Cardiovascular parameters:*** *(Hemodynamics OR Atrial Pressure OR Baroreflex OR Blood Pressure OR Arterial Pressure OR Pulmonary Wedge Pressure OR Cerebral Blood Volume OR Erythrocyte Volume OR Plasma Volume OR Cardiac Output OR Stroke Volume OR Cardiac Volume OR Heart Rate OR Respiratory Sinus Arrhythmia OR Heart Sounds OR Hemorheology OR Blood Flow Velocity OR Blood Viscosity OR Pulsatile Flow OR Kallikrein-Kinin System OR Pulse OR Renin-Angiotensin System OR Valsalva Maneuver OR Vascular Capacitance OR Vascular Resistance OR Capillary Resistance OR Vasoconstriction OR Vasodilatation OR Ventricular Pressure)*

To be continued…

Table S2 *Continuation*

Databases	Search strategies
LILACS	***LANGUAGE: Spanish*** ***Bebida energizante:*** *(tw:(Bebida Energética)) AND* ***Frecuencia cardíaca:*** *(tw:(Frecuencia cardíaca)) OR (tw:(Cronotropismo cardíaco)) OR (tw: (Frecuencia cardíaca)) (tw:(Frecuencia cardíaca)) OR* ***Presión arterial:*** *(tw: (tw:(Presión arterial))* ***Función endotelial:*** *(tw: (Endotelio)) OR (tw: (Función endotelial)) OR (tw: (Endotelio vascular))* ***LANGUAGE: Portuguese*** ***Bebida Energética:*** *(tw:(Bebida Energética)) OR (tw:(Bebidas Isotônicas)) OR (tw:(Bebidas Isotônicas)) (tw:(Repositores Hidroeletrolíticos)) AND* ***Frequência cardíaca:*** *(tw:(Frequência cardíaca)) OR (tw:(Cronotropismo Cardíaco)) OR (tw:(Frequência de Pulsação)) (tw:(Frequência de Pulso)) OR* ***Função endotelial:*** *(tw:(Endotélio)) OR (tw:(Função endotelial)) OR (tw:(Endotélio vascular)) OR* ***Pressão arterial:*** *(tw:(Pressão Arterial)) OR (tw:(Monitorização Ambulatorial da Pressão Arterial))* ***LANGUAGE: English*** ***Energy Drink:*** *(tw:(Energy Drink)) AND* ***Heart rate:*** *(tw:(Heart rate)) OR (tw:(Cardiac Chronotropism)) OR (tw:(Pulse Rate)) (tw:(Pulse Rate)) OR* ***Endothelial function:*** *(tw:(Endothelium)) OR (tw:(Endothelial function)) OR (tw:(Vascular endothelium)) OR* ***Blood pressure:*** *(tw:(Arterial Pressure)) OR (tw:(Blood Pressure Monitoring, Ambulatory))*
Web of Science	***Energy Drink:*** ("Energy Drinks" OR "Drinks, Energy" OR "Drink, Energy" OR "Energy Drink") AND ***Cardiovascular parameters:*** ("Hemodynamics" OR "Atrial Pressure" OR "Baroreflex OR Blood Pressure" OR "Arterial Pressure" OR "Pulmonary Wedge Pressure" OR "Cerebral Blood Volume" OR "Erythrocyte Volume" OR "Plasma Volume" OR "Cardiac Output" OR "Stroke Volume" OR "Cardiac Volume" OR "Heart Rate" OR "Respiratory Sinus Arrhythmia" OR "Heart Sounds" OR "Hemorheology" OR "Blood Flow Velocity" OR "Blood Viscosity" OR "Pulsatile Flow" OR "Kallikrein-Kinin System" OR "Pulse" OR "Renin-Angiotensin System" OR "Valsalva Maneuver" OR "Vascular Capacitance" OR "Vascular Resistance" OR "Capillary Resistance" OR "Vasoconstriction" OR "Vasodilatation" OR "Ventricular Pressure")
SPORTDiscus	***Energy Drink:*** *(Energy Drinks OR Drinks, Energy OR Drink, Energy OR Energy Drink) AND* ***Cardiovascular parameters:*** *(Hemodynamics OR Atrial Pressure OR Baroreflex OR Blood Pressure OR Arterial Pressure OR Pulmonary Wedge Pressure OR Cerebral Blood Volume OR Erythrocyte Volume OR Plasma Volume OR Cardiac Output OR Stroke Volume OR Cardiac Volume OR Heart Rate OR Respiratory Sinus Arrhythmia OR Heart Sounds OR Hemorheology OR Blood Flow Velocity OR Blood Viscosity OR Pulsatile Flow OR Kallikrein-Kinin System OR Pulse OR Renin-Angiotensin System OR Valsalva Maneuver OR Vascular Capacitance OR Vascular Resistance OR Capillary Resistance OR Vasoconstriction OR Vasodilatation OR Ventricular Pressure)*

Table S3

Search strategies that will be applied in gray literature databases

Databases	Search strategies
OpenGrey	*Energy Drinks OR Energy Drink*
*Brazilian Coordination for the Improvement of Higher Education Personnel (CAPES) Bank of Theses and Dissertations**	*Bebidas energéticas*
*ReBEC***	*Bebidas energéticas*
*ClinicalTrials****	*Energy Drinks*
WHO*****	*Energy Drinks*

** Filter: major area of knowledge (Health Sciences), area of assessment (Physical Education, Medicine I-II-III, Nutrition). Language: Portuguese.*

*** Filter: type of study (interventional), recruitment status (ongoing recruitment, complete recruitment, complete data analysis). Language: Portuguese.*

**** Filter: type of study (interventional (clinical trial)), status (ongoing, complete, closed).*

***** Filter: Recruitment status (ALL)*

Box S1

Interpretation of heterogeneity results

Interpretation of I^2
• 0% to 40%: might not be important;
• 30% to 60%: may represent moderate heterogeneity*;
• 50% to 90%: may represent substantial heterogeneity*;
• 75% to 100%: considerable heterogeneity*.

* The importance of the value of I^2 depends on the magnitude and direction of effects and the strength of evidence for heterogeneity (I^2 confidence interval: uncertainty of the value of I^2 is substantial when there is a small number of studies).

Box S2

Initial script for data analysis using RStudio

- library (readxl)
- EnergyDrink <- read_excel ("C:/Metanalysis_Pedro/database_analysis/EnergyDrink.xlsx")
- View (EnergyDrink)
- Meta_1 = EnergyDrink <- metacont (t_n, t_mean, t_dp, c_n, c_mean, c_dp, Study, predict = TRUE, data = EnergyDrink, sm = "MD")
- Meta_1
- forest (Meta_1, sortvar = Study, xlim = c (-10.0, 10.0), predict = TRUE, col.square = "grey", col.diamond = "black", digits = 2)
- forest (Meta_1, comb.fixed = FALSE, sortvar = Study, xlim = c (-10.0, 10.0), digits.sd = 2, digits.I2= 2, print.I2.ci = TRUE , digits.tau2 = 2, digits.pval.Q = 3, squaresize = 0.5, lab.e = "Experimental", lab.c = "Control", col.inside = "black", col.square = "grey", col.diamond = "black",col.predict = "transparent", digits = 2)
- baujat (Meta_1, ylim = c (-1.0, 1.0), xlim = c (-200, 200))
- metainf (Meta_1, pooled = "random")
- metabias (Meta_1, method.bias = "linreg")
- funnel (meta_ED)

APÊNDICE B – Material suplementar do Artigo II

Supplementary material

ACUTE EFFECTS OF ENERGY DRINKS CONSUMPTION ON CARDIOVASCULAR PARAMETERS IN HEALTHY ADULTS: A SYSTEMATIC REVIEW WITH META-ANALYSIS OF RANDOMIZED CLINICAL TRIALS

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Supplementary Materials

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Supplementary Figure S3 **Subgroup analysis comparing studies classified by rob2 with some concerns and high risk of bias on systolic blood pressure [SBP].** Time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (D) ≥120 minutes. * Preliminary study conducted in 1997 and published in 2001 along with another study. 150

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Supplementary Figure S4 **Subgroup analysis comparing studies classified by rob2 with some concerns and high risk of bias on diastolic blood pressure [DBP].** time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (D) ≥120 minutes. * Preliminary study conducted in 1997 and published in 2001 along with another study. 152

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Supplementary Figure S7 **Subgroup analysis comparing studies classified by rob2 with some concerns and high risk of bias on heart rate [HR].** Time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (D) ≥120 minutes. * Preliminary study conducted in 1997 and published in 2001 along with another study 157

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Supplementary Table S1 **Cardiovascular outcomes mean baseline values of the studies included in the meta-analysis (n= 17).**

Cardiovascular parameters	Intervention group (n= 350)	Control group (n= 346)
Systolic blood pressure (mmHg)	117 ± 3.5	117 ± 3.7
Diastolic blood pressure (mmHg)	74.3 (64.3 - 77.0)	74.8 (65.1 - 77.7)
Resting heart hate (bpm)	68.9 ± 6.7	69.0 ± 6.2
Cardiac output (L/min)	5.3 (4.8 – 5.3)	5.1 ± 0.2
Interval QT (ms)	393 ± 15.1	397 ± 10.1
Interval QTc (ms)	410 ± 12.0	410 ± 12.1

Data are presented as mean ± standard deviation and median (minimum - maximum). Data normality by means of the Shapiro-Wilk test and descriptive analysis were performed via JAMOVI software.

Supplementary Table S2 **Description of studies that evaluated the effects of energy drinks on cardiovascular parameters and were included in previously published systematic reviews.**

References	Sample	Outcomes	Authors (year)	Study design	Intervention group (caffeine concentration)	Control group (caffeine concentration)
Shah et al (2016)[S1, #]	Healthy adults	SBP, DBP, HR	Al-Fares et al (2015)	R, SB, PC, C	Energy drink (unknown)	Placebo (none)
		SBP, DBP, HR	Doerner et al (2015)	OL, AC, C	Energy drink (105 mg)	Caffeinated drink (105 mg)
		SBP, DBP, HR	Hajsadeghi et al (2015)	OL, NC	Energy drink (80 mg)	None
		SBP, DBP, HR	Svatikova et al (2014)	R, DB, PC, C	Energy drink (240 mg)	Placebo (none)
		SBP	Fletcher et al (2014)	R, DB, AC, C	Energy drink (unknown)	Caffeinated drink (unknow)
		SBP, DBP, HR	Grasser et al (2014)	OL, R, PC, C	Energy drink (114 mg)	Placebo (none)
		SBP, DBP, HR	Marczinski et al (2014)	PC, C	Energy drink (200 mg)	Decaffeinated drink (6 mg)
		SBP, DBP, HR	Phan and Shah (2014)	R, DB, AC, C	Energy drink (200 mg)	Decaffeinated drink (6 mg)
		SBP, DBP, HR	Kurtz et al (2013)	R, DB, AC, C	Energy drink (200 mg)	Decaffeinated drink (6 mg)
		SBP, DBP, HR	Menci et al (2013)	OL, PC, C	Energy drink (unknown)	Placebo (none)
		SBP, DBP, HR	Ragsdale et al (2010)	DB, P	Energy drink (80 mg)	Placebo (none)
		SBP, DBP, HR	Walker et al (2010)	R, DB, PC, C	Caffeinated drink (5 mg/kg)	Placebo (none)
		SBP, DBP, HR	Rashti et al (2009)	R, DB, PC C	Energy drink (230 mg)	Placebo (none)
		SBP, DBP, HR	Steinke et al (209)	OL, NC	Energy drink (200 mg)	Placebo (none)
		SBP, DBP, HR	Alford 1997 (2001)	R, DB, C	Energy drink (80 mg)	Placebo (none)
Lasheras et al (2021)[S2, #&]	Healthy adults	HR, QTc	Kozik et al (2016)	OL, NC	Energy drink (320 mg)	None
		HR, QTc	Shah et al (2019)	R, DB, PC, C	Energy drink (414 mg)	Placebo (none)
		HR, QTc	Shah et al (2019)	R, DB, PC, C	Energy drink (320 mg)	Placebo (none)

		HR, QTc	Fletcher et al (2017)	R, DB, AC, C	Energy drink (320 mg)	Caffeinated drink (320 mg)
		HR	Del Coso et al (2012)	R, DB, PC, C	Energy drink (207 mg)	Placebo (none)
		HR	An (2014)	SB, PC, P	Energy drink (90 mg)	Placebo (none)
		HR	An (2014)	SB, PC, P	Energy drink (180 mg)	Placebo (none)
		HR	Peveler et al (2018)	R, DB, PC, C	Energy drink (180 mg)	Placebo (none)
		HR	Peveler et al (2018)	R, DB, PC, C	Energy drink (163 mg)	Placebo (none)
		HR	Peveler et al (2018)	R, DB, PC, C	Energy drink (103 mg)	Placebo (none)
		HR	Petreli et al (2018)	OL, NC	Energy drink (114 mg)	None
		HR	Alford (2001)	R, DB, PC, C	Energy drink (80 mg)	Placebo (none)
		HR	Alford (2001)	R, DB, PC, C	Energy drink (80 mg)	Placebo (none)
Lasheras et al. (2021)[S2] #&	Healthy adults	QTc	Kozik et al (2018)	R, OL, PC, C	Energy drink (320 mg)	None
		QTc	Shah et al (2016)	R, DB, PC, C	Energy drink (414 mg)	Placebo (none)
		HR, QTc	Wiklund et al (2009)	OL, NC	Energy drink (240 mg)	None
		HR	Rashti et al (2009)	R, DB, PC, C	Energy drink (89 mg)	Placebo (none)
		HR	Steinke et al (2009)	OL, NC	Energy drink (200 mg)	None
		HR	Sillivent (2012)	R, DB, PC, C	Energy drink (250 mg)	Placebo (none)
		HR	Franks et al (2012)	R, OL, AC, C	Energy drink (80 mg)	Caffeinated drink (80 mg)
		HR	Kurtz et al (2013)	R, DB, AC, C	Energy drink (207 mg)	Decaffeinated drink (6 mg)
		QTc	Alsunni et al (2015)	OL, NC	Energy drink (1,6 mg/kg)	None
		HR	Grasser et al (2014)	R, OL, PC, C	Energy drink (114 mg)	Placebo (none)
		HR	Elitok et al (2015)	OL, NC	Energy drink (114 mg)	None
		HR	Doerner et al (2015)	OL, AC, C	Energy drink (105 mg)	Caffeinated drink (105 mg)

		HR	Svatikova et al (2015)	R, DB, PC, C	Energy drink (240 mg)	Placebo (none)
Lasheras et al. (2021)[S2] #&	Healthy adults	HR	Miles-chan et al (2015)	R, SB, PC, AC, C	Energy drink (114 mg)	Placebo (none)
		HR	Nowak et al (2019)	SB, PC, AC, P	Energy drink (64 mg)	Placebo (none)
		HR, QTc	Hajsadeghi (2016)	OL, NC	Energy drink (80 mg)	None
		HR	Nowak (2018)	R, OL, PC, C	Energy drink (32 mg)	Placebo (none)
		HR	Quinlivan et al (2015)	R, DB, PC, C	Energy drink (248 mg)	Placebo (none)
		HR	Gray et al (2017) $	R, DB, PC, C	Energy drink (160 mg)	Placebo (none)

Abbreviations: AC, active control; C, crossover; DB, double-blind; DBP, diastolic blood pressure; HR, heart rate; NC, noncontrolled; OL, open-label; P, parallel; PC, placebo-controlled; QTc, QTc interval; R, randomized; SB, single-blind; SBP, systolic blood pressure. $ Participants had long QT syndrome. # For both meta-analyses there was no protocol article published, PROSPERO registration, analysis of the risk of bias of individual studies and analysis of quality of individual studies. & No assessment of the study quality is available.

