UNIVERSIDADE DE BRASÍLIA

FACULDADE DE CIÊNCIAS DA SAÚDE

PROGRAMA DE PÓS-GRADUAÇÃO EM NUTRIÇÃO HUMANA

VALIDAÇÃO DO QUESTIONÁRIO DE EXPECTATIVA À CAFEÍNA PARA A POPULAÇÃO BRASILEIRA E ASSOCIAÇÃO AOS POLIMORFISMOS DOS GENES *CYP1A2* E *ADORA2A*

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Validação do questionário de expectativa à cafeína para a população brasileira e associação aos polimorfismos dos genes *CYP1A2* e *ADORA2A*.

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RESUMO

A expectativa de efeitos da cafeína pode ser registrada em questionários validados para observar padrões favoráveis, ou não, ao uso de fontes cafeína. Esta individualidade biológica está relacionada com os polimorfismos genéticos podem interferir no modo como os indivíduos metabolizam a cafeína, gene *CYP1A2* (rs 762551), genótipo AA, fenótipo rápidos metabolizadores, e a sua ação nos receptores de adenosina *ADORA2A* (rs 5751876), genótipo TT, fenótipo maior sensibilidade. Portanto, o presente estudo teve como objetivo avaliar a capacidade do CaffEQ-BR na diferenciação dos polimorfismos dos genes *CYP1A2* e *ADORA2A*, conforme as expectativas de efeito da cafeína medidas pelo instrumento. O estudo foi composto por três etapas: (i) processo de tradução com dois tradutores bilingues, validação semântica por meio de técnica de juízes (n = 20), análise de reprodutibilidade e consistência interna com amostra de conveniência (n = 50) e validação externa por meio da análise fatorial confirmatória com amostra composta por 4.202 participantes de todas as Unidades da Federação; (ii) desenvolvimento e validação da versão curta do instrumento (B-CaffEQ-BR); (iii) aplicação do CaffEQ-BR (versão completa e curta) a uma amostra (n = 71) de atletas brasileiros treinados em desenvolvimento, consumidores habituais de cafeína com determinação prévia para os polimorfismos dos genes *CYP1A2* e *ADORA2A*. O questionário se mostrou adequado quanto à confiabilidade, clareza e compreensão. A reprodutibilidade e a validação foram confirmadas pelo alfa de Cronbach (α) de 0,948, e foi observado um coeficiente de correlação intraclasse de 0,976. Os sete fatores apresentaram um bom ajuste para a raiz do erro quadrático médio de aproximação – RMSEA = 0,0332 (IC 95%: 0,0290–0,0375). Após a validação externa, o CaffEQ-BR passou por modelagem estatística com vistas a reduzir o número de itens, com três itens por fator, mantendo os sete fatores (CaffEQ-BR versão curta com 21 itens) com reprodutibilidade interobservador e a consistência interna tão satisfatória quanto o CaffEQ-BR (α de Cronbach $\geq$ 0,729) e reprodutibilidade global (ICC $\geq$ 0,915) para todo o questionário e seus sete fatores. As versões completa e curta foram aplicados em indivíduos (n = 71) com genotipagem prévia para os polimorfismos dos genes *CYP1A2* e *ADORA2A*. A frequência observada dos genótipos AA para o gene *CYP1A2* foi de 47,9% (n=34) e portadores do alelo C (AC e CC) foi de 52,1% (n=37). Para o gene *ADORA2A* foi observado 22,7% (n=15) como portadores do genótipo TT e 77,3%

(n=51) portadores C (TC e CC). Com exceção ao fator "ansiedade/efeitos físicos negativos", os demais escores do CaffEQ-BR (completo e curto), obtiveram ICC > 0,75. Indivíduos que pontuaram > 4 na escala *Likert* ("um pouco provável") no fator ansiedade/efeitos negativos no B-CaffEQ-BR apresentaram capacidade discriminatória para o genótipo TT para *ADORA2A* (p = 0,01) de acordo com a curva ROC, mas com representatividade muito baixa (n = 2). Portanto, na presente amostra estudada, o CaffEQ-BR não foi capaz de diferenciar, por meio da expressão dos fenótipos de rápida metabolização hepática e maior sensibilidade na ação da cafeína nos receptores de adenosina, associado aos genótipos para os genes *CYP1A2* e *ADORA2A* em amostra de conveniência de atletas brasileiros treinados em desenvolvimento. Sugere-se que pesquisas futuras utilizem amostras mais amplas, com grupo controle composto por indivíduos com consumo baixo ou irregular consumo de cafeína, calibrando o questionário com maior foco em aspectos da ansiedade e efeitos negativos na busca em diferenciar o genótipo TT para *ADORA2A*.

Palavras-chave: Cafeína; *CYP1A2*; *ADORA2A*; Polimorfismo; Questionário; Expectativa; Valores Preditivos; Ansiedade.

Validation of the Caffeine Expectancy Questionnaire for the Brazilian population and association with *CYP1A2* and *ADORA2A* gene polymorphisms.

ABSTRACT

The expected effects of caffeine can be recorded in validated questionnaires to observe patterns favorable or not to the use of caffeine sources. Genetic polymorphisms can interfere with how individuals metabolize caffeine, *CYP1A2* gene (rs 762551), AA genotype, rapid metabolizer phenotype, and its action on adenosine receptors *ADORA2A* (rs 5751876), TT genotype, increased sensitivity phenotype. Therefore, the present study aimed to evaluate the ability of CaffEQ-BR to measure the *CYP1A2* and *ADORA2A* polymorphism genes, according to the effects of caffeine. The study consisted of three stages: (i) translation process with two bilingual translators, semantic validation using the judges' technique (n = 20), reproducibility and internal consistency analysis with a convenience sample (n = 50) and validation external through confirmatory factor analysis with a sample composed of 4,202 participants from all Federation Units; (ii) development and validation of the instrument's brief version (B-CaffEQ-BR); (iii) application of CaffEQ-BR (complete and brief version) to a sample (n = 71) of Brazilian trained/developmental athletes habitual caffeine consumers with previous determination for *CYP1A2* and *ADORA2A* gene polymorphisms. The questionnaire proved adequate in terms of reliability, clarity, and understanding. Reproducibility and validation were confirmed by Cronbach's alpha (α) of 0.948, and an intraclass correlation coefficient of 0.976 was observed. The seven factors showed a good fit for the root mean square error of approximation – RMSEA = 0.0332 (95% CI: 0.0290–0.0375). After external validation, the CaffEQ-BR underwent statistical modeling to reduce the number of items, with three items per factor, keeping the seven factors (CaffEQ-BR short version with 21 items) with inter-observer reproducibility and internal consistency as satisfactory as the CaffEQ-BR (Cronbach's α ≥ 0.729) and global reproducibility (ICC ≥ 0.915) for the entire questionnaire and its seven factors. The full and brief versions were applied to individuals (n = 71) with previous genotyping for *CYP1A2* and *ADORA2A* gene polymorphisms. The observed frequency of AA genotypes for the *CYP1A2* gene was 47.9% (n=34), and the frequency of carriers of the C allele (AC and CC) was 52.1% (n=37). For the *ADORA2A* gene, 22.7% (n=15) were carriers of the TT genotype and 77.3% (n=51) were C carriers (TC and CC). Except for

the "anxiety/negative physical effects" factor, the other CaffEQ-BR scores (complete and brief) obtained ICC > 0.75. Individuals who scored > 4 on the Likert scale ("a little likely") in the anxiety/negative effects factor on the B-CaffEQ-BR showed a discriminatory capacity for the TT genotype for *ADORA2A* (p = 0.01) according to the ROC curve, but with very low representation (n = 2). In conclusion, CaffEQ-BR was not able to differentiate, through the expression of the phenotypes of rapid hepatic metabolism and greater sensitivity in the action of caffeine on adenosine receptors, associated with the genotypes for the *CYP1A2* and *ADORA2A* in a convenience sample of Brazilian trained/developmental athletes. It is suggested that future research uses broader samples, with a control group composed of individuals with low or irregular caffeine consumption, calibrating the questionnaire with a greater focus on aspects of anxiety and negative effects in the search to differentiate the TT genotype from *ADORA2A*.

LISTA DE SIGLAS

ADORA2A: *Adenosine A2A receptor*

AUC: *Area Under Curve*

B-CaffEQ-BR: *Brief Caffeine Expectancy Questionnaire in Brazil*

CAF: Cafeína

CaffEQ: *Caffeine Expectancy Questionnaire*

CaffEQ-BR: *Caffeine Expectancy Questionnaire in Brazil*

CaffCo: *Caffeine habits and consumption questionnaire*

CEQ: *Caffeine Expectation Questionnaire*

CYP1A2: *Cytochrome P450 1A2*

ICC: *Intraclass Correlation Coeficiente*

IMC: Índice de Massa Corporal

MAE: *Mean Absolute Error*

OMS: Organização Mundial de Saúde

RMSEA: *Root Mean Square Error of Approximation*

ROC: *Receiver Operating Characteristic*

SNC: Sistema Nervoso Central

SNP: *Single Nucleotide Polymorphism*

TCLE: Termo de Consentimento Livre e Esclarecido

SUMÁRIO

ESTRUTURA DA TESE

Esta tese está estruturada em três capítulos. O Capítulo 1 é composto de introdução, referencial teórico, objetivos, e materiais e métodos. No Capítulo 2, composto dos resultados e da discussão, onde estão dispostos os artigos resultantes desta pesquisa: "*Translation and Validation of the Caffeine Expectancy Questionnaire in Brazil (CaffEQ-BR)*", publicado em 2020 no periódico Nutrients (FI: 6.7); "*Brief Version of Caffeine Expectancy Questionnaire in Brazil (B-CaffEQ-BR)*" publicado em 2021 no periódico Frontiers in Nutrition (FI: 6.5); "*Can the Brazilian Caffeine Expectancy Questionnaires Differentiate the CYP1A2 and ADORA2A Gene Polymorphisms?—An Exploratory Study with Brazilian Athletes*" publicado em 2022 no periódico *Nutrients* (FI: 6.7). Por fim, o Capítulo 3 expõe a conclusão do estudo e as referências bibliográficas.

1. INTRODUÇÃO

A cafeína, de nomenclatura científica 1,3,7-trimetilxantina, é o princípio ativo mais presente no café, mate, guaraná, chá verde, cacau e seus derivados (HECKMAN; WEIL; DE MEJIA, 2010). É amplamente estudada e apresenta várias diretrizes para forma de uso, posologia e limites seguros de consumo (POOLE et al., 2017; WIKOFF et al., 2017; MAUGHAN et al., 2018; GRGIC et al., 2019). A cafeína é a substância psicoativa lícita mais utilizada no mundo (REYES; CORNELIS, 2018), e tem sido observado que o consumo de cafeína pode apresentar respostas fisiológicas diferentes ao estímulo da cafeína, e parte desses efeitos estão associados à variabilidade genética do indivíduo (FULTON et al., 2018; GRGIC et al., 2019; PICKERING, 2019). Ágoston et al. (2018) relata que a ingestão de produtos que contenham cafeína não está associada apenas às suas características sensoriais e hábitos alimentares, mas também às expectativas dos indivíduos acerca dos efeitos da cafeína em seu organismo e suas associações com aspectos fisiológicos (ÁGOSTON et al., 2018a).

Estudos confirmam que o efeito esperado da cafeína desempenha um papel subjetivo na crença em torno do seu consumo (DÖMÖTÖR; SZEMERSZKY; KÖTELES, 2015; SHABIR et al., 2018, 2019). Dessa forma, as expectativas associadas ao consumo e efeitos da cafeína podem desempenhar um papel importante no desenvolvimento, manutenção e reforço de seus padrões de consumo, mostrando a importância do conhecimento acerca das percepções subjetivas associadas ao consumo da cafeína (HEINZ; KASSEL; SMITH, 2009; HUNTLEY; JULIANO, 2012; FULTON et al., 2018). Neste sentido, uma das formas de levantamento de informações sobre percepções subjetivas é a aplicação de questionários padronizados construídos e avaliados a partir de técnicas psicométricas (PASQUALI, 2009). No caso das

percepções subjetivas associadas ao consumo da cafeína, estudos procuram associar o consumo habitual de cafeína com mudanças no humor, apetite, sono/vigília, desempenho físico e outros fatores por meio de instrumentos validados (HEINZ; KASSEL; SMITH, 2009; HUNTLEY; JULIANO, 2012).

Outro aspecto que pode alterar a forma que o indivíduo percebe os efeitos da cafeína é a variabilidade genética associada aos genes −163C> A (*CYP1A2*) relacionado à metabolização hepática da cafeína no citocromo P450 e o gene 1976T> C (*ADORA2A*) relacionado à ação da cafeína nos receptores de adenosina (NEHLIG, 2018). A forma como se apresentam os alelos dos genótipos, pode proporcionar ao seu portador um fenótipo de uma metabolização da cafeína mais rápida (AA) ou lenta (portadores do alelo C), assim como perceber melhor a ação da cafeína, o que significa uma ação mais sensível nos receptores de adenosina (alelos TT) no sistema nervoso central (SNC), se comparado aos portadores do alelo C do gene *ADORA2A* (GUEST et al., 2021). Assim, usualmente as pessoas tendem a consumir uma quantidade de cafeína na qual se sentem confortáveis (BALTAZAR-MARTINS et al., 2019). Esse mecanismo de autorregulação provavelmente se baseia nas experiências pessoais de reações à cafeína (FULTON et al., 2018).

Até o presente momento não há na literatura um instrumento validado para língua portuguesa para avaliar a expectativa relacionada ao consumo da cafeína. Também não foram encontrados instrumentos validados no intuito de diferenciar o fenótipo relacionado aos polimorfismos genéticos rs762551 (−163C> A) no gene *CYP1A2* que codifica a enzima citocromo P450 família 1 subfamília A membro 2, e o rs5751876 (1976T> C) no gene *ADORA2A* que codifica para o receptor de adenosina 2A2, interferem no metabolismo e na percepção cerebral a cafeína, respectivamente. Portanto, buscou-se validar um instrumento para avaliação das expectativas

relacionadas ao consumo da cafeína no Brasil e, a partir disso, surgiu a hipótese que o instrumento CaffEQ-BR pode ter capacidade discriminatória em relação aos polimorfismos dos genes *CYP1A2* e *ADORA2A* de acordo com o fenótipo apresentado aos efeitos da cafeína.

2. REVISÃO DA LITERATURA

2.1 A cafeína, suas fontes e metabolização

A cafeína (1,3,7-trimetilxantina) é um pseudoalcalóide da família das metilxantinas, que possui como fórmula $C_8H_{10}N_4O_2$ e massa molar de 198,19 g/mol. Em temperatura ambiente, a cafeína se apresenta em forma de pó incolor, inodoro e branco, possuindo como característica organoléptica mais perceptível um sabor amargo (FARAH, 2019; VERSTER; KOENIG, 2018). Ela está naturalmente presente no café (*Coffea sp.*), na planta do chá-da-índia (*Camellia sinensis*), no guaraná (*Paullinia cupana*), no cacaueiro (*Theobroma cacao*), dentre outras fontes. Frequentemente é incorporada a bebidas energéticas, múltiplos medicamentos e suplementos alimentares (HECKMAN; WEIL; DE MEJIA, 2010; WICKHAM; SPRIET, 2018; DEPAULA; FARAH, 2019).

Segundo Nehlig (2018), a cafeína é rapidamente absorvida no trato gastrointestinal (aproximadamente 45 minutos), sendo 80% absorvida no intestino delgado e cerca de 20% absorvida ainda no estômago. Uma pequena fração é metabolizada por agentes orais ou após sua absorção no intestino delgado via circulação porta hepática. A maior parte logo que absorvida entra rapidamente em todos os tecidos do corpo e atravessam livremente a barreira hematoencefálica, placentária e testiculares. Com meia vida plasmática de 2 a 8 horas, os principais metabólitos da cafeína em humanos são a paraxantina, teobromina e teofilina (NEHLIG, 2018).

A paraxantina, principal metabólito da cafeína, sofre desmetilação do N-3 e catalisação principalmente pelo citocromo P-450 (*CYP1A2*). A atividade do *CYP1A2* é responsável por 95% da metabolização da cafeína. Paraxantina, teofilina e teobromina mais adiante são metabolizadas e depois excretadas na urina na forma de ácido 1metil úrico (NEHLIG, 2018; PURKIEWICZ et al., 2022). Com a fácil difusão da cafeína para

todos os tecidos, sua ação age sobre o SNC, como antagonista dos receptores de adenosina A1 e A2A, que são expressos principalmente nos gânglios da base, envolvida na atividade motora (MUÑOZ et al., 2020; NEHLIG, 2018). Por isso seu consumo está intimamente associado a sua ergogenicidade no esporte (GRGIC et al., 2021) e nos ambientes de trabalho e estudos (ÁGOSTON et al., 2018a).

2.2 Consumo de café e cafeína no Brasil e seus fatores determinantes

A cafeína é a substância psicoativa mais consumida no mundo (REYES; CORNELIS, 2018), consumida principalmente por meio do café, que faz parte do hábito do brasileiro (PEREIRA et al., 2015; SOUSA; DA COSTA, 2015). A cultura do café no Brasil tem origem histórica em sua capacidade produtiva, pois é o maior exportador de café do mercado mundial (INTERNATIONAL COFFEE ORGANIZATION. TRADE STATISTICS., 2019). A produção de café no Brasil corresponde a um terço da produção mundial, tornando-se o maior produtor mundial, posição que ocupa há mais de 150 anos, sendo um dos produtos responsáveis pela modernização, urbanização e desenvolvimento de algumas cidades (TOLEDO, 2012). O café é uma bebida amplamente apreciada em todo o país, o consumo anual per capita brasileiro é de 6,02 kg, o que representa 13% da demanda mundial (ASSOCIAÇÃO BRASILEIRA DE INDUSTRIA DO CAFÉ - ABIC, 2019). O fácil acesso ao café influencia naturalmente a cultura de consumo dos brasileiros (SOUZA et al., 2013). O café é a principal bebida consumida no Brasil, com média de 163 ml por dia, sendo também o segundo alimento mais consumido, sendo a região Nordeste a maior consumidora de café (PEREIRA et al., 2015; SOUSA; DA COSTA, 2015).

No Brasil e no mundo, a principal fonte de cafeína é o café (REYES; CORNELIS, 2018). Globalmente, o consumo habitual de café varia de cerca de uma a

mais de cinco xícaras por dia, o que indica que a dose diária pode ser definida por vários motivos, como estilo de vida, gênero, expectativa dos efeitos da cafeína, cultura, genética, efeitos na saúde, entre outros (BOOLANI et al., 2020; DHARMASENA; CAPPS; CLAUSON, 2011; DÓREA; DA COSTA, 2005; KOLB; KEMPF; MARTIN, 2020). A cafeína está presente como princípio ativo no café, mas também em outros produtos como mate, guaraná, cacau e seus derivados (HECKMAN; WEIL; DE MEJIA, 2010; DEPAULA; FARAH, 2019).

E esses alimentos também estão presentes no hábito dos brasileiros, com consumo enraizado na cultura em regiões específicas do Brasil. Como exemplo, o consumo per capita de erva-mate no Brasil é estimado em 1,2 kg por ano, consumidos na forma quente, denominado "Chimarrão" na região sul, e o mate frio denominado "Terere" na região Centro-Oeste (GEBARA et al., 2017). Já o extrato de guaraná é majoritariamente consumido na região Norte do Brasil, com per capita nacional de 20 gramas ao ano (SCHIMPL et al., 2013). O chocolate é a forma mais comum de consumo do cacau, hábito mais frequente nas regiões produtoras no sul e sudeste do país, mas é disseminado por todo o país com consumo per capita de aproximadamente 2,7 kg ao ano (BRASIL. MINISTÉRIO DA INDÚSTRIA, 2018).

As diferenças na individualidade biológica, nos fatores culturais e nas respostas do organismo associadas ao consumo de cafeína podem influenciar os hábitos de consumo de cafeína (ÁGOSTON et al., 2018a; MAHONEY et al., 2019). Portanto, a ingestão de produtos que contenham cafeína não está associada apenas às suas características sensoriais e hábitos alimentares, mas também às expectativas associadas aos efeitos da cafeína no organismo (HEINZ; KASSEL; SMITH, 2009; HUNTLEY; JULIANO, 2012; ÁGOSTON et al., 2018; CHAN; MAGLIO, 2019).

Há evidências na literatura científica que o efeito placebo associado à suplementação de cafeína estão provavelmente relacionados à expectativa que os indivíduos apresentam em torno dos efeitos da cafeína no organismo. Os autores Beedie et al. (2006) e Saunders et al. (2017) conduziram estudos duplo-cegos que mostraram o efeito do tratamento com placebo percebido como cafeína melhoraram o desempenho nos exercícios de forma semelhante quando comparados com a ingestão de cafeína. A expectativa positiva associada à ingestão de cafeína pareceu impulsionar esse efeito, uma vez que os indivíduos que acreditam que ingeriram cafeína aumentaram a percepção de efeito médio da cafeína (BEEDIE et al., 2006; SAUNDERS et al., 2017). No entanto, esses resultados não foram observados em variáveis fisiológicas, como frequência cardíaca e pressão arterial (DÖMÖTÖR; SZEMERSZKY; KÖTELES, 2015), reforçando ainda mais a noção de que o efeito esperado no organismo após o consumo da cafeína desempenha um papel subjetivo na crença em torno do seu consumo (SHABIR et al., 2018). Em relação à expectativa relacionada aos efeitos da cafeína no organismo, fatores como motivação e crença podem influenciar a resposta ergogênica da cafeína em adultos (SHABIR et al., 2018). Portanto, as expectativas associadas ao consumo/resultado da cafeína podem desempenhar um papel importante no desenvolvimento, manutenção e reforço de seus padrões de consumo e essa expectativa de efeito da cafeína parece ser ainda maior em atletas e desportistas (HEINZ; KASSEL; SMITH, 2009; HUNTLEY; JULIANO, 2012; SHABIR et al., 2018; ÁGOSTON et al., 2018; GRGIC, 2021).

Estudos verificaram associação entre o consumo habitual de cafeína com mudanças no humor, apetite, sono/vigilância, desempenho de exercícios e outros fatores (HUNTLEY; JULIANO, 2012; SCHOTT; BEIGLBÖCK; NEUENDORFF, 2016; KEARNS et al., 2018; ROWE et al., 2020; GRGIC, 2021). A ingestão total de cafeína

em homens geralmente é maior, como observados por vários estudos (SOUSA; DA COSTA, 2015 GIOVANINI DE OLIVEIRA SARTORI; VIEIRA DA SILVA, 2016; CHAN; MAGLIO, 2019). Provavelmente, essas diferenças de gênero estão relacionadas a fatores culturais e comportamentais em homens, bem como às diferenças nas respostas fisiológicas à cafeína (DENDEN et al., 2016; DILLON et al., 2019; TEMPLE; ZIEGLER, 2011). Outro aspecto relevante é a influência da cultura local sobre o consumo alimentar, como nas Américas e Europa, o fácil acesso e disponibilidade das bebidas cafeinadas, podem aumentar o seu consumo, reforçando assim o hábito (ÁGOSTON et al., 2018a; DEPAULA; FARAH, 2019; REYES; CORNELIS, 2018).

Outros determinantes também estão associados ao reforço no consumo de fontes de cafeína. Os autores Chan & Maglio (2019), reforçam a tese de que a exposição a estímulos relacionados ao café e chás estimulantes podem aumentar a excitação, mesmo na ausência de ingestão real. Nas sociedades ocidentais, o café está associado a uma maior excitação comparado ao chá, e o inverso ocorre entre os orientais. Assim, os autores observaram que a exposição ao café (vs. preparar chá) sugere maior aumento da excitação mental que aqueles observados entre os consumidores habituais de chá. Isso pode ser explicado em parte pelo maior teor de cafeína e experiências sensoriais com café, ou com o perfil do consumidor ocidental (CHAN; MAGLIO, 2019).

Diversas organizações de saúde avaliaram a segurança do consumo da cafeína, certificando-se da ingestão aguda e diária estimada a qual não acarreta prejuízos para a população saudável em geral, e populações específicas, como atletas (DHARMASENA; CAPPS; CLAUSON, 2011; MAUGHAN et al., 2018; VERSTER; KOENIG, 2018).

O consumo da cafeína pode ocasionar efeitos adversos leves a moderados em curto e longo prazo (GRGIC, 2021; TEMPLE; DEWEY; BRIATICO, 2010; WIKOFF et al., 2017). Em curto prazo, está relacionado a distúrbios do SNC favorecendo

episódios de ansiedade, mudanças comportamentais, interrupção de sono, e até a presença de cafeína no leite materno (ÁGOSTON et al., 2018b; GUEST et al., 2021; PURKIEWICZ et al., 2022). Em longo prazo, o consumo excessivo de cafeína (> 400 mg/dia) está relacionado com as doenças cardiovasculares (sobretudo aumento da pressão arterial) e em mulheres grávidas pode ser observado um desenvolvimento anormal do feto (DÖMÖTÖR; SZEMERSZKY; KÖTELES, 2015; TEMPLE; DEWEY; BRIATICO, 2010; WIKOFF et al., 2017).