Supplementary Table S3 **Main database search strategies.**

Databases	Search strategies
MEDLINE (PubMed)	Energy Drink: (Drink, Energy OR Drinks, Energy OR Energy Drink) AND Cardiovascular parameters: (Hemodynamics OR Atrial Pressure OR Baroreflex OR Blood Pressure OR Arterial Pressure OR Pulmonary Wedge Pressure OR Venous Pressure + Blood Volume OR Cerebral Blood Volume OR Erythrocyte Volume OR Plasma Volume OR Cardiac Output OR Stroke Volume OR Cardiac Volume OR Heart Rate OR Heart Rate, Fetal OR Respiratory Sinus Arrhythmia OR Heart Sounds OR Hemorheology OR Blood Flow Velocity OR Blood Viscosity OR Pulsatile Flow OR Kallikrein-Kinin System OR Pulse OR Renin-Angiotensin System OR Valsalva Maneuver OR Vascular Capacitance OR Vascular Resistance OR Capillary Resistance OR Vasoconstriction OR Vasodilation OR Ventricular Pressure) AND Type of study: (Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw])
EMBASE	Energy Drink: ('drink, energy':ab,ti OR 'drinks, energy':ab,ti OR 'energy drink':ab,ti) AND Cardiovascular parameters: (hemodynamics:ab,ti OR 'atrial pressure':ab,ti OR baroreflex:ab,ti OR 'blood pressure':ab,ti OR 'arterial pressure':ab,ti OR 'pulmonary wedge pressure':ab,ti OR 'venous pressure + blood volume':ab,ti OR 'cerebral blood volume':ab,ti OR 'erythrocyte volume':ab,ti OR 'plasma volume':ab,ti OR 'cardiac output':ab,ti OR 'stroke volume':ab,ti OR 'cardiac volume':ab,ti OR 'heart rate':ab,ti OR 'heart rate, fetal':ab,ti OR 'respiratory sinus arrhythmia':ab,ti OR 'heart sounds':ab,ti OR hemorheology:ab,ti OR 'blood flow velocity':ab,ti OR 'blood viscosity':ab,ti OR 'pulsatile flow':ab,ti OR 'kallikrein-kinin system':ab,ti OR pulse:ab,ti OR 'renin-angiotensin

	system':ab,ti OR 'valsalva maneuver':ab,ti OR 'vascular capacitance':ab,ti OR 'vascular resistance':ab,ti OR 'capillary resistance':ab,ti OR vasoconstriction:ab,ti OR vasodilation:ab,ti OR 'ventricular pressure':ab,ti)
COCHRANE	*Energy Drink: (Energy Drinks OR Drinks, Energy OR Drink, Energy OR Energy Drink) AND* *Cardiovascular parameters: (Hemodynamics OR Atrial Pressure OR Baroreflex OR Blood Pressure OR Arterial Pressure OR Pulmonary Wedge Pressure OR Cerebral Blood Volume OR Erythrocyte Volume OR Plasma Volume OR Cardiac Output OR Stroke Volume OR Cardiac Volume OR Heart Rate OR Respiratory Sinus Arrhythmia OR Heart Sounds OR Hemorheology OR Blood Flow Velocity OR Blood Viscosity OR Pulsatile Flow OR Kallikrein-Kinin System OR Pulse OR Renin-Angiotensin System OR Valsalva Maneuver OR Vascular Capacitance OR Vascular Resistance OR Capillary Resistance OR Vasoconstriction OR Vasodilatation OR Ventricular Pressure)*
LILACS	*LANGUAGE: Spanish* *Bebida energizante: (tw:(Bebida Energética)) AND* *Frecuencia cardíaca: (tw:(Frecuencia cardíaca)) OR (tw:(Cronotropismo cardíaco)) OR (tw: (Frecuencia cardíaca)) (tw:(Frecuencia cardíaca)) OR* *Presión arterial: (tw: (tw:(Presión arterial))* *Función endotelial: (tw: (Endotelio)) OR (tw: (Función endotelial)) OR (tw: (Endotelio vascular))* *LANGUAGE: Portuguese* *Bebida Energética: (tw:(Bebida Energética)) OR (tw:(Bebidas Isotônicas)) OR (tw:(Bebidas Isotônicas)) (tw:(Repositores Hidroeletrolíticos)) AND*

Frequência cardíaca: (tw:(Frequência cardíaca)) OR (tw:(Cronotropismo Cardíaco)) OR (tw:(Frequência de Pulsação)) (tw:(Frequência de Pulso)) OR

Função endotelial: (tw:(Endotélio)) OR (tw:(Função endotelial)) OR (tw:(Endotélio vascular)) OR

Pressão arterial: (tw:(Pressão Arterial)) OR (tw:(Monitorização Ambulatorial da Pressão Arterial))

LANGUAGE: English

Energy Drink: (tw:(Energy Drink)) AND

Heart rate: (tw:(Heart rate)) OR (tw:(Cardiac Chronotropism)) OR (tw:(Pulse Rate)) (tw:(Pulse Rate)) OR

Endothelial function: (tw:(Endothelium)) OR (tw:(Endothelial function)) OR (tw:(Vascular endothelium)) OR

Blood pressure: (tw:(Arterial Pressure)) OR (tw:(Blood Pressure Monitoring, Ambulatory))

Web of Science	*Energy Drink:* (“Energy Drinks” OR “Drinks, Energy” OR “Drink, Energy” OR “Energy Drink”) AND *Cardiovascular parameters:* (“Hemodynamics“ OR “Atrial Pressure“ OR “Baroreflex OR Blood Pressure“ OR “Arterial Pressure“ OR “Pulmonary Wedge Pressure“ OR “Cerebral Blood Volume“ OR “Erythrocyte Volume“ OR “Plasma Volume“ OR “Cardiac Output“ OR “Stroke Volume“ OR “Cardiac Volume“ OR “Heart Rate“ OR “Respiratory Sinus Arrhythmia“ OR “Heart Sounds“ OR “Hemorheology“ OR “Blood Flow Velocity“ OR “Blood Viscosity“ OR “Pulsatile Flow“ OR “Kallikrein-Kinin System“ OR “Pulse“ OR “Renin-Angiotensin System“ OR “Valsalva Maneuver“ OR “Vascular Capacitance“ OR “Vascular Resistance“ OR “Capillary Resistance“ OR “Vasoconstriction“ OR “Vasodilatation“ OR “Ventricular Pressure“)
SPORTDiscus	*Energy Drink: (Energy Drinks OR Drinks, Energy OR Drink, Energy OR Energy Drink) AND* *Cardiovascular parameters: (Hemodynamics OR Atrial Pressure OR Baroreflex OR Blood Pressure OR Arterial Pressure OR Pulmonary Wedge Pressure OR Cerebral Blood Volume OR Erythrocyte Volume OR Plasma Volume OR Cardiac Output OR Stroke Volume OR Cardiac Volume OR Heart Rate OR Respiratory Sinus Arrhythmia OR Heart Sounds OR Hemorheology OR Blood Flow Velocity OR Blood Viscosity OR Pulsatile Flow OR Kallikrein-Kinin System OR Pulse OR Renin-Angiotensin System OR Valsalva Maneuver OR Vascular Capacitance OR Vascular Resistance OR Capillary Resistance OR Vasoconstriction OR Vasodilatation OR Ventricular Pressure)*

Supplementary Table S4 **Search strategies used in grey literature and unpublished studies.**

Databases	Search strategies
OpenGrey	*Energy Drinks OR Energy Drink*
*Brazilian Coordination for the Improvement of Higher Education Personnel (CAPES) Bank of Theses and Dissertations**	*Bebidas energéticas*
*ReBEC***	*Bebidas energéticas*
*ClinicalTrials****	*Energy Drinks*
WHO*****	*Energy Drinks*

* Filter: major area of knowledge (Health Sciences), area of assessment (Physical Education, Medicine I-II-III, Nutrition). Language: Portuguese.

** Filter: type of study (interventional), recruitment status (ongoing recruitment, complete recruitment, complete data analysis). Language: Portuguese.

*** Filter: type of study (interventional (clinical trial)), status (ongoing, complete, closed).

**** Filter: Recruitment status (ALL)

Supplementary Table S5 **Excluded references and the reasons for their exclusion.**

Author, year	Reference	Reason for exclusion
AdibSaber et al (2022)[S3]	AdibSaber F, Ansari S, Elmieh A, Rajabzadeh H. Effect of an Energy Drink On Muscle and Liver Damage Enzymes, And Cardiovascular Indices in Soccer Players. *Sci Med Footb*. 2022: 1-7. doi: 10.1080/24733938.2022.2051728	Lack of open access and non-availability by authors upon request
An (2016)[S4]	An SM, Park JS, Kim SH. Effect of energy drink dose on exercise capacity, heart rate recovery and heart rate variability after high-intensity exercise. *J Exerc Nutrition Biochem*. 2014;18(1):31-39. doi: 10.5717/jenb.2014.18.1.31	Wrong study design, not a randomized clinical trial
Bloomer et al (2015)[S5]	Bloomer RJ, Majaj R, Moran R, MacDonnchadh J. Comparison of 5-Hour ENERGY and caffeine on cognitive performance and subjective feelings in young men and women. *J Caffeine Res*. 2015; 5(3):130-139. doi: 10.1089/jcr.2015.0005	Lack of relevant data to conduct quantitative analysis
Brothers et al (2017)[S6]	Brothers RM, Christmas KM, Patik JC, Bhella PS. Heart rate, blood pressure and repolarization effects of an energy drink as compared to coffee. *Clin Physiol Funct Imaging*. 2017; 37(6):675-681. doi: 10.1111/cpf.12357	Lack of relevant data to conduct quantitative analysis
Cavka et al (2015)[S7]	Cavka A, Stupin M, Panduric A, et al. Adrenergic system activation mediates changes in cardiovascular and psychomotoric reactions in young individuals after red bull© energy drink consumption. *Int J Endocrinol.* 2015;2015. doi: 10.1155/2015/751530	Wrong study design, not a randomized clinical trial

Del Coso et al (2012)[S8]	Del Coso, J, Salinero, JJ, González-Millán, C, Abián-Vicén, C, Pérez-González, B. Dose response effects of a caffeine-containing energy drink on muscle performance: a repeated measures design. *J Int Soc Sports Nutr*. 2012; 9(1):21. doi: 10.1186/1550-2783-9-21	Lack of relevant data to conduct quantitative analysis
García et al (2017)[S9]	García A, Romero C, Arroyave C, Giraldo F, Sánchez L, Sánchez J. Acute effects of energy drinks in medical students. *Eur J Nutr*. 2017;56:2081-20191. doi: 10.1007/s00394-016-1246-5	Lack of relevant data to conduct quantitative analysis
Kurtz et al (2013)S[10]	Kurtz AM, Leong J, Anand M, Dargush AE, Shah SA. Effects of caffeinated versus decaffeinated energy shots on blood pressure and heart rate in healthy young volunteers. *Pharmacotherapy*. 2013;33(8):779-786. doi: 10.1002/phar.1296	Wrong control group, the beverage contained caffeine in its composition
Nelson (2014)[S11]	Nelson MT, Blitz HR, Dengel DR. Cardiovascular and ride time-to-exhaustion effects of an energy drink. *J Int Soc Sports Nutr*. 2014;11:1-7. doi: 10.1186/1550-2783-11-2	Lack of relevant data to conduct quantitative analysis
Phan (2014)S[12]	Phan JK, Shah SA. Effect of caffeinated versus noncaffeinated energy drinks on central blood pressures. *Pharmacotherapy*. 2014;34(6):555-560. doi: 10.1002/phar.1419	Wrong control group, the beverage contained caffeine in its composition
Rashti et al (2009)[S13]	Rashti SL Ratamess NA, Kang J, Faigenbaum AD, Chilakos A, Hoffman JR. Thermogenic effect of meltdown RTD™ energy drink in young healthy women: a double blind, cross-over design study. *Lipids Health Dis*. 2009;8(57):1-7. doi: 10.1186/1476-511X-8-57	Wrong intervention, another substance was used in parallel with the energy drink as an intervention
Scholey (2004)[S14]	Scholey AB, Kennedy DO. Cognitive and physiological effects of an "energy drink": an evaluation of the whole drink and of glucose,	Wrong intervention, a physical stimulus, painful and/or cognitive stressor, was used in parallel to the energy drink as an intervention

	caffeine and herbal flavouring fractions. *Psychopharmacology*. 2004;176(3-4):320-330. doi: 10.1007/s00213-004-1935-2	
Sheehan (2010)[S15]	Sheehan KM, Hartzler LK. Effects of XS® energy drink on aerobic exercise capacity of athletes. *Int J Exerc Sci*. 2011;4(2): 52-163.	Lack of relevant data to conduct quantitative analysis
Sillivent (2012)[S16]	Sillivent J, Blevins-McNaughton J, Peak K. Energy drinks: ergolytic or ergogenic? *Int J Exerc Sci*. 2012;5(3):214-222.	Wrong control group, the beverage contained caffeine in its composition
Szotowska et al (2013)[S17]	Szotowska M, Bartmanska M, Wyskida K, et al. The influence of so called „energy drinks" on the blood pressure and the pulse rate in young, healthy adults. *Arterial Hypertension*. 2013;17(2):169-174.	Lack of relevant data to conduct quantitative analysis
Wiklund et al (2009)[S18]	Wiklund U, Karlsson M, Öström M, Messner T. Influence of energy drinks and alcohol on post-exercise heart rate recovery and heart rate variability. *Clin Physiol Funct Imaging*. 2009;29(1):74-80. doi: 10.1111/j.1475-097X.2008.00837.x	Wrong study design, not a randomized clinical trial
Worthley et al (2010)[S19]	Worthley MI, Prabhu A, Sciscio PD, Schultz C, Sanders P, Willoughby SR. Detrimental effects of energy drink consumption on platelet and endothelial function. *Am J Med*. 2010;123(2):184-187. doi: 10.1016/j.amjmed.2009.09.013	Wrong study design, not a randomized clinical trial

Supplementary Table S6 **List of authors contacted, data requested, means of communication used, authors responses and decisions made.**

Author, year	Requested data	Media	Answer / Decision
AdibSaber (2022)[S3]	Access to full article	E-mail	The authors did not answer the message / The paper was excluded
Basrai et al. (2019)[S4]	HR (SD) (Pre and post values of the groups: intervention and control)	E-mail	The authors did not answer the message / The paper included and only this variable was not included in the quantitative analysis
Bloomer et al (2015)[S5]	SBP, DBP and HR (SD) (Pre and post values of the groups: intervention and control);	E-mail	The authors did not answer the message / Article was excluded because the authors did not have the requested data
Brothers et al (2016)[S6]	SBP, DBP, HR and QTcB (SD) (Pre and post values of the groups: intervention and control)	E-mail	The authors did not answer the message / The paper was excluded
Del Coso et al (2012)[S8]	SBP, DBP and HR (SD) (Pre values of the groups: intervention and control)	E-mail	The authors did not answer the message / The paper was excluded
García et al (2015)[S9]	SBP, DBP and HR (SD) (Post values of the groups: intervention and control)	E-mail	The authors did not answer the message / The paper was excluded
Grasser et al (2014)[S21]	SBP, DBP, HR and CO (SD) (Post values of the groups: intervention and control)	E-mail	The authors –answered the message, however without the requested data / The paper was included and data extracted via software
Miles-Chan et al (2015)[S22]	SBP, DBP, HR and CO (SD) (Post values of the groups: intervention and control)	E-mail	The authors did not answer the message / The paper was included and data extracted via software

Nelson et al (2014)[S11]	HR (SD) (Pre values of the groups: intervention and control)	E-mail	The authors did not answer the message / The paper was excluded
Nowak et al (2018)[S23]	Intervention drink brand	E-mail	The authors did not answer the message / The paper was included, as the variable would not influence the quantitative analysis
Nowak et al (2019)[S24]	SBP, DBP and HR (SD) (Values after 60 and 120 minutes of groups: intervention and control)	E-mail	The authors did not answer the message / The paper was included, as the variable would not influence the quantitative analysis
Polito (2017)[S25]	Intervention drink brand	E-mail	The authors answered the message, however without the requested data / The paper was included, as the variable would not influence the quantitative analysis
Ragsdale et al (2010)[S26]	QT (SD) (Pre and post values of the groups: intervention and control); Study design	E-mail	The authors answered the message and provided the requested data / The paper was included
Rashti et al (2009)[S13]	Control drink ingredients	E-mail	The authors answered the message and provided the requested data/ The paper was excluded, because the intervention drink was associated with another substance
Seehan (2010)[S15]	HR (SD) (Pre and post values of the groups: intervention and control)	E-mail	The authors did not answer the message / The paper was excluded due to lack of data that would influence the quantitative analysis

Shah et al (2019)[S27]	Intervention drink brand and ingredients	E-mail and ResearchGate	The authors did not answer the message / The paper was included, as the variable would not influence the quantitative analysis
Sillivent (2012)[S16]	SBP, DBP and HR (SD) (Post values of the groups: intervention and control)	E-mail and ResearchGate	The authors did not answer the message / The paper was excluded, because the control drink contained caffeine in its composition
Szotowska et al (2013)[S17]	SBP and DBP (SD) (Pre and post values of the groups: intervention and control); Intervention drink brand and ingredients	E-mail	The authors did not answer the message / The paper was excluded due to lack of data that would influence the quantitative analysis
Worthley et al (2010)[S19]	SBP, DBP and HR (SD) (Pre and post values of the groups: intervention and control); Study design; Intervention drink brand	E-mail	The authors answered the message and provided the requested data / The paper was excluded because it is not an RCT

Abbreviations: DBP, diastolic blood pressure; HR, heart hate; QT, interval QT; QTcB, interval QT corrected by Bazett's formula; SBP, systolic blood pressure; SD, standard error.