Dessa forma, instrumentos validados que consigam apresentar uma tendência de perfil de consumo são de interesse para profissionais de saúde, e é preconizado pela Organização Mundial da Saúde (OMS) (WORLD HEALTH ORGANIZATION, 2014). Ademais, destaca-se a importância de se avaliar as expectativas associadas ao consumo dos alimentos fontes de cafeína na população, por se tratar da substância psicoativa lícita mais consumida no Brasil e no mundo (REYES; CORNELIS, 2018), com alimentos fonte amplamente comercializados e consumidos (ASSOCIAÇÃO BRASILEIRA DE INDUSTRIA DO CAFÉ - ABIC, 2019; SOUSA; DA COSTA, 2015).

2.3 Questionário para avaliar a expectativa aos efeitos da cafeína

Frequentemente, profissionais e especialistas em saúde necessitam medir estados subjetivos, como atitudes, sentimentos, qualidade de vida, desempenho e aptidão de seus pacientes (VOGELZANG, 2015). Técnicas de escalas de medição, com utilização de análise fatorial exploratória e confirmatória, são aplicadas no desenvolvimento de escalas para medir resultados em saúde às vezes não tangíveis por outros métodos objetivos (PASQUALI, 2009; VOGELZANG, 2015).

A esse respeito, alguns questionários validados para o monitoramento do consumo da cafeína e percepção dos seus efeitos foram publicados nas últimas décadas, se apoiando no pressuposto de que as expectativas de resultados para o uso da cafeína sejam à base das propriedades de reforço do seu consumo. Os autores Heinz et al. (2009) em estudo em duas fases com 89 indivíduos propuseram um questionário com 37 itens para examinar a expectativa aos efeitos da cafeína compreendendo quatro fatores: (i) "sintomas de abstinência" ($\alpha = 0.91$), (ii) "efeitos positivos" ($\alpha = 0.90$), (iii) "efeitos negativos agudos" ($\alpha = 0.89$) e (iv) "efeitos do humor" ($\alpha = 0.87$). Seus resultados apresentaram correlação significativa e positiva entre os escores do instrumento e o padrão de consumo (195 ± 112 mg/dia). A limitação desse estudo foi a necessidade de uma amostra mais heterogênea para avaliar a confiabilidade e a validade da medida, em um amplo contexto populacional (HEINZ; KASSEL; SMITH, 2009).

Posteriormente, Huntley e Juliano (2012) com base em dois estudos preliminares com participação de 1.046 indivíduos, propuseram o *Caffeine Expectancy Questionnaire*, um questionário estruturado baseado em uma revisão detalhada da literatura e uma série de estudos preliminares para construção dos itens. Uma amostra independente de 665 indivíduos completou o CaffEQ e outras medidas, e uma subamostra (n = 440) completou o CaffEQ novamente aproximadamente 2 semanas depois. A análise fatorial confirmatória revelou um bom ajuste do modelo e a confiabilidade teste-reteste foi muito boa ($\alpha = 0.96$). A versão final do CaffEQ (originalmente em inglês, projetado para os Estados Unidos da América - EUA) inclui 47 itens, avaliados por meio de uma escala *Likert* de seis pontos (de "muito improvável" a "muito provável"), distribuídos em sete fatores: (i) "dependência", (ii) "melhoria de energia/trabalho", (iii) "supressão do apetite", (iv) "melhora social/do humor", (v) "melhora do desempenho físico", (vi) "ansiedade/efeitos físicos negativos" e (vii)

"distúrbios do sono" (HUNTLEY; JULIANO, 2012). Seus resultados apresentaram correlação significativa e positiva entre os escores do instrumento e o padrão de consumo (323 ± 297 mg/dia) observado em uma população mais jovem, contendo muitos estudantes universitários. Além de ser utilizado na língua inglesa, o CaffEQ também foi traduzido e validado para países de língua alemã (Alemanha, Suíça e Áustria) pelos autores Schott et al. (2016) que apresentou excelentes medidas de reprodutibilidade e consistência (n = 352; α = 0,98), que se correlacionou positiva e significativamente com padrão de consumo observado (236 ± 235 mg/dia) (SCHOTT; BEIGLBÖCK; NEUENDORFF, 2016). Após a validação do CaffEQ, Kearns et al. (2018) propuseram uma versão curta do questionário, reduzido de 47 para 20 itens preservando os 7 domínios originais, com consistência interna e externa melhor que o CaffEQ original, afirmando que o uso de questionários curtos tem melhor aceitação do público-alvo, principalmente no contexto de autopreenchimento (KEARNS et al., 2018).

No entanto, como a validação e padronização do questionário CaffEQ foram realizadas apenas para populações de língua inglesa e alemã, atualmente não há estudos com países da América Latina utilizando o CaffEQ devido às barreiras linguísticas e diferenças culturais que dificultam a aplicação do questionário original. Nesse sentido, até o momento, nenhum estudo se propôs a avaliar as expectativas quanto aos efeitos da cafeína na população brasileira devido à falta de um questionário válido na língua portuguesa do Brasil.

A importância da elaboração de versões curtas de questionários está relacionada prioritariamente à economia de tempo e recursos, assim como a melhor adesão dos participantes. Completar um questionário está inversamente associado à carga de resposta e um dos principais fatores que afetam a carga de resposta é tamanho do

questionário (número de itens e volume de texto) (ROLSTAD; ADLER; RYDÉN, 2011).

2.4 Percepção subjetiva aos efeitos da cafeína e variabilidade genética

Os efeitos no desempenho físico e cognitivo proporcionados pelo consumo da cafeína tem relação com a sua metabolização hepática e ação nos receptores A1, A2A e A2B da adenosina em tecidos extra-hepáticos, especialmente no SNC e periférico (MUÑOZ et al., 2020).

Esse efeito ocorre devido à regulação de uma enzima hepática chave do metabolismo da cafeína pelo citocromo P450. A enzima hepática citocromo P450 1A2 (*CYP1A2*) é responsável por aproximadamente 95% do metabolismo da cafeína, enquanto a cafeína exerce muito dos seus efeitos via ligação antagonista aos receptores da adenosina A2A (*ADORA2A*) (NEHLIG, 2018). Por isso a relevância em examinar os polimorfismos de nucleotídeo único funcional (em inglês, *single nucleotide polymorphism;* SNP) em *CYP1A2* (SNP rs762551 -163C > A) e *ADORA2A* (SNP rs5751876 1976T > C) para detectar suas influências sobre os efeitos da cafeína no organismo (GUEST et al., 2021). Os mais recentes estudos associam diferenças na resposta ergogênica à ingestão aguda de cafeína a uma distribuição entre os alelos do gene *CYP1A2* (−163C> A, rs762551) caracterizado como metabolizadores de cafeína "rápidos" (genótipo AA) e "lentos" (portadores do alelo C) com uma distribuição entre os genótipos estimada de 56% e 44%, respectivamente (GRGIC et al., 2020b; GUEST et al., 2020). Para o gene *ADORA2A* (1976T > C; rs5751876) caracterizado por "alta" (genótipo TT) ou "baixa" sensibilidade à cafeína (portadores do alelo C), a literatura aponta uma distribuição de 61% e 39%, respectivamente (GRGIC et al., 2020a; MUÑOZ et al., 2020).

Na última década, um número crescente de estudos estão se debruçando sobre a associação da variabilidade genética em torno na metabolização e ação da cafeína e seus efeitos sobre o desempenho físico e cognitivo (GRGIC et al., 2021; GUEST et al., 2021). Em uma cronologia de publicações, inicialmente os autores Womack et al.(2012), Loy et al. (2015), Salinero et al. (2017) e Puente et al. (2018) realizaram ensaios clínicos controlados com uso do placebo e cafeína, nas mais diferentes doses ergogênicas (3 – 6 mg/kg peso), comparando seu efeito conforme o polimorfismo dos genes *CYP1A2* e *ADORA2A*, relativos à metabolização e à ação da cafeína no organismo dos participantes desses experimentos (LOY et al., 2015; PUENTE et al., 2018; SALINERO et al., 2017; WOMACK et al., 2012). O que se observa, assim como descrito claramente no estudo de Salinero et al. (2017) e Puente, et al. (2018), é que os efeitos positivos sobre a ergogenicidade e cognição da cafeína estão associadas ao polimorfismo do genótipo AA para o gene *CYPA12*, que apresenta rápida metabolização da hepática da cafeína. Já os sintomas negativos percebidos com a suplementação aguda de cafeína podem estar associados a outro gene relacionado à sensibilidade à cafeína, *ADORA2A*. Segundo Grgic et al., (2019), há uma associação entre as sensações negativas da cafeína com a alta sensibilidade na ação da cafeína nos receptores de adenosina, ou seja, os portadores homozigotos TT para *ADORA2A* (GRGIC et al., 2020a).

Os autores Rahimi et al. (2018), Guest, et al. (2018), e Giersch et al. (2018) encontraram resultados controversos sobre a associação da rápida metabolização da cafeína e melhor ergogenicidade da cafeína, uma comparação entre os portadores do genótipo AA e os portadores do alelo C (GIERSCH et al., 2018; GUEST et al., 2018; RAHIMI R., 2018).

Por fim, os autores Grgic et al. (2020), Carswell et al. (2020) e Muñoz et al. (2020), usando dose de cafeína no padrão 3 mg/kg peso, avaliando polimorfismo do gene *CYPA12* em modelos experimentais cruzados controlados por placebo, observaram melhores resultados para os portadores do genótipo AA, e baixa associação de melhora cognitiva ou ergogênica para genótipo TT no gene *ADORA2A* associado a alta sensibilidade para cafeína (CARSWELL et al., 2020; GRGIC et al., 2020b, 2020a; MUÑOZ et al., 2020).

Após essa revisão cronológica da literatura verifica-se em pesquisas científicas, e na prática clínica, a manifestação dos resultados nulos ou controversos dos indivíduos considerados *outlayer* (GRGIC, 2018). Esses são, por definição, participantes de pesquisas e pacientes que não se mostram responsivos aos efeitos da cafeína, pelo menos a expectativas de efeitos apresentados nos *guidelines* (MAUGHAN et al., 2018; PICKERING; KIELY, 2018). Possivelmente porque, até pouco tempo, a literatura científica sobre o uso de cafeína não abordava a variação interindividual na ergogenicidade da cafeína, o que justifica o crescente interesse científico nessa temática (GRGIC et al., 2021; GUEST et al., 2021). Assim, destaca-se a importância de estudos de validação de instrumento capaz de discriminar o polimorfismo genético com base nas expectativas de efeito da cafeína, como uma alternativa de baixo custo, rápida e prática aplicação e menos invasiva.

3. OBJETIVOS

3.1 Objetivo Geral

Este estudo teve como objetivo avaliar a capacidade do CaffEQ-BR na diferenciação dos polimorfismos dos genes *CYP1A2* e *ADORA2A*, conforme as expectativas de efeito da cafeína medidas pelo instrumento.

3.2 Objetivos Específicos

- Validar um instrumento que avalie as expectativas aos efeitos da cafeína para o Brasil;
- Avaliar as expectativas de efeito da cafeína em participantes adultos brasileiros;
- Desenvolver a versão curta do instrumento;
- Analisar a capacidade do CaffEQ-BR para a discriminação do perfil genético dos participantes em função dos diferentes polimorfismos dos genes *CYP1A2* e *ADORA2A*.

4. MÉTODOS

4.1 Tipo do estudo e aspectos éticos

Trata-se de um estudo prospectivo de observação de dados primários, dividido em três fases: a primeira fase foi composta por (i) Tradução, adaptação cultural e avaliação semântica; (ii) Análise de consistência interna e reprodutibilidade do CaffEQ-BR; (iii) Aplicação CaffEQ-BR em todo o Brasil. A segunda fase foi composta por validar a versão curta do CaffEQ-BR, se propondo em reduzir pela metade o número de itens em relação a versão completa.

A terceira e última fase foi composta por um estudo quantitativo, transversal e observacional, que se propõe a explorar as aplicações do CaffEQ-BR em discriminar os polimorfismos dos genes *CYP1A2* e *ADORA2A*, conforme os registros de expectativa aos efeitos da cafeína de participantes que realizaram a genotipagem previamente por meio de parceria com os pesquisadores da Universidade de São Paulo (USP) e da Universidade Federal de Alagoas (UFAL), que realizaram a coleta de amostras biológicas, extração de DNA e o sequenciamento genético e determinação dos polimorfismos para os genes *CYP1A2* (rs762551) e *ADORA2A* (rs5751876).

As fases do estudo relacionado à tradução, validação e aplicação do questionário em território nacional, foi aprovada pelo Comitê de Ética em Pesquisa (CAAE: 23019319.3.0000.0029) (ANEXO A) destacado junto ao Termo de Consentimento Livre e Esclarecido – TCLE (APÊNDICE A) e seguiu as diretrizes estabelecidas pela Declaração de Helsinki. Os voluntários foram informados sobre o protocolo do estudo e forneceram seu consentimento no formulário online.

4.2 Tradução, adaptação cultural e avaliação semântica

Em função da necessidade de avaliar as expectativas em relação aos efeitos da cafeína na população brasileira, foi realizada uma busca de um questionário validado para essa finalidade. Para esse fim, o questionário *Caffeine Expectancy Questionnaire* foi selecionado em função de ter sido elaborado por meio de uma revisão detalhada da literatura em conjunto com uma série de estudos preliminares para sua construção (HUNTLEY; JULIANO, 2012).

Esse questionário foi traduzido para o português passando por uma adaptação semântica e cultural ao perfil da população brasileira, de acordo com as recomendações da Organização Mundial da Saúde (OMS) (WORLD HEALTH ORGANIZATION, 2014). Um pesquisador bilíngue nativo em português foi convidado para traduzir a versão original do CaffEQ (em inglês) para o português do Brasil. O convite se estendeu a outro pesquisador bilíngue, nativo da língua inglesa (residente no Brasil), sem conhecimento da obra original, para fazer a retradução da versão em português do Brasil feita pelo primeiro tradutor novamente para o inglês. Em seguida, três pesquisadores compararam a versão retraduzida em inglês com o questionário original e analisaram a versão traduzida para o português do Brasil. Ajustes semânticos foram realizados em caso de não conformidade. A versão final foi revisada pelos tradutores bilíngues como etapa final do processo de tradução.

O questionário foi posteriormente analisado e revisado por um painel de profissionais especialistas em saúde (n = 20) compostos por mestres, doutores e pós-doutores. Os especialistas analisaram individualmente a adaptação cultural e avaliação semântica usando parâmetros de 'importância' e 'clareza' de cada item do questionário (n = 47) em escala *Likert* de cinco pontos, onde 1 indica "discordo totalmente do item"; 2— "Discordo parcialmente do item"; 3— "Não concordo nem discordo do item"; 4— "Concordo parcialmente com o item"; e 5— "Concordo plenamente com o item". O

objetivo foi alcançado quando foi obtido mais de 80% de concordância entre os especialistas (*Likert* com média > 3) para cada questão (MEIJERING; KAMPEN; TOBI, 2013). Os itens que não atingiram concordância foram ajustados de acordo com as observações dos especialistas e devolvidos a eles para nova análise. Esse processo ocorreu até que todos os itens obtiveram pelo menos 80% de concordância com média na escala *Likert* > 3. O grau de concordância entre os especialistas na avaliação da 'importância' e 'clareza' das questões foi realizado pelo coeficiente de correlação de Kendall (W) variando de 0 a 1. Um valor $W \geq 0,66$ indica que os especialistas aplicaram os mesmos padrões de avaliação e valores de W <0,66 sugerem discordância entre os especialistas. Para a aprovação de um item, foi considerado necessário que pelo menos 80% de concordância entre os especialistas (valores de $W \geq 0,8$) (MEIJERING; KAMPEN; TOBI, 2013).

4.3 Consistência interna e reprodutibilidade

A consistência interna e reprodutibilidade do instrumento traduzido e adaptado (CaffEQ-BR) foi analisada antes da aplicação nacional, pois, antes da aplicação em uma amostra grande, é importante testar a reprodutibilidade (confiabilidade) e consistência interna com um tamanho amostral reduzido. A consistência interna refere-se à variação nas medições feitas sob condições de mudança e a reprodutibilidade avalia a concordância entre quaisquer duas medições feitas no mesmo sujeito (HAIR et al., 2010).

Dessa forma, o questionário foi aplicado por meio da plataforma *online* Google Forms® em uma amostra de conveniência (n= 50) de adultos brasileiros (> 19–59 anos) consumidores regulares de diversas fontes de cafeína. Os participantes foram convidados por meio de anúncios nas mídias sociais (Facebook®, Instagram® e

WhatsApp®). O questionário foi respondido duas vezes (teste-reteste) por cada pessoa. O segundo questionário foi enviado 24 horas após o envio do primeiro questionário e solicitado sua devolução ao menos nas próximas 48 horas para sua inclusão amostral (prazo máximo, 15 dias após o segundo envio). O procedimento de teste-reteste avaliou a reprodutibilidade do questionário. É importante destacar que os participantes não foram previamente informados que iriam responder o questionário uma segunda vez. A análise da confiabilidade teste-reteste (reprodutibilidade) foi realizada pelo coeficiente de correlação intraclasse (em inglês, *intraclass correlation coefficient* – ICC) e a consistência interna dos fatores foram verificadas pelo coeficiente alfa de Cronbach (α) (CICCHETTI, 1994; STREINER; STREINER, 2016).

4.4 Aplicação nacional do CaffEQ-BR

Para validar o CaffEQ-BR no Brasil e avaliar a população adulta brasileira quanto às expectativas em relação aos efeitos da cafeína, foi utilizado um questionário composto por três partes: (1) questões sociodemográficas e de saúde; (2) avaliação do consumo de cafeína; e (3) o CaffEQ-BR. De acordo com Hair et al. (2010), o processo de validação de um questionário requer 20 respondentes por item (20:1). Nesse sentido, o tamanho mínimo da amostra foi estimado em 940 participantes para validar o CaffEQ-BR, que é composto por 47 itens. Além disso, por se tratar de um estudo de validação externa nacional, o tamanho da amostra adotou para o cálculo, o último censo nacional brasileiro (IBGE, 2010), com adequação maior ou igual a 70% da distribuição da amostra segundo as Unidades Federativas (UF) do Brasil. Por exemplo, o estado do Rio de Janeiro, a população de 17.264.943, representa 8,22% da população do Brasil. Portanto, a amostra para obter 100% de adequação, deve ter 8,22% de sua amostra total

composta por participantes do estado do Rio de Janeiro. Dessa forma, a amostra foi balanceada entre as UF do Brasil.

O questionário foi aplicado por meio da plataforma *online* Google Forms® a uma amostra de conveniência de adultos brasileiros de todas as 27 unidades federativas. Os participantes foram recrutados por publicidade nas redes sociais, em páginas criadas especificamente para divulgação da pesquisa (Facebook®, Instagram® e WhatsApp®), estratégia utilizada de acordo com o estudo de Schott et al. (2016) que validaram o CaffEQ para língua germânica.

A página inicial da pesquisa *online* apresentou o termo de consentimento livre e esclarecido com detalhes dos critérios de inclusão: (1) adultos (19-59 anos) residentes no Brasil; (2) consumidor regular de fontes de cafeína (pelo menos três vezes por semana), essa informação foi posteriormente confirmada pelo questionário de do consumo de cafeína.

Aqueles que não concordaram em participar da pesquisa foram direcionados para uma página de agradecimento, enquanto os que concordaram foram direcionados para a primeira página do questionário com questões sociodemográficas e relacionadas à saúde, em seguida, avaliação do consumo de cafeína e então o CaffEQ-BR (APÊNDICE B).

4.5 Dados sociodemográficos e de saúde

As variáveis sociodemográficas autorreferidas (APÊNDICE C) foram registradas: gênero, autoidentificação de etnia, estado da federação de residência atual, maior nível de escolaridade e renda familiar média mensal (R$). As variáveis referentes aos aspectos de saúde autorreferidos: altura (m) e peso (kg), ≥150 min de exercício físico semanal e diagnóstico prévio de doenças crônicas com a medicação em uso.

4.6 Consumo autorreferido de cafeína

O questionário de avaliação do consumo de cafeína foi utilizado para avaliar a quantidade de cafeína consumida nas últimas duas semanas antes do preenchimento do questionário (ANEXO B). Esse questionário foi obtido a partir de uma tradução literal e adaptação do *Caffeine Consumption Questionnaire* proposto incialmente por Shohet e Landrum (2001), e mais tarde validado por Irons et al. (2016) (IRONS et al., 2016; SHOHET; LANDRUM, 2001). Os participantes foram solicitados a indicar o número de porções em uma lista categorizada em oito grupos de fontes de cafeína: 1. café filtrado ou expresso, quente ou gelado; 2. chás fontes de cafeína como mate, chá verde e chá preto; 3. chocolate com teor ≥ 50% cacau; 4. bebidas de chocolate com teor ≥ 50% de cacau; 5. refrigerantes à base de noz de cola ou guaraná; 6. medicamentos associados com cafeína; 7. bebidas energéticas contendo cafeína ou bebida com extrato de guaraná; 8. suplementos esportivos contendo cafeína. Doses padronizadas de café, em medidas caseiras, foram adotadas conforme estudo de referência nacional (BRASIL, 2010). O tamanho típico da porção e os valores de cafeína foram baseados nas informações do fabricante dos produtos e em tabela de composição dos alimentos (DEPAULA; FARAH, 2019; DHARMASENA; CAPPS; CLAUSON, 2011).

4.7 Análise Estatística

A reprodutibilidade do questionário entre o comparativo teste e reteste foi analisada pelo ICC. O mesmo processo foi realizado para os sete fatores do questionário. Dessa forma foi possível considerar o questionário (e seus itens) como reprodutível quando valor de ICC for maior que 0,7 (CICCHETTI, 1994).

O cálculo de alfa de Cronbach foi utilizado para verificar a consistência interna dos domínios do questionário, onde valor maior que 0,8 indica que os domínios são consistentes (STREINER; STREINER, 2016). Para o cálculo do alfa de Cronbach (α) foi considerado como referência o primeiro questionário enviado. A análise fatorial confirmatória para verificação da validade dos fatores foi avaliada pela raiz quadrada média do erro de aproximação (em inglês, *Root Mean Square Error of Approximation* – RMSEA). O RMSEA varia de 0 a 1, onde o valor 0 indica um ajuste perfeito do modelo e um valor de 0,05 ou menos é indicativo de um ajuste de modelo aceitável. A ingestão de cafeína foi expressa como média ± desvio padrão (DP). O teste de Shapiro-Wilk foi usado para avaliar a normalidade da distribuição. O teste *t* para amostras independentes foi utilizado para comparar as médias entre os sexos. Todos os testes foram realizados considerando nível de significância de 5%. Foram utilizados para as análises os pacotes estatísticos IBM SPSS® (*Statistical Package for Social Sciences*) versão 22 (IBM SPSS *Statistics* para Windows, IBM Corp, Armonk, NY, EUA) e IBM SPSS AMOS® (*Analysis of Moment Structures*) versão 22 (Amos, IBM SPSS, Chicago, IL, EUA).

4.8 CaffEQ-BR versão curta

A versão curta do questionário foi obtida combinando procedimentos qualitativos e quantitativos. Na análise qualitativa, os especialistas confirmaram a relevância do item, quando de forma unânime concordaram que deve manter ou excluir o item, até restarem três itens por fator nesse processo de afunilamento em várias etapas. A análise quantitativa selecionou todas as possíveis versões com três itens por fator cujos fatores apresentarem um *Mean Absolute Error* – MAE (com base na versão completa) menor do que 0,5 e consistência interna alfa de cronbach ≥ 0,8 (STREINER; STREINER, 2016; WILLMOTT; MATSUURA, 2005). O MAE representa a

divergência média dos escores das versões curta e completa, sendo que o valor zero indica concordância perfeita. A condição MAE < 0,5 significa que, em média, essa divergência é menor do que 0,5 (ou 10% em uma escala de cinco pontos, por exemplo) (WILLMOTT; MATSUURA, 2005).

Finalmente, a versão curta selecionada foi aquela aprovada pelo método quantitativo e que mais se aproximou da seleção do grupo de especialistas. Após essa etapa foi avaliada a versão curta do CaffEQ-BR em contraste com o CaffEQ-BR completo. Para isso foi selecionada uma nova amostra de adultos brasileiros (n = 80) consumidores regulares de cafeína. Desses, 20 participantes aleatoriamente preencheram o CaffEQ-BR completo, e depois de 48h foram convidados a preencher a versão curta do CaffEQ-BR. A outra subamostra (n = 20) fez o processo inverso, e responderam inicialmente a versão curta do CaffEQ-BR e 48h depois o CaffEQ-BR completo. Finalmente, outra subamostra (n=40) responderam a versão curta do CaffEQ-BR duas vezes no intervalo de 48h para confirmar a consistência interna do instrumento, viabilizando o uso da versão curta do CaffEQ-BR após sua publicação.

4.9 CaffEQ-BR e determinação de polimorfismos nos genes CYPIA2 e ADORA2A

Para a terceira fase da pesquisa, a intenção foi verificar a capacidade do CaffEQ-BR (versão completa e curta) em discriminar os polimorfismos dos genes *CYP1A2* (rs762551) e *ADORA2A* (rs5751876), associado à expectativa aos efeitos da cafeína registrado pelo questionário. Para isso, foram convidados os atletas dos estudos de Spineli et al., (2020) (n = 100) e Barreto et al. (n = 50) (dados ainda não publicados). Os critérios de inclusão foram: (i) adulto brasileiro (19-59 anos), residente no Brasil, consumidor regular de cafeína (pelo menos 3x por semana) de diversas fontes, ter

aceitado participar do preenchimento das versões completa e curta do CaffEQ-BR; (ii) todos os participantes tiveram seus genótipos CYP1A2 −163C>A e ADORA2A 1976T>C determinados previamente.

No estudo de Spineli et al. (2020) os participantes eram atletas saudáveis, treinados, e em desenvolvimento que praticavam vôlei, atletismo ou futebol competitivo amador (idade: 15 ± 2 anos; altura: $1,69 \pm 0,10$ m; massa corporal: $58,8 \pm 11,9$ kg; VO2máx: $44,0 \pm 2,7$ ml·kg−1·min−1) (SPINELI et al., 2020). Enquanto o estudo de Barreto et al. (dados ainda não publicados) os participantes eram ciclistas saudáveis treinados, homens e mulheres (idade: 37 ± 6 e 40 ± 2 anos; altura: $1,76 \pm 0,04$ e $1,63 \pm 0,04$ m; massa corporal: $74,1 \pm 6,7$ e $61,5 \pm 7,3$ kg; V̇O2max: $51,1 \pm 5,2$ e $42,3 \pm 8,12$ ml·kg−1·min−1). É importante ressaltar que os atletas da pesquisa de Spineli et al. (2020) eram adolescentes durante o período de coleta do estudo original. A aplicação das versões do CaffEQ-BR ocorreu quatro anos depois e todos os voluntários tinham mais de 19 anos (adultos) no momento do preenchimento dos questionários.

A distribuição entre os genótipos geralmente inclui menos participantes homozigotos carregando os genótipos CC para *CYP1A2* e TT para *ADORA2A*, que representam menos de 10% e 20% da população, respectivamente (ERBLANG et al., 2019; GUEST et al., 2020). Assim, o objetivo foi obter uma amostra onde cada subgrupo de genótipo tivesse pelo menos 10 participantes. Considerando a formação de quatro subgrupos com pelo menos 10 portadores do alelo C (AC e CC) e genótipo (AA) para *CYP1A2* e portadores do alelo C (CT e TT) e genótipo (TT) *ADORA2A*, a amostra mínima seria de 40 participantes. No entanto, há uma predominância de genótipo AA para *CYP1A2* e portadores do alelo C para *ADORA2A*, e uma prevalência menor para CC para *CYP1A2*, e TT para *ADORA2A*. Portanto, buscou-se uma amostra superior a 40 participantes.

O questionário foi aplicado via Google Forms® e os participantes foram contatados por telefone, e-mail ou mídia social (Facebook®, Instagram® ou WhatsApp®). O período de coleta de dados ocorreu entre outubro de 2021 e abril de 2022. Antes de revelar os genótipos, como processo de cegamento, esses participantes responderam a versão completa e curta do CaffEQ-BR com intervalo mínimo de 48 horas e máximo de 15 dias entre o primeiro e o segundo questionário. A ordem de preenchimento dos questionários foi com um desenho contrabalanceado, em que parte da amostra iniciou com a versão completa e depois a versão curta, e a outra parte realizou a ordem inversa (MENDES et al., 2021). Dos 150 indivíduos convidados, 71 aceitaram e participaram da pesquisa.

Para as amostras do estudo de Spineli et al., (2020) os métodos de coleta de amostra biológica, extração e purificação do DNA, ampliação e análise genética dos procedimento de extração dos genes *CYP1A2* e *ADORA2A* e determinação dos polimorfismos foram descritos detalhadamente segundo artigos de referência na literatura (CORNELIS; EL-SOHEMY; CAMPOS, 2004; DECKERT et al., 1998). Para as amostras do estudo de Barreto et al. (dados ainda não publicados) os métodos de coleta de amostra biológica, extração e purificação do DNA, ampliação e análise genética dos procedimento de extração dos genes *CYP1A2* e *ADORA2A* e determinação dos polimorfismos foram descritos detalhadamente segundo artigos de referência na literatura (MUÑOZ et al., 2020; SALINERO et al., 2017). A genotipagem foi bem-sucedida em todos os participantes para *CYP1A2* (rs762551). Entretanto, cinco participantes do grupo de Spineli et al., (2020) não obtiveram sucesso na determinação do polimorfismo do gene *ADORA2A* (rs5751876).

Para análise estatística foram realizadas análises descritivas aplicando-se frequências e percentuais para variáveis categóricas e média e desvio padrão para

variáveis numéricas (escores CaffEQ-BR). A concordância do CaffEQ-BR entre as versões completa e curta foi verificada por meio do coeficiente de correlação intraclasse (ICC). O tipo de ICC adotado foi o de concordância absoluta, sendo considerada a média de concordância das duas aplicações. O cálculo do ICC foi baseado em um modelo misto de duas vias. De acordo com Cicchetti (1994), considera-se excelente concordância do ICC quando foi encontrado valor ≥ 0,75 pontos entre duas respostas (CICCHETTI, 1994). A capacidade do CaffEQ-BR em identificar a presença (ou ausência) dos genótipo dos genes *CPY1A2* e *ADORA2A* foi avaliada pela curva *receiver operating characteristic* – ROC (HAJIAN-TILAKI, 2013). A área sob a curva (*area under curve* – AUC) varia de 0 a 1, uma AUC = 0,5 indica que o CaffEQ-BR não possui capacidade de discriminação e AUC = 0 ou 1 corresponde à discriminação perfeita. Além disso, AUC 0,0-0,5 ou 0,5-1,0 indica que valores mais baixos/mais altos de CaffEQ-BR (respectivamente) indicam evidência de um estado positivo (HAJIAN-TILAKI, 2013).

Para avaliar a capacidade do CaffEQ-BR (versão completa e curta) em discriminar os genótipos dos genes *CYP1A2* e *ADORA2A*, as amostras foram agrupadas em *cluster* de dois níveis contendo portadores do alelo C e portadores do genótipo AA para *CYP1A2* e TT para *ADORA2A*. Assim como *cluster* de três níveis, sendo AA, AC e CC para *CYP1A2*, e TT, CT e CC para *ADORA2A*. Os genótipos só foram revelados após a análise estatística, como forma de cegamento de todo processo. As estimativas de ICC e AUC são apresentadas com seus respectivos intervalos de confiança de 95% e foram avaliadas pelo IBM SPSS Software versão 22 (IBM SPSS Statistics® for Windows, IBM Corp, Armonk, NY, EUA).

CAPÍTULO 2

Os resultados e discussão desta tese estão apresentados em forma de artigos científicos. Os artigos "*Translation and Validation of the Caffeine Expectancy Questionnaire in Brazil (CaffEQ-BR)*" (MENDES et al., 2020), "*Brief Version of Caffeine Expectancy Questionnaire in Brazil*" (MENDES et al., 2021) e "*Can the Brazilian Caffeine Expectancy Questionnaires differentiate the CYP1A2 and ADORA2A gene polymorphisms?*" (MENDES et al., 2022) foram publicados em 2020, 2021 e 2022.

5. RESULTADOS

5.1 1º ARTIGO PUBLICADO - MENDES, Guilherme Falcão, et al. Translation and validation of the caffeine expectancy questionnaire in Brazil (CaffEQ-BR). *Nutrients*, 2020, 12.8: 2248. https://doi.org/10.3390/nu12082248

![nutrients logo] MDPI

Translation and Validation of the Caffeine Expectancy Questionnaire in Brazil (CaffEQ-BR)

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Abstract: Caffeine is the world's most commonly used stimulant of the central nervous system. Caffeine is present in coffee and other beverages such as tea, soft drinks, and cocoa-based foods. The caffeine expectancy questionnaire was developed to investigate the effects of caffeine expectations and thus contribute to knowledge about its usage and subjective effects (response expectancies). This study aimed to evaluate caffeine expectation psychometrically in a sample of the Brazilian population. The original version of the "Caffeine Expectancy Questionnaire (CaffEQ)" was translated and validated into Brazilian-Portuguese and adapted to Brazilian culture to be used in the Brazilian adult (19–59 y) population. After the translation and back-translation processes of the original CaffEQ questionnaire, the content and semantic validation were performed by a group of experts. The Brazilian-Portuguese version of the questionnaire consists of 47 items, in seven factors, which assess subjective perceptions about the effects of caffeine. Interobserver reproducibility and internal consistency of the questionnaire were tested with a convenience sample ($n = 50$) of Brazilian adult consumers of caffeine sources, who completed the Brazilian CaffEQ (CaffEQ-BR) on two occasions separated by 24 h. All of the 47 questions were adequate regarding reliability, clarity, and comprehension. Psychometric properties could be replicated consistently. Appropriate internal consistency and validation were confirmed by Cronbach's alpha (α) 0.948, and an intraclass correlation coefficient of 0.976 was observed. The CaffEQ-BR was applied using a web-based platform to a convenience sample of Brazilian adults from all 27 Brazilian states ($n = 4202$ participants), along with measures of sociodemographic and caffeine consumption data. Factor validity was verified by confirmatory factor analysis. The seven factors presented a good fit for Root Mean Square Error of Approximation—RMSEA = 0.0332 (95% CI: 0.0290–0.0375). By confirming the validity and reliability of CaffEQ-BR, a useful tool is now available to assess caffeine expectations in the Brazilian adult population.

Keywords: caffeine; subjective; expectancy; instrument; validation; Brazilian; Portuguese

1. Introduction

Caffeine (1,3,7-trimethylxanthine) is the most widely consumed psychoactive substance in the world [1,2] with several guidelines addressing the form of use, dosage, and limits for safe consumption [3–5]. Worldwide, and in Brazil, caffeine intake occurs primarily through coffee consumption [1]. The estimation of the Brazilian population's average daily coffee intake is 163 mL [6], being the most consumed non-alcoholic drink in Brazil [7,8]. In addition, caffeine is also widely consumed in other foods and beverages such as cola, cocoa, chocolate, guarana, and in matte, black, and green teas [9]. Furthermore, a range of energy drinks and sports supplements also contain caffeine in their composition [5]. The differences in biological individuality and cultural factors can influence the habits of caffeine consumption [10,11]. Therefore, the ingestion of products that contain caffeine is not only associated with their sensorial characteristics and eating habits but also with caffeine effect expectations [12].

It is well established that placebo effects are associated with caffeine supplementation, likely due to an expectancy surrounding its effects. Double-blind studies have shown that participants receiving a placebo treatment perceived to be caffeine improved exercise performance to a similar extent when compared with caffeine ingestion [13,14]. Positive expectation associated with caffeine ingestion appeared to drive this effect since individuals correctly believing that they had ingested caffeine improved to a greater extent than the average effect of caffeine [13,15]. However, these results were not observed in physiological variables, such as heart rate and blood pressure [16], further reinforcing the notion that the expected effect of caffeine plays a subjective role in the belief around its consumption [16,17]. Regarding expectancy, factors such as motivation and belief can influence the ergogenic response of caffeine in adults [17]. Therefore, expectancies associated with caffeine use/outcome may play an important role in the development, maintenance, and reinforcement of its consumption patterns [12,18,19]. Studies have attempted to associate habitual caffeine consumption with changes in mood, appetite, sleep/alertness, exercise performance, and other factors [19–21]. Based on these observations, standardized questionnaires were constructed using psychometric techniques [22] to assess expectancy about caffeine consumption [19–21], or to evaluate the motives for caffeine consumption [12].

In this regard, Heinz et al. (2009) [18] proposed a questionnaire with 37 items to examine caffeine expectancy comprising four factors: 'withdrawal symptoms', 'positive effects', 'acute negative effects', and 'mood effects'. Subsequently, Huntley and Juliano (2012) [20] proposed the Caffeine Expectancy Questionnaire (CaffEQ), a structured questionnaire based on a detailed review of the literature and a series of preliminary studies for construction of the items. The final version of the CaffEQ (originally in English, designed for the United States of America) includes 47 items, evaluated using a six-point Likert scale, distributed across seven factors: 'withdrawal/dependence', 'energy/work enhancement', 'appetite suppression', 'social/mood enhancement', 'physical performance enhancement', 'anxiety/negative physical effects' and 'sleep disturbance'. Besides its use in the English language, the CaffEQ was also translated and validated for German-speaking countries (Germany, Switzerland, and Austria) by the authors Schott et al. (2016) [21].

However, since the validation and standardization of the CaffEQ questionnaire were performed only for English and German speaking populations [19–21], there are currently no studies with Latin American countries using the CaffEQ due to linguistic barriers and cultural differences that cause difficulties in using the original questionnaire. In this sense, there has been no study proposed to evaluate caffeine expectations in the Brazilian population due to the lack of a valid questionnaire in the Brazilian-Portuguese language. Therefore, this study aimed to translate, culturally adapt, and validate the CaffEQ to the Brazilian population (CaffEQ-BR), and also to evaluate caffeine expectations in Brazilian adult participants. We expect that this study can provide a questionnaire with internal and external validity to characterize caffeine expectations in the Brazilian adult population and be an easy questionnaire to incorporate into research and clinical contexts.

2. Materials and Methods

The present study used the original CaffEQ and translated it from the English version to Brazilian-Portuguese [20]. The CaffEQ is composed of 47 items, evaluated using a six-point Likert scale. In order to create the CaffEQ for the Brazilian population (CaffEQ-BR), our study was conducted in four stages: (1) Translation, Cultural Adaptation, and Semantic Evaluation; (2) Internal Consistency and Reproducibility of CaffEQ-BR; (3) Brazilian nationwide CaffEQ-BR application; (4) Statistical analysis. The study was approved by the Ethics Committee of the University Católica of Brasília (Brasília, Brazil) (number: 23019319.3.0000.0029) and followed the guidelines established by the Declaration of Helsinki. The volunteers were informed about the study protocol and provided web-based consent.

In the present study, the survey was carried out using Google Forms™ web-based platform [23]. The online form maintained the original CaffEQ version layout and content [20]. The expert panel suggested inserting an explanation about the meaning of the word caffeine (as well as about its main sources) in the questionnaire heading for a better understanding of the questionnaire by the general public, since the term "caffeine" is not common to the Brazilian population.

2.1. Translation, Cultural Adaptation, and Semantic Assessment

The translation and cultural adaptation of the questionnaire was performed according to World Health Organization (WHO) recommendations [24]. A bilingual researcher native in Portuguese (T.H.M.d.C.) translated the original version (in English) of the CaffEQ into the Brazilian-Portuguese language. Subsequently, another bilingual researcher, a native English speaker (resident in Brazil for eight years) (B.S.), with no knowledge of the original work, back-translated the Brazilian-Portuguese version (made by T.H.M.d.C.) into English. After that, three collaborators (G.F.M.; C.E.G.R.; R.P.Z.) compared the back-translated version (in English, made by B.S.) with the original questionnaire and analyzed the Brazilian-Portuguese translation version to make adjustments in case of non-conformities. The final version was agreed upon by the bilingual translators (T.H.M.d.C. and B.S.) as a final step in the translation process.

The questionnaire was subsequently analyzed and revised by a panel of health professional experts ($n = 20$) distributed across the following academic degrees: Master's ($n = 7$; 35%), Doctorate ($n = 9$; 45%) and Post-doctorate ($n = 4$; 20%), all associated with universities and all residents in Brasília Federal District [22]. The experts individually analyzed the cultural adaptation and semantic assessment using parameters of the 'importance' and 'clarity' of each question ($n = 47$) on a Likert scale of 1 to 5, where 1 indicates "I totally disagree with the item"; 2—"I partially disagree with the item"; 3—"I neither agree nor disagree with the item"; 4—"I partially agree with the item"; and 5—"I fully agree with the item". The objective was to achieve more than 80% agreement among the experts (mean > 3) for each question [25,26]. Pending items were adjusted according to the experts' observations and sent back to them for compliance analysis. This process occurred until all items achieved at least 80% agreement (mean > 3). The degree of agreement among experts in the evaluation of the 'importance' and 'clarity' of the questions was performed by the Kendall correlation coefficient (W) ranging from 0 to 1. A W-value ≥ 0.66 indicates that the experts applied the same evaluation standards, and W-values < 0.66 suggest disagreement between experts. To approve an item, it was deemed necessary that at least 80% agreement was achieved among the experts (W values ≥ 0.8) [26].

2.2. Internal Consistency and Reproducibility of CaffEQ-BR

The reproducibility of the translated and adapted instrument CaffEQ-BR was analyzed before nationwide application since, before application in a large sample, it is important to test the reproducibility (reliability) and internal consistency with a small sample size [27]. Internal consistency refers to the variation in measurements made under changing conditions and reproducibility evaluates the agreement between any two measurements made on the same subject [27].

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For this purpose, the questionnaire was applied using the Google Forms™ platform to a convenience sample ($n = 50$) of Brazilian adults (>19–59 y) who were regular consumers of caffeine from various sources. Participants were invited through pilot advertising on social media (for example, Facebook™, Instagram™, and WhatsApp™). The questionnaire was answered twice (test-retest) by each person. The second questionnaire was sent within 24 h and returned within the next 24 h. The test-retest questionnaires evaluated reproducibility. It is important to note that the participants did not previously know that they would have to answer the questionnaire a second time. The test-retest reliability (reproducibility) analysis was performed using the intraclass correlation coefficient (ICC), and the internal consistency of the factors was verified using Cronbach's alpha (α). The number of individuals used in this step was considered sufficient once the results were statistically significant ($p < 0.05$) and the effect size was significant (alpha > 0.9 and ICC > 0.6) [28,29].

2.3. Brazilian Nationwide Application of CaffEQ-BR

In order to validate the CaffEQ-BR in Brazil and also to evaluate the Brazilian adult population, we used a questionnaire composed of three parts: (i) sociodemographic and health-related questions; (ii) evaluation of caffeine consumption; and (iii) the CaffEQ-BR. According to Hair et al. (2010) [30], the process of validating a questionnaire requires 20 respondents per item (20:1). In this sense, the minimum sample size was estimated as 940 participants to validate this questionnaire composed of 47 items. In addition, as this is a nationally external validation study, the sample size adopted for calculation was in accordance with the last Brazilian national census [26], with adequacy greater than or equal to 70% of the sample distribution, according to the various states of Brazil. In the example of the state of Rio de Janeiro, the population of 17,264,943, represents 8.22% of the population of Brazil. Therefore, the CaffEQ-BR sample, to obtain 100% adequacy, must have 8.22% of its total sample composed of participants from the state of Rio de Janeiro. In this way, we balanced the sample among the states of Brazil.

The questionnaire was applied using the Google Forms™ platform to a convenience sample of Brazilian adults from all 27 Brazilian states. Participants were recruited by advertising on social media (e.g., Facebook™, Instagram™, and WhatsApp™) [21]. The data collection period occurred from December 2019 to April 2020.

The initial page of the online survey presented the informed consent form with details of the inclusion criteria: (i) adults (>19–59 y) [31,32]) living in Brazil; (ii) regular consumer of caffeine sources (at least three times per week [33]), later confirmed by the caffeine consumption questionnaire. Those who did not agree to participate were directed to a page thanking them for their time, while those who agreed were directed to the first page of the questionnaire with sociodemographic and health-related questions, then caffeine consumption assessment and the 47-item CaffEQ-BR.

2.3.1. Sociodemographic and Health Data

Sociodemographic variables were gender; self-identification of ethnicity; state of the federation of current residence; education level; and average monthly income (BRL/month/person or family). The variables concerning health aspects were height (m) and weight (kg) (self-reported); ≥150 min weekly physical exercise; and previous diagnosis of self-reported chronic diseases with current medication.

2.3.2. Caffeine Consumption

The caffeine consumption questionnaire [33,34] was used to assess the caffeine consumed over the past two weeks prior to the completion of the questionnaire. Participants were asked to indicate the number of servings of coffee, tea, soft drinks, energy drinks, and other caffeine-containing products consumed. The questionnaire also includes a list categorized into eight groups of caffeine sources: 1. Filtered or espresso, hot or iced coffee; 2. Tea sources of caffeine like mate, green and black tea; 3. Pure chocolate with 50% cocoa; 4. Chocolate beverages with 50% cocoa; 5. Cola or guarana based soft drinks; 6. Caffeinated drugs; 7. Commercial drink sources of anhydrous caffeine or guarana

extract beverage; 8. Sports supplements sources of anhydrous caffeine. Standardized doses of coffee, in homemade measures, were adopted according to the national reference study [35]. The typical serving size and caffeine values were based on the products' manufacturer information and the food composition table [36].

2.4. Statistical Analysis

A confirmatory factor analysis verified the factor validity. The factor validity was evaluated by the Root Mean Square Error of Approximation (RMSEA). The RMSEA ranges from 0 to 1, where the value 0 indicates a perfect model fit. A value of 0.05 or less is indicative of an acceptable model fit. Caffeine intake was expressed as a mean ± standard deviation (SD). Shapiro-Wilk test was used to evaluate the normality of distribution. The independent samples t-test was used to compare means between gender. All tests were conducted considering a significance level of 5%. The statistical packages IBM SPSS (Statistical Package for Social Sciences) version 22 (IBM SPSS Statistics for Windows, IBM Corp, Armonk, NY, USA) and IBM SPSS AMOS (Analysis of Moment Structures) version 22 (Amos, IBM SPSS, Chicago, IL, USA) were used for the analyses.

3. Results

3.1. Translation, Cultural Adaptation, Semantic Evaluation, and Content Validation

The CaffEQ-BR (available in Brazilian-Portuguese in Appendix A) was constructed considering the translation/back-translation process and the suggestions made by the expert panel. Following the translation/back-translation phase, the first stage of semantic evaluation and content validation was carried out by the panel of 20 experts who decided to keep 47 items with cultural and semantic adaptations, since we chose to follow the original CaffEQ questionnaire [20]. Throughout three rounds of assessment, with modifications in the items regarding cultural and semantic aspects, the experts reached agreement (≥80%) on the evaluation of the 47 items in the questionnaire. After that, with a convenience sample of 50 Brazilian adults (60% female, 36.4 ± 12.4 y, 62.2% self-identification as white), the internal consistency and reproducibility of CaffEQ-BR were verified. A summary of the translation, cultural adaptation, semantic evaluation, and content validation processes for CaffEQ-BR is shown in Figure 1.

3.2. Reproducibility and Internal Consistency of the CaffEQ-BR

All seven factors of the CaffEQ-BR showed no significant difference (ICC > 0.9) in the responses from the same individual ($n = 50$) (Table 1). As shown in Table 1, all seven factors indicated good internal consistency ($\alpha \geq 0.8$) [29,37].

Table 1. Reproducibility and internal consistency of the instrument and factors of the Caffeine Expectancy Questionnaire in Brazil (CaffEQ-BR) *.