Supplementary Table S7 **Summary of Findings Table (SoFT) for changes in systolic blood pressure after consumption of energy drinks compared to a control drink in healthy adults.**

Population: Healthy adults

Setting: Acute effects of energy drink consumption on systolic blood pressure

Intervention: Energy drink

Comparison: Water or control drink

Certainty assessment	№ of patients	Effect	Certainty	Importance

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Energy drink	Control drink	Absolute (95% CI)		
Systolic blood pressure (< 20min) (assessed with: Auscultatory or oscillometric methods)											
2	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	43	43	MD **2.18 mmHg higher** (2 lower to 6.37 higher)	⊕◯◯◯ Very low	NOT IMPORTANT
Systolic blood pressure (30-40 min) (assessed with: Auscultatory or oscillometric methods)											
12	randomised trials	serious[c]	not serious	not serious	serious[d]	none	198	151	MD **3.23 mmHg higher** (1.19 higher to 5.28 higher)	⊕⊕◯◯ Low	IMPORTANT
Systolic blood pressure (60-80 min) (assessed with: Auscultatory or oscillometric methods)											
15	randomised trials	serious[e]	not serious	not serious	not serious	none	278	231	MD **4.71 mmHg higher** (2.97 higher to 6.45 higher)	⊕⊕⊕◯ Moderate	IMPORTANT
Systolic blood pressure (90-100 min) (assessed with: Auscultatory or oscillometric methods)											
6	randomised trials	not serious	not serious	not serious	serious[d]	none	113	96	MD **4.1 mmHg higher** (1.63 higher to 6.56 higher)	⊕⊕⊕◯ Moderate	IMPORTANT
Systolic blood pressure (> 120 min) (assessed with: Auscultatory or oscillometric methods)											

10	randomised trials	not serious	not serious	not serious	not serious	none	215	194	MD **3.64 mmHg higher** (1.66 higher to 5.63 higher)	⊕⊕⊕⊕ High	IMPORTANT

CI: confidence interval; **MD:** mean difference

Explanations:

a. The weight of studies with high risk of bias is greater than 50% (-2 levels).

b. The minimum number of total participants (> 400) has not been reached and the summary estimate the confidence interval cross the null line (-2 levels).

c. Only the point estimate of the group with high risk of bias is significant (-1 level).

d. The total minimum number of participants (> 400) has not been reached. (-1 level).

Supplementary Table S8 **Summary of Findings Table (SoFT) for changes in diastolic blood pressure after consumption of energy drinks compared to a control drink in healthy adults.**

Population: Healthy adults

Setting: Acute effects of energy drink consumption on diastolic blood pressure

Intervention: Energy drink

Comparison: Water or control drink

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Energy drink	Control drink	Absolute (95% CI)		
Diastolic blood pressure (< 20 min) (assessed with: Auscultatory or oscillometric methods)											
2	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	43	43	MD **3.15 mmHg higher** (0.73 lower to 7.03 higher)	⊕◯◯◯ Very low	NOT IMPORTANT
Diastolic blood pressure (30-40 min) (assessed with: Auscultatory or oscillometric methods)											
12	randomised trials	not serious	not serious	not serious	serious[c]	none	198	151	MD **2.37 mmHg higher** (0.99 higher to 3.74 higher)	⊕⊕⊕◯ Moderate	IMPORTANT
Diastolic blood pressure (60-80 min) (assessed with: Auscultatory or oscillometric methods)											
15	randomised trials	serious[e]	not serious	not serious	not serious	none	278	231	MD 3**.07 mmHg higher** (1.86 higher to 4.28 higher)	⊕⊕⊕◯ Moderate	IMPORTANT

Diastolic blood pressure (90-100 min) (assessed with: Auscultatory or oscillometric methods)

6	randomised trials	serious[d]	not serious	not serious	serious[c]	none	113	96	MD **3.60 mmHg higher** (1.86 higher to 5.35 higher)	⊕⊕◯◯ Low	IMPORTANT

Diastolic blood pressure (> 120 min) (assessed with: Auscultatory or oscillometric methods)

10	randomised trials	serious[d]	serious[f]	not serious	not serious	none	215	194	MD **4.51 mmHg higher** (2.60 higher to 6.42 higher)	⊕⊕◯◯ Low	IMPORTANT

CI: confidence interval; **MD:** mean difference

Explanations:

a. Weight of high risk of bias studies greater than 50% (-2 levels).

b. The minimum number of total participants (> 400) has not been reached and the summary estimate the confidence interval cross the null line (-2 levels).

c. The minimum number of total participants (> 400) has not been reached (-1 level).

d. The effect estimate of both groups (some concerns and high risk of bias) are statistically significant, but the group with high risk of bias has higher values and may promote greater influence on the final estimate (-1 level).

e. The effect estimate of both groups (some concerns and high risk of bias) are statistically significant, and also present approximate values, and may affect the final estimate in a similar way (-1 level).

f. There are confidence intervals that do not overlap with the others, besides showing moderate heterogeneity, although not significant (-1 level).

Supplementary Table S9 **Summary of Findings Table (SoFT) for changes in heart rate after consumption of energy drinks compared to a control drink in healthy adults.**

Population: Healthy adults

Setting: Acute effects of energy drink consumption on heart rate

Intervention: Energy drink

Comparison: Water or control drink

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Energy drink	control drink	Absolute (95% CI)		
Heart rate (< 20 min) (assessed with: Portable cardiotachometer or electrocardiography)											
2	randomised trials	very serious[a]	not serious	not serious	very serious[b]	None	43	43	MD **0.02 bpm higher** (3.3 lower to 3.33 higher)	⨁◯◯◯ Very low	IMPORTANT
Heart rate (30-40 min) (assessed with: Portable cardiotachometer or electrocardiography)											
11	randomised trials	serious[d]	serious[e]	not serious	very serious[b]	None	178	131	MD **1.18 bpm higher** (0.75 lower to 3.11 higher)	⨁◯◯◯ Very low	NOT IMPORTANT
Heart rate (60-80 min) (assessed with: Portable cardiotachometer or electrocardiography)											

13	randomised trials	serious[c]	very serious[f]	not serious	serious[g]	None	235	188	MD **2.36 bpm higher** (1.26 lower to 5.98 higher)	⊕◯◯◯ Very low	NOT IMPORTANT

Heart rate (90-100 min) (assessed with: Portable cardiotachometer or electrocardiography)

5	randomised trials	serious[c]	serious[h]	not serious	very serious[b]	None	93	76	MD **1.12 bpm higher** (1.76 lower to 3.99 higher)	⊕◯◯◯ Very low	NOT IMPORTANT

Heart rate (> 120 min) (assessed with: Portable cardiotachometer or electrocardiography)

9	randomised trials	serious[d]	serious[e]	not serious	very serious[b]	None	195	174	MD **1.49 bpm higher** (0.52 lower to 3.49 higher)	⊕◯◯◯ Very low	NOT IMPORTANT

CI: confidence interval; **MD:** mean difference

Explanations:

a. The weight of studies with high risk of bias is greater than 50% (-2 levels).

b. The minimum number of total participants (> 400) has not been reached and the summary estimate and the confidence interval cross the null line (-2 levels).

c. Only the point estimate of the group with a high risk of bias is significant (-1 level).

d. Both groups (some concerns and high risk of bias) showed no significant differences, consequently the final estimate also showed no difference (- 1 level).

e. There are inconsistent point estimates, the confidence intervals do not overlap with the others (-1 level).

f. There are inconsistent point estimates, the confidence intervals that do not overlap with the others, as well as showing considerable and significant heterogeneity. Through subgroup analysis, it is possible that the group classified as "some concerns" explains some of the heterogeneity (-2 level).

g. The summary estimate cross the null line (-1 level).

h. There are inconsistent point estimates, and it also has moderate but not significant heterogeneity.

Supplementary Table S10 **Summary of Findings Table (SoFT) for changes in cardiac output after consumption of energy drinks compared to a control drink in healthy adults.**

Population: Healthy adults

Setting: Acute effects of energy drink consumption on cardiac output

Intervention: Energy drink

Comparison: Water or control drink

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Energy drink	control drink	Absolute (95% CI)		
Cardiac output (< 20 min) (assessed with: Invasive and non-invasive methods)											
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	25	25	MD **0.15 L higher** (0.13 lower to 0.43 higher)	⨁◯◯◯ Very low	NOT IMPORTANT
Cardiac output (30-40 min) (assessed with: Invasive and non-invasive methods)											
2	randomised trials	very serious[a]	serious[d]	not serious	serious[c]	none	33	33	MD **0.43 L higher** (0.08 higher to 0.77 higher)	⨁◯◯◯ Very low	IMPORTANT
Cardiac output (60-80 min) (assessed with: Invasive and non-invasive methods)											

3	randomised trials	very serious[a]	serious[d]	not serious	serious[c]	none	53	53	MD **0.41 L higher** (0.1 higher to 0.71 higher)	⊕◯◯◯ Very low	IMPORTANT

Cardiac output (90-100 min) (assessed with: Invasive and non-invasive methods)

2	randomised trials	very serious[a]	serious[d]	not serious	very serious[b]	none	33	33	MD **0.15 l higher** (0.11 lower to 0.41 higher)	⊕◯◯◯ Very low	NOT IMPORTANT

Cardiac output (> 120 min) (assessed with: Invasive and non-invasive methods)

2	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	33	33	MD **0 L** (0.24 lower to 0.23 higher)	⊕◯◯◯ Very low	NOT IMPORTANT

CI: confidence interval; **MD:** mean difference

Explanations:

a. The weight of studies with high risk of bias is greater than 50% (-2 levels).

b. The minimum number of total participants (> 400) has not been reached and the summary estimate and the confidence interval cross null line (-2 levels).

c. The minimum number of total participants (> 400) is not reached (-1 level).

d. There are inconsistent point estimates, the confidence intervals do not overlap with the others (-1 level).

Supplementary Table S11 **Summary of Findings Table (SoFT) for changes in QT interval after consumption of energy drinks compared to a control drink in healthy adults.**

Population: Healthy adults

Setting: Acute effects of energy drink consumption on QT interval

Intervention: Energy drink

Comparison: Water or control drink

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Energy drink	control drink	Absolute (95% CI)		
QT interval (30-40 min) (assessed with: Electrocardiogram)											
3	randomised trials	not serious	serious[b]	not serious	very serious[a]	none	52	35	MD **1.95 ms higher** (7.12 lower to 11.02 higher)	⊕◯◯◯ Very low	NOT IMPORTANT
QT interval (60-80 min) (assessed with: Electrocardiogram)											
5	randomised trials	serious[c]	not serious	not serious	very serious[a]	none	104	87	MD **4.67 ms higher** (0.06 lower to 9.4 higher)	⊕◯◯◯ Very low	IMPORTANT
QT interval (90-100 min) (assessed with: Electrocardiogram)											

3	randomised trials	not serious	not serious	not serious	very serious[a]	none	60	43	MD **4.09 ms higher** (3.77 lower to 11.95 higher)	⊕⊕◯◯ Low	IMPORTANT

QT interval (> 120 min) (assessed with: Electrocardiogram)

4	randomised trials	serious[c]	very serious[d]	not serious	very serious[a]	none	78	61	MD **4.23 ms higher** (7.15 lower to 15.61 higher)	⊕◯◯◯ Very low	IMPORTANT

CI: confidence interval; **MD:** mean difference

Explanations:

a. The minimum number of total participants (> 400) has not been reached and the summary estimate and the confidence interval cross the null line (-2 levels).

b. There are inconsistent point estimates, the confidence intervals do not overlap with the others (-1 level).

c. The weight of studies with high risk of bias is more than 25% but less than 50% (-1 level).

d. There are inconsistent point estimates, confidence intervals that do not overlap with others, and considerable and significant heterogeneity (-2 level).

Supplementary Table S12 **Summary of Findings Table (SoFT) for changes in corrected QT interval after consumption of energy drinks compared to a control drink in healthy adults.**

Population: Healthy adults

Setting: Acute effects of energy drink consumption on corrected QT interval

Intervention: Energy drink

Comparison: Water or control drink

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Energy drink	control drink	Absolute (95% CI)		
Corrected QT interval (30-40 min) (assessed with: Electrocardiogram)											
3	randomised trials	not serious	not serious	not serious	very serious[a]	none	52	36	MD **1.72 ms lower** (10.44 lower to 7 higher)	⊕⊕◯◯ Low	NOT IMPORTANT
Corrected QT interval (60-80 min) (assessed with: Electrocardiogram)											
6	randomised trials	not serious	not serious	not serious	very serious[a]	none	125	108	MD **0.3 ms higher** (4.28 lower to 4.88 higher)	⊕⊕◯◯ Low	NOT IMPORTANT
Corrected QT interval (90-100 min) (assessed with: Electrocardiogram)											

3	randomised trials	not serious	serious[b]	not serious	very serious[a]	none	60	43	MD **0.5 ms lower** (7.77 lower to 6.78 higher)	⊕◯◯◯ Very low	NOT IMPORTANT

Corrected QT interval (> 120 min) (assessed with: Electrocardiogram)

3	randomised trials	not serious	serious[b]	not serious	very serious[a]	none	61	44	MD **5 ms higher** (1.09 lower to 11.09 higher)	⊕◯◯◯ Very low	NOT IMPORTANT

CI: confidence interval; **MD:** mean difference

Explanations:

a. The minimum number of total participants (> 400) has not been reached and the summary estimate and the confidence interval cross the null line (-2 levels).

b. There are inconsistent point estimates, the confidence intervals do not overlap with the others (-1 level).

Tables References

S1. Shah SA, Chu BW, Lacey CS, Riddock IC, Lee M, Dargush AE. Impact of acute energy drink consumption on blood pressure parameters: a meta-analysis. *Ann Pharmacother*. 2016; 50(10):808-815. https://doi.org/10.1177/1060028016656433

S2. Lasheras I, Seral P, Alonso-Ventura V, Santabárbara J. The impact of acute energy drink consumption on electrical heart disease: A systematic review and meta-analysis. *J Electrocardiol*. 2021;65: 128-135. https://doi.org/10.1016/j.jelectrocard.2021.01.020

S3. AdibSaber F, Ansari S, Elmieh A, Rajabzadeh H. Effect of an Energy Drink On Muscle and Liver Damage Enzymes, And Cardiovascular Indices in Soccer Players. *Sci Med Footb*. 2022:1-7. https://doi.org/10.1080/24733938.2022.2051728

S4. An SM, Park JS, Kim SH. Effect of energy drink dose on exercise capacity, heart rate recovery and heart rate variability after high-intensity exercise. *J Exerc Nutrition Biochem*. 2014;18(1):31-39. https://doi.org/10.5717/jenb.2014.18.1.31

S5. Bloomer RJ, Majaj R, Moran R, MacDonnchadh J. Comparison of 5-Hour ENERGY and caffeine on cognitive performance and subjective feelings in young men and women. *J Caffeine Res*. 2015; 5(3):130-139. https://doi.org/10.1089/jcr.2015.0005

S6. Brothers RM, Christmas KM, Patik JC, Bhella PS. Heart rate, blood pressure and repolarization effects of an energy drink as compared to coffee. *Clin Physiol Funct Imaging*. 2017; 37(6):675-681. https://doi.org/10.1111/cpf.12357

S7. Cavka A, Stupin M, Panduric A, et al. Adrenergic system activation mediates changes in cardiovascular and psychomotoric reactions in young individuals after red bull© energy drink consumption. *Int J Endocrinol.* 2015;2015. doi: https://doi.org/10.1155/2015/751530

S8. Del Coso, J, Salinero, JJ, González-Millán, C, Abián-Vicén, C, Pérez-González, B. Dose response effects of a caffeine-containing energy drink on muscle performance: a repeated measures design. *J Int Soc Sports Nutr*. 2012; 9(1):21. https://doi.org/10.1186/1550-2783-9-21

S9. García A, Romero C, Arroyave C, Giraldo F, Sánchez L, Sánchez J. Acute effects of energy drinks in medical students. *Eur J Nutr*. 2017;56:2081-20191. https://doi.org/10.1007/s00394-016-1246-5

S10. Kurtz AM, Leong J, Anand M, Dargush AE, Shah SA. Effects of caffeinated versus decaffeinated energy shots on blood pressure and heart rate in healthy young volunteers. *Pharmacotherapy*. 2013;33(8):779-786. doi: https://doi.org/10.1002/phar.1296

S11. Nelson MT, Blitz HR, Dengel DR. Cardiovascular and ride time-to-exhaustion effects of an energy drink. *J Int Soc Sports Nutr*. 2014;11:1-7. https://doi.org/10.1186/1550-2783-11-2

S12. Phan JK, Shah SA. Effect of caffeinated versus noncaffeinated energy drinks on central blood pressures. *Pharmacotherapy*. 2014;34(6):555-560. doi: https://doi.org/10.1002/phar.1419

S13. Rashti SL Ratamess NA, Kang J, Faigenbaum AD, Chilakos A, Hoffman JR. Thermogenic effect of meltdown RTD™ energy drink in young healthy women: a double blind, cross-over design study. *Lipids Health Dis*. 2009;8(57):1-7. doi: https://doi.org10.1186/1476-511X-8-57

S14. Scholey AB, Kennedy DO. Cognitive and physiological effects of an "energy drink": an evaluation of the whole drink and of glucose, caffeine and herbal flavouring fractions. *Psychopharmacology*. 2004;176(3-4):320-330. doi: https://doi.org/10.1007/s00213-004-1935-2

S15. Sheehan KM, Hartzler LK. Effects of XS® energy drink on aerobic exercise capacity of athletes. *Int J Exerc Sci*. 2011;4(2): 52-163.

S16. Sillivent J, Blevins-McNaughton J, Peak K. Energy drinks: ergolytic or ergogenic? *Int J Exerc Sci*. 2012;5(3):214-222.

S17. Szotowska M, Bartmanska M, Wyskida K, et al. The influence of so called „energy drinks" on the blood pressure and the pulse rate in young, healthy adults. *Arterial Hypertension*. 2013;17(2):169-174.

S18. Wiklund U, Karlsson M, Öström M, Messner T. Influence of energy drinks and alcohol on post-exercise heart rate recovery and heart rate variability. *Clin Physiol Funct Imaging*. 2009;29(1):74-80. doi: https://doi.org/10.1111/j.1475-097X.2008.00837.x

S19. Worthley MI, Prabhu A, Sciscio PD, Schultz C, Sanders P, Willoughby SR. Detrimental effects of energy drink consumption on platelet and endothelial function. *Am J Med*. 2010;123(2):184-187. https://doi.org/10.1016/j.amjmed.2009.09.013

S20. Basrai M, Schweinlin A, Menzel J, et al. Energy Drinks Induce Acute Cardiovascular and Metabolic Changes Pointing to Potential Risks for Young Adults: A Randomized Controlled Trial. *Journal of Nutrition*. 2019;149(3):441-450. https://doi.org/10.1093/jn/nxy303

S21. Grasser EK, Yepuri G, Dulloo AG, Montani J. Cardio- and cerebrovascular responses to the energy drink Red Bull in young adults: a randomized cross-over study. *Eur J Nutr*. 2014;53:1561-1571. https://doi.org/10.1007/s00394-014-0661-8

S22. Miles-Chan JL, Charrière N, Grasser EK, Montani J, Dulloo AG. The blood pressure-elevating effect of Red Bull energy drink is mimicked by caffeine but through different hemodynamic pathways. *Physiological Reports*. 2015;3(2):e12290. https://doi.org/10.14814/phy2.12290

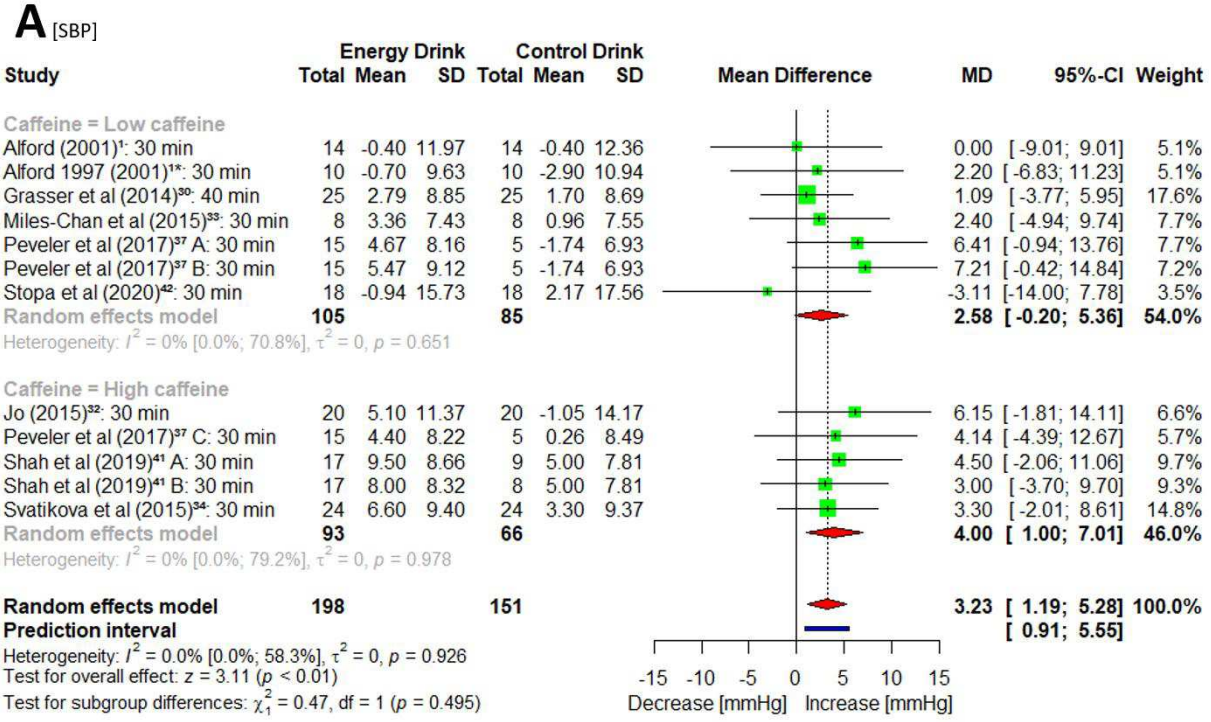
S23. Nowak D, Gośliński M, Nowatkowska K. The Effect of Acute Consumption of Energy Drinks on Blood Pressure, Heart Rate and Blood Glucose in the Group of Young Adults. *Int J Environ Res Public Health*. 2018;15(3):544. https://doi.org/10.3390/ijerph15030544

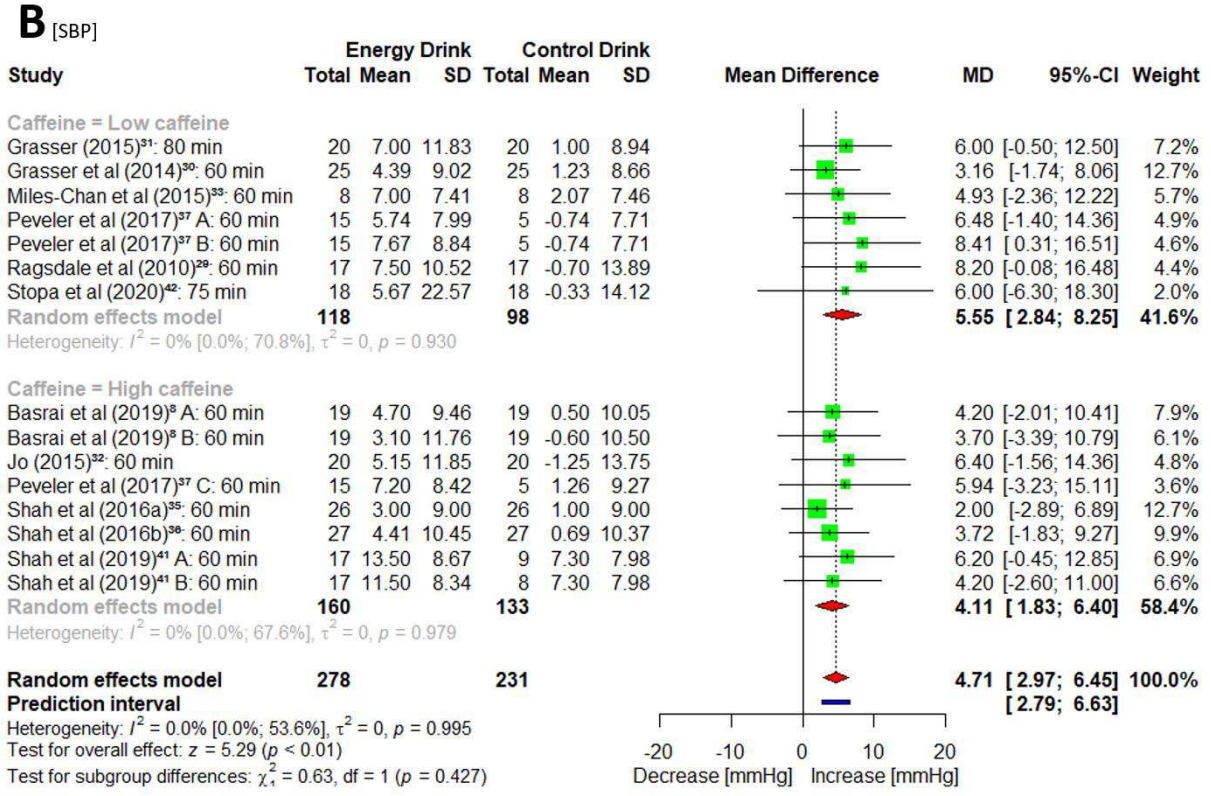
S24. Nowak D, Golinski M, Wesolowska A, Berenda K, Poplawski C. Effects of Acute Consumption of Noni and Chokeberry Juices vs. Energy Drinks on Blood Pressure, Heart Rate, and Blood Glucose in Young Adults. *Evid Based Complement Alternat Med*. 2019:1-9. https://doi.org/10.1155/2019/6076751

S25. Polito M, Souza D, França D. The acute energy drink intake improve performance in resistance exercises. *R. Bras. Ci. E Mov.* 2017;25(3):61-66.

S26. Ragsdale FR, Gronli TD, Batool N, et al. Effect of Red Bull energy drink on cardiovascular and renal function. *Amino Acids*. 2010;38:1193-1200. https://doi.org/10.1007/s00726-009-0330-z

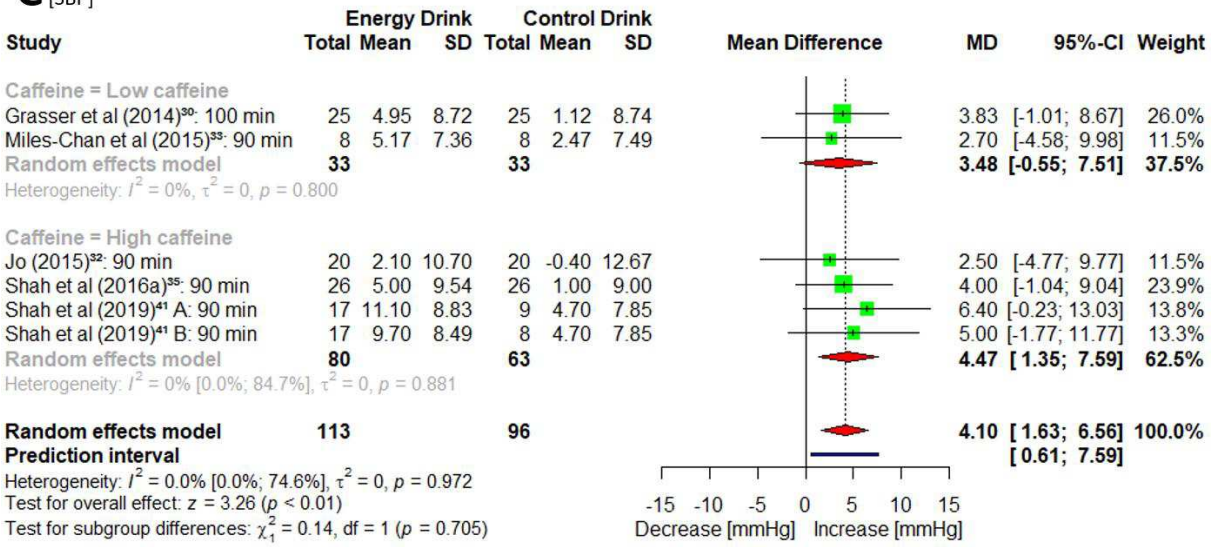
S27. Shah SA, Szeto AH, Farewell R, et al. Impact of High Volume Energy Drink Consumption on Electrocardiographic and Blood Pressure Parameters: A Randomized Trial. *J Am Heart Assoc*. 2019;8:e011318. https://doi.org/10.1016/j.ijcard.2016.05.007





Supplementary Figure S1 **Subgroup analysis comparing low-caffeine and high-caffeine energy drinks on systolic blood pressure [SBP].** Time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (D) ≥120 minutes. * Preliminary study conducted in 1997 and published in 2001 along with another study.

C [SBP]



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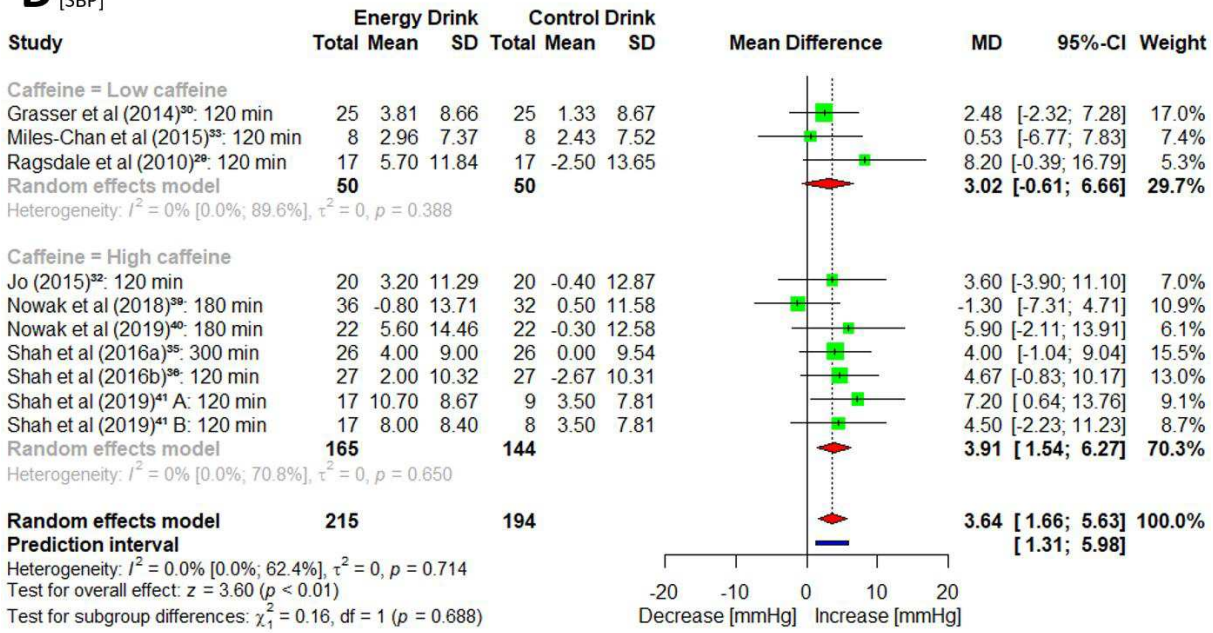