Factors	N. Items	Internal Consistency Cronbach Alpha (95% CI)	Reproducibility Intraclass Correlation Coefficient (95% CI)
Withdrawal/dependence	12	0.948 (0.923–0.968)	0.983 (0.969–0.991)
Energy/work enhancement	8	0.926 (0.888–0.923)	0.953 (0.912–0.975)
Appetite suppression	5	0.872 (0.802–0.923)	0.951 (0.903–0.974)
Social/mood enhancement	6	0.889 (0.829–0.932)	0.949 (0.900–0.973)
Physical performance enhancement	3	0.924 (0.875–0.956)	0.965 (0.936–0.981)
Anxiety/negative physical effects	9	0.872 (0.807–0.921)	0.953 (0.907–0.976)
Sleep disturbance	4	0.941 (0.907–0.965)	0.970 (0.945–0.983)
Overall	47	0.948 (0.923–0.967)	0.976 (0.935–0.989)

* For reproducibility and internal consistency of items and factors of the CaffEQ-BR, conducted with a convenience sample of 50 Brazilian adults: 60% female, 36.4 ± 12.4 y, 62.2% of self- identification as white.
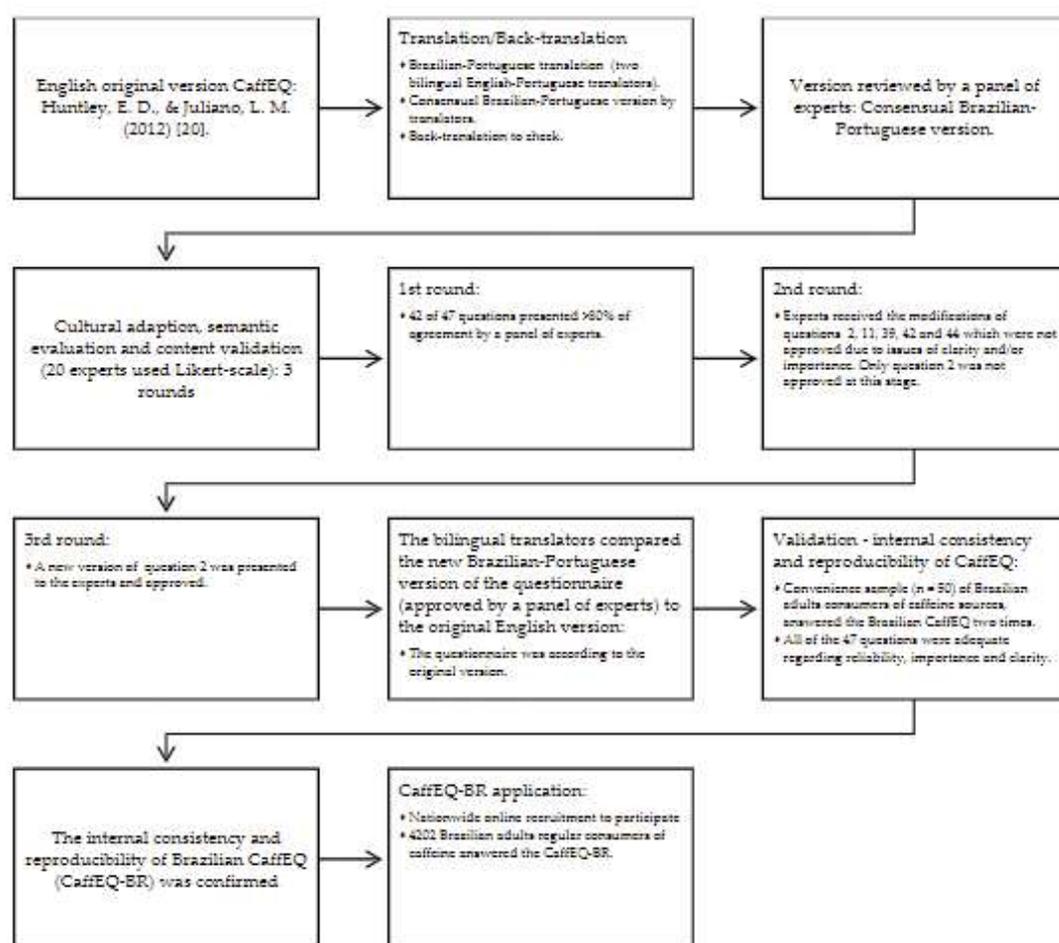
Figure 1. Flowchart of translation, cultural adaptation, semantic evaluation, content validation processes and application of the Caffeine Expectancy Questionnaire in Brazil (CaffEQ-BR).

3.3. Brazilian Nationwide Application of the CaffEQ-BR

3.3.1. Participants

From 4339 individuals who responded to the online CaffEQ-BR questionnaire, the final sample was composed of 4202 participants, since some participants ($n = 137$) did not provide all the data necessary for their inclusion in the survey. The nationwide distribution of the participants among the Brazilian states is presented in Figure 2. Participants were mostly from the Southeast Brazilian region ($n = 1390$; 33.08%), followed by the Northeast ($n = 1175$; 27.96%), Midwest ($n = 716$; 17.04%), South ($n = 566$; 13.47%) and North ($n = 355$; 8.45%). The state with the highest participation was São Paulo-Southeast region ($n = 683$; 16.25%), and the lowest was Acre-North region ($n = 18$; 0.43%). Figure 2 shows the methodological rigor of adequacy of 70% or more in the sample representation, according to the last national census [38], since all Brazilian states achieved this goal. Figure 2 also displays the mean of participants' caffeine and coffee consumption by each Brazilian state.

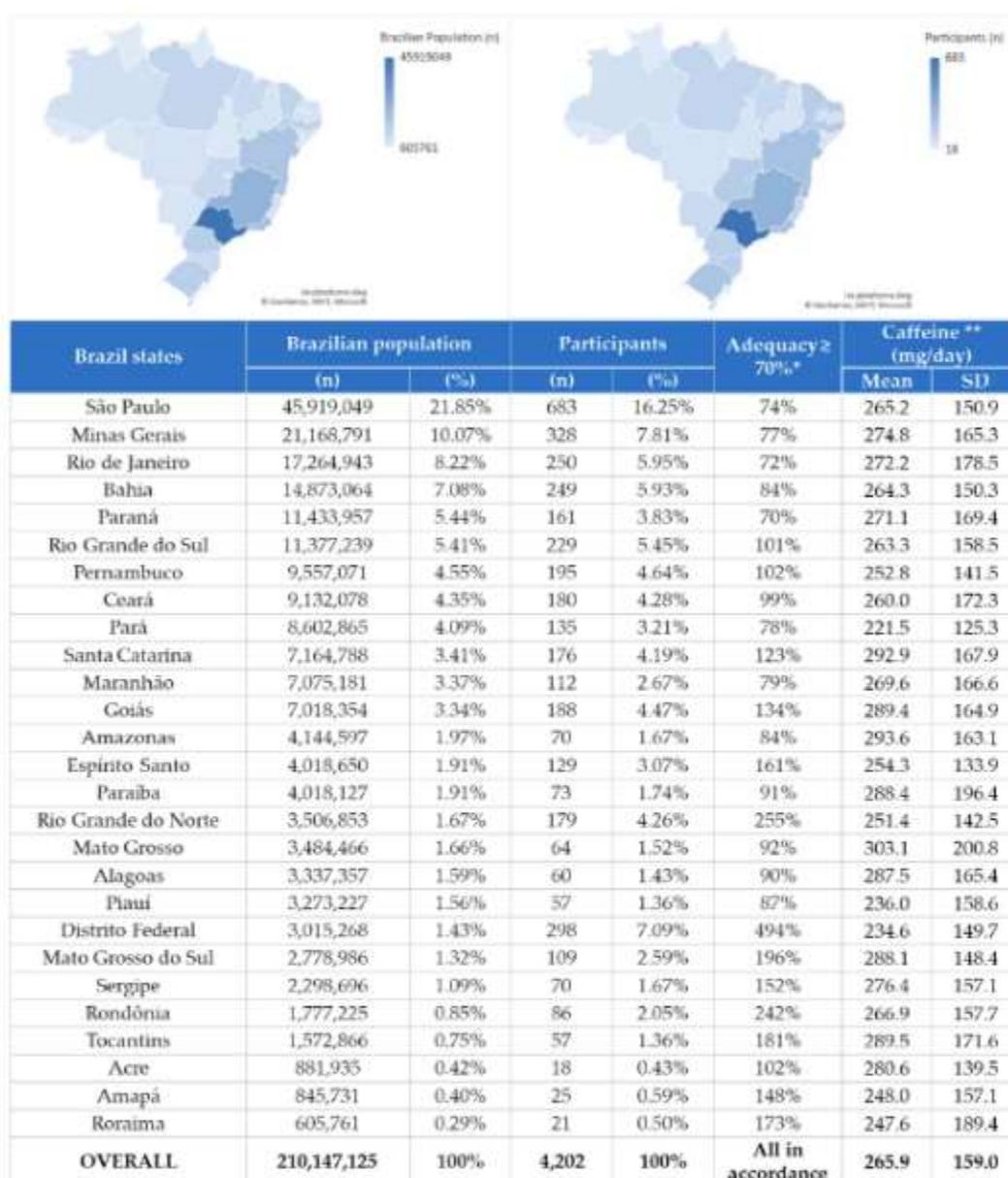| Brazil states	Brazilian population		Participants		Adequacy ≥ 70%*	Caffeine ** (mg/day)	
	(n)	(%)	(n)	(%)		Mean	SD
São Paulo	45,919,049	21.85%	683	16.25%	74%	265.2	150.9
Minas Gerais	21,168,791	10.07%	328	7.81%	77%	274.8	165.3
Rio de Janeiro	17,264,943	8.22%	250	5.95%	72%	272.2	178.5
Bahia	14,873,064	7.08%	249	5.93%	84%	264.3	150.3
Paraná	11,433,957	5.44%	161	3.83%	70%	271.1	169.4
Rio Grande do Sul	11,377,239	5.41%	229	5.45%	101%	263.3	158.5
Pernambuco	9,557,071	4.55%	195	4.64%	102%	252.8	141.5
Ceará	9,132,078	4.35%	180	4.28%	99%	260.0	172.3
Pará	8,602,865	4.09%	135	3.21%	78%	221.5	125.3
Santa Catarina	7,164,788	3.41%	176	4.19%	123%	292.9	167.9
Maranhão	7,075,181	3.37%	112	2.67%	79%	269.6	166.6
Goiás	7,018,354	3.34%	188	4.47%	134%	289.4	164.9
Amazonas	4,144,597	1.97%	70	1.67%	84%	293.6	163.1
Espírito Santo	4,018,650	1.91%	129	3.07%	161%	254.3	133.9
Paraíba	4,018,127	1.91%	73	1.74%	91%	288.4	196.4
Rio Grande do Norte	3,506,853	1.67%	179	4.26%	255%	251.4	142.5
Mato Grosso	3,484,466	1.66%	64	1.52%	92%	303.1	200.8
Alagoas	3,337,357	1.59%	60	1.43%	90%	287.5	165.4
Piauí	3,273,227	1.56%	57	1.36%	87%	236.0	158.6
Distrito Federal	3,015,268	1.43%	298	7.09%	494%	234.6	149.7
Mato Grosso do Sul	2,778,986	1.32%	109	2.59%	196%	288.1	148.4
Sergipe	2,298,696	1.09%	70	1.67%	152%	276.4	157.1
Rondônia	1,777,225	0.85%	86	2.05%	242%	266.9	157.7
Tocantins	1,572,866	0.75%	57	1.36%	181%	289.5	171.6
Acre	881,935	0.42%	18	0.43%	102%	280.6	139.5
Amapá	845,731	0.40%	25	0.59%	148%	248.0	157.1
Roraima	605,761	0.29%	21	0.50%	173%	247.6	189.4
OVERALL	**210,147,125**	**100%**	**4,202**	**100%**	**All in accordance**	**265.9**	**159.0**

Figure 2. National distribution of participants and average caffeine consumption. * As this is an external validation study of national scope, the sample calculation was performed according to the last Brazilian national census [38], with adequacy greater than or equal to 70% of the sample distribution according to the states of Brazil; ** caffeine in general sources. Northeast Region-Alagoas, Bahia, Ceará, Maranhão, Paraíba, Pernambuco, Piauí, Rio Grande do Norte, Sergipe; North Region-Acre, Amazonas, Amapá, Pará, Rondônia, Roraima, Tocantins; Midwest Region-Distrito Federal, Goiás, Mato Grosso, Mato Grosso do Sul; South Region-Paraná, Santa Catarina, Rio Grande do Sul; Southeast Region-Espírito Santo, Minas Gerais, Rio de Janeiro, São Paulo.

Table 2 shows the balanced distribution of participants by gender, with the highest frequency of participants aged between 31 and 59 y ($n = 2625$; 62.5%) and the majority of people of normal weight (classified by BMI between 18.5–24.9 kg/m^2 [31]). More than half of the sample ($n = 2328$; 55.4%) was white, as well as physically active ($n = 2278$; 54.2%). Graduates and postgraduates were the most

frequent educational level (n = 2477; 59%). A monthly income between 3000.01 and 5000.00 (BRL) was the most frequent (n = 865; 20.6%). A large part of the sample did not report having any chronic disease (n = 3397; 80.8%). More information on sociodemographic aspects is shown in Table 2.

Table 2. Sociodemographic data, sample profile of the CaffEQ-BR study (2019–2020).

	Categories	Total (n = 4202)	
		n	%
Gender	Male	2063	49.1
	Female	2139	50.9
Age	19–24	822	19.5
	25–30	755	18.0
	31–40	1331	31.7
	41–59	1294	30.8
Body Mass Index * (kg/m²)	<18.5	106	2.5
	18.5–24.9	1751	41.7
	25–29.9	1498	35.6
	≥30	847	20.2
Self-Identified ethnicity	Asia descendants	114	2.7
	White	2328	55.4
	Indigenous	41	1.0
	Pardo	1330	31.6
	Black	309	7.4
	Without description	80	1.9
Physical Exercises ≥ 150 min/week	No	1924	45.8
	Yes	2278	54.2
Educational Level	No schooling	3	0.1
	Incomplete elementary school	17	0.4
	Completed elementary school	37	0.9
	Incomplete high school	101	2.4
	Completed high school	596	14.2
	Incomplete higher education	955	22.7
	Higher education graduate	1162	27.6
	Postgraduate studies	1315	31.3
	Without description	16	0.4
Monthly Income (BRL) **	1000.00	407	9.7
	1000.01 to 2000.00	769	18.3
	2000.01 to 3000.00	669	15.9
	3000.01 to 5000.00	865	20.6
	5000.01 to 10,000.00	796	18.9
	Above 10,000.00	575	13.7
	Without description	121	2.9
Self-Reported Chronic Diseases	No	3397	80.8
	Yes	805	19.2

* Body mass index (BMI) followed the criteria adopted by the World Health Organization (WHO) [39] underweight (BMI < 18.5 kg/m²), adequate (BMI between 18.5 and 24.9 kg/m²), overweight (BMI between 25 and 29.9 kg/m²) and obesity (BMI ≥ 30 kg/m²). ** 5.55 BRL = 1.00 USD on the last day of data collection, April 2020.

3.3.2. Caffeine Consumption

Based on weekly consumption of caffeine sources, the average daily intake observed was 265 ± 159 mg (minimum 49 mg; maximum 1200 mg). The total caffeine intake for males (274 ± 162 mg/day) and for females (256 ± 155 mg/day) was statistically different (t = 3703; df = 4200; $p < 0.001$). Figure 2 shows descriptive data of average caffeine consumption by Brazilian states. A very similar pattern of consumption was observed between states. The average consumption by regions was as follows: North (n = 355; caffeine consumption: 253 ± 150 mg/day); Northeast (n = 1175; caffeine consumption: 262 ± 157 mg/day); Midwest (n = 716; caffeine consumption: 267 ± 162 mg/day); Southeast (n = 1390; caffeine consumption: 267 ± 158 mg/day); South (n = 566; caffeine consumption: 274 ± 164 mg/day). Thus, the highest absolute consumption of caffeine was in the southern region. Table 3 shows the distribution of consumption of caffeine sources and the time of the day that these were consumed.

Table 3. Distribution frequency of regular consumption of sources of caffeine per week (n = 4202).

Caffeine Sources [1]		Coffee [2]	Tea [3]		Chocolate [4]		Chocolate Beverages [5]		Soft Drinks [6]		Medication [7]		Energy Drinks [8]		Sports Supplements [9]	
		N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Time of the Day	Early morning (00:00–06:00)	202	4.8%	79	1.9%	153	3.6%	70	1.7%	149	3.5%	115	2.7%	109	2.6%	19	0.5%
	Morning (06:00–12:00)	3853	91.7%	503	12.0%	644	15.3%	653	15.5%	362	8.6%	505	12.0%	188	4.5%	333	7.9%
	Afternoon (12:00–18:00)	2829	67.3%	686	16.3%	1594	37.9%	523	12.4%	1361	32.4%	396	9.4%	324	7.7%	206	4.9%
	Evening (18:00–24:00)	1508	35.9%	878	20.9%	1291	30.7%	563	13.4%	1058	25.2%	699	16.6%	348	8.3%	122	2.9%
N° of Servings Per Day	1	971	23.1%	1178	28.0%	1647	39.2%	908	21.6%	985	23.4%	824	19.6%	530	12.6%	463	11.0%
	2	1958	46.6%	322	7.7%	537	12.8%	273	6.5%	543	12.9%	209	5.0%	141	3.4%	78	1.9%
	3	983	23.4%	92	2.2%	235	5.6%	89	2.1%	209	5.0%	111	2.6%	43	1.0%	19	0.5%
	4	139	3.3%	12	0.3%	64	1.5%	22	0.5%	58	1.4%	35	0.8%	7	0.2%	1	0.0%
Total Recorded		4051	96.4%	1604	38.2%	2483	59.1%	1292	30.7%	1795	42.7%	1179	28.1%	721	17.2%	561	13.4%

[1] Standardization of the portions in the consumption frequency table was adopted based on the dose of 50 mg of caffeine/portion. The percentages exceed 100% because consumption can occur in two or more periods. [2] Filtered or espresso, hot or iced coffee. [3] Tea sources of caffeine like mate, green and black tea. [4] Pure chocolate with ≥ 50% cocoa. [5] Chocolate beverages with ≥ 50% cocoa. [6] Cola nut or guarana based soft drinks. [7] Caffeinated medication. [8] Commercial drink sources of anhydrous caffeine or guarana extract beverage. [9] Sports supplements sources of anhydrous caffeine.

The participants' main source of caffeine was coffee, mostly consumed in the morning. In the afternoon, soft drinks and chocolates were the primary sources of caffeine. In the evening, the consumption of coffee, teas, chocolate, soft drinks, caffeine medications, and energy drinks was more frequent. Chocolate beverages showed no difference in consumption during the day. Caffeine-based sports supplements were most frequent in the morning. Coffee was the only source of caffeine with a predominance (73.3%) of consumption of two or more servings daily.

3.3.3. Confirmatory Factor Analysis and Associations of the CaffEQ-BR

Based on the national sample (n = 4202), the external factor validity of CaffEQ-BR was verified by confirmatory factor analysis. The seven factors presented RMSEA = 0.0332 (95% CI: 0.0290–0.0375), which shows satisfactory external validity.

Table 4 shows the results of the Pearson correlation coefficient between the CaffEQ-BR scores, divided between the seven factors, and the consumption of caffeine. All correlation between caffeine consumption and CaffEQ-BR factors (F1 to F6) were positive weak ($r < 0.4$) and significant ($p < 0.001$), except for F7 ($-0.074; p < 0.001$). Therefore, the higher the consumption, the higher the score. Despite the weak correlation ($r < 0.4$), the association between caffeine consumption and the CaffEQ-BR scores were all significant ($p < 0.001$), due to the large sample size (n = 4202).

Table 4. Correlations Between Caffeine Expectancy Questionnaire in Brazil (CaffEQ-BR) Factors and Caffeine-Related Variables (n = 4202).

Sources	Factors of the CaffEQ-BR *						
	F1	F2	F3	F4	F5	F6	F7
Caffeine ** (mg/day)	0.085 ***	0.102 ***	0.081 ***	0.141 ***	0.097 ***	0.095 ***	−0.074 ***

* Factors of the CaffEQ-BR: F1 Withdrawal/dependence; F2 Energy/work enhancement; F3 Appetite suppression; F4 Social/mood enhancement; F5 Physical performance enhancement; F6 Anxiety/negative physical effects; F7 Sleep disturbance; ** Caffeine in general sources (Tea, coffee, chocolate above 50% cocoa, chocolate beverages, cola nut or guarana based soft drinks, caffeinated drugs, commercial drinks and sports supplements sources of anhydrous caffeine or guarana extract beverage); Pearson correlation *** $p < 0.001$.

In Table 5, the region of Brazil with the highest average for F1 factor (withdrawal/dependence) was the southeast. The F2 (energy/work) enhancement factor resulted in the highest average score among all factors and was similar between regions in Brazil. The F3 factor (appetite suppression) was below 3 on the six-point Likert scale for all regions of Brazil. The factors F4 (social/mood enhancement) and F5 (physical performance enhancement) were above 3 on the Likert scale, with emphasis on the upper average for F4 in the north region, and the lower average for F5 in the south region of Brazil. The F6 factor (anxiety/negative physical effects) resulted in the lowest average score among all factors, with a similarity between regions. The F7 factor (sleep disturbance) was also below 3 on the Likert scale, with the lowest average for the south region of Brazil.

Table 5. Mean and Standard Deviation (SD) of the scores on a six-point Likert scale of the seven factors of the Caffeine Expectancy Questionnaire in Brazil (CaffEQ-BR) by regions of Brazil (n = 4202).

Regions **	Factors of the CaffEQ-BR * Mean (SD)						
	F1	F2	F3	F4	F5	F6	F7
North	3.48 (1.49)	4.16 (1.37)	2.21 (1.15)	3.56 (1.45)	3.49 (1.55)	1.78 (0.69)	2.51 (1.60)
Northeast	3.44 (1.41)	4.15 (1.31)	2.24 (1.14)	3.44 (1.38)	3.55 (1.53)	1.81 (0.77)	2.45 (1.58)
Midwest	3.34 (1.39)	4.08 (1.32)	2.13 (1.14)	3.25 (1.34)	3.50 (1.53)	1.85 (0.82)	2.62 (1.69)
Southeast	3.60 (1.45)	4.17 (1.33)	2.26 (1.18)	3.41 (1.38)	3.47 (1.49)	1.75 (0.75)	2.44 (1.62)
South	3.47 (1.43)	4.08 (1.30)	2.36 (1.24)	3.42 (1.34)	3.24 (1.48)	1.74 (0.75)	2.36 (1.57)
Brazil	3.48 (1.43)	4.14 (1.32)	2.24 (1.17)	3.41 (1.38)	3.47 (1.51)	1.78 (0.77)	2.47 (1.62)

* Factors of the CaffEQ-BR, range: 1.00–6.00: F1 Withdrawal/dependence; F2 Energy/work enhancement; F3 Appetite suppression; F4 Social/mood enhancement; F5 Physical performance enhancement; F6 Anxiety/negative physical effects; F7 Sleep disturbance. ** Regions of Brazil: North Region-Acre, Amazonas, Amapá, Pará, Rondônia, Roraima, Tocantins; Northeast Region-Alagoas, Bahia, Ceará, Maranhão, Paraíba, Pernambuco, Piauí, Rio Grande do Norte, Sergipe; Midwest Region-Distrito Federal, Goiás, Mato Grosso, Mato Grosso do Sul; South Region-Paraná, Santa Catarina, Rio Grande do Sul; Southeast Region-Espírito Santo, Minas Gerais, Rio de Janeiro, São Paulo.

4. Discussion

In this original study, we developed and validated the Brazilian version of the CaffEQ. Until now, there has been no adaptation of CaffEQ to Brazilian-Portuguese in the cultural context of Brazil, or in Latin American countries. Its application may assist in observational studies for clinical trials that assess caffeine consumption in Brazil. The selected questionnaire also allowed us to make comparisons with data available from other countries that used the same questionnaire [19–21]. The CaffEQ-BR is a questionnaire designed to identify the expectations that Brazilian individuals have about the subjective effects of caffeine on the biopsychosocial aspects involved in its consumption [19–21].

In order to create the CaffEQ-BR, the translation and back-translation process (linguistic validation of the instrument) was necessary, since the original questionnaire was developed in another language and there was no translated and validated version in the target language [24]. Therefore, the first step of this study was to translate/retranslate the original version of CaffEQ from English to Brazilian-Portuguese to English following the scientific guidelines proposed by the WHO [12,24]. After this, the questionnaire was sent to experts for evaluation, since semantic evaluation is necessary to ensure its clarity and comprehension [40,41]. In this sense, CaffEQ-BR presented cultural and semantic adequacy according to the consensus of the experts (at least 80% of agreement). After this stage, the test-retest with 50 individuals was used to assess the reliability of the CaffEQ-BR, which analyzes the questionnaire's ability to reproduce consistent results [29,41]. The internal consistency of CaffEQ-BR was measured by Cronbach's alpha coefficient (α = 0.94), considered acceptable when ≥0.8 [28,37]. This result was similar to the findings of Huntley and Juliano (2012) [20] (n = 1046; α = 0.96), and Schott et al. [21] (n = 352; α = 0.98) for the same questionnaire in English and German, respectively. In addition, the CaffEQ-BR presented excellent measures of reproducibility (ICC = 0.97). This result confirms that the questionnaire is able to consistently measure the subjective effects of caffeine perceived by the interviewed user. Every scale used to measure health results needs this reliability performed by exploratory and confirmatory factor analysis [37].

After internal validation of the CaffEQ-BR, we conducted a national study in Brazil, using a sample of all 27 Brazilian states (Figure 2) with uniform distribution of age and sex (Table 2), similar to the last available national census (Brazil-IBGE (Instituto Brasileiro de Geografia e Estatística) 2010) [42]. The national census is usually held every decade, and the 2020 edition is in progress. The first five most populous Brazilian states (Figure 2) had two or more rounds of dissemination of the survey on social networks, to achieve the established interview number goal. The Federal District had the highest representation in percentage points because the research group is based in Brasília, Federal District. Naturally, in a convenience sample, there was greater participation in our hometown.

The sociodemographic data of the CaffEQ-BR participants are closer to the measures of the adult Brazilian population on gender and age than the sample of the original study (CaffEQ) [20], which had a predominance of young female students. Although the CaffEQ-BR sample is representative of the population distribution parameters in the Brazilian states [38], there is a selection bias in relation to the respondents' education and socioeconomic level, which was above the national average family income (1439 BRL per month in 2019) [43] directly influencing educational status [44]. Another factor was the use of social networks to disseminate the research questionnaire. Other nationwide surveys in Brazil from our institution/research groups, released through web-base, also observed greater access by higher economic classes compared to the national average [45,46]. Therefore, it is not possible to extrapolate our results to the entire Brazilian adult population. This is not a national census or national sample representation.