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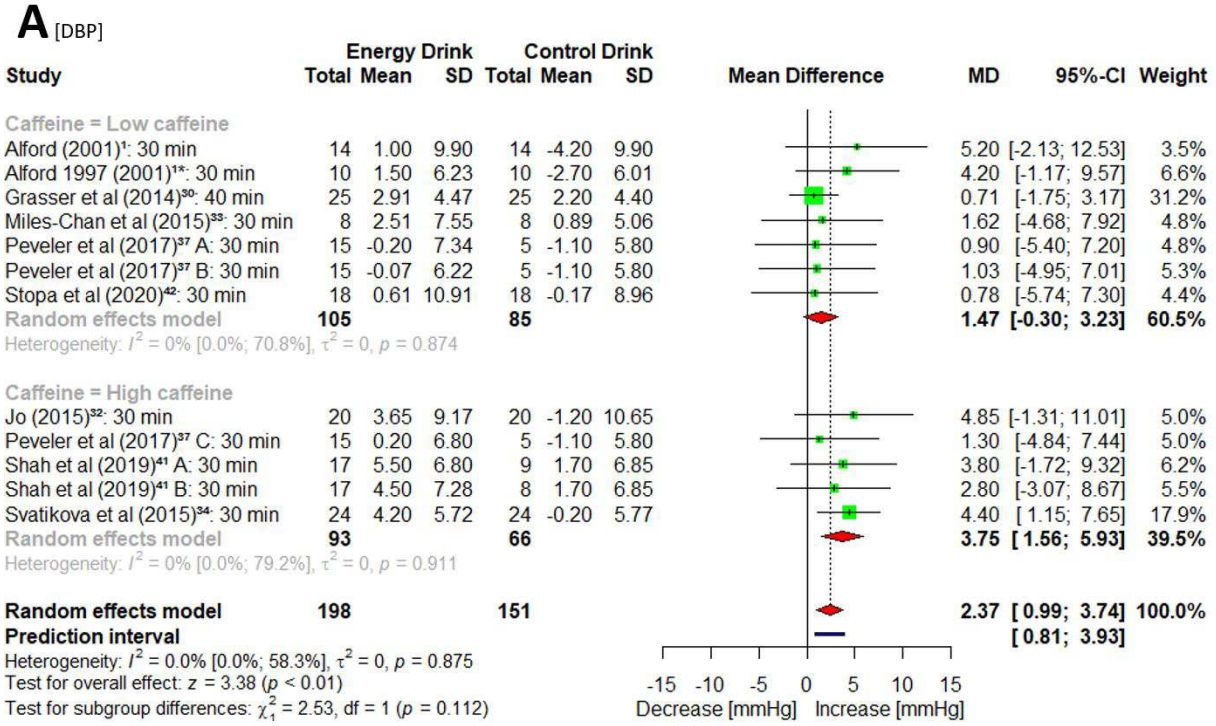
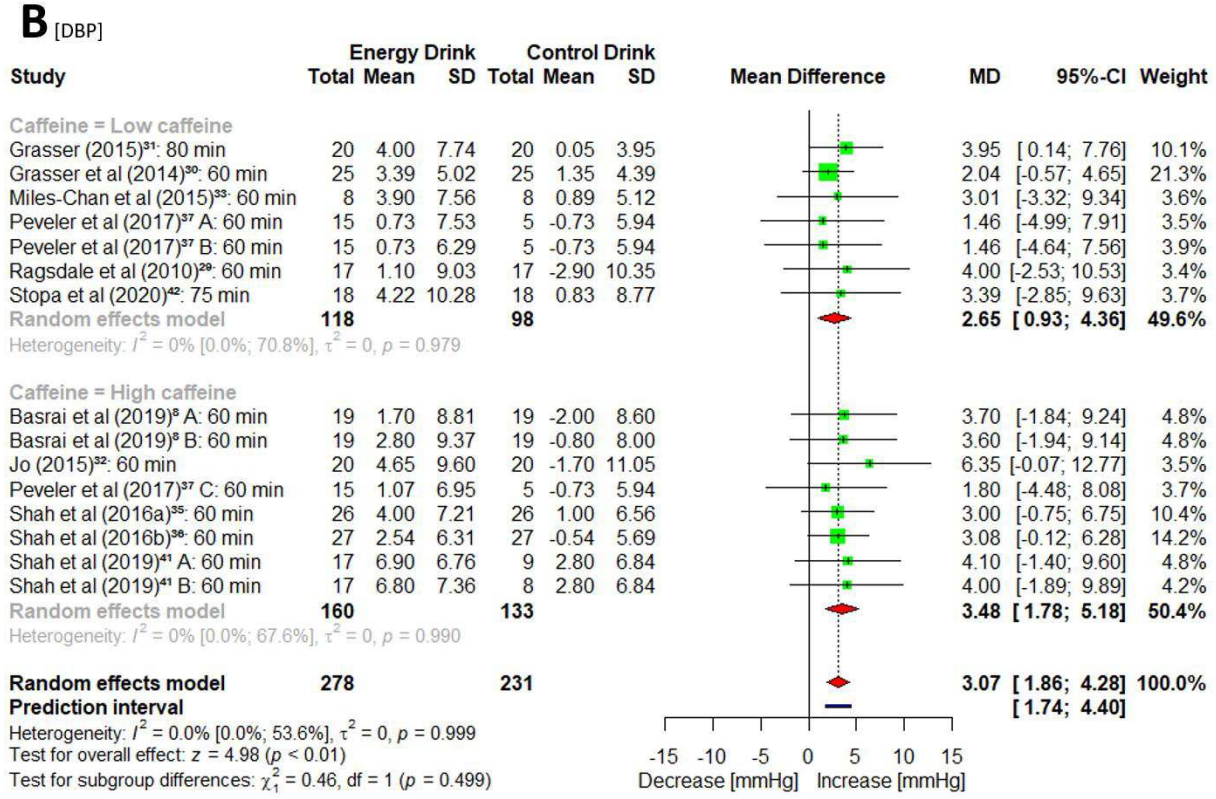
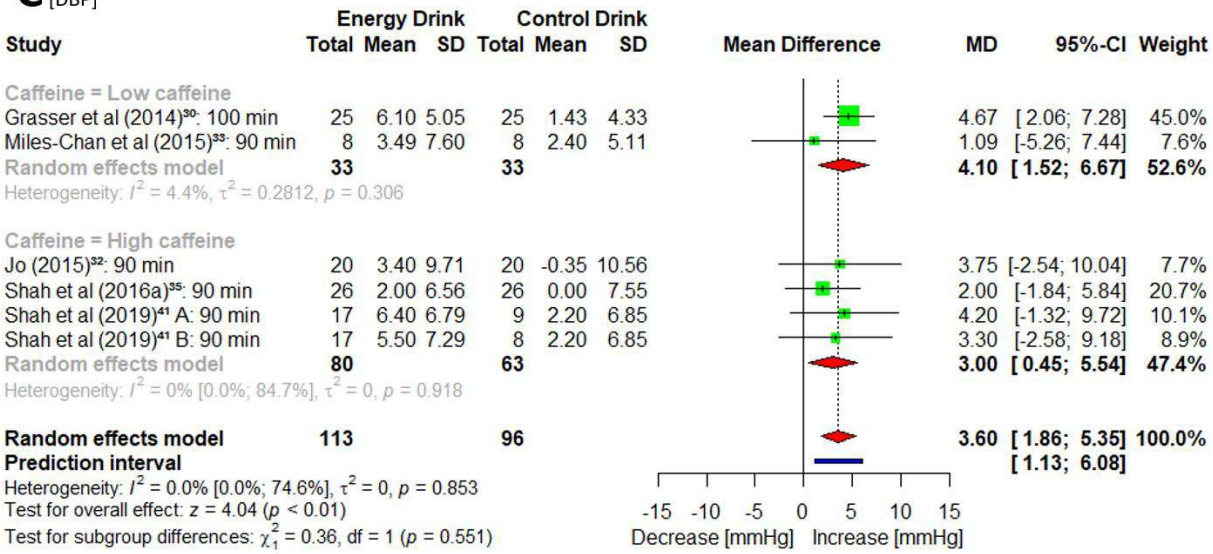


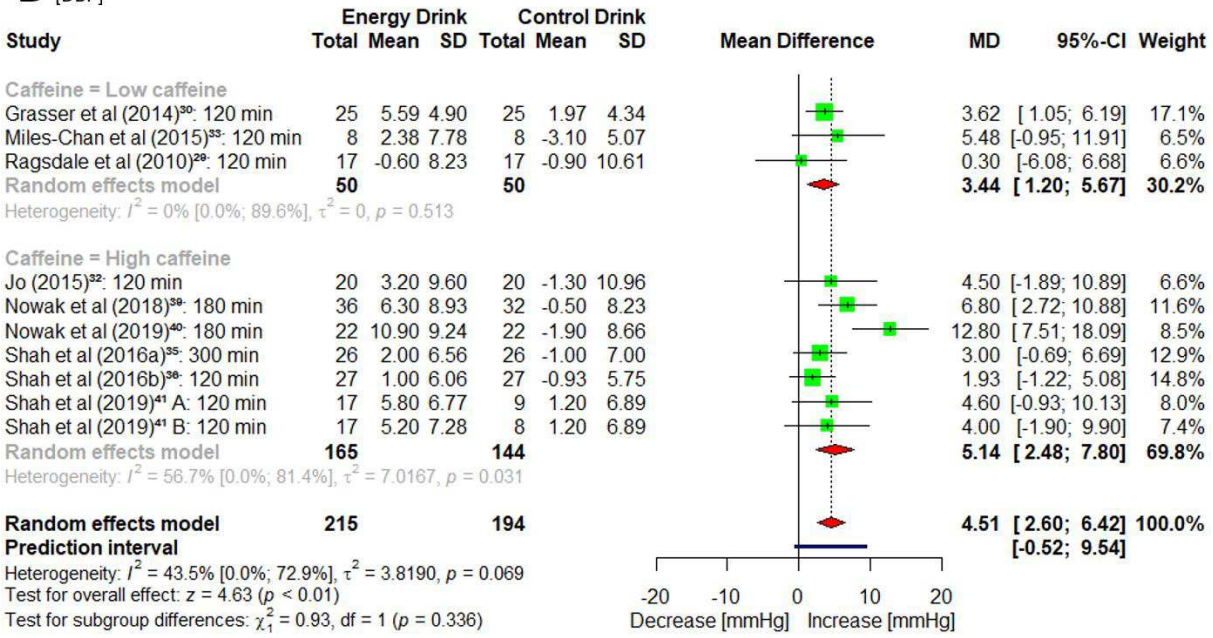


Supplementary Figure S2 **Subgroup analysis comparing low-caffeine and high-caffeine energy drinks on diastolic blood pressure [DBP].** Time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (D) ≥120 minutes. * Preliminary study conducted in 1997 and published in 2001 along with another study.

C [DBP]



D [DBP]



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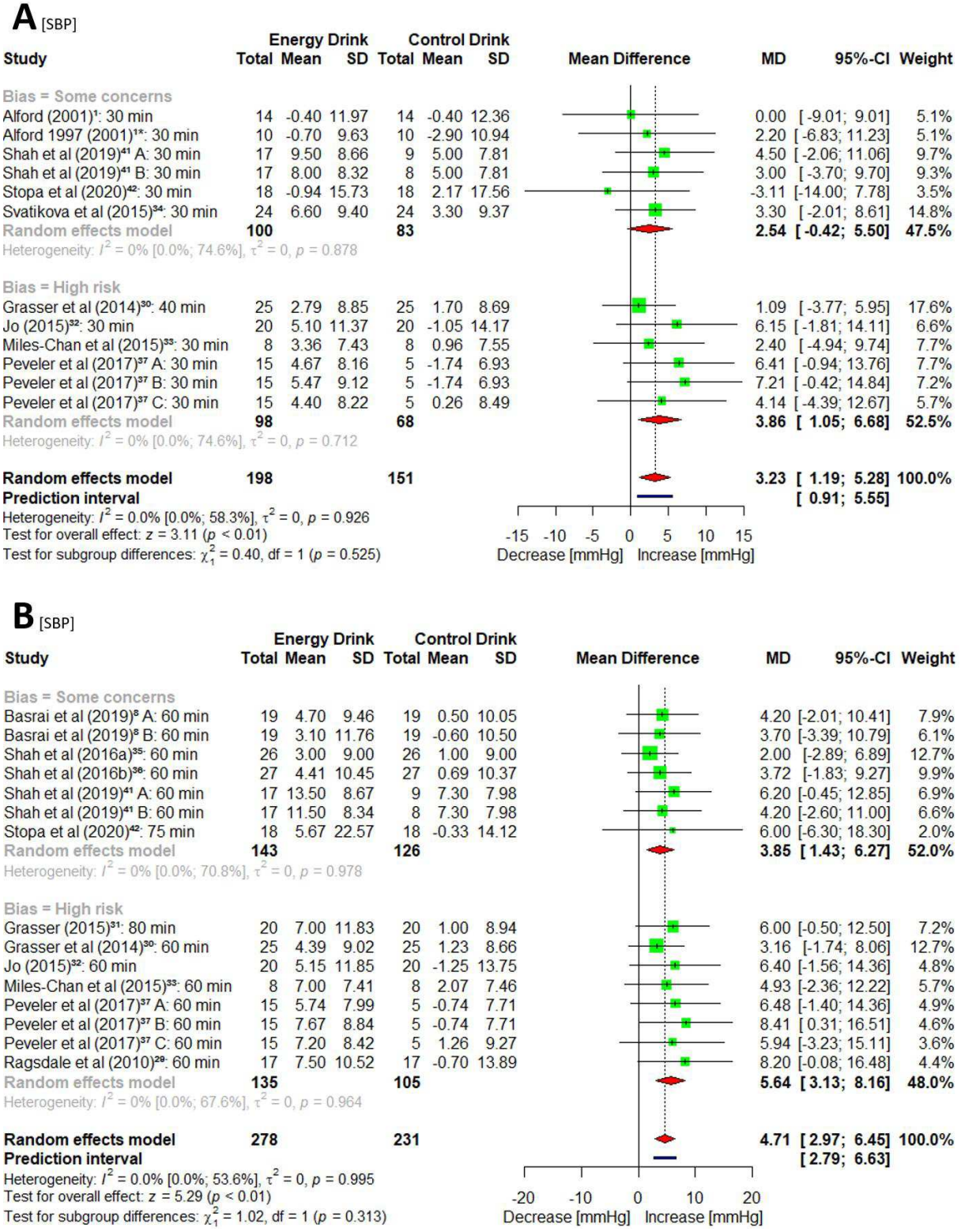
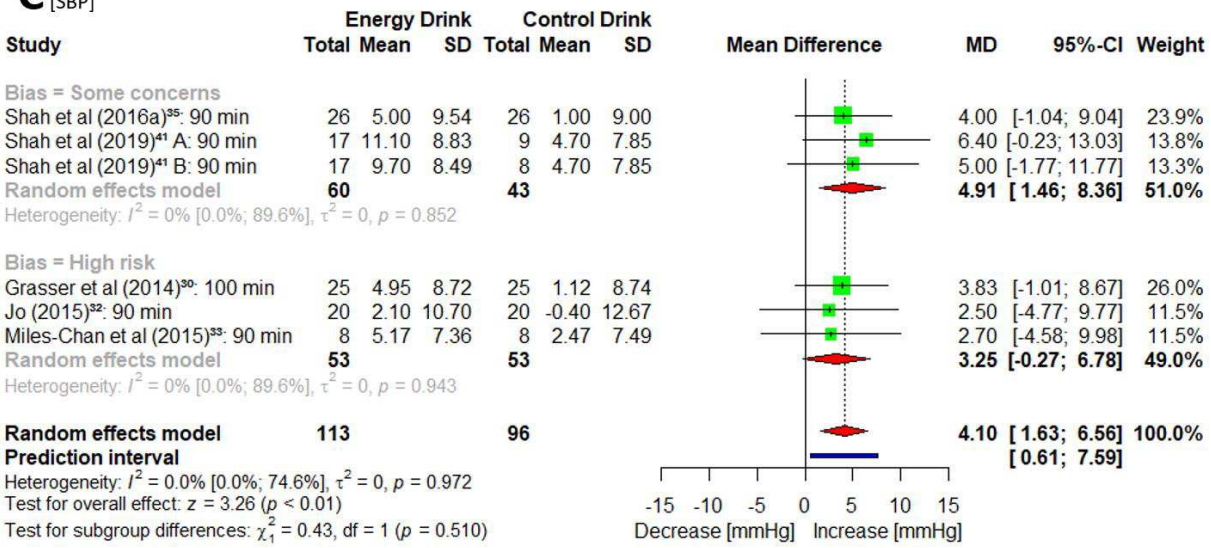
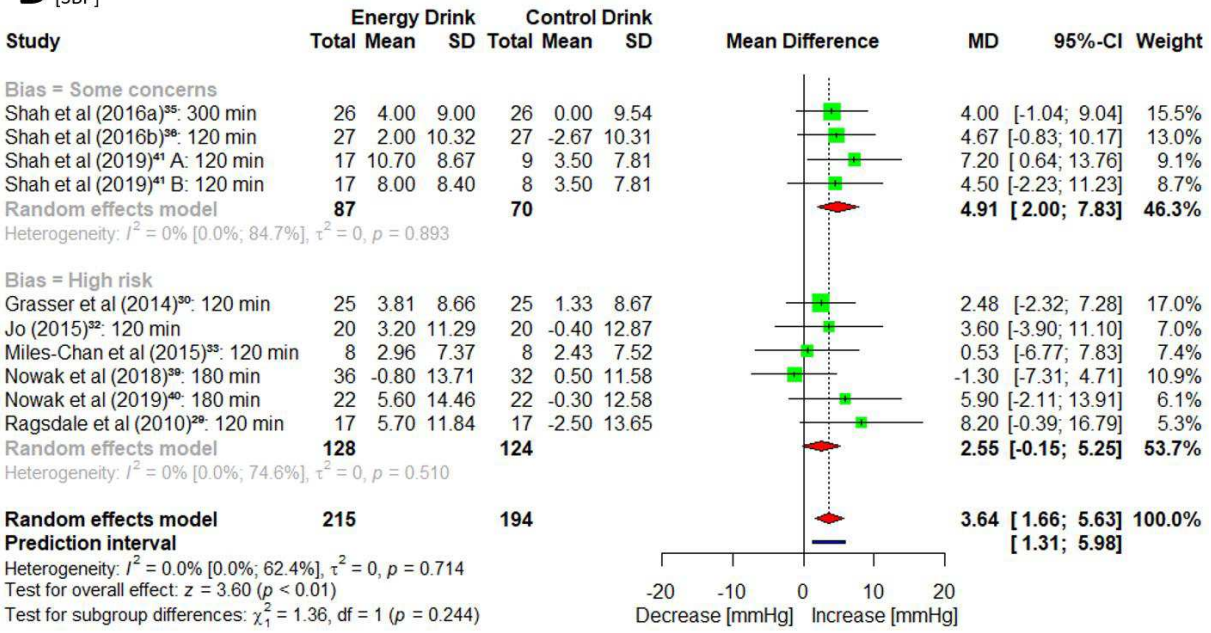


Supplementary Figure S3 **Subgroup analysis comparing studies classified by RoB2 with some concerns and high risk of bias on systolic blood pressure [SBP].** Time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (D) ≥120 minutes. * Preliminary study conducted in 1997 and published in 2001 along with another study.

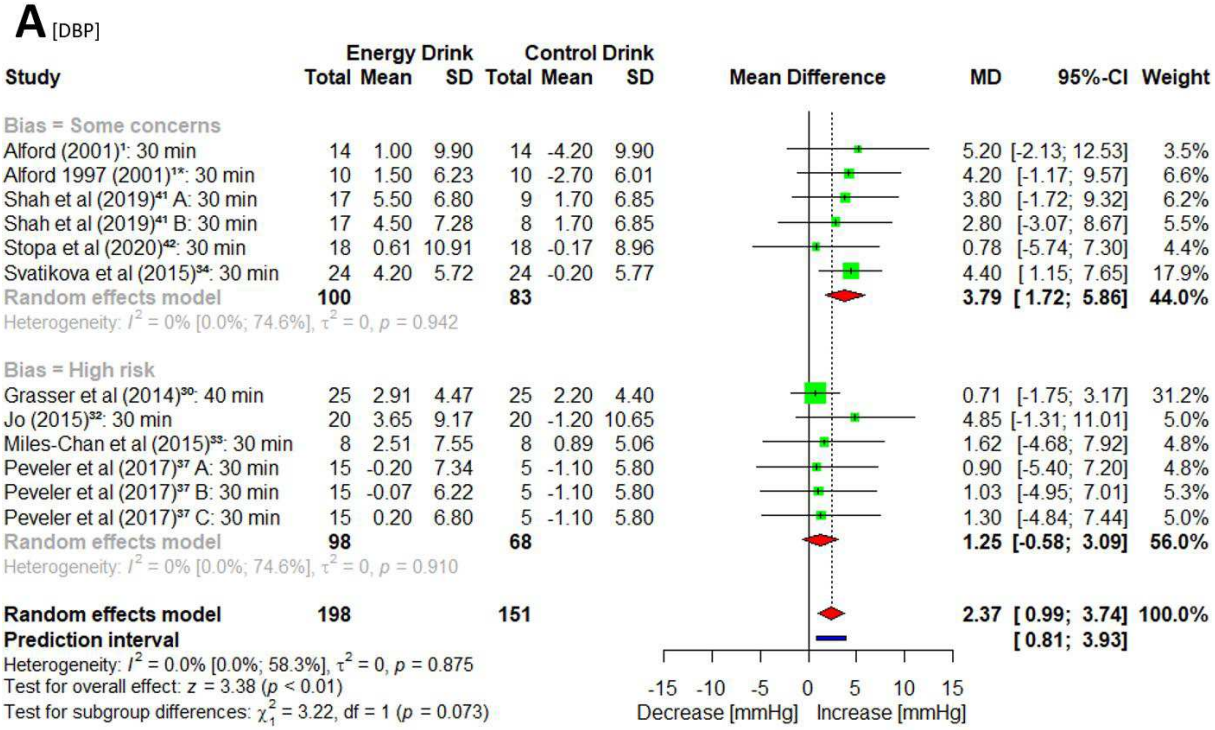
C [SBP]

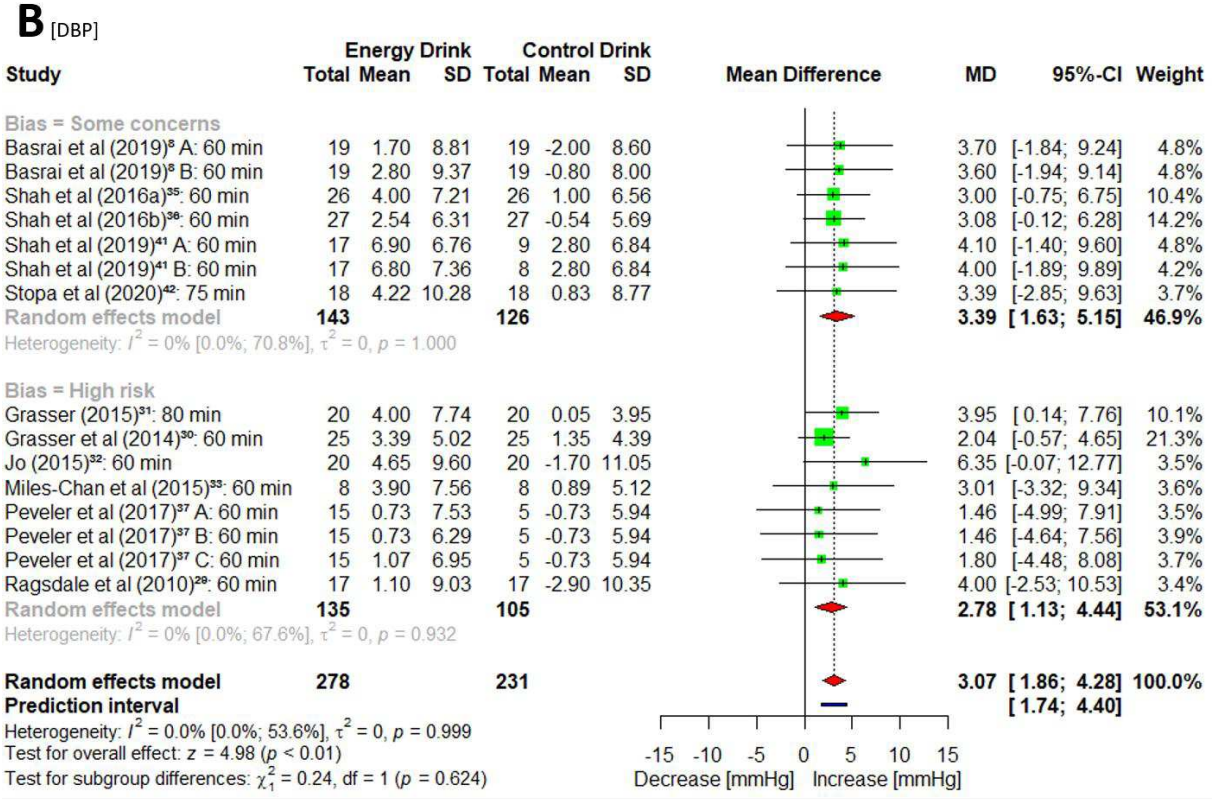


D [SBP]

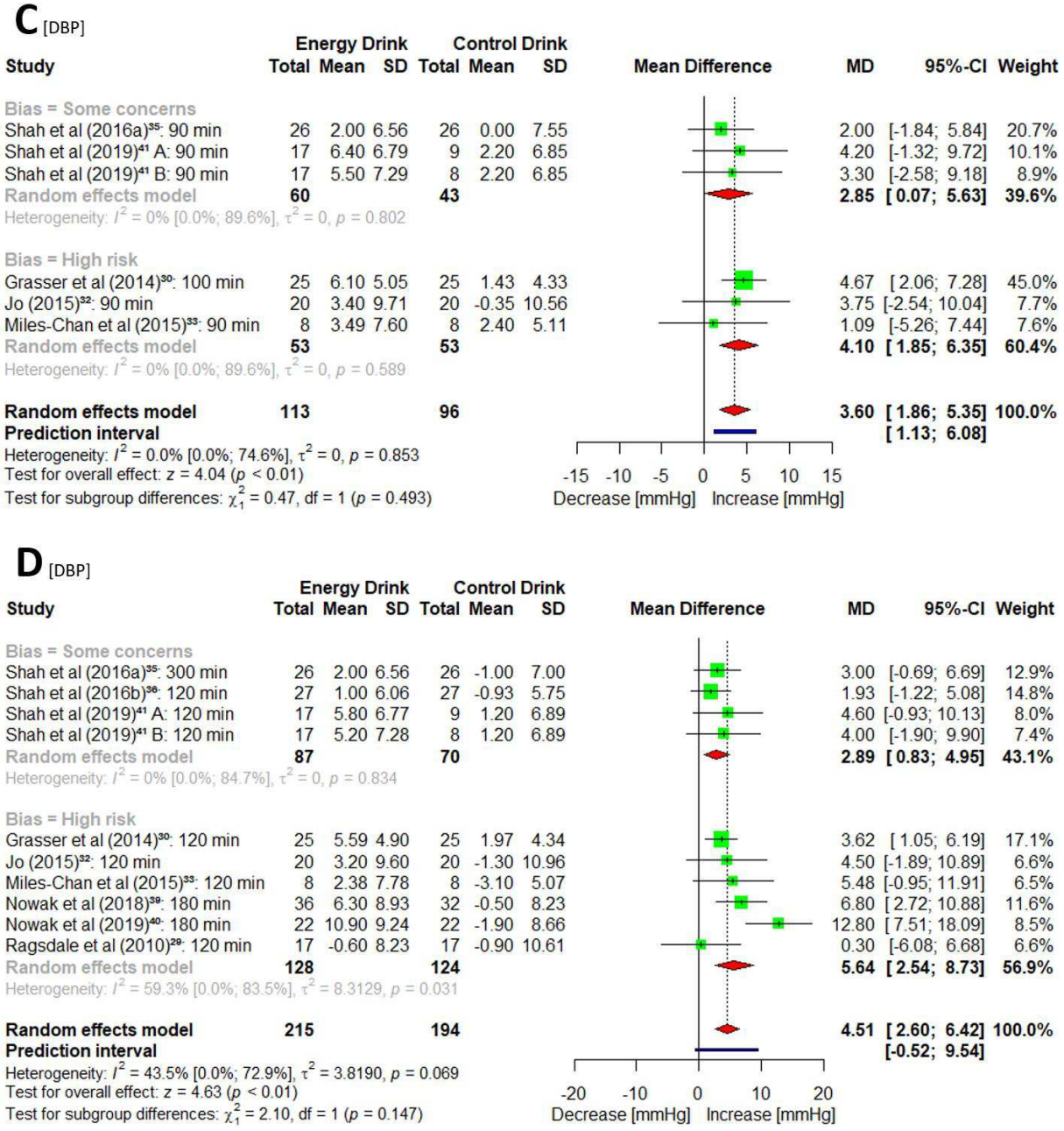


Supplementary Figure S3 **Continued.**

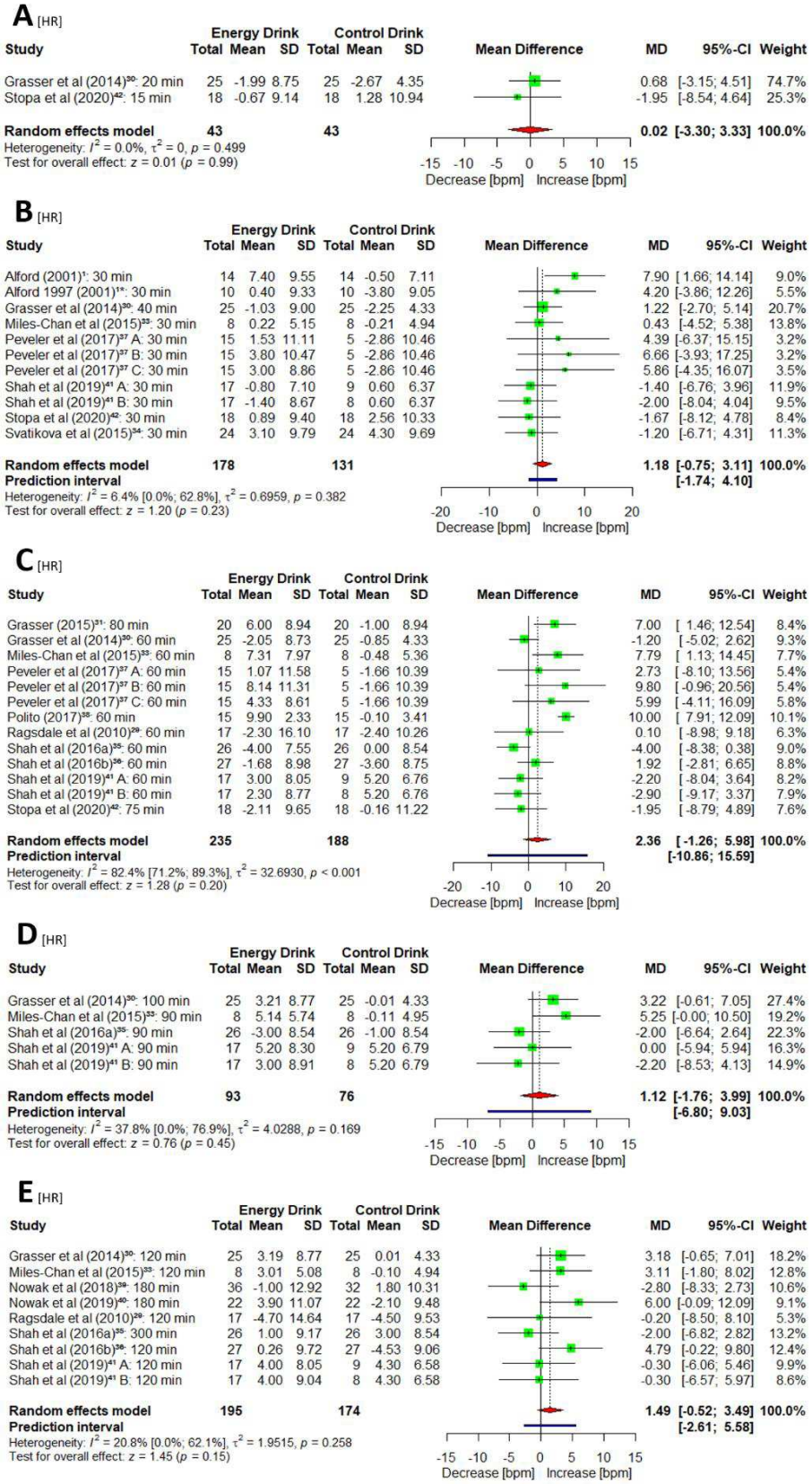




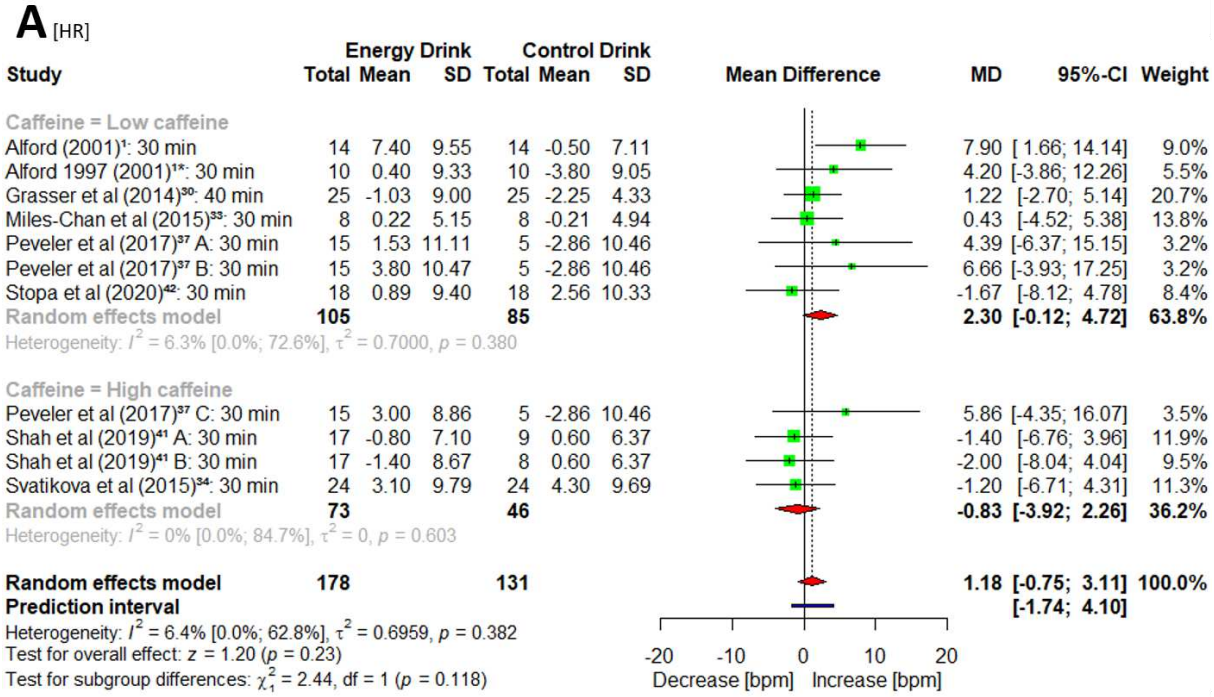
Supplementary Figure S4 **Subgroup analysis comparing studies classified by RoB2 with some concerns and high risk of bias on diastolic blood pressure [DBP].** Time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (D) ≥120 minutes. * Preliminary study conducted in 1997 and published in 2001 along with another study.