Regarding the self-reported categories for BMI $\geq$ 25 and chronic disease being treated, our sample data showed a lower incidence of these two variables (55.8%; 19.2%, respectively) compared to the results of the Brazilian national study "Surveillance of risk and protective factors for chronic diseases by telephone research" (VIGITEL 2019) (75.7%; 31.9%, respectively). However, our sample showed a higher frequency of people who self-reported being physically active: 54.2%, compared to the last VIGITEL (2019) which showed 39.5% [47]. The VIGITEL study used a representative random sample only from the state capitals of Brazil, through phone interviews. Our survey did not cover capitals only, with a convenience sample by invitation on social networks with predominant access via mobiles. There was an inclination towards greater sample composition of middle-aged adults, with a higher level of education and income for the CaffEQ-BR. There are studies that indicate a greater preference, especially for coffee, in individuals with this sociodemographic profile [6–8]. The VIGITEL study in different periods of time (2006 to 2019) showed that that part of the population that has more years of schooling ($\geq$12 years) is less overweight, sedentary, and chronically ill. The reverse context, low income and education level and high morbidity rate, are also observed [48]. The self-reported ethnicity comparison between the National Household Sample Survey (2018/2019) [43] and that obtained in the CaffEQ-BR was: 45.2–55.4% of Brazilians that declared themselves as white, 45.0–31.6% as pardo, 8.8–8% as black, 0.47–2.7% as Asian descendants and 0.38–1.0% as indigenous.

The average caffeine intake in our sample (265 $\pm$ 159 mg/day) is above the published standards for Brazil (115 $\pm$ 96 mg/day) [49]. According to Sartori et al., the survey on caffeine consumption in Brazil was based on food sources, extracted from data from the national survey of 2008 and 2009 [49]. In addition to the difference in the observation periods (2008/09 vs. 2019/20), our survey included other sources of caffeine as supplements and medications. This fact is relevant according to Arrais et al. (2016) [50], as self-medication is a recurrent practice in Brazil, including among young adults, mainly associated with the use of non-prescription medications, such as analgesics and muscle relaxants. In the national market, these drugs take in their composition, on average, 30 to 50 mg of caffeine per serving. Our study also focused on individuals who are regular consumers of caffeine (from different sources); therefore, we expect that the participants' average usual intake could be higher than the general Brazilian population. These values were similar to those found by Schott et al. (from Germany, Switzerland, and Austria: 236 $\pm$ 235 mg/day) [21] but considerably below the consumption found by Huntley and Juliano (from U.S.: 323 $\pm$ 297 mg/day), which was based on the consumption of a younger population, containing many college/university students [20]. Another point is that the volume of coffee consumed in Brazil is not a standard variable to be compared with a North American or European study, since Brazilians and inhabitants of other Latin American countries usually drink small portions of stronger coffee (approx. 50 mL of small cups) compared to the American culture of large cups (approx. 250 mL) of lighter coffee, a fact observed by De Paula and Farah (2019) [51]. Total caffeine intake in males (274 $\pm$ 162 mg/day) was higher than in females (256 $\pm$ 155 mg/day), similar to the results observed by other studies [8,49,52]. Probably these gender differences are related to cultural and behavioral factors in males as well as to the gender differences in physiological responses to caffeine [53–56]. A study showed that males differ in cardiovascular responses to caffeine,

while females did not differ in their responses as a function of typical caffeine use [55]. Males also presented greater decreases in heart rate in response to caffeine than did females, probably related to changes in circulating steroid hormone, in which increased circulating estradiol increases the physiological and subjective effects associated with caffeine, influencing the high consumption of caffeine on males [53].

Across previous CaffEQ studies, caffeine was consumed mainly in coffee, a habit also observed in Brazil [6–8]. Globally, habitual coffee consumption ranges from about 1 to more than 5 cups per day, which indicates that the daily dose is defined by several reasons, like lifestyle, gender, expectance of caffeine effects, culture, genetics, health effects, among others [2,36,57]. Most of our sample (69%) are used to consuming 2 or 3 portions of coffee daily (Table 3). The culture of coffee in Brazil has a historical origin in its production capacity, as it is the largest coffee exporter in the world market [58]. Brazil accounts for one-third of the world's coffee production, making it the world's largest producer, a position it has occupied for more than 150 years. In Brazil, at the beginning of the 19th century, coffee was already treated as an investment. With the expansion of plantations in the country, there was also an expansion of investment favoring urbanization, such as the construction of railroads responsible for the national distribution and export of coffee, in addition to the arrival of immigrants. Thus, in Brazil, coffee is considered one of those products responsible for the modernization, urbanization and development of some cities [59], and it is still widely consumed and appreciated throughout the country. Annual per capita Brazilian consumption is 6.02 kg, which represents 13% of world demand [60]. Easy access to coffee naturally influences the consumption culture of Brazilians [8]. Coffee is the main drink consumed, with an average of 163 mL per day, and is also the second most consumed food [6,7].

In Brazil, coffee consumption is widespread [6]. This reflects a very similar average consumption between regions [6], as observed in the CaffEQ-BR survey. The differences are greater when other eating habits are associated with the daily use of coffee. For example, the habit of consuming a hot mate called "Chimarrão" in the south region, a cold mate called "Terere" in the Midwest region [61] and guarana extract in the northern region of Brazil [62]. The fact that the Northeast region is the largest consumer of coffee was also confirmed by the study of Sousa and Da Costa [6]. We also emphasize that coffee and other caffeine sources are also sources of other bioactive compounds, including polyphenols and chlorogenic acids [63]. However, the main substance with psychoactive properties is caffeine, confirmed by several meta-analyses [4]. The construction of the original CaffEQ [20] takes into account the estimated average consumption of caffeine in general (from all sources), without the intention of associating it with other compounds present in food sources of caffeine.

The statistical correlations ($r < 0.4$) shown between CaffEQ factors, scores and caffeine consumption were also observed in previous studies that used the original CaffEQ in the United States [20] and the translated and validated version in German-speaking countries [21].

When observing the descriptive results of the CaffEQ-BR scores divided into seven factors using the original questionnaire [20], it is possible to observe similarity in the factors Withdrawal/dependence 3.48 (1.43)–3.22 (1.45), Energy/work enhancement 4.14 (1.32)–3.92 (1.17), Appetite suppression 2.24 (1.17)–2.70 (1.20), Social/mood enhancement 3.41 (1.38)–2.98 (1.21), respectively. However, there was a difference of approximately one point for the factors Physical performance enhancement 3.47 (1.51)–2.41 (1.07), Anxiety/negative physical effects 1.78 (0.77)–2.68 (1.04) and Sleep disturbance 2.47 (1.62)–3.20 (1.45). Differences in mean scores in the seven factors were also observed in the other cultures where CaffEQ was studied [20,21].

Data from the latest survey published by the Brazilian Institute of Geography and Statistics showed that three out of four Brazilians in metropolitan capitals (Belém (Pará), Fortaleza (Ceará), Recife (Pernambuco), Salvador (Bahia), Belo Horizonte (Minas Gerais), Rio (Rio de Janeiro), São Paulo (São Paulo), Curitiba (Paraná) and Porto Alegre (Rio Grande do Sul)) have access to the Internet, and the number of households with landlines dropped from 33.6 % to 31.5%, while ownership of devices with mobile internet increased from 92.6% to 93.2% [64]. The smartphone was also the main

tool used to access the internet. Therefore, although web-based research may be limited because it is not possible to reach every portion of the population, it can still be considered a viable strategy since our web search could be answered on any device with internet. There is also the limitation of memory and intake bias, which is intrinsically related to frequency questionnaires [65].

There is no other scientifically validated Brazilian research questionnaire that evaluates consumption related to caffeine. Therefore, there are no parameters for comparison except with the original version of the CaffEQ [20] and the German version [21]. Another important factor is the heterogeneity of the Brazilian-Portuguese language in the national territory. Certainly, there are aspects of regionality, but despite these limitations, due to the construction process in several stages and the wide statistical confirmation, the Brazilian version of CaffEQ represents a reliable and valid questionnaire to assess expectations of caffeine intake. Analytical item analysis confirms the quality of the translated items. Overall, the CaffEQ's translation and validation for Portuguese and Brazilian culture were successful.

5. Conclusions

The full version of the Caffeine Expectancy Questionnaire in Brazil (CaffEQ-BR) is available for Brazilian adults, translated into Portuguese and adapted to Brazilian culture. This study confirmed the validity and reliability of the CaffEQ-BR. Its internal and external consistency allows its use throughout the national territory, if the sampling conditions are similar. The CaffEQ-BR observed the pattern of consumption of caffeine sources by Brazilian adults, confirming the national preference for coffee as the main source of daily caffeine. Future studies may validate the CaffEQ-BR in children, adolescents and the elderly, since caffeine is widely consumed across the lifespan. The present study contributes to a better understanding of the expectations of the most used psychoactive substance in Brazil, systematizing several expectations in seven factors that can be explored and categorized. Thus, the CaffEQ-BR can be used to facilitate our understanding of the use of caffeine. Other studies may also replicate our results, pointing out the temporal stability of the CaffEQ-BR, monitoring changes in expectations in longitudinal exposure to caffeine.

Appendix A

Questionário de Expectativa de efeitos da Cafeína/café, versão brasileira (CaffEQ-BR)

Instruções: Estamos interessados em suas crenças sobre os efeitos que a cafeína tem sobre você. Abaixo há uma lista de possíveis efeitos da cafeína presentes nos produtos listados na tabela acima preenchida. Usando a escala como guia, avalie cada afirmação em termos de quanto é PROVÁVEL ou IMPROVÁVEL para esses efeitos como consequências do consumo da cafeína. As possibilidades de respostas são: 1 = Muito improvável; 2 = Improvável; 3 = Um pouco improvável; 4 = Um pouco provável; 5 = Provável; 6 = Muito provável. Baseie suas respostas no produto com cafeína que escolheu.

Se você usa muitos tipos de produtos com cafeína, escolha o mais usual para basear suas respostas, ou você pode optar por basear suas respostas em "cafeína/café".

Itens	Muito Improvável	Improvável	Um Pouco Improvável	Um Pouco Provável	Provável	Muito Provável
1. Cafeína/café me dá ânimo quando estou cansado	☐	☐	☐	☐	☐	☐
2. Eu fico extrovertido quando tomo cafeína/café	☐	☐	☐	☐	☐	☐
3. Cafeína/café me ajuda a não comer mais do que deveria	☐	☐	☐	☐	☐	☐
4. Fico facilmente estressado depois de tomar cafeína/café	☐	☐	☐	☐	☐	☐
5. Cafeína/café melhora meu desempenho físico	☐	☐	☐	☐	☐	☐
6. Fico menos cansado depois de tomar cafeína	☐	☐	☐	☐	☐	☐
7. A cafeína/café tira minha fome	☐	☐	☐	☐	☐	☐
8. Fico triste quando não tomo cafeína/café	☐	☐	☐	☐	☐	☐
9. Cafeína/café melhora meu humor	☐	☐	☐	☐	☐	☐
10. Eu fico ansioso quando não tomo cafeína/café	☐	☐	☐	☐	☐	☐
11. Eu me sinto angustiado quando tomo cafeína/café	☐	☐	☐	☐	☐	☐
12. Eu me exercito melhor depois de tomar cafeína/café	☐	☐	☐	☐	☐	☐
13. Eu sinto muita falta de cafeína/café quando não tomo	☐	☐	☐	☐	☐	☐
14. Eu não gosto do jeito que eu me sinto após tomar cafeína/café	☐	☐	☐	☐	☐	☐
15. Eu me sinto mal se ficar sem cafeína/café	☐	☐	☐	☐	☐	☐
16. Cafeína/café aumenta minha motivação para trabalhar	☐	☐	☐	☐	☐	☐
17. Eu me sinto mais confiante depois de tomar cafeína/café	☐	☐	☐	☐	☐	☐
18. Tomar cafeína/café a qualquer hora do dia atrapalha o meu sono	☐	☐	☐	☐	☐	☐
19. Quando tomo cafeína/café fico nervoso(a)	☐	☐	☐	☐	☐	☐
20. Quando tomo cafeína/café fico mais alerta	☐	☐	☐	☐	☐	☐
21. Mesmo quando tomo uma pequena quantidade de cafeína/café fico ansioso	☐	☐	☐	☐	☐	☐
22. Cafeína/café melhora minha concentração	☐	☐	☐	☐	☐	☐
23. Quando tomo cafeína/café fico mais amigável	☐	☐	☐	☐	☐	☐
24. Eu tenho que tomar cafeína/café todos os dias	☐	☐	☐	☐	☐	☐
25. Cafeína/café me faz suar	☐	☐	☐	☐	☐	☐
26. Cafeína/café me faz pular refeições	☐	☐	☐	☐	☐	☐
27. Tenho muita vontade de tomar cafeína/café se não tiver tomado a quantidade de sempre	☐	☐	☐	☐	☐	☐
28. Tomar cafeína/café na hora de dormir atrapalha meu sono	☐	☐	☐	☐	☐	☐
29. Cafeína/café me deixa irritado	☐	☐	☐	☐	☐	☐
30. Eu desejo cafeína/café o tempo todo	☐	☐	☐	☐	☐	☐

Itens	Muito Improvável	Improvável	Um Pouco Improvável	Um Pouco Provável	Provável	Muito Provável
31. Cafeína/café me ajuda a trabalhar por mais tempo	□	□	□	□	□	□
32. Cafeína/café me faz sentir feliz	□	□	□	□	□	□
33. Eu não funciono sem tomar cafeína/café	□	□	□	□	□	□
34. Quando tomo cafeína/café meu coração acelera	□	□	□	□	□	□
35. Eu tenho dificuldade em começar o dia sem tomar cafeína/café	□	□	□	□	□	□
36. Sinto dor de estômago quando tomo cafeína/café	□	□	□	□	□	□
37. Eu não conseguiria parar de tomar cafeína/café	□	□	□	□	□	□
38. Tomar cafeína/café no final da tarde atrapalha o meu sono	□	□	□	□	□	□
39. Cafeína/café me ajuda a regular o peso	□	□	□	□	□	□
40. Quanto não tomo cafeína/café sinto dor de cabeça	□	□	□	□	□	□
41. Cafeína/café melhora minha atenção	□	□	□	□	□	□
42. Eu fico mais extrovertido(a) quando tomo cafeína/café	□	□	□	□	□	□
43. Cafeína/café me ajuda a me exercitar por mais tempo	□	□	□	□	□	□
44. Sinto-me mais disposto quando tomo cafeína/café	□	□	□	□	□	□
45. Cafeína/café me faz sentir com mais energia	□	□	□	□	□	□
46. Cafeína/café diminui o meu apetite	□	□	□	□	□	□
47. Tomar cafeína/café no final do dia não me deixa dormir	□	□	□	□	□	□

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5.2 - 2º ARTIGO PUBLICADO - MENDES, Guilherme Falcão, et al. Brief Version of Caffeine Expectancy Questionnaire in Brazil. *Frontiers in nutrition*, 2021, 8. https://doi.org/10.3389/fnut.2021.695385

Brief Version of Caffeine Expectancy Questionnaire in Brazil

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The use of extensive questionnaires has the limitation of filling time bias, related to the ability to focus and accurately respond to many items, justifying the necessity for a brief version. This study aimed to build a brief version of the Caffeine Expectancy Questionnaire in Brazil (B-CaffEQ-BR) composed of 21 items divided into seven factors, with as adequate consistency and reproducibility as the full version. Quantitative procedures using statistical modeling were applied using the CaffEQ-BR (full version) database keeping the Mean Absolute Error (MAE) (based on the full version) <0.5 and Cronbach's α and Intraclass Correlation Coefficient (ICC) ≥ 0.7. The expert panel ($n = 3$), in a blind design, evaluated the semantic structuring within the options indicated by previous statistical modeling until the agreement of the expert panel. The participants ($n = 62$), Brazilian adults who were regular caffeine consumers (175.8 ± 94.4 mg/day), of whom 62.9% were women, 33.1 ± 9.7 years, 24.5 ± 3.8 kg/m², and 62.9% of whom self-identified as white, were asked to respond twice to the online questionnaire in 48–72 h. The first sample ($n = 40$) tested interobserver reproducibility with the double application of B-CaffEQ-BR. Another sample ($n = 22$) answered the CaffEQ-BR (full version) and B-CaffEQ-BR, and the last sample ($n = 18$) performed the reverse process. The B-CaffEQ-BR presented excellent internal consistency (Cronbach's $\alpha \geq 0.729$) and overall reproducibility (ICC ≥ 0.915) for the entire questionnaire and its seven factors. The B-CaffEQ-BR can be a valuable tool in caffeine research with the Brazilian adult population.

Keywords: short, brief, questionnaire, assessment, caffeine, expectancy, Brazilian-Portuguese

INTRODUCTION

Caffeine is the most consumed psychoactive substance globally (1), used mainly in coffee, which forms a part of Brazilian eating habits (2–4). In addition, caffeine is the most common active ingredient in coffee, mate, guarana, green tea, cocoa, and its derivatives (5). Caffeine is widely studied and presents several guidelines for use, dosage, and safe consumer limits (<400 mg/day) (6–8). The intake of products containing caffeine is associated with its taste characteristics, population eating habits, and the expectations related to the effects of caffeine on the body (i.e., physiological and performance aspects) (9).

Studies confirm that the expected effects of caffeine play a subjective role in the belief around its consumption (10–12). Thus, the expectations associated with caffeine consumption and its effects can play an essential role in the development, maintenance, and reinforcement of their consumption showing the importance of knowledge about the subjective perceptions of caffeine

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consumption (9, 12, 13). In this regard, validated questionnaires to assess caffeine expectancy have been recently published to understand the expectations of caffeine effects (i.e., mood, appetite, sleep/wakefulness, physical performance, and other factors) and consumption (9, 13–15).

Chronologically, Heinz et al. (12) developed the Caffeine Expectation Questionnaire (CEQ) composed of 37 items distributed in four factors that represent (i) "withdrawal symptoms," (ii) "positive effects," (iii) "acute negative effects," and (iv) "mood effects." Subsequently, Huntley and Juliano (14) developed the Caffeine Expectancy Questionnaire (CaffEQ), which consists of 47 items divided into seven factors: (i) "addiction," (ii) "energy and mental activity," (iii) "appetite suppression," (iv) "improved mood/sociability," (v) "improved physical performance," (vi) "anxiety and negative effects," and (vii) "sleep disorders." In the process of translation and cultural validation, Schott et al. (15) validated the CaffEQ for the adult German-speaking population (Germany, Austria, and Switzerland). More recently, Kearns et al. (13) proposed a brief English version of CaffEQ validated in a sample ($n =$ 975) of undergraduate adult students from the United States of America (US). They reduced the questionnaire from 47 to 20 items preserving the original seven factors, with satisfactory internal and external consistency, stating that the use of short questionnaires is better accepted by the public, especially in the context of a self-applied questionnaire.

Our group recently published the Caffeine Expectancy Questionnaire in Brazil (CaffEQ-BR) (16) with semantic translation and cultural validation to Brazilian–Portuguese language based on the wide application covering all the states of the Brazilian territory ($n = 4,202$). CaffEQ-BR presented satisfactory consistency and reproducibility as the original version (CaffEQ), maintaining the seven factors and the 47 items. One of the difficulties presented in our CaffEQ-BR study was to apply a lengthy questionnaire in a large population sample, with a frequent complaint of repetitive items and the long time required for attentive completion (16). The time to complete a questionnaire (due to the number of items and volume of text/words) is inversely associated with the response rate and accuracy. The length of the questionnaire (47 items) may hinder the widespread application of this tool (17). Therefore, brief versions of questionnaires validated to specific populations are emphasized to save time and resources, and to increase the adherence of participants to the studies. Hence, the development of the brief version of the Caffeine Expectancy Questionnaire in Brazil (B-CaffEQ-BR) is justified given the current context of online self-filling application questionnaires having become a worldwide trend (18).

Smith et al. (19) reported that some questions must be considered when developing a brief version of the questionnaire: (i) developing the brief version of a previously sufficiently validated full version; (ii) showing that the brief version preserves the coverage of the content of each factor and the scale of each factor is measured in the same way; (iii) showing that the brief version has an adequate variety of equivalent overlap and the

ability to reproduce the factorial structure; (iv) showing that each factor in the brief form is valid in an independent sample, with similar or better consistency indexes than the full version; and (v) showing that the brief version offers significant savings in time and/or resources. All these assumptions were fully observed in the construction of the B-CaffEQ-BR.

Even with the brief English CaffEQ (13) questionnaire previously available in the literature, it is important to emphasize that the translation and cultural validation of an instrument in the brief version does not guarantee the achievement of the same result based on the full version (14). For this reason, we initially translated and validated the full version of CaffEQ-BR (16) into Portuguese and Brazilian culture. Therefore, it was more appropriate to construct the B-CaffEQ-BR version based on the data obtained in the full version (CaffEQ-BR) with the treatment of construct from a qualitative and quantitative methodological perspective.

Therefore, this study aimed to validate the B-CaffEQ-BR. We hope this study can provide a questionnaire with as satisfactory internal and external validation as the full CaffEQ-BR version. The brief version aims to have a similar ability to characterize according to the expectations of caffeine use in the Brazilian adult population, with more straightforward application in large populations, which can be useful in future caffeine studies.

MATERIALS AND METHODS

The present study used the dataset from the full version CaffEQ-BR, previously validated in the Brazilian–Portuguese language (16). The CaffEQ-BR consists of seven factors and 47 items, assessed using a six-point Likert scale. For the construction of the B-CaffEQ-BR, the present study was carried out in four stages: (1) Quantitative evaluation by statistical modeling, (2) Qualitative assessment of semantic structure by the panel of experts, (3) Internal consistency and reproducibility analysis, and (4) Survey of full and brief versions by the mixed two-way model.

The study was approved by the Ethics Committee of the Catholic University of Brasília (Brasília, Brazil) (number: 23019319.3.0000.0029) and followed the guidelines established by the Declaration of Helsinki. The volunteers were informed about the study protocol and provided web-based consent. The research was conducted using a web platform, Google Forms™ (20). The online form maintained the layout, content, and the general instructions contained in the original version of CaffEQ-BR, in addition to self-reported identification data and average weekly consumption of caffeine sources as described in detail by Mendes et al. (16).

Quantitative Evaluation by Statistical Modeling

For the quantitative analysis, from the preliminary information obtained from the database of full CaffEQ-BR ($n = 4,202$), it was possible to obtain all combinations of three items by a factor whose present Mean Absolute Error (MAE) (21) is <0.5 and internal alpha consistency of Cronbach's $\alpha \geq 0.7$

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(22). This previous procedure was paramount to providing a ranking of options for the subsequent semantic analysis of the specialist panel. The objective of this stage before the qualitative assessment was to reduce the structure of the full CaffEQ-BR (seven factors/47 items) (16) for a brief version with seven factors and 21 items (three items per factor).

Qualitative Assessment of Semantic Structure by the Expert Panel

In the qualitative analysis, an expert panel ($n = 3$) assessed the semantic relevance of items from the ranking indicated by the quantitative analysis. The funneling process (in a blind design) was carried out in several stages when the experts unanimously agreed to maintain or delete the item until three items per factor remained. Finally, the brief version selected and approved by the quantitative and qualitative analysis (seven factors/21 items) was applied to a convenience sample of Brazilian adults living in Brazil to assess the internal consistency and reproducibility.

Internal Consistency and Reproducibility

The internal consistency and reproducibility of the B-CaffEQ-BR were analyzed using a convenience sample of Brazilian adults ($n = 40$) who were regular caffeine consumers (188.7 ± 106.5 mg/day) and who never had contact with the questionnaire. They answered the B-CaffEQ-BR twice (test and retest) within 48–72 h intervals (16, 23). These data were applied to analyze internal consistency and reproducibility due to the convergence of responses in the test and retest (24).

Survey of Full and Brief Version by the Mixed Two-Way Model

The composition and psychometric properties of the brief version were compared with full CaffEQ-BR. Therefore, another convenience sample ($n = 40$) of regular caffeine consumers (160.0 ± 71.8 mg/day) was recruited in which half of the participants ($n = 20$) first filled out the full CaffEQ-BR and after 48–72 h (16, 23), they were asked to fill in the B-CaffEQ-BR. The other half did the reverse process, initially answering the B-CaffEQ-BR and then the full CaffEQ-BR (within 48–72 h interval). This method aims to determine whether there was interference from the "learning bias" issue. According to Smith et al. (19), this methodological care reinforces the quality and applicability of the construct.

Statistical Analysis

The MAE test was used to perform the qualitative analysis, representing the average divergence of the brief and scores of the full versions, with the zero-value indicating perfect agreement. The condition of MAE <0.5 means that, on average, this divergence is <0.5 (i.e., 10% error on a five-point scale) (21).

The reproducibility of the questionnaire between the test and retest was analyzed by the Intraclass Correlation Coefficient (ICC). The absolute agreement was used to determine ICC, considering the average agreement of the two applications. According to Cicchetti (25), an excellent ICC agreement between evaluators is considered when the value ≥0.75 and good agreement is between 0.74 and 0.60. Cronbach's α was used to check the internal consistency of questionnaire factors, where values ≥0.7 indicate that the factors are consistent (22). The agreement of the B-CaffEQ-BR scores compared to the full version was assessed using the ICC (absolute agreement) obtained through a mixed two-way model.