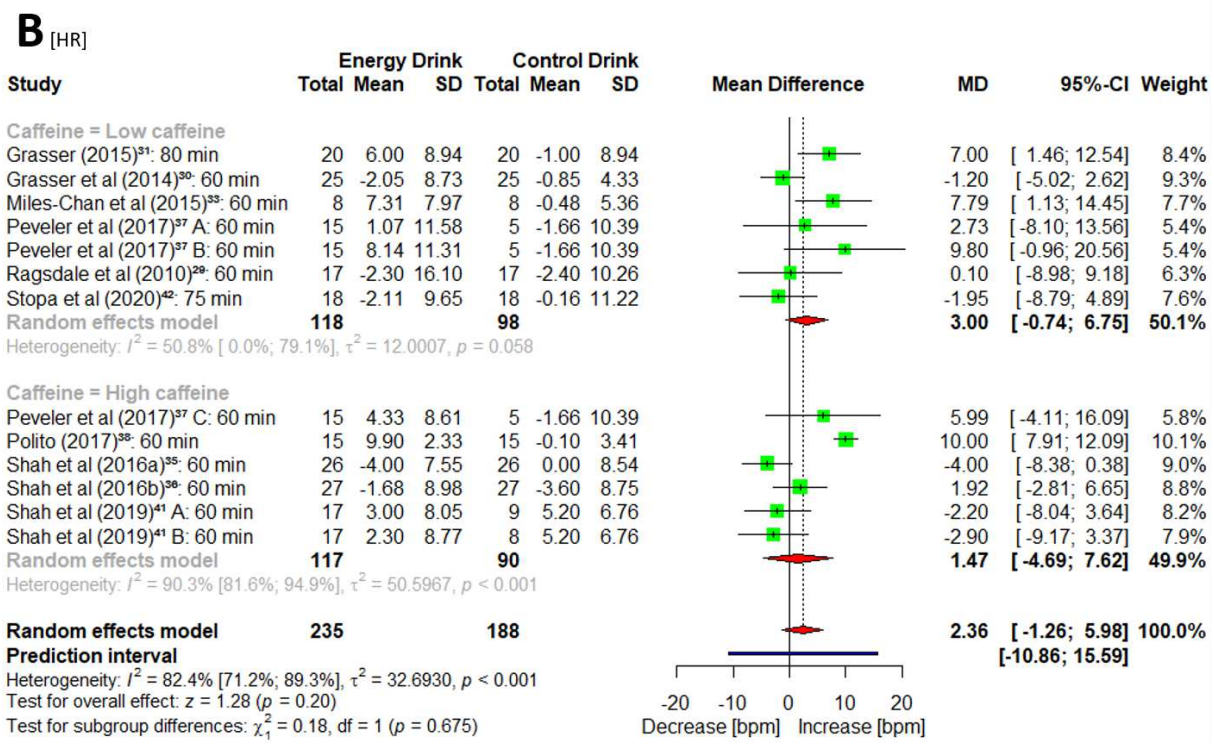


Supplementary Figure S4 **Continued.**



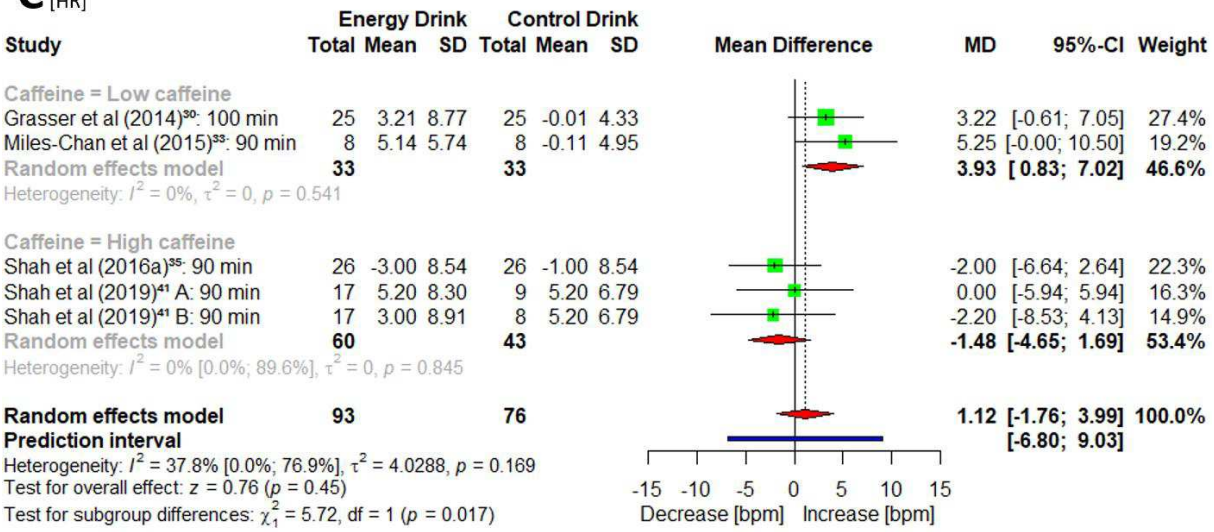
Supplementary Figure S5 **Meta-analysis of the acute effects of energy drink consumption compared to a control drink on heart rate [HR] in healthy adults.** Time frames: (A) ≤20 minutes, (B) 30-40 minutes, (C) 60-80 minutes, (D) 90-100 minutes and (E) ≥120 minutes. * Preliminary study conducted in 1997 and published in 2001 along with another study.



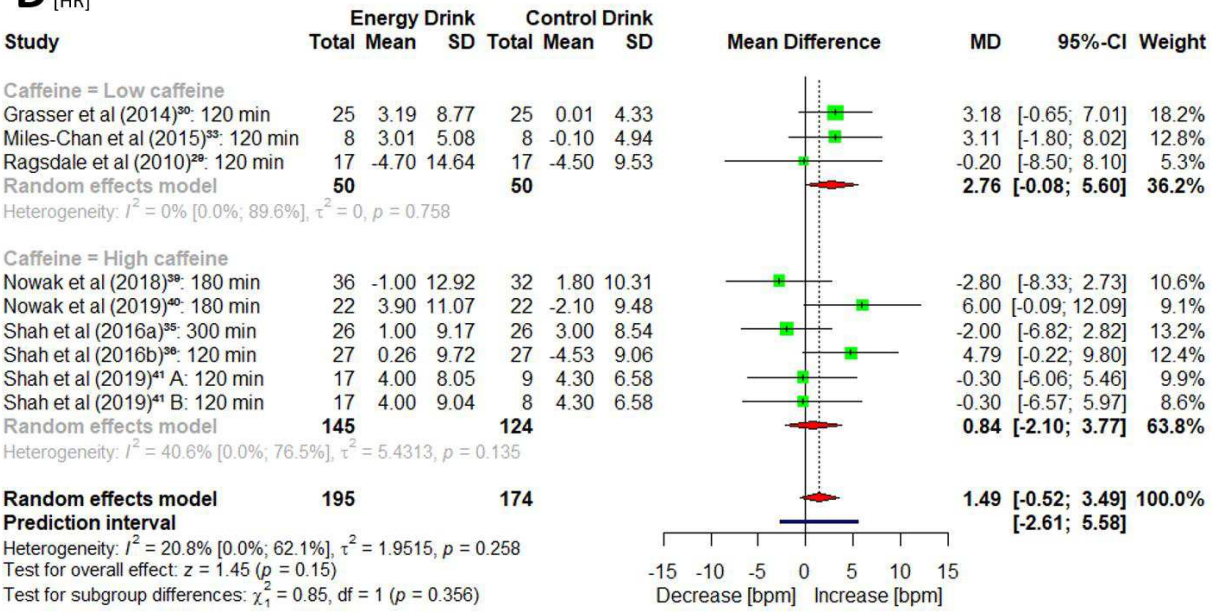


Supplementary Figure S6 **Subgroup analysis comparing low-caffeine and high-caffeine energy drinks on heart rate [HR].** Time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (D) ≥120 minutes. * Preliminary study conducted in 1997 and published in 2001 along with another study.

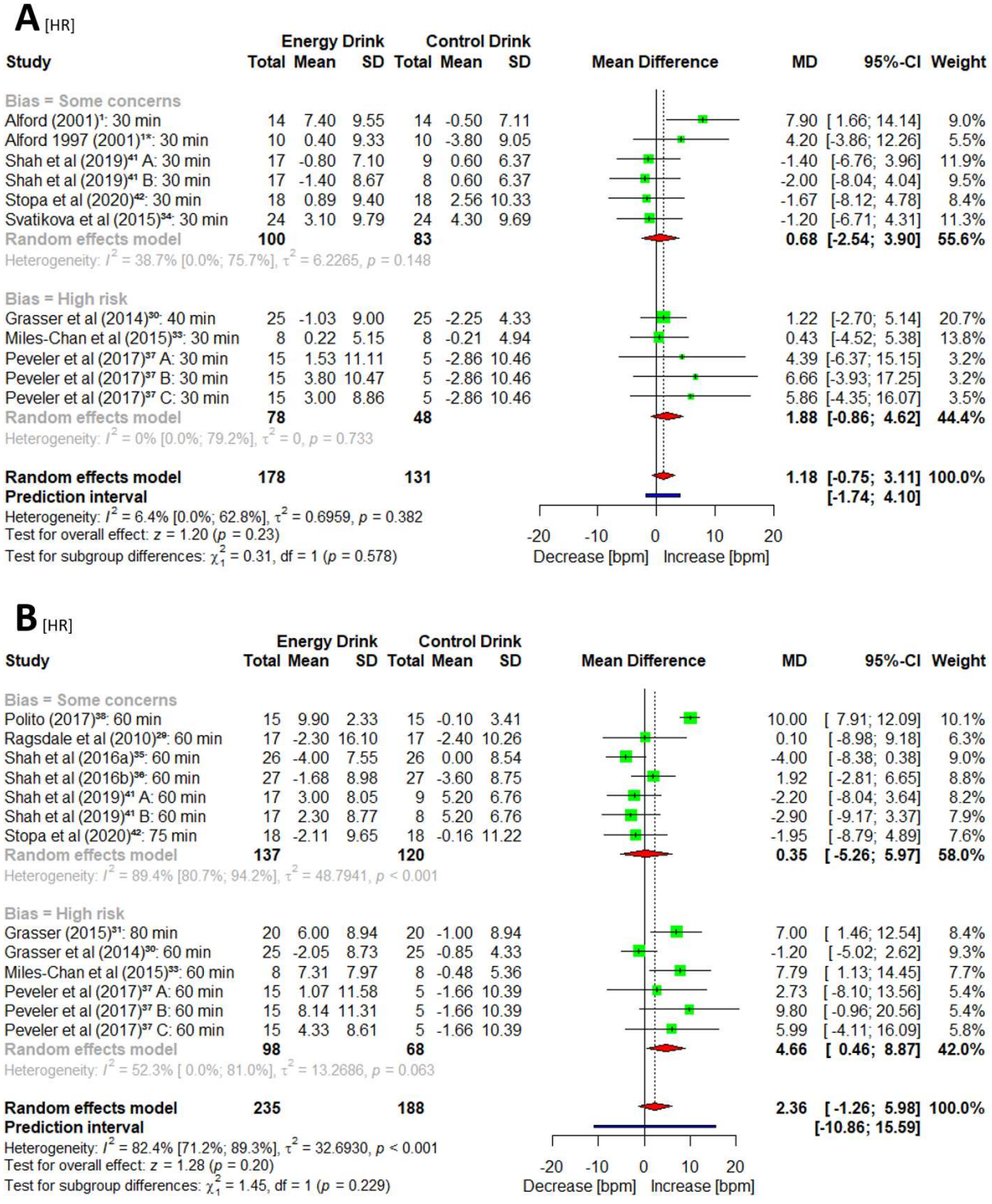
C [HR]



D [HR]

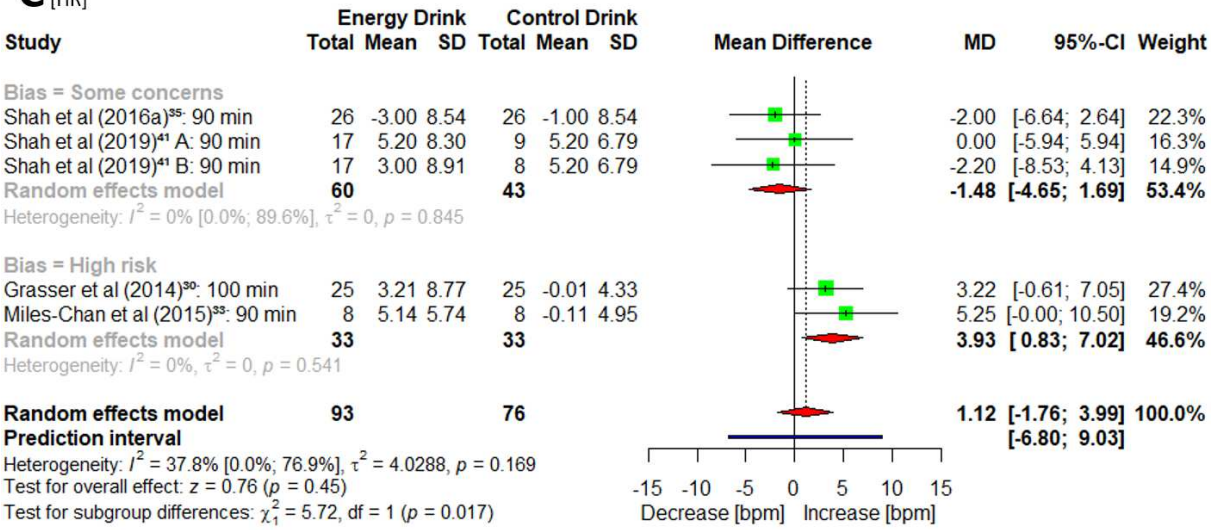


Supplementary Figure S6 **Continued.**

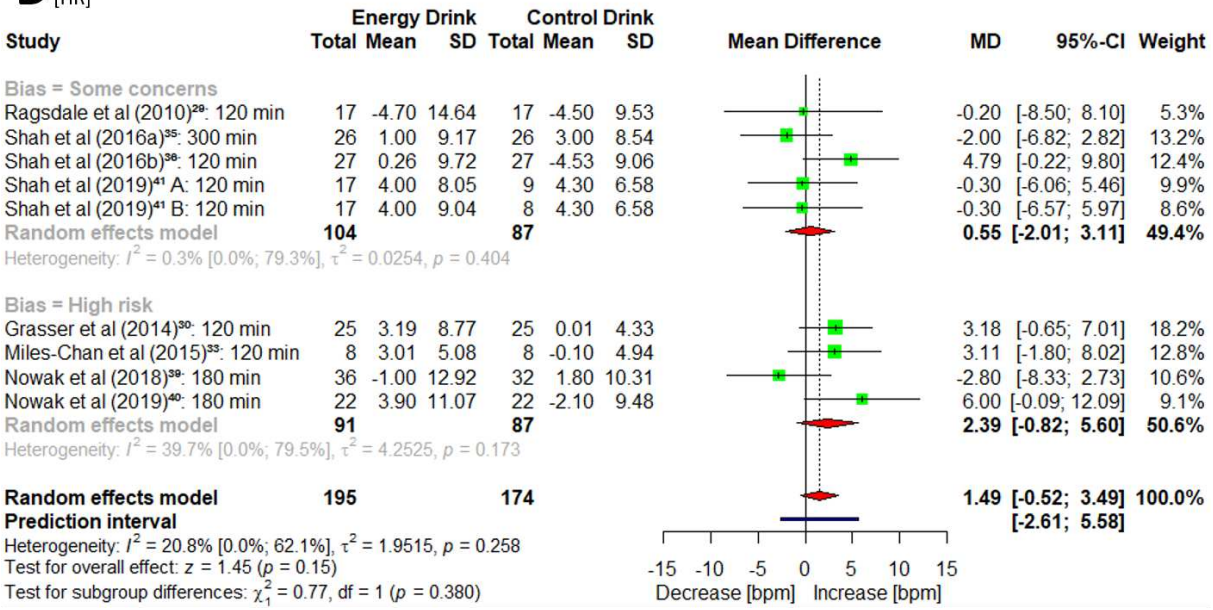


Supplementary Figure S7 **Subgroup analysis comparing studies classified by RoB2 with some concerns and high risk of bias on heart rate [HR].** Time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (D) ≥120 minutes. * Preliminary study conducted in 1997 and published in 2001 along with another study.

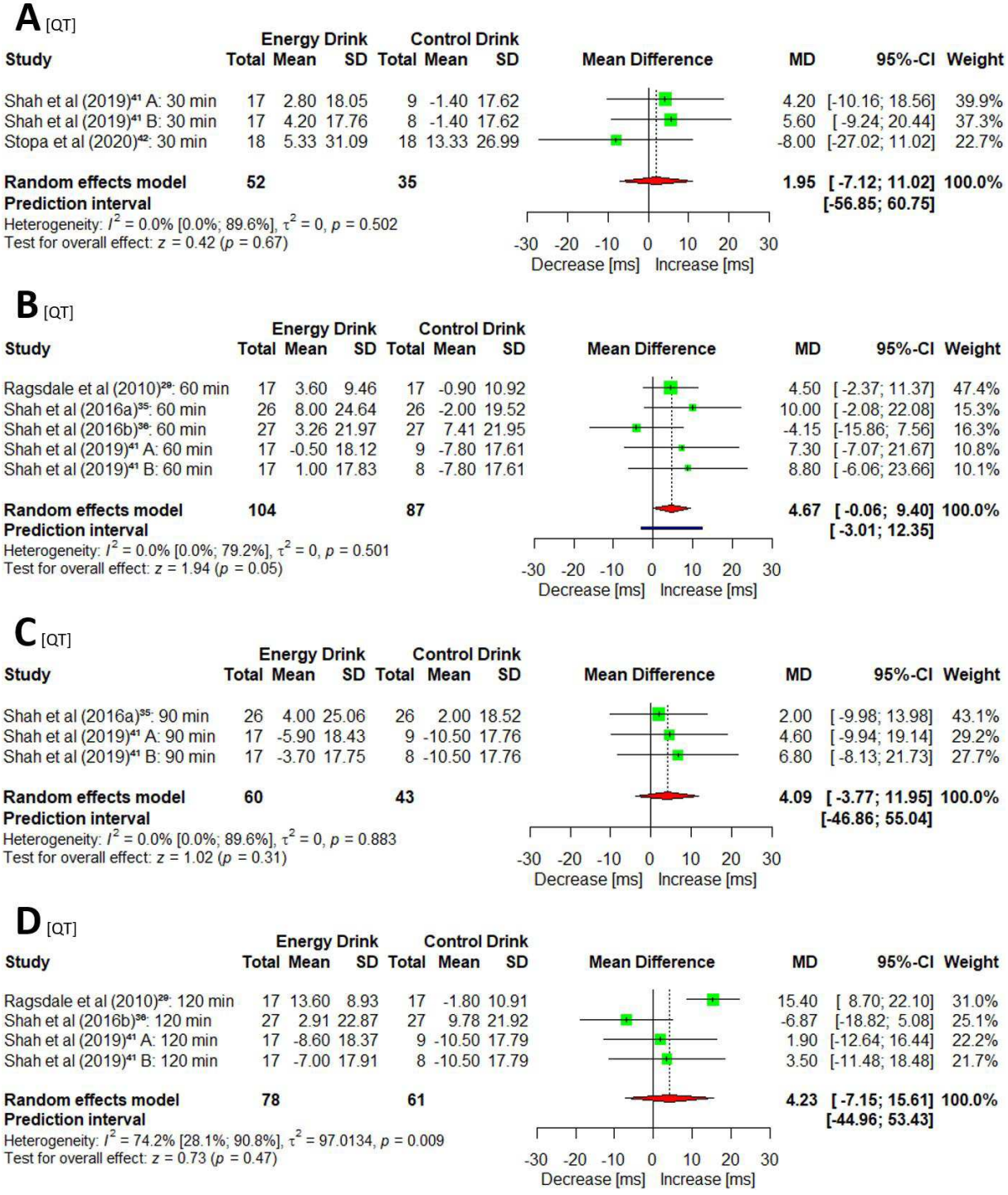
C [HR]