All tests were performed considering a significance level of 5%, using the statistical packages IBM SPSS (Statistical Package for Social Sciences) version 22 (IBM SPSS Statistics for Windows, IBM Corp, Armonk, NY, US) and IBM SPSS AMOS (Analysis of Moment Structures) version 22 (Amos, IBM SPSS, Chicago, IL, US).

RESULTS

In **Figure 1**, the flowchart shows the results obtained with the multiple steps described in the methods. The results present convergence of the quantitative analysis results by statistical modeling and semantic agreement obtained by the expert panel. The B-CaffEQ-BR was performed with a convenience sample of 62 Brazilian adult usual consumers of caffeine (175.8 ± 94.4 mg/day). The sample profile composed of 62.9% females, 33.1 ± 9.7 years, body mass index 24.5 ± 3.8 kg/m², self-identified as white 62.9%, 80.6% without a diagnosis of chronic diseases, 71% physically active (>150 weekly min of physical exercise), 53.2% with postgraduate education, and 40.3% with average monthly family income from BRL 10,001.00 to 20,000.00 (BRL 5.76 = USD 1.00) on the last day of data collection, October 2020.

Internal Consistency of B-CaffEQ-BR

Table 1 shows the internal consistency of Cronbach's α values ($\alpha \geq 0.729$) for all seven factors and the entire questionnaire ($\alpha = 0.906$). These results were obtained with a 55.3% reduction of the questionnaire, from 47 to 21 items.

Reproducibility and Agreement of CaffEQ-BR Versions

The overall reproducibility showed an excellent ICC agreement (brief–brief = 0.978 and full–brief = 0.920) for the entire questionnaire. Regardless of the order of the applications of questionnaires (brief–brief or full–brief) the ICC values are excellent (≥0.780) for all seven factors, except for "anxiety/negative physical effects" on full x brief analysis (ICC = 0.726; good agreement) (**Table 2**). These findings confirm the agreement between the two versions of CaffEQ-BR.

DISCUSSION

The B-CaffEQ-BR, a brief version of the questionnaire, showed excellent reproducibility and adequate internal consistency, similar to the full CaffEQ-BR version ($n = 4,202$; $\alpha = 0.948$; and ICC = 0.976) as previously published (16). These findings confirm that the convenience sample of Brazilian adult habitual caffeine consumers was sufficient to verify the reproducibility and internal consistency of B-CaffEQ-BR. The expectations of the
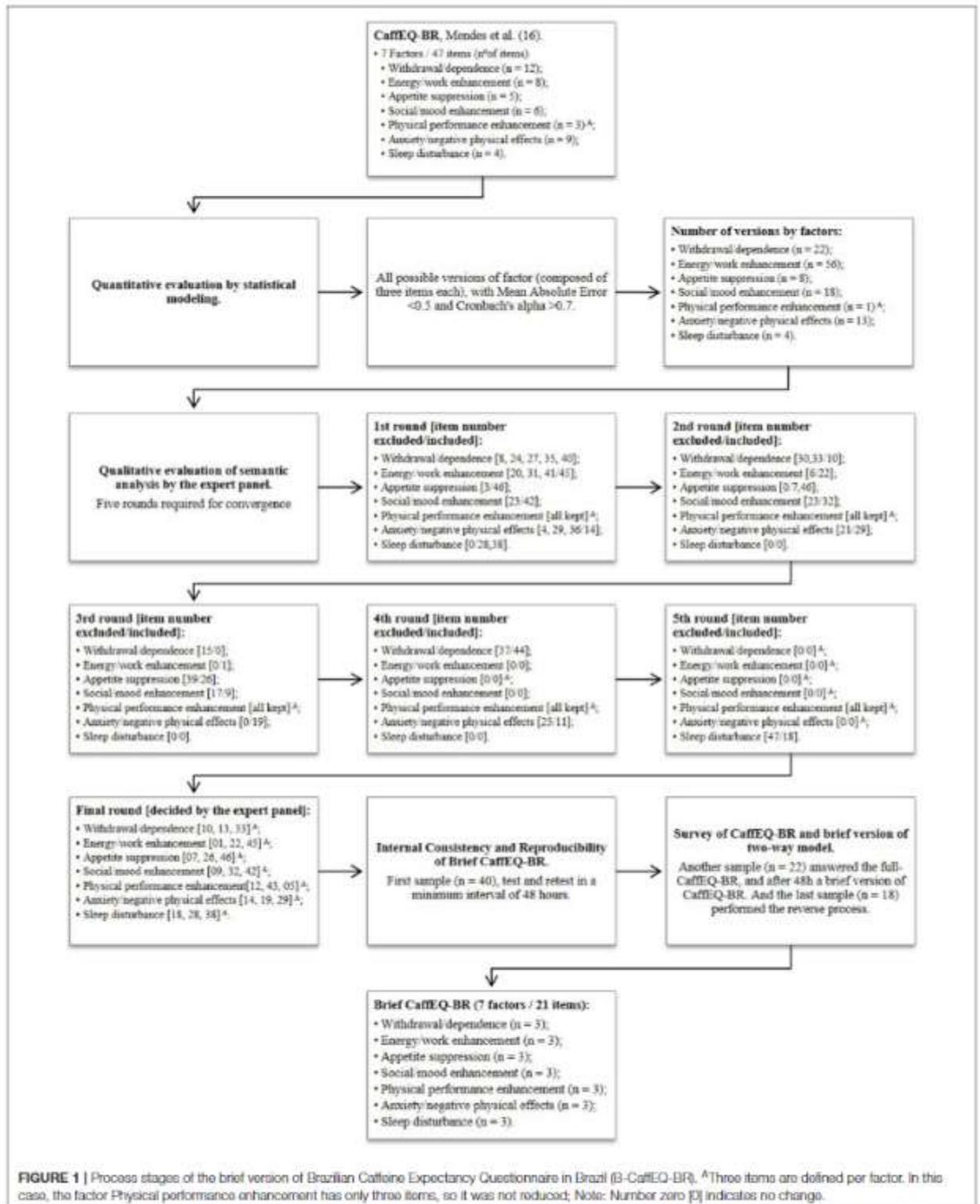
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FIGURE 1 | Process stages of the brief version of Brazilian Caffeine Expectancy Questionnaire in Brazil (B-CaffEQ-BR). ^AThree items are defined per factor. In this case, the factor Physical performance enhancement has only three items, so it was not reduced; Note: Number zero [0] indicates no change.

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TABLE 1 | Internal consistency of the brief version of Caffeine Expectancy Questionnaire in Brazil (B-CaffEQ-BR) ($n = 62^A$).

Factors	N. items	Cronbach's α
Withdrawal/dependence	3	0.729
Energy/work enhancement	3	0.799
Appetite suppression	3	0.819
Social/mood enhancement	3	0.774
Physical performance enhancement	3	0.909
Anxiety/negative physical effects	3	0.837
Sleep disturbance	3	0.859
Entire questionnaire	**21**	**0.906**

$^A n = 62$ participants in total, regular adult caffeine consumers in Brazil (175.8 ± 94.4 mg/day). Subsamples: $n = 18$ brief to brief to full + $n = 22$ only brief to brief + $n = 22$ full to brief.

caffeine effects were similar across all seven factors of B-CaffEQ-BR compared to the full version (16).

In addition, B-CaffEQ-BR obtained a significant reduction from 47 to 21 items, presenting a real time saver for completion (reduction from ~10 to 5 min) (internal data). This substantial saving of time is important to popularize online surveys (18). Therefore, the B-CaffEQ-BR fits better to web-based research demands, and the current model is widely used through the internet and social networks (13, 15, 16, 20). The questionnaire is semantically adapted to the Brazilian language and culture and can be applied to the Brazilian adult population of habitual caffeine consumers. This instrument is essential for the proper screening of research participants around caffeine studies (26). Sometimes, sample heterogeneity can compromise the internal or external validation of the study (27). The sample profile regarding the expectations of caffeine effects reduces the possible confounding variables in the analysis (26, 28).

The application of a methodological and statistical approach allowed the reduction of the questionnaire resulting in excellent internal consistency and overall reproducibility for the entire questionnaire and its seven factors (**Tables 1, 2**). The possibility of using the robust database from the full CaffEQ-BR allowed a targeted selection of the 21 items of the brief version. Thereby, this study was able to achieve reproducibility and internal consistency of the brief version without the intention of assessing the expectations of caffeine effects through the B-CaffEQ-BR.

Regarding **Table 1**, the internal consistency of the entire questionnaire is not the average of the factors, but Cronbach's α scores considering the whole instrument. The isolated factors presented a satisfactory Cronbach's α (α ≥ 0.729), and the entire questionnaire showed a very satisfactory internal consistency (α = 0.906). It reinforces the need for factor analysis of the entire questionnaire (22). Another important aspect was the semantic evaluation of the panel of experts. In addition to the statistical approach, semantic analyses were performed by funneling process to reduce from 47 to 21 items with the seven factors preserved. The brief English version of the CaffEQ also presented a similar reduction from 47 to 20 items keeping the

seven factors and showed a satisfactory internal consistency ($n = 975$; α = 0.93) (13), similar to the original CaffEQ version ($n = 1,046$; α = 0.96) (14).

Concerning the composition of the B-CaffEQ-BR (21 items) compared with the brief English version (20 items) (13), we found that 11 items (47.6%) converge between versions (items: 1, 7, 12, 13, 19, 26, 28, 42, 43, 45, and 46). The English and Portuguese–Brazilian versions are different, not only in linguistic and cultural adaptation but also in the selected items in the questionnaire. Therefore, they must be applied to their respective populations, for which they were validated.

The adoption of the mixed two-way model was essential to confirm that, regardless of the order of application (brief–brief or brief–full), the instrument presented an excellent overall reproducibility (ICC = 0.978 and 0.920, respectively) (**Table 2**), of the full version (ICC = 0.976) (16). This methodological strategy is an additional precaution to control the learning bias since the time interval between tests (48–72 h) should solve this issue. The inversion application order of the questionnaires can avoid this memorization/learning risk of bias (29).

A relevant result obtained was the high mean value (3.90–4.26) observed in the "Energy/work enhancement" factor showing a probable effect on the expectation of stimulating caffeine effects by the responders. The opposite (improbable effect) was observed for the "Anxiety factor/negative physical effects" factor, which presented a mean value <2.0. In all studies that applied the CaffEQ, the samples were composed of regular caffeine consumers (13–16). People who presented negative effects after caffeine consumption are probably not regular consumers (11, 14). Therefore, a tendency to express more positive than negative effects is expected (14, 30). Many people possibly scored high value for "Energy/work enhancement" due to the expectation of productivity at work and studies, a fact more observed in Western consumers (30), such as the Brazilian adults participating in the present study. Other studies show high consumption of caffeine sources above the population average in specific groups, such as University students (31, 32) and men of working age at work (3, 31). In any case, our sample is similar on the sociodemographic aspects, caffeine consumption, and expectancy recorded in the CaffEQ-BR full version (16).

The Caffeine Expectancy Questionnaire in Brazil, in full and brief versions, aims to discover individual caffeine expectancy. However, the benefits of the brief version are accuracy (as well as the full version) and quick and easy application. In the sporting context, performance-related factors have more relevance (e.g., "energy/work enhancement," "social/mood enhancement," "physical performance enhancement," and "anxiety/negative physical effects"). Understanding these expectations is critical to assess the risk of bias in clinical trials in sports science due to the ergogenic or ergolytic effects of placebo associated with the effects of caffeine. Literature shows how the placebo effect (33, 34), either due to excess or lack of expectation about the effect of caffeine (12, 14, 35, 36), can represent a possible risk of bias for the main findings of the research. For example, scores above the national average for factors may indicate a tendency to respond to caffeine supplementation. In the comparison of the average results in **Table 2**, with the averages observed nationally (16),

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TABLE 2 | Mean (SD) of Caffeine Expectancy Questionnaire in Brazil (CaffEQ-BR) full and brief scores and measure of agreement.

Factors (n° items Full to Brief)	Brief × Brief (n = 40)[A]			Full × Brief (n = 40)[A]		
	Brief 1 Mean (SD)	Brief 2 Mean (SD)	ICC[B]	Full Mean (SD)	Brief Mean (SD)	ICC[B]
Withdrawal/dependence (12 to 3)	3.04 (1.49)	2.98 (1.50)	0.953	2.55 (1.50)	2.69 (1.37)	0.931
Energy/work enhancement (8 to 3)	4.07 (1.36)	4.09 (1.49)	0.920	3.90 (1.36)	4.26 (1.30)	0.829
Appetite suppression (5 to 3)	2.12 (1.37)	2.16 (1.41)	0.975	1.82 (1.19)	1.69 (1.07)	0.908
Social/mood enhancement (6 to 3)	3.19 (1.47)	3.26 (1.45)	0.949	3.07 (1.37)	2.89 (1.27)	0.780
Physical performance enhancement (3 to 3)	3.81 (1.50)	3.87 (1.65)	0.960	3.45 (1.57)	3.90 (1.57)	0.885
Anxiety/negative physical effects (9 to 3)	1.94 (1.08)	1.95 (1.25)	0.915	1.48 (0.66)	1.86 (0.76)	0.726
Sleep disturbance (4 to 3)	3.31 (1.62)	3.08 (1.62)	0.946	2.88 (1.65)	2.65 (1.69)	0.882
Entire questionnaire	3.07 (0.97)	3.05 (0.98)	0.978	2.74 (0.90)	2.79 (0.80)	0.920

[A]n = 18 brief–full and 22 full–brief subsample, regular adult caffeine consumers in Brazil (160.0 ± 71.8 mg/day); [B]ICC, Intraclass Correlation Coefficient (absolute agreement) obtained through a mixed two-way model; Likert scale from 1 = Very unlikely to 6 = Very likely.

by factors: withdrawal/dependence, averages between 2.55 and 3.04, national 3.48 (1.43); energy/work enhancement, between 3.90 and 4.26, national 4.14 (1.32); appetite suppression, between 1.69 and 2.16, national 2.24 (1.17); social/mood enhancement, between 2.89 and 3.26, national 3.41 (1.38); physical performance enhancement, between 3.45 and 3.90, national 3.47 (1.51); anxiety/negative physical effects, between 1.48 and 1.95, national 1.78 (0.77); sleep disturbance, between 2.65 and 3.31, national 2.47 (1.62). Moreover, its application in clinical practice, to know the caffeine expectancy profile, can help to adjust the caffeine prescription. However, further studies are necessary to evaluate other applications of CaffEQ-BR with more specific purposes.

Some limitations of the present study must be observed. Web-based research has an inherent selection bias, limited to those with access to computers and internet resources, a fact described and observed in other studies with CaffEQ (13–16). Web-based research is limited to control environmental factors during the research application that may add some risk of bias to the data collected. However, the robustness and consistency of our results suggest that respondents answered the questions consciously. A fact observed in the present study is that the average daily self-reported caffeine intake (175.8 ± 94.4 mg/day) was lower than that observed in the full CaffEQ-BR (265 ± 159 mg/day) (16) and slightly higher than Brazil nationwide estimation (115 ± 96 mg/day) (37). This provides indirect evidence that our sample is regular caffeine consumers with a weekly and daily average that may reflect the consumption profile of the general population.

CONCLUSION

The B-CaffEQ-BR is available for the Brazilian adult population. This study provides a reliability questionnaire, expressed by adequate internal consistency and reproducibility, similar to the full version of the CaffEQ-BR. The brief version can characterize the expectations of the effect of caffeine on adult Brazilian consumers, with more straightforward and feasible online applications in large populations, and may be helpful in future studies on caffeine.

DATA AVAILABILITY STATEMENT

The original contributions generated for this study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the University Católica of Brasília (Brasilia, Brazil) (number: 23019319.3.0000.0029) and followed the guidelines established by the Declaration of Helsinki. The volunteers were informed about the study protocol and provided web-based consent. The patients/participants provided their written informed consent to participate in this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.695385/full#supplementary-material

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Brief version of Caffeine Expectancy Questionnaire Brazil (B-CaffEQ-BR)

Supplementary Material

Versão curta do Questionário de Expectativa de Efeitos da Cafeína, Brasil (B-CaffEQ-BR)

Instruções: Estamos interessados em suas crenças sobre os efeitos que a cafeína tem sobre você. Abaixo há uma lista de possíveis efeitos da cafeína quando consumida. Usando a escala como guia, avalia cada afirmação em termos de quanto é PROVÁVEL ou IMPROVÁVEL para esses efeitos como consequência do consumo da cafeína. As possibilidades de respostas são: 1 = Muito improvável; 2 = Improvável; 3 = Um pouco improvável; 4 = Um pouco provável; 5 = Provável; 6 = Muito provável. Baseie suas respostas com base nas fontes de cafeína mais usuais na sua rotina, ou você pode optar por basear suas respostas em "cafeína/café".

Itens	Muito improvável	Improvável	Um pouco improvável	Um pouco provável	Provável	Muito provável
1. Cafeína/café me dá ânimo quando estou cansado(a).	☐	☐	☐	☐	☐	☐
2. Cafeína/café melhora meu desempenho físico.	☐	☐	☐	☐	☐	☐
3. A cafeína/café tira minha fome.	☐	☐	☐	☐	☐	☐
4. Cafeína/café melhora meu humor.	☐	☐	☐	☐	☐	☐
5. Eu fico ansioso(a) quando não tomo cafeína/café.	☐	☐	☐	☐	☐	☐
6. Eu me exercito melhor depois de tomar cafeína/café.	☐	☐	☐	☐	☐	☐
7. Eu sinto muita falta de cafeína/café quando não tomo.	☐	☐	☐	☐	☐	☐
8. Eu não gosto do jeito que eu me sinto após tomar cafeína/café.	☐	☐	☐	☐	☐	☐
9. Tomar cafeína/café a qualquer hora do dia atrapalha o meu sono.	☐	☐	☐	☐	☐	☐
10. Quando tomo cafeína/café fico nervoso(a).	☐	☐	☐	☐	☐	☐
11. Cafeína/café melhora minha concentração.	☐	☐	☐	☐	☐	☐
12. Cafeína/café me faz pular refeições.	☐	☐	☐	☐	☐	☐
13. Tomar cafeína/café na hora de dormir atrapalha meu sono.	☐	☐	☐	☐	☐	☐
14. Cafeína/café me deixa irritado(a).	☐	☐	☐	☐	☐	☐
15. Cafeína/café me faz sentir feliz.	☐	☐	☐	☐	☐	☐
16. Eu não funciono sem tomar cafeína/café.	☐	☐	☐	☐	☐	☐
17. Tomar cafeína/café no final da tarde atrapalha o meu sono.	☐	☐	☐	☐	☐	☐
18. Eu fico mais extrovertido(a) quando tomo cafeína/café.	☐	☐	☐	☐	☐	☐
19. Cafeína/café me ajuda a me exercitar por mais tempo.	☐	☐	☐	☐	☐	☐
20. Cafeína/café me faz sentir com mais energia.	☐	☐	☐	☐	☐	☐
21. Cafeína/café diminui o meu apetite.	☐	☐	☐	☐	☐	☐

5.3 - 3º ARTIGO – MENDES, Guilherme Falcão, et al. Can the Brazilian Caffeine Expectancy Questionnaires Differentiate the CYP1A2 and ADORA2A Gene Polymorphisms? —An Exploratory Study with Brazilian Athletes. *Nutrients*. 2022; 14(16):3355. https://doi.org/10.3390/nu14163355

Can the Brazilian Caffeine Expectancy Questionnaires Differentiate the *CYP1A2* and *ADORA2A* Gene Polymorphisms?—An Exploratory Study with Brazilian Athletes

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Abstract: This study investigated the ability of the Brazilian Caffeine Expectancy Questionnaire (CaffEQ-BR), full and brief versions, to differentiate genetic profiles regarding the polymorphisms of the *CYP1A2* (rs 762551) and *ADORA2A* (rs 5751876) genes in a cohort of Brazilian athletes. One-hundred and fifty participants were genotyped for *CYP1A2* and *ADORA2A*. After the recruitment and selection phase, 71 (90% male and 10% female, regular caffeine consumers) completed the CaffEQ-BR questionnaires and a self-report online questionnaire concerning sociodemographic data, general health status, and frequency of caffeine consumption. The order of completion of the CaffEQ-BR questionnaires was counterbalanced. The concordance between the full and brief versions of the CaffEQ-BR was analyzed using the intraclass correlation coefficient (ICC). To determine the discriminatory capacity of the questionnaires for genotype, the receiver operating characteristic (ROC) curve was applied for sensitivity and specificity (significance level of 5%). Mean caffeine intake was 244 ± 161 mg·day^{-1}. The frequency of AA genotypes for *CYP1A2* was 47.9% ($n = 34$) and 52.1% ($n = 37$) for C-allele carriers (AC and CC). The frequencies of TT genotypes for *ADORA2A* were 22.7% ($n = 15$) and 77.3% ($n = 51$) for C-allele carriers (TC and CC). All CaffEQ-BR factors, for the full and brief versions, were ICCs > 0.75, except for factor 6 (anxiety/negative effects; ICC = 0.60), and presented ROC curve values from 0.464 to 0.624 and 0.443 to 0.575 for *CYP1A2* and *ADORA2A*. Overall, the CaffEQ-BR (full and brief versions) did not show discriminatory capacity for *CYP1A2* and *ADORA2A* gene polymorphisms. In conclusion, the CaffEQ-BR was not able to differentiate genotypes for the *CYP1A2* or *ADORA2A* genes in this group of Brazilian athletes.

Keywords: caffeine; *CYP1A2*; *ADORA2A*; polymorphism; expectancy questionnaire

1. Introduction

Caffeine is the most consumed psychoactive substance worldwide, and coffee is the most common source on a global scale [1]. In addition, caffeine can be found in guarana, yerba mate, green tea, cocoa and its derivatives, cola-based beverages, supplements (e.g., energy drinks and chewing gum), and medicines [2,3]. To improve strength,

power, and endurance sports performance, the recommended dose varies from 3 to 6 mg·kg^{-1} body mass (BM) [4–6]. To improve cognitive aspects and wakefulness, 1 to 3 mg·kg^{-1} BM is an effective dose [7,8]. It is recommended that individuals who have never used caffeine supplementation or those who are sensitive to caffeine use lower doses [9]. Furthermore, high doses can be associated with increased adverse effects, such as irritation, anxiety, tachycardia, and sleep disturbance, depending on the genetic profile of the individual [10].

Genetic variants can affect caffeine metabolism [11], potentially inducing different effects of caffeine regarding the perception of effort, fatigue, sleep, appetite, and adverse or beneficial effects across a range of exercise modalities, including endurance, team sports, short-duration high-intensity exercise, and resistance exercise [12,13]. In nutrigenetic studies, caffeine is one of the most studied substances in clinical trials assessing the interactions between gene polymorphisms and sports performance [14–17]. Differences in the effect of caffeine may be explained in part by the polymorphism in the single nucleotide polymorphism (SNP) of the cytochrome P450 enzyme *CYP1A2* (SNP rs762551 −163C > A; AA and C-carriers genotypes), which is related to the hepatic metabolization of caffeine [11]. C allele carriers (AC and CC genotypes) are considered slow caffeine metabolizers and AA genotypes are fast metabolizers [10]. In addition, a SNP on the *ADORA2A* gene (SNP rs5751876 1976T > C; TT and C-carriers genotypes) is related to the sensitivity and responsiveness to caffeine [18]. TT homozygotes experience high sensitivity to the effects of caffeine, likely due to a greater effect of caffeine on the central nervous system (CNS) adenosine receptors, whereas C allele carriers (TC and CC genotypes) present lower caffeine sensitivity [10]. This effect may lead to feelings of anxiety, irritation, tachycardia, and sleep disturbance in TT homozygotes [19].

Understanding how the *CYP1A2* and *ADORA2A* genotypes affect the responsiveness and sensitivity of caffeine in the CNS is of great scientific and clinical relevance [12], including for sports performance, to individualize caffeine supplementation [10,14,20,21]. In clinical practice, this knowledge is important to avoid prescriptions disregarding the patient's genotype characteristics, or to prevent unnecessary use or sub-optimal caffeine doses according to the patient's profile [22,23]. In clinical trials, it is important to understand the caffeine expectation profile to minimize the risk of bias related to the individual's expectancy of caffeine's effects on exercise performance [7,24]. Thus, it is of interest to determine the *CYP1A2* and *ADORA2A* genotypes of any individuals undergoing caffeine consumption, be it in research or in the real world, since these genes may alter responses. Nonetheless, genotyping is a time consuming and expensive process that is not easily available, meaning alternative, more cost-effective methods are desirable.

Therefore, assessing the expectations about caffeine's effects is important due to its impacts on mood and sports performance. The Brazilian caffeine expectancy questionnaires (full and brief versions) (CaffEQ-BR) were developed to investigate expectations relating to caffeine ingestion in the adult Brazilian population, specifically regarding factors related to dependence, energy/work improvement, social/mood enhancement, physical performance, anxiety, and sleep disturbances [25,26]. Understanding these expectations can be a useful tool to assess the potential ergogenic or ergolytic response to caffeine supplementation. Physical performance may be differentially affected by caffeine depending on *CYP1A2* genotype [15], whereas anxiety and sleep disturbance have been associated with the *ADORA2A* gene [27]. Thus, genetic differences in caffeine metabolism (e.g., *CYP1A2*) and sensitivity (e.g., *ADORA2A*) may lead to different response profiles to the CaffEQ-BR questionnaires.

The present study aimed to examine the ability of the CaffEQ-BR questionnaires (full and brief versions) to differentiate the polymorphisms of the *CYP1A2* and *ADORA2A* genes. The study hypothesis was that the CaffEQ-BR instrument could differentiate the polymorphisms of the *CYP1A2* and *ADORA2A* genes. If this holds true, these questionnaires may be a cost-efficient method capable of identifying different genotypes that could be implemented in clinical research and practice to guide caffeine recommendations.

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2. Materials and Methods

This was a cross-sectional study involving 71 participants genotyped for *CYP1A2* and *ADORA2A* polymorphisms who completed the full and brief versions of the CaffEQ-BR [25,26]. The present study was approved by the Ethics Committee of the Universidade Católica de Brasília (CAAE 23019319.3.0000.0029) and followed the guidelines established by the Declaration of Helsinki. Volunteers were informed about the study protocol and provided their consent using an online form.

2.1. Participants

Participants were recruited among individuals who participated in the study by Spineli et al. [28] ($n = 100$) and Barreto et al. ($n = 50$) (data not yet published). Inclusion criteria were: (i) Brazilian adult (19–59 years old), resident in Brazil, regular consumer of caffeine ($\geq 3x$ a week) from various sources, and agreement to complete the full and brief versions of CaffEQ-BR; (ii) had *CYP1A2* $-163C > A$ and *ADORA2A* 1976T > C genotypes determined.

In the Spineli et al. study [28], the participants were healthy, trained/developmental athletes [29] engaged in volleyball, athletics, or competitive soccer (age: 15 ± 2 years; height: 1.69 ± 0.10 m; BM: 58.8 ± 11.9 kg; VO$_{2max}$: 44.0 ± 2.7 mL·kg^{-1}·min^{-1}) [28]; and in Barreto et al. (unpublished), participants were healthy male and female trained cyclists [30] (age: 37 ± 6 and 40 ± 2 y; height: 1.76 ± 0.04 and 1.63 ± 0.04 m; BM: 74.1 ± 6.7 and 61.5 ± 7.3 kg; VO$_{2max}$: 51.1 ± 5.2 and 42.3 ± 8.12 mL·kg^{-1}·min^{-1}, respectively). It is important to emphasize that the athletes in the Spineli et al. study [28] were teenagers during the collection period of the original study. However, the application of the CaffEQ-BR occurred four years later, and all volunteers were over 19 years old when completing the questionnaires.

The distribution across genotypes generally includes fewer homozygous participants carrying the CC genotype for *CYP1A2* and TT for *ADORA2A*, which represent less than 10% and 20% of the population, respectively [15,27]. Thus, the objectives were to obtain a sample where each allele subgroup had at least 10 genotyped participants. Considering the formation of four subgroups with at least 10 carriers of the C allele (AC and CC) and A homozygote polymorphism (AA) for *CYP1A2* and carriers of the C allele (CT and TT) and T homozygote (TT) *ADORA2A*, the minimum sample would be 40 participants. Of the 150 individuals invited, 71 participated in the research.

2.2. Questionnaires Application

Participants completed the full and brief versions of the CaffEQ-BR questionnaire. We have previously shown the full (overall ICCs > 0.9) [25] and brief (overall ICCs > 0.9) [26] versions of the questionnaires to have excellent reliability in the Brazilian population. The questionnaires were applied via Google Forms™ (Google LLC, Mountain View, CA, US) to a convenience sample of adult Brazilian athletes [25,26]. Participants were contacted via phone calls, email, or social media like Facebook™, Instagram™, or WhatsApp™ (Meta Inc., Menlo Park, CA, US) [31]. The data collection period took place between October 2021 and April 2022. First, the participants completed a self-report online questionnaire concerning sociodemographic data, general health status, and frequency of caffeine consumption. Then, they answered the full and brief version of the CaffEQ-BR with a minimum interval of 48 h and a maximum of 15 days between the first and second questionnaires [32]. This step was used to analyze the agreement between the full and short versions of the CaffEQ-BR. The order of completion of the questionnaires was counterbalanced, in which part of the sample started with the full version and then the brief version, and the other part was performed in reverse order [26].

2.3. Genetic Analysis

For the samples of Spineli et al. [28], the *CYP1A2* gene extraction procedure followed the protocol proposed by Cornelis et al. [33], and for *ADORA2A*, that by Deckert et al. [34].

For the samples of Barreto et al. (unpublished), the *CYP1A2* gene extraction procedure followed the protocol proposed by Salinero et al. [35], and for *ADORA2A*, that by Muñoz et al. [18]. Genotyping for *CYP1A2* (rs762551) was successful in all participants. However, five participants were not successful in determining the polymorphism of the *ADORA2A* gene (rs5751876). The researchers and participants were blinded to their genetic polymorphisms until all statistical analyses had been completed.

2.4. Statistical Analysis

Descriptives analysis are presented through frequencies and percentages for categorical variables and mean and standard deviation for numerical variables (CaffEQ-BR scores). The CaffEQ-BR concordance between full and brief versions was verified using the intraclass correlation coefficient (ICC). The type of ICC adopted was the absolute agreement considering the average agreement of the two applications. The ICC calculation was based on a two-way mixed model. According to Cicchetti [36], an excellent ICC agreement was considered when ≥0.75 was found between the two responses. The ability of CaffEQ-BR to identify the presence (or absence) of the *CPY1A2* and *ADORA2A* gene polymorphisms was evaluated by the receiver operating characteristic (ROC) curve. The area under the ROC curve (AUC) ranged from 0 to 1, an AUC = 0.5 indicates that CaffEQ-BR has no discrimination capability, and AUC = 0 or 1 corresponds to perfect discrimination. In addition, AUC 0.0–0.5 or 0.5–1.0 indicates that lower/higher CaffEQ-BR values indicate evidence of a positive state [37]. The analyses were performed with two-tier sample clusters using C allele carriers and homozygous AA genotype for *CYP1A2* and TT homozygotes for *ADORA2A*, and three-tier clusters using AA, AC, and CC genotypes for *CYP1A2* and TT, CT, and CC genotypes for *ADORA2A*. The ICC and AUC estimates are presented with their respective 95% confidence intervals and were evaluated by IBM SPSS Software version 22 (IBM SPSS Statistics for Windows, IBM Corp, Armonk, NY, USA).

3. Results

3.1. Sample Profile

This study was conducted with 71 Brazilian adults who were habitual caffeine consumers (244 ± 161 mg·day^{-1}). The sample profile consisted of 90.1% males, 25 ± 8 y, body mass index 23.7 ± 3.9 kg/m^2 (69.0% eutrophic [38]), 33.8% completed high school, and 83.1% presented an average monthly family income above one minimum wage (R\$ 1212 = US\$ 246.63) (May 2022) (Table 1).

Table 1. Sociodemographic data and sample profile ($n = 71$).

	Categories	Total (N = 71)	
		n	%
Sex	Male	64	90.1
	Female	7	9.9
Age	<30 years	55	77.5
	≥30 years	16	22.5
Body Mass Index (kg/m²) *	<18.5	2	2.8
	18.5–24.9	49	69.0
	25–29.9	14	19.7
	≥30	6	8.5
Self-identification	Asia descendants	5	7.0
	White	24	33.8
	Indigenous	3	4.3
	Pardo	29	40.8
	Black	9	12.7
	Without description	1	1.4

Table 1. Cont.

	Categories	Total (N = 71)	
		n	%
Physical Exercises	No	26	36.6
(≥ 150 min/week) **	Yes	45	63.4
Degree of Education	Complete elementary school	1	1.4
	Incomplete high school	9	12.7
	Complete high school	24	33.8
	Incomplete graduated	22	30.0
	Graduated	6	8.5
	Postgraduate studies	9	12.7
Income (BRL) ***	Up to 1000.00	12	16.9
	1000.01 to 2000.00	18	25.4
	2000.01 to 3000.00	17	24.0
	3000.01 to 5000.00	15	21.1
	5000.01 to 10,000.00	5	7.0
	Above 10,000.00	4	5.6
Self-reported chronic diseases	No	67	94.4
	Yes	4	5.6

Note: * Body mass index (BMI) followed the criteria adopted by the World Health Organization (WHO) [38]: underweight (BMI < 18.5kg/m^2), adequate (BMI between 18.5 and 24.9kg/m^2), overweight (BMI between 25 and 29.9kg/m^2), and obesity (BMI ≥ 30kg/m^2); ** The cutoff point according to the WHO [39] was adopted, with a minimum workload that indicates whether the participant was physically active at the time of participating in the research; *** 5.00 BRL = 1.00 USD on May 2022.

3.2. CYP1A2 and ADORA2A Genotypes

The frequency of AA homozygotes for the *CYP1A2* gene was 47.9% (n = 34), and that of C allele carriers (AC and CC genotypes) was 52.1% (n = 37). For the *ADORA2A* gene, 22.7% (n = 15) were TT homozygotes and 77.3% (n = 51) were C allele carriers (TC and CC genotypes).

3.3. CaffEQ-BR Full and Brief Questionnaires Agreement

All factors showed excellent agreement (ICC > 0.75; Table 2), except item 6: "Anxiety/negative physical effects" (ICC = 0.6). The scores obtained for the full and brief CaffEQ-BR showed an ICC agreement between the two versions (full with 47 items and brief with 21 items) (Table 2).

Table 2. Means (DP) and intra-class correlation coefficients (ICC) between scores of the CaffEQ-BR full and brief versions (n = 71).

Factors	Full	Brief	ICC * (CI 95%)
1. Withdrawal/dependence	2.33 (1.24)	2.06 (1.22)	0.851 (0.754–0.909)
2. Energy/work enhancement	3.17 (1.43)	3.13 (1.41)	0.879 (0.806–0.924)
3. Appetite suppression	1.87 (0.97)	1.70 (0.93)	0.769 (0.631–0.856)
4. Social/mood enhancement	2.62 (1.29)	2.55 (1.34)	0.907 (0.850–0.942)
5. Physical performance enhancement	3.16 (1.51)	2.94 (1.46)	0.891 (0.824–0.932)
6. Anxiety/negative physical effects	1.84 (0.89)	1.53 (0.80)	0.600 (0.356–0.751)
7. Sleep disturbance	2.58 (1.41)	2.49 (1.38)	0.858 (0.772–0.911)
Overall	2.44 (0.98)	2.34 (0.90)	0.856 (0.777–0.910)

* An excellent ICC agreement is considered when ≥ 0.75 was found between the two responses.

3.4. CaffEQ-BR Discriminatory Capacity for CYP1A2 and ADORA2A Genotypes

The analyses performed with two-tier clusters (C allele carriers and homozygous carriers—AA for *CYP1A2* and TT for *ADORA2A*) obtained a better discriminatory capacity than with three-tier clusters (AA, AC, and CC for CYP1A2; and TT, CT, and CC for ADORA2A) (data not presented).

Table 3 shows the AUC results for CaffEQ-BR full and brief versions for the *CYP1A2* gene with the AA homozygotes as the reference level. Note that all seven factors and the overall result presented values near to 0.5, which indicates no discriminatory capacity for the *CYP1A2* genotypes. Figure 1 shows the CaffEQ-BR factor lines do not deviate from the reference diagonal line when compared to the pattern of responses recorded by genotype AA for CYP1A2, used as a reference for fast caffeine metabolism.

Table 3. Area under the ROC curve (AUC) of CaffEQ-BR full and brief versions for *CYP1A2* genotypes.

Factors	AUC * (CI 95%)	
	Full	Brief
1. Withdrawal/dependence	0.513 (0.376–0.651)	0.496 (0.360–0.632)
2. Energy/work enhancement	0.464 (0.329–0.599)	0.504 (0.369–0.640)
3. Appetite suppression	0.537 (0.402–0.672)	0.443 (0.304–0.582)
4. Social/mood enhancement	0.548 (0.411–0.686)	0.514 (0.376–0.651)
5. Physical performance enhancement	0.472 (0.336–0.608)	0.467 (0.332–0.602)
6. Anxiety/negative physical effects	0.624 (0.492–0.757)	0.575 (0.441–0.709)
7. Sleep disturbance	0.528 (0.391–0.665)	0.453 (0.318–0.589)
Overall	0.529 (0.393–0.665)	0.504 (0.367–0.640)

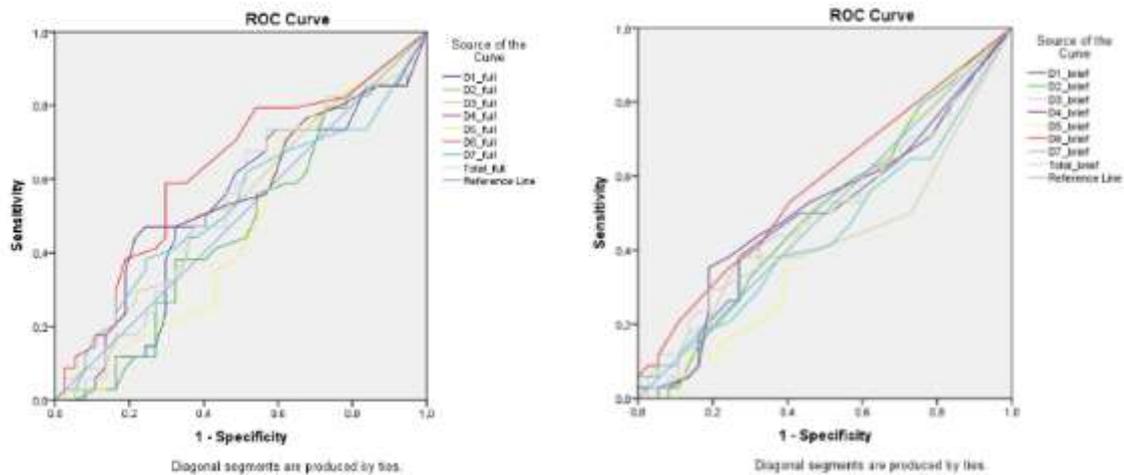* Genotype AA group is the reference level (0.5 = no discriminatory effects).

Figure 1. ROC curve of the CaffEQ-BR full (**left**) and brief (**right**) versions. The colored lines are the recorded scores of the 7 CaffEQ-BR factors for discrimination of the *CYP1A2* genotypes considering AA group as the reference level (0.5 = reference diagonal line, no discriminatory for sensitivity or specificity). Factors: D1: withdrawal/dependence; D2: energy/work enhancement; D3: appetite suppression; D4: social/mood enhancement; D5: physical performance enhancement; D6: anxiety/negative physical effects; D7: sleep disturbance.

Table 4 shows the AUC results for the CaffEQ-BR full and brief versions for the *ADORA2A* gene with the TT homozygote group as the reference level. Note that of all seven factors, only factor 6 (anxiety/negative physical effects) showed discriminatory ability for the *ADORA2A* genotypes in the brief questionnaire (AUC = 0.293). In Figure 2, only factor 6 for the brief CaffEQ-BR is far from the reference diagonal line, which indicates its discriminatory capacity for *ADORA2A* genotypes.

Table 4. Area under the ROC curve (AUC) of CaffEQ-BR full and brief versions for *ADORA2A* genotypes.

Factors	AUC * (CI 95%)	
	Full	Brief
1. Withdrawal/dependence	0.415 (0.245–0.585)	0.385 (0.233–0.537)
2. Energy/work enhancement	0.516 (0.324–0.708)	0.414 (0.250–0.578)
3. Appetite suppression	0.358 (0.199–0.516)	0.422 (0.267–0.577)
4. Social/mood enhancement	0.498 (0.330–0.666)	0.417 (0.257–0.577)
5. Physical performance enhancement	0.529 (0.350–0.709)	0.444 (0.279–0.609)
6. Anxiety/negative physical effects	0.356 (0.201–0.510)	0.293 (0.155–0.431)
7. Sleep disturbance	0.461 (0.290–0.632)	0.455 (0.289–0.621)
Overall	0.443 (0.271–0.616)	0.367 (0.211–0.522)

* Genotype TT group is the reference level (0.5 = no discriminatory effects).
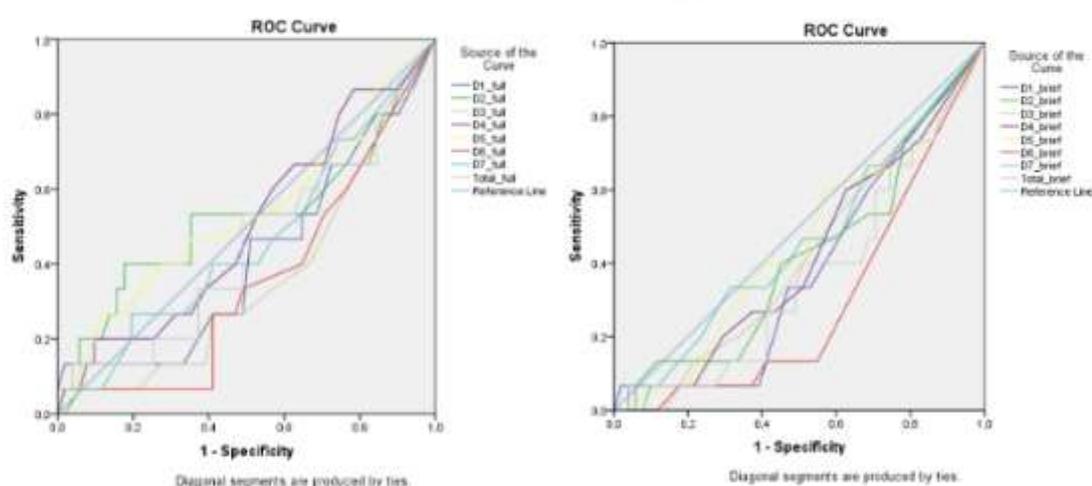

Figure 2. ROC curves of the CaffEQ-BR full (left) and brief (right) versions. The colored lines are the recorded scores of the 7 CaffEQ-BR factors for discrimination of the *ADORA2A* genotypes considering TT group as the reference level (0.5 = reference diagonal line, no discriminatory for sensitivity or specificity). Factors: D1: withdrawal/dependence; D2: energy/work enhancement; D3: appetite suppression; D4: social/mood enhancement; D5: physical performance enhancement; D6: anxiety/negative physical effects; D7: sleep disturbance.

4. Discussion

This is the first study that evaluated if an instrument (full and brief CaffEQ-BR questionnaires) can differentiate the polymorphisms of the *CYP1A2* and *ADORA2A* genes. Data showed that the full and brief versions of CaffEQ-BR were not able to differentiate the *CYP1A2* or *ADORA2A* genotypes in these adult Brazilian athletes. Of all factors, only factor 6 (anxiety/negative physical effects) in the brief questionnaire showed any discriminatory capacity for the genotype TT for the *ADORA2A* gene. However, the sample size was limited to two individuals, which precluded generalizing this result to an external population. Specifically, factor 6 in the brief CaffEQ-BR is composed of three questions related to the expected anxiety and negative physical effects of caffeine: "I don't like the way I feel after drinking caffeine/coffee" (portuguese: *Não gosto de como me sinto depois de tomar cafeína/café*). "When I drink caffeine/coffee I get nervous" (portuguese: *Quando bebo cafeína/café fico nervoso*). "Caffeine/coffee makes me irritable" (portuguese: *Cafeína/café me deixa irritado*). Anxiety and sleep disturbance (factors 6 and 7) have been associated with the *ADORA2A* gene [27]; therefore, future studies should consider these factors when developing a questionnaire capable of discriminating between *ADORA2A* polymorphisms.

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The CaffEQ-BR questionnaires were not capable of discriminating between genotypes for *CYP1A2*, suggesting differences in caffeine metabolism do not lead to different expectations regarding caffeine effects. The importance of caffeine metabolism for exercise performance following supplementation is still unclear and inconsistent [12,14]. Most studies have shown no influence of *CYP1A2* genotype on caffeine's ergogenic effect [18,35,40,41], though some studies do suggest that those with slower metabolism (i.e., C-allele carriers) might have less benefit [15,17,42]. No study has shown differential effects of caffeine on physiological measurements or side-effects between *CYP1A2* genotypes. Differences in caffeine metabolism may not sufficiently alter variables that would modify caffeine expectancy, as the questionnaires here may provide questions that are too vague and generalized to detect differences in *CYP1A2* genotypes. It cannot be ruled out that other questionnaires related to how symptoms develop and persist over time following caffeine ingestion may provide a more accurate method of determining an individual's caffeine metabolism genotype.

Studies that aim to find differences in the polymorphisms of the *ADORA2A* gene seem more consistent, especially regarding the negative effects of caffeine in more sensitive individuals (TT homozygotes), such as increased anxiety and sleep disturbance at higher doses (>6 mg·day^{-1}) [10]. In the articles published by the present research group [25,26] and in all studies using the CaffEQ [24,43,44], the Likert scale scores were low (<3) in factor 6 (anxiety/negative physical effects). Huntley and Juliano [24] showed that daily consumers of caffeine presented high scores ($\geq$4) in factors 1, 2, 3, 4, and 5 (related to expectation of dependence and beneficial effects of caffeine). However, irregular consumers of caffeine presented high scores ($\geq$4) for factors 6 and 7 (related to negative effects such as anxiety and sleep disturbance). Studies suggest that individuals who may experience more adverse effects from caffeine, especially with dosages exceeding the safe limit (> 6 mg·day^{-1}), are likely TT homozygotes for the *ADORA2A* gene [27,45]. Thus, it was surprising, and contrary to our hypothesis, that the questionnaires used here could not differentiate between *ADORA2A* genotypes.

Individuals with high dependency scores present strong correlation and high scores in CaffEQ factors 1, 2, 3, 4, and 5 (related to expectation of dependence and beneficial effects). However, individuals who reported a desire to reduce or eliminate caffeine consumption from their routines had high scores on factors 6 and 7 (related to anxiety/negative physical effects and sleep disturbance) [24]. In the study by Kearns et al. [44], factor 6 was associated with other validated questionnaires about anxiety, appetite suppression, and sleep disturbance. Schott et al. [43], who validated the CaffEQ for German-speaking countries, also found a negative correlation between mean consumption of caffeine and negative symptoms. This reinforces the hypothesis that habitual caffeine consumers are usually people with the genetic profiles to experience favorable effects from caffeine intake, and consequently greater chances of dependence. In addition, people who are very sensitive to caffeine may experience more adverse effects and avoid its consumption.

In all versions of the CaffEQ, the questionnaire presents more factors to support people who experience beneficial effects or a possible dependence on caffeine than negative effects, such as anxiety and sleep disturbance [24–26,43,44]. Therefore, the instrument to discriminate the individuals' genetic variations regarding *ADORA2A* needs to be calibrated to have high sensitivity and specificity for those individuals who experience negative effects from caffeine. The present results suggest that future studies should include more individuals with low/irregular caffeine intake, as these may be, to a large extent, of the TT genotype for the *ADORA2A* gene.

A recent caffeine expectancy questionnaire (CaffCo) stressed the methodological caution needed to balance the number of positive/negative caffeine effects factors in the development of this kind of questionnaire [46]. The CaffCo may be an alternative questionnaire to be tested in the future for the capacity to discriminate the polymorphisms for *CYP1A2* and *ADORA2A* genes. Furthermore, a good alternative could be to carry out an exploratory factor analysis, followed by a confirmatory analysis based on a biobank

of individuals genotyped for *CYP1A2* and *ADORA2A* polymorphisms in an attempt to assess the ability to differentiate the genotypes according to the responses to the caffeine expectancy questionnaire.

The current data suggest that the CaffEQ-BR questionnaire cannot be used to differentiate individuals for the *CYP1A2* and *ADORA2A* genotypes. Nonetheless, regarding the practical applications, the CaffEQ-BR remains a useful tool to understand the expectation of caffeine intake to assess any potential risk of bias in clinical trials in sports science due to the possible ergogenic effects of placebo associated with the expected effects of caffeine in the placebo/control group [47,48], since higher or lower expectations about the effect of caffeine may alter outcomes measures [12,14].

The strengths of the present study are that we explored the capacity of both full and brief versions of the CaffEQ-BR questionnaires to discriminate between *CYP1A2* and *ADORA2A* genotypes; importantly, we also showed good agreement between both versions of the questionnaire, confirming our previous work [26]. Some potential limitations include the small sample size of homozygous participants (CC for *CYP1A2* and TT for *ADORA2A*) and the small number of female participants. However, it is unclear if the questionnaire could lead to different discriminatory capacities for genotypes between men and women. Nevertheless, we recommended that future studies balance the sample profile in terms of gender. The research was conducted with the participants previously enrolled in the study of Spineli et al. [28] and Barreto et al. (unpublished), who performed the genotype analysis of their athletes. Furthermore, considering the COVID-19 pandemic period during the study conduction, it was not possible to increase our sample size or female representativeness.