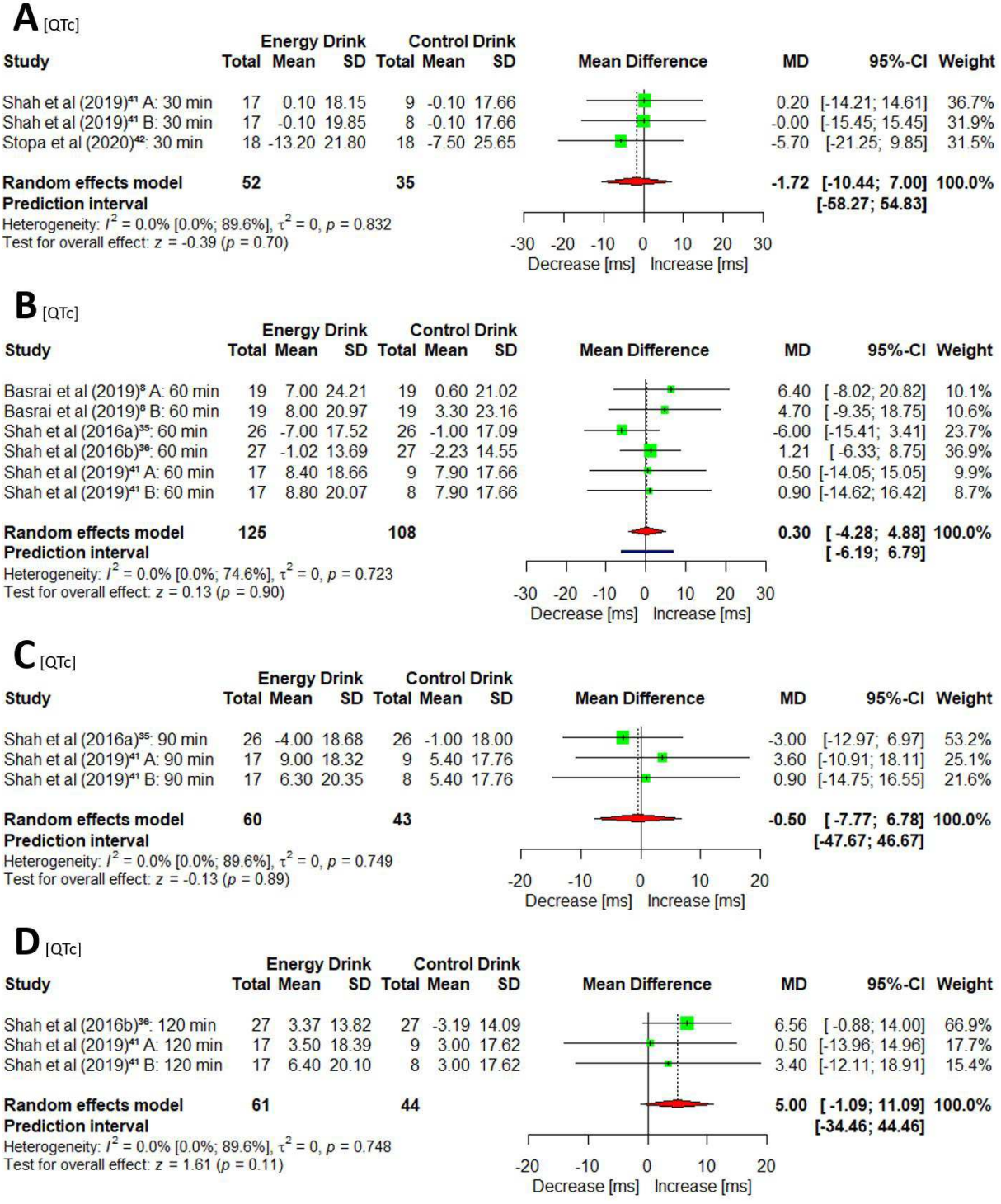
D [HR]



Supplementary Figure S7 **Continued.**



Supplementary Figure S8 **Meta-analysis of the acute effects of energy drink consumption compared to a control drink on QT interval [QT] in healthy adults.** Time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (D) ≥120 minutes.



Supplementary Figure S9 **Meta-analysis of the acute effects of energy drink consumption compared to a control drink on corrected QT interval [QTc] in healthy adults.** Time frames: (A) 30-40 minutes, (B) 60-80 minutes, (C) 90-100 minutes and (D) ≥120 minutes.

Supplementary Box S1 **Interpretation of heterogeneity results.**

Interpretation of I^2
0% to 40%: might not be important;
30% to 60%: may represent moderate heterogeneity*;
50% to 90%: may represent substantial heterogeneity*;
75% to 100%: considerable heterogeneity*.

* The importance of the value of I^2 depends on the magnitude and direction of effects and the strength of evidence for heterogeneity (I^2 confidence interval: uncertainty of the value of I^2 is substantial when there is a small number of studies).

Supplementary Box S2 **Example of the script used to perform the meta-analysis by RStudio.**

```
## 1st step: Upload meta-analysis package

library(meta)


## 2nd step: Detail and perform the meta-analysis

Meta.SBP <- metacont(tto_n, tto_mean, tto_dp,

                     cont_n, cont_mean, cont_dp,

                     paste(Study),

                     data = SBP,

                     fixed = FALSE,

                     prediction = TRUE,

                     method.tau = "DL")


Meta.SBP


## 3rd step: Incorporate combinations for multiple meta-analyses

Meta.SBP.B <- subset (SBP, Combination!= "A" & Combination!= "C" & Combination!= "D" & Combination!= "E" & Combination!= "BB" & Combination!= "CC" & Combination!= "EE" & Combination!= "DD" & Combination!= "XX")


Meta.SBP.B


Meta.SBP.B <- metacont(tto_n, tto_mean, tto_dp,
```

```
            cont_n, cont_mean, cont_dp,
            paste(Study),
            data = Meta.SBP.B,
            fixed = FALSE,
            prediction = TRUE,
            method.tau = "DL")

Meta.SBP.B

## 4th step: Create Forest plot of the meta-analysis
forest(Meta.SBP.B)

## 5th step: Customize Forest plot of the meta-analysis
forest(Meta.SBP.B,
    comb.fixed = FALSE,
    sortvar = Study,
    xlim = c (-15.0, 15.0),
    squaresize = 0.6,
    col.square = "green",
    col.diamond = "red",
    col.predict = "blue",
    digits.sd = 2,
    digits.tau = 1,
    digits.pval.Q = 3,
    digits.I2 = 1,
    print.I2.ci = TRUE,
    label.e = "Energy Drink",
    label.c = "Control Drink",
    label.left = "Decrease [mmHg]",
    label.right = "Increase [mmHg]",
    test.overall = TRUE)
```

```
## Step 6: Incorporate combinations for subgroup analysis (Low Caffeine vs. High Caffeine)

Meta.SBP.B <- subset(SBP, Combination!= "A" & Combination!= "C" & Combination!= "D" & Combination!= "E" & Combination!= "BB" & Combination!= "CC" & Combination!= "EE" & Combination!= "DD" & Combination!= "XX")


## 7th step: Perform subgroup analysis

Meta.SBP.B <- metacont(tto_n, tto_mean, tto_dp,
                       cont_n, cont_mean, cont_dp,
                       paste(Study),
                       byvar = Caffeine,
                       data = Meta.SBP.B,
                       fixed = FALSE,
                       prediction = TRUE,
                       method.tau = "DL")


Meta.SBP.B


## 8th step: Create Forest plot from subgroup analysis

forest(Meta.SBP.B)


## 9th step: Customize Forest plot of subgroup analysis

forest(Meta.SBP.B,
     comb.fixed = FALSE,
     sortvar = Study,
     xlim = c(-15.0, 15.0),
     squaresize = 0.7,
     col.square = "green",
     col.diamond = "red",
     col.predict = "blue",
     digits.sd = 2,
```

```
    digits.tau = 1,
    digits.pval.Q = 3,
    digits.I2 = 1,
    print.I2.ci = TRUE,
    label.e = "Energy Drink",
    label.c = "Control Drink",
    label.left = "Decrease [mmHg]",
    label.right = "Increase [mmHg]",
    test.overall = TRUE)


## 10th step: Incorporate combinations for subgroup analysis (Some Concerns vs. High Risk)
Meta.SBP.B <- subset(SBP, Combination!="A" & Combination!= "C" & Combination!= "D" & Combination!= "E" & Combination!= "BB" & Combination!= "CC" & Combination!= "EE" & Combination!= "DD" & Combination!= "XX")


## 11th step: Perform subgroup analysis
Meta.SBP.B <- metacont(tto_n, tto_mean, tto_dp,
                       cont_n, cont_mean, cont_dp,
                       paste(Study),
                       byvar = Bias,
                       data = Meta.SBP.B,
                       fixed = FALSE,
                       prediction = TRUE,
                       method.tau = "DL")


Meta.SBP.B


## 11th step: Create Forest plot from subgroup analysis
forest(Meta.SBP.B)


## 12th step: Customize Forest plot of subgroup analysis
```

```
forest(Meta.SBP.B,
      comb.fixed = FALSE,
      sortvar = Study,
      xlim = c (-15.0, 15.0),
      squaresize = 0.7,
      col.square = "green",
      col.diamond = "red",
      col.predict = "blue",
      digits.sd = 2,
      digits.tau = 1,
      digits.pval.Q = 3,
      digits.I2 = 1,
      print.I2.ci = TRUE,
      label.e = "Energy Drink",
      label.c = "Control Drink",
      label.left = "Decrease [mmHg]",
      label.right = "Increase [mmHg]",
      test.overall = TRUE)

## 13th step: Create and customize Funnel plot
      metabias (Meta.SBP.B,
            method.bias = "linreg",
            k.min=10)

      funnel (Meta.SBP.B)

      col.contour = c ("gray75",
                  "gray85",
                  "gray95")

      funnel.meta (Meta.SBP.B,
```

```
            xlim = c(-15.0, 15.0),
            contour = c(0.9, 0.95, 0.99),
            col.contour = col.contour)

    legend (x = 9.5,
        y = 0.10,
        legend = c ("p < 0.1", "p < 0.05", "p < 0.01"),
        fill = col.contour)

## 14th step: Create and perform publication bias analysis
baujat(Meta.SBP.B)

metainf (Meta.SBP.B, pooled= "random")
```

ANEXO A – Protocolo de registro no prospero

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Acute effects of energy drink consumption on cardiovascular parameters in adults: a systematic review with meta-analysis

Citation

Luis Fernando Deresz, Gustavo Waclawovsky, Pedro Ian Barbalho Gualberto, Vinícius Vieira Benvindo. Acute effects of energy drink consumption on cardiovascular parameters in adults: a systematic review with meta-analysis. PROSPERO 2022 CRD42022295335 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022295335

Review question

What are cardiovascular parameters acute responses after energy drink consumption in healthy adults?

Searches

The electronic databases to be used in this review will be: MEDLINE via PubMed, EMBASE, Cochrane Library, Web of Science, LILACS and SPORTDiscus. To minimize the risk of publication bias, searches will also be carried out in the gray literature, including OpenGrey and the Banco de Teses e Dissertações da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

Clinical trials registry databases will be used to consult studies that are ongoing or that have not yet been published, they will be: Clinical Trial.gov, Brazilian Clinical Trials Registry (REBEC), International Clinical Trials Registry Platform.

There will be no publication period and language restrictions.

The date of the first search in bases was 01/11/2021 and will be done again on 01/05/2022.

Types of study to be included

Randomized clinical trials

Condition or domain being studied

Healthy subjects' cardiovascular parameters

Participants/population

- Inclusion criteria:

Randomized clinical trials performed with healthy adult individuals aged 18 years or over, with cardiovascular parameters measured by:

a) Blood pressure: Auscultatory, oscillometric, or ambulatory blood pressure monitoring (ABPM);

b) Heart rate at rest: Portable cardio tachometer or electrocardiography;

c) Cardiac output: Invasive and non-invasive methods;

d) Endothelial function: Ultrasonography using the flow-mediated dilation (FMD) technique, Plethysmography using the reactive hyperemia (RH) technique, or Plethysmography using the infusion of vasoactive agents.

e) QT and QTc interval: Electrocardiography.

- Exclusion criteria:

Studies that used, in addition to energy drinks, other interventions such as juices, teas, alcohol, coffee, medications, energy bars, sports supplementation, physical activity, psychological/emotional stimulation will be excluded. Studies with similar characteristics, but published in different journals will be reviewed and, if necessary, will be excluded for being considered as a duplicate publication.

Intervention(s), exposure(s)

Commercialized energy drinks. These, unlike traditional energy drinks (coffee, tea, and sports drinks), have high caffeine content, which is usually combined with large amounts of vitamins, minerals, taurine, amino acids, and different mixtures of phytochemicals. This components combination may change cardiovascular parameters acutely.

Comparator(s)/control

Placebo drink. Water with or without artificial coloring and flavoring or a drink in which it doesn't interfere with study outcomes.

Context

Some studies indicate that energy drinks consumption may increase heart rate and blood pressure levels acutely. However, there is no consensus on the effects of energy drinks on these cardiovascular parameters and others, such as cardiac output, endothelial function, and QT interval, and QTc interval.

Thus, our aim is to evaluate energy drink consumption's acute effects on blood pressure, resting heart rate, cardiac output, endothelial function, and QT/QTc interval in healthy adults.

Main outcome(s)

- Rest mean, systolic, and diastolic blood pressure;

- Rest Heart rate;

- Rest cardiac output;

- Rest endothelial function;

- QT/QTc interval.

Measures of effect

Mean differences or standardized mean difference

Additional outcome(s)

Analysis of subgroups or subsets

Only randomized clinical trials involving healthy adults (>17 years old) will be eligible for the systematic review. To investigate the consistency of the energy drink effect across studies, the analysis of the degree of heterogeneity (relative variability in effect estimates attributed to heterogeneity) will be tested with the Higgins inconsistency test (I^2) for each pairwise comparison. In case of heterogeneity (0% to 40%: may not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity), it will be explored. To explore the heterogeneity ($p< 0.05$), subgroup analyzes (observational) or meta-regression (statistics; if there are more than 10 studies) will be used for effect modifiers with normal distribution in a quartile-quartile plot (qq-plot) and confirmed by the Shapiro-Wilk test ($p> 0.05$). Associated with this, to identify discrepant data from the meta-analysis, the imprecision of the effect estimate described by heterogeneity will also be visually observed using the absence of overlapping 95% CI in the forests plot to identify possible outliers. Potential effect modifiers for cardiovascular factors such as age, body mass index, sex, the volume of energy drink consumed will be analyzed separately. When heterogeneity is significant and we do not have data to explain it, the meta-analysis will not be performed, but we will present estimates of the effects of the studies' interventions individually. Statistical tests will be two-tailed and significance as $p< 0.05$. The data will be modeled in RStudio software (version 1.3.959) using the "Meta" package.

Contact details for further information

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Organisational affiliation of the review

Universidade Federal de Juiz de Fora

https://www2.ufjf.br/gv/

Review team members and their organisational affiliations

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Dr Gustavo Waclawovsky. Fundação Universitária de Cardiologia

Pedro Ian Barbalho Gualberto. Universidade Federal de Juiz de Fora

Vinícius Vieira Benvindo. Universidade Federal de Juiz de Fora

Type and method of review

Meta-analysis, Systematic review

Anticipated or actual start date

01 November 2021

Anticipated completion date [1 change]

30 April 2022

Funding sources/sponsors

Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) - Brazil

Conflicts of interest

The authors do not have any personal, religious, cultural, or business potential conflict of interest to declare.

None known

Language

English

Country

Brazil

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Adult; Energy Drinks; Humans

Date of registration in PROSPERO

06 January 2022

Date of first submission

06 December 2021

Stage of review at time of this submission [1 change]

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

Revision note

No major changes were made to the protocol, only the steps were updated and the expected completion date was postponed.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

06 January 2022

06 January 2022

02 February 2023

ANEXO B – Comprovante de submissão do Artigo II

Nutrition Reviews

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Author

Review

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Submission Confirmation

Print

Thank you for your submission

Submitted to
Nutrition Reviews

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Title
Acute effects of energy drink consumption on cardiovascular parameters in healthy adults: a systematic review with meta-analysis of randomized clinical trials

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Date Submitted
12-May-2023