The analyses were even less discriminatory when performed with three-tier clusters (AA, AC, and CC for *CYP1A2*; and TT, CT, and CC for *ADORA2A*), due to high sample segmentation and analysis with small groups. To achieve a more expressive number of genotypes of CC and TT for the *CYP1A2* and *ADORA2A* genes (respectively), future studies should enroll larger samples due to the small presence of these homozygous individuals in the general population. We also encourage further studies to evaluate other applications of the CaffEQ-BR with more specific purposes, such as its application to the effect of placebo-controlled caffeine supplementation in clinical trials, as performed by Shabir et al. [49], with heart rate variability monitorization [50] and salivary paraxanthine level [51] as control covariates.

5. Conclusions

The CaffEQ-BR (full and brief versions) was not able to differentiate genotypes for the *CYP1A2* and *ADORA2A* genes in this healthy adult Brazilian athlete population. Future studies should replicate this research in a large sample, and include low caffeine consumers as a control group, thereby calibrating the caffeine expectancy questionnaire to focus on aspects of anxiety and increased negative effects in search of discriminating the TT genotype for the *ADORA2A* gene.

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CAPÍTULO 3

6 - CONCLUSÃO

O presente estudo objetivou avaliar a capacidade do CaffEQ-BR na determinação dos polimorfismos dos genes *CYP1A2* (rs762551) e *ADORA2A* (rs5751876), conforme as expectativas de efeito da cafeína medidas pelo instrumento. De fato, foi possível validar o CaffEQ-BR, um instrumento que avalia as expectativas aos efeitos da cafeína para adultos brasileiros. Assim como foi possível avaliar as expectativas de efeito da cafeína em participantes adultos brasileiros de todas as unidades da federação, com uma amostra representativa e balanceada. Além disso, foi possível validar a versão curta do instrumento, que possibilita uma aplicação mais rápida e efetiva, principalmente em formulários eletrônicos encaminhados por meio das redes sociais, por exemplo. Entretanto, o CaffEQ-BR (versão completa e curta) não foi capaz de diferenciar os genótipos para os genes *CYP1A2* e *ADORA2A* em uma amostra de atletas brasileiros. Pesquisas futuras devem replicar essa pesquisa em uma amostra substancialmente maior, incluindo consumidores de baixas quantidades de cafeína como grupo controle, calibrando o questionário de expectativa de cafeína com maior foco nos aspectos de ansiedade e aumento dos efeitos negativos na busca de discriminar o genótipo TT para o gene *ADORA2A*.

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8. APÊNDICES

APÊNDICE A – TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

O (a) senhor(a) está sendo convidado(a) a participar do projeto: **TRADUÇÃO PARA LÍNGUA PORTUGUESA E VALIDAÇÃO PARA CULTURA BRASILEIRA DO QUESTIONÁRIO DE EXPECTATIVA DOS EFEITOS DA CAFEÍNA/CAFÉ**, sob responsabilidade do professor e pesquisador da Universidade Católica de Brasília, Guilherme Falcão Mendes.

A cafeína é a substância estimulante mais consumida no mundo, sua forma de consumo mais habitual é pelo café, mas também é encontrada em chás, bebidas energéticas, chocolate, alguns medicamentos e suplementos esportivos. Logo, é importante estudar os efeitos positivos e negativos da cafeína no organismo.

Dessa forma o objetivo desta pesquisa é traduzir para a língua portuguesa e validar para cultura brasileira o Questionário de Expectativa de Cafeína, originalmente chamado de *Caffeine Expectancy Questionnaire* (CaffEQ), que avalia a percepção subjetiva de expectativa aos efeitos da cafeína/café. Essa pesquisa é importante para validação desse instrumento no Brasil, que irá auxiliar pesquisas na área de Nutrição.

O(a) senhor(a) receberá todos os esclarecimentos necessários antes e no decorrer da pesquisa e lhe asseguramos que seu nome não aparecerá, sendo mantido o mais rigoroso sigilo por meio da omissão total de quaisquer informações que permitam identificá-lo(a). O (a) senhor(a) pode se recusar a responder qualquer questão (do questionário) que lhe traga constrangimento, podendo desistir de participar da pesquisa em qualquer momento, sem nenhum prejuízo. A sua participação será da seguinte forma: responder por meio de formulário *online* um questionário sobre expectativa de efeitos subjetivos da cafeína/café. O tempo médio para preenchimento do formulário varia de 15 a 25 minutos. Os resultados da pesquisa serão divulgados na Universidade Católica de Brasília podendo ser publicados posteriormente em outros meios. Os dados e materiais utilizados na pesquisa ficarão sob a guarda do pesquisador.

Este projeto possui os seguintes benefícios: melhor compreensão pessoal sobre a sua relação com os possíveis efeitos positivos e negativos do consumo de cafeína/café.

O risco da pesquisa é mínimo, considerando a possibilidade do constrangimento ao responder às perguntas do questionário. É de nossa responsabilidade a assistência integral caso ocorra danos que estejam diretamente ou indiretamente relacionados à pesquisa. Esta pesquisa não lhe trará custos e despesas.

Se o(a) Senhor(a) tiver qualquer dúvida em relação à pesquisa, por favor telefone para: Prof. Guilherme Falcão Mendes, na instituição Universidade Católica de Brasília, telefone: 61 98426-5574, de segunda a sexta no horário das 8 às 18h.

Este projeto foi aprovado pelo Comitê de Ética em Pesquisa da UCB, número do protocolo CAAE: 23019319.3.0000.0029. As dúvidas com relação à assinatura do TCLE ou os direitos do sujeito da pesquisa podem ser obtidas no CEP/UCB pelo telefone: (61) 3356-9784. O CEP da UCB está localizado na sala K-239, no endereço Campus I - QS 07 – Lote 01 – EPCT – Águas Claras – Brasília – DF.

Declaro que, após convenientemente esclarecido pelo pesquisador e ter entendido o que me foi explicado, consinto em participar do presente Projeto de Pesquisa.

Eu aceito participar da pesquisa: SIM (   ) NÃO (   )

Nome completo do participante: Nome do pesquisador responsável:

_____   GUILHERME FALCÃO MENDES

Assinatura: Assinatura:

Brasília-DF, ____ de _____ de _____

Questionário de Expectativa de efeitos da Cafeína, versão brasileira (CaffEQ-BR)

Instruções: Estamos interessados em suas crenças sobre os efeitos que a cafeína tem sobre você. Abaixo há uma lista de possíveis efeitos da cafeína presentes nos produtos listados na tabela acima preenchida. Usando a escala como guia, avalia cada afirmação em termos de quanto é PROVÁVEL ou IMPROVÁVEL para esses efeitos como consequências do consumo da cafeína. As possibilidades de respostas são: 1 = Muito improvável; 2 = Improvável; 3 = Um pouco improvável; 4 = Um pouco provável; 5 = Provável; 6 = Muito provável. Baseie suas respostas no produto com cafeína que escolheu. Se você usa muitos tipos de produtos com cafeína, escolha o mais usual para basear suas respostas, ou você pode optar por basear suas respostas em "cafeína/café".

Itens	Muito improvável	Improvável	Um pouco improvável	Um pouco provável	Provável	Muito provável
1. Cafeína/café me dá ânimo quando estou cansado(a)	☐	☐	☐	☐	☐	☐
2. Eu fico extrovertido(a) quando tomo cafeína/café	☐	☐	☐	☐	☐	☐
3. Cafeína/café me ajuda a não comer mais do que deveria	☐	☐	☐	☐	☐	☐
4. Fico facilmente estressado(a) depois de tomar cafeína/café	☐	☐	☐	☐	☐	☐
5. Cafeína/café melhora meu desempenho físico	☐	☐	☐	☐	☐	☐
6. Fico menos cansado(a) depois de tomar cafeína	☐	☐	☐	☐	☐	☐
7. A cafeína/café tira minha fome	☐	☐	☐	☐	☐	☐
8. Fico triste quando não tomo cafeína/café	☐	☐	☐	☐	☐	☐
9. Cafeína/café melhora meu humor	☐	☐	☐	☐	☐	☐
10. Eu fico ansioso(a) quando não tomo cafeína/café	☐	☐	☐	☐	☐	☐
11. Eu me sinto angustiado(a) quando tomo cafeína/café	☐	☐	☐	☐	☐	☐
12. Eu me exercito melhor depois de tomar cafeína/café	☐	☐	☐	☐	☐	☐
13. Eu sinto muita falta de cafeína/café quando não tomo	☐	☐	☐	☐	☐	☐
14. Eu não gosto do jeito que eu me sinto após tomar cafeína/café	☐	☐	☐	☐	☐	☐
15. Eu me sinto mal se ficar sem cafeína/café	☐	☐	☐	☐	☐	☐
16. Cafeína/café aumenta minha motivação para trabalhar	☐	☐	☐	☐	☐	☐
17. Eu me sinto mais confiante depois de tomar cafeína/café	☐	☐	☐	☐	☐	☐
18. Tomar cafeína/café a qualquer hora do dia atrapalha o meu sono	☐	☐	☐	☐	☐	☐
19. Quando tomo cafeína/café fico nervoso(a)	☐	☐	☐	☐	☐	☐
20. Quando tomo cafeína/café fico mais alerta	☐	☐	☐	☐	☐	☐
21. Mesmo quando tomo uma pequena quantidade de cafeína/café fico ansioso(a)	☐	☐	☐	☐	☐	☐
22. Cafeína melhora minha concentração	☐	☐	☐	☐	☐	☐
23. Quando tomo cafeína/café fico mais amigável	☐	☐	☐	☐	☐	☐
24. Eu tenho que tomar cafeína/café todos os dias	☐	☐	☐	☐	☐	☐
25. Cafeína/café me faz suar	☐	☐	☐	☐	☐	☐
26. Cafeína/café me faz pular refeições	☐	☐	☐	☐	☐	☐
27. Tenho muita vontade de tomar cafeína/café se não tiver tomado a quantidade de sempre	☐	☐	☐	☐	☐	☐
28. Tomar cafeína/café na hora de	☐	☐	☐	☐	☐	☐

dormir atrapalha meu sono

29. Cafeína/café me deixa irritado(a)	☐	☐	☐	☐	☐	☐
30. Eu desejo cafeína/café o tempo todo	☐	☐	☐	☐	☐	☐
31. Cafeína/café me ajuda a trabalhar por mais tempo	☐	☐	☐	☐	☐	☐
32. Cafeína/café me faz sentir feliz	☐	☐	☐	☐	☐	☐
33. Eu não funciono sem tomar cafeína/café	☐	☐	☐	☐	☐	☐
34. Quando tomo Cafeína/café meu coração acelera	☐	☐	☐	☐	☐	☐
35. Eu tenho dificuldade em começar o dia sem tomar cafeína/café	☐	☐	☐	☐	☐	☐
36. Sinto dor de estômago quando tomo cafeína/café	☐	☐	☐	☐	☐	☐
37. Eu não conseguiria parar de tomar cafeína/café	☐	☐	☐	☐	☐	☐
38. Tomar cafeína/café no final da tarde atrapalha o meu sono	☐	☐	☐	☐	☐	☐
39. Cafeína/café me ajuda a regular o peso	☐	☐	☐	☐	☐	☐
40. Quanto não tomo cafeína/café sinto dor de cabeça	☐	☐	☐	☐	☐	☐
41. Cafeína/café melhora minha atenção	☐	☐	☐	☐	☐	☐
42. Eu fico mais extrovertido(a) quando tomo cafeína/café	☐	☐	☐	☐	☐	☐
43. Cafeína/café me ajuda a me exercitar por mais tempo	☐	☐	☐	☐	☐	☐
44. Sinto-me mais disposto(a) quando tomo cafeína/café	☐	☐	☐	☐	☐	☐
45. Cafeína/café me faz sentir com mais energia	☐	☐	☐	☐	☐	☐
46. Cafeína/café diminui o meu apetite	☐	☐	☐	☐	☐	☐
47. Tomar cafeína/café no final do dia não me deixa dormir	☐	☐	☐	☐	☐	☐

Versão curta do Questionário de Expectativa de Efeitos da Cafeína, Brasil (B-CaffEQ-BR)

1. Cafeína/café me dá ânimo quando estou cansado(a).	☐	☐	☐	☐	☐	☐
2. Cafeína/café melhora meu desempenho físico.	☐	☐	☐	☐	☐	☐
3. A cafeína/café tira minha fome.	☐	☐	☐	☐	☐	☐
4. Cafeína/café melhora meu humor.	☐	☐	☐	☐	☐	☐
5. Eu fico ansioso(a) quando não tomo cafeína/café.	☐	☐	☐	☐	☐	☐
6. Eu me exercito melhor depois de tomar cafeína/café.	☐	☐	☐	☐	☐	☐
7. Eu sinto muita falta de cafeína/café quando não tomo.	☐	☐	☐	☐	☐	☐
8. Eu não gosto do jeito que eu me sinto após tomar cafeína/café.	☐	☐	☐	☐	☐	☐
9. Tomar cafeína/café a qualquer hora do dia atrapalha o meu sono.	☐	☐	☐	☐	☐	☐
10. Quando tomo cafeína/café fico nervoso(a).	☐	☐	☐	☐	☐	☐
11. Cafeína/café melhora minha concentração.	☐	☐	☐	☐	☐	☐
12. Cafeína/café me faz pular refeições.	☐	☐	☐	☐	☐	☐
13. Tomar cafeína/café na hora de dormir atrapalha meu sono.	☐	☐	☐	☐	☐	☐
14. Cafeína/café me deixa irritado(a).	☐	☐	☐	☐	☐	☐
15. Cafeína/café me faz sentir feliz.	☐	☐	☐	☐	☐	☐
16. Eu não funciono sem tomar cafeína/café.	☐	☐	☐	☐	☐	☐
17. Tomar cafeína/café no final da tarde atrapalha o meu sono.	☐	☐	☐	☐	☐	☐
18. Eu fico mais extrovertido(a) quando tomo cafeína/café.	☐	☐	☐	☐	☐	☐
19. Cafeína/café me ajuda a me exercitar por mais tempo.	☐	☐	☐	☐	☐	☐
20. Cafeína/café me faz sentir com mais energia.	☐	☐	☐	☐	☐	☐
21. Cafeína/café diminui o meu apetite.	☐	☐	☐	☐	☐	☐

APÊNDICE C – Questionário de identificação, sociodemográfico e aspectos da saúde.

Instruções: Você, adulto(a) brasileiro(a), residente no Brasil. Estamos interessados em conhecer melhor o perfil da amostra estudada na pesquisa. Dessa forma, assim como descrito no Termo de Consentimento Livre e Esclarecido que você assinou, seus dados serão mantidos em sigilo, e utilizados unicamente para fins de pesquisa científica. Agradecemos a sua compreensão!

Qual seu:	Respostas
Sexo	Masculino
	Feminino
Idade em anos	De 19 a 59, qual:
Peso (kg)	
Altura (m)	
Auto identificação de cor de pele	Amarelo
	Branco
	Indígena
	Pardo
	Preto
	Sem descrição
Faz 150, ou mais minutos de exercícios físicos por semana	Não
	Sim
Grau de ensino	Sem instrução
	Fundamental incompleto
	Fundamental completo
	Ensino médio incompleto
	Ensino médio completo
	Graduação incompleta
	Graduação
	Pós-graduação
	Sem descrição
Faixa de renda mensal familiar (R$)	1.000,00
	1.000,01 a 2.000,00
	2.000,01 a 3.000,00
	3.000,01 a 5.000,00
	5.000,01 a 10.000,00
	Acima de 10.000,00
	Sem descrição
Doença crônica auto referida em uso de medicação	Não
	Sim

9. ANEXOS

ANEXO A – APROVAÇÃO PELO COMITÊ DE ÉTICA EM PESQUISA

Universidade Católica de Brasília

UNIVERSIDADE CATÓLICA DE BRASÍLIA - UCB

Plataforma Brasil

COMPROVANTE DE ENVIO DO PROJETO

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Tradução para língua portuguesa e validação para cultura brasileira do questionário de expectativa dos efeitos da cafeína/café.

Pesquisador: Guilherme Falcão Mendes

Versão: 1

CAAE: 23019319.3.0000.0029

Instituição Proponente: Curso de Nutrição

DADOS DO COMPROVANTE

Número do Comprovante: 131008/2019

Patrocionador Principal: FUNDACAO DE APOIO A PESQUISA DO DISTRITO FEDERAL

Informamos que o projeto Tradução para língua portuguesa e validação para cultura brasileira do questionário de expectativa dos efeitos da cafeína/café. que tem como pesquisador responsável Guilherme Falcão Mendes, foi recebido para análise ética no CEP Universidade Católica de Brasília - UCB em 08/10/2019 às 15:05.

Endereço: QS 07 Lote 01 EPCT - Bloco R, Sala 201
Bairro: Taguatinga   **CEP:** 71.966-700
UF: DF   **Municipio:** BRASILIA
Telefone: (61)3356-9451   **Fax:** (61)33563-9784   **E-mail:** cep@ucb.br

Continuação do Parecer: 3.686.958

Após a realização da pesquisa é compromisso dos/das proponentes a entrega do relatório final ou versão final do trabalho.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_P ROJETO_1449774.pdf	08/10/2019 15:03:47		Aceito
Projeto Detalhado / Brochura Investigador	SUBMISSAO_CEP_PLATAFORMA_BR ASIL_UCB_VALIDACAO.pdf	08/10/2019 15:03:12	Guilherme Falcão Mendes	Aceito
Outros	CARTA_DE_ENCAMINHAMENTO.pdf	08/10/2019 15:01:25	Guilherme Falcão Mendes	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_CEP_2019_VALIDACAO.pdf	08/10/2019 15:00:32	Guilherme Falcão Mendes	Aceito
Folha de Rosto	FOLHA_DE_ROSTO_ASS.pdf	08/10/2019 13:47:32	Guilherme Falcão Mendes	Aceito

Situação do Parecer:
Aprovado
Necessita Apreciação da CONEP:
Não

BRASILIA, 06 de Novembro de 2019

Assinado por:
Adriana Cardoso Furtado
(Coordenador(a))

Endereço: QS 07 Lote 01 EPCT - Anexo Bloco Central - Bloco- K Sala - 239
Bairro: Taguatinga   **CEP:** 71.966-700
UF: DF   **Município:** BRASILIA
Telefone: (61)3356-9784   **Fax:** (61)3356-3010   **E-mail:** cep@ucb.br

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Efeito do genótipo e consumo habitual de cafeína nas respostas individuais a suplementação aguda de cafeína

Pesquisador: Bruno Gualano

Área Temática:

Versão: 5

CAAE: 71618417.1.0000.5391

Instituição Proponente: UNIVERSIDADE DE SAO PAULO

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.996.200

Apresentação do Projeto:

Trata-se de emenda (no. 1) do projeto de pesquisa.

O pesquisador responsável notifica o CEP do Centro proponente (Escola de Educação Física e Esporte da USP) que, por questões logísticas, parte das coletas de dados do projeto, que serão obtidas na visita 2 dos participantes, relacionadas à ingestão da cafeína e subsequentes análises sanguíneas, passarão a ser realizadas no Laboratório do Grupo de Pesquisa em Fisiologia Aplicada e Nutrição na Faculdade de Medicina da Universidade de São Paulo, LIM17 (Sala 3148), cujo pesquisador responsável pelo projeto, é também, um dos coordenadores do referido Laboratório.

Continuação do Parecer: 2.996.200

Recomendações:

Sem recomendações.

Conclusões ou Pendências e Lista de Inadequações:

Este CEP toma CIÊNCIA da notificação de mudança do local de parte da coleta de dados do projeto, as quais passarão a ser realizadas no Laboratório do Grupo de Pesquisa em Fisiologia Aplicada e Nutrição na Faculdade de Medicina da Universidade de São Paulo, LIM17 (Sala 3148).

Contudo, esta Comissão ressalta que é de responsabilidade do pesquisador a aprovação da realização dessas coletas na referida Instituição (Faculdade de Medicina da Universidade de São Paulo).

Considerações Finais a critério do CEP:

Aprovado

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_123910 6_E1.pdf	15/10/2018 10:25:07		Aceito
Declaração de Pesquisadores	AmendmentLetterCaffeine.pdf	15/10/2018 10:24:28	Bryan Saunders	Aceito
Projeto Detalhado / Brochura Investigador	Projeto.pdf	15/10/2018 10:24:17	Bryan Saunders	Aceito
Outros	Carta_BrunoGualano.pdf	03/04/2018 19:57:10	Bryan Saunders	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_ProjetoCafeina_V3.pdf	14/01/2018 06:42:14	Bryan Saunders	Aceito
Outros	CAFProjeto_Assinado.pdf	17/07/2017 14:52:41	Bryan Saunders	Aceito
Folha de Rosto	FolhodeRosto_CAF_Assinado.pdf	17/07/2017 14:50:00	Bryan Saunders	Aceito

Situação do Parecer:

Aprovado

Endereço: Av. Profº Mello Moraes, 65
Bairro: Cidade Universitária   CEP: 05.508-030
UF: SP   Município: SAO PAULO
Telefone: (11)3091-3097   Fax: (11)3812-4141   E-mail: cep39@usp.br

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ASSOCIAÇÃO ENTRE OS POLIMORFISMOS I/D DA ENZIMA CONVERSORA DE ANGIOTENSINA (ECA), C/A DO CYP1A2, C/T DO RECEPTOR A2A DE ADENOSINA (ADORA2A) E SUPLEMENTAÇÃO DE CAFEÍNA SOBRE O DESEMPENHO AERÓBIO E ANAERÓBIO EM JOVENS ATLETAS

Pesquisador: Gustavo Gomes de Araujo

Área Temática: Genética Humana:
(Trata-se de pesquisa envolvendo Genética Humana que não necessita de análise ética por parte da CONEP;);

Versão: 3

CAAE: 51191915.8.0000.5013

Instituição Proponente: Universidade Federal de Alagoas

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.541.599

Apresentação do Projeto:

Introdução: O desempenho físico humano tem sido alvo de estudos durante muito tempo e sabe-se que vários fatores podem influenciar os resultados desse desempenho. Algumas décadas atrás, alguns pesquisadores resolveram ir mais afundo para encontrar essas respostas e começou -se os estudos sobre o DNA e suas variações, determinadas polimorfismos genéticos, como contribuição para o desempenho. Foi descoberto alguns

Continuação do Parecer: 1.541.599

Assentimento / Justificativa de Ausência	TCLE.docx	21:56:27	Araujo	Aceito
Projeto Detalhado / Brochura Investigador	poli.docx	02/03/2016 01:00:20	Gustavo Gomes de Araujo	Aceito
Outros	RES_.jpg	21/11/2015 15:43:34	Gustavo Gomes de Araujo	Aceito
Declaração de Pesquisadores	PES_.jpg	21/11/2015 15:42:19	Gustavo Gomes de Araujo	Aceito
Declaração de Instituição e Infraestrutura	LAB_.jpg	21/11/2015 15:41:30	Gustavo Gomes de Araujo	Aceito
Declaração de Instituição e Infraestrutura	QUADRA_.jpg	21/11/2015 15:40:58	Gustavo Gomes de Araujo	Aceito
Declaração de Manuseio Material Biológico / Biorepositório / Biobanco	MANUSEIO_.jpg	21/11/2015 15:38:18	Gustavo Gomes de Araujo	Aceito
Folha de Rosto	Doc2.pdf	10/09/2015 20:58:17	Gustavo Gomes de Araujo	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

MACEIO, 12 de Maio de 2016

_____

Assinado por:
Deise Juliana Francisco
(Coordenador)

ANEXO B – QUESTIONÁRIO DE CONSUMO DE CAFEÍNA

Por favor, preencha o questionário abaixo a respeito de seu uso frequente de cafeína. Indique o número de vezes que você consome os seguintes produtos durante uma semana. Forneça um valor aproximado de acordo com as porções estipuladas para cada grupo de alimentos\produtos.

	Manhã (6 - 11h59)	Tarde (12 - 17h59)	Noite (18 - 23h59)	Madrugada (24 - 5h59)
CAFÉ (Porções de 200ml = 1 xícara): em pó, orgânico, expresso, instantâneo, descafeinado, extraforte, cappuccino				
CHÁ (Porções 200ml = 1 xícara): chá verde, preto ou mate				
CHOCOLATE (Porções 147g / semana): chocolate meio amargo, com 50%, 70%, ou mais cacau				
BEBIDAS COM CACAU (Porções de 240ml = 01 copo americano): Chocolate amargo ou cacau em pó				
REFRIGERANTES (Porções de 240ml = 01 copo americano): Refrigerante a base de Noz de Cola, Coca, Pepsi, ou Guaraná				
MEDICAMENTOS (comprimidos / semana): Excedrin, Torsilax, Sedalgina, Neosaldina, Tandrilax, Benegrip, Coristina D, Engov, Tylenol				

BEBIDAS ENERGÉTICAS (1 colher de chá 5g para 50ml) de Extrato de guaraná OU (01 lata = 250 ml): Redbull, Burn, Flying Horse, Monster Energy Drink, TNT				
SUPLEMENTOS À BASE DE CAFEÍNA (1 cápsula ou dosador >= 210 mg): Cafeína anidra, termogênicos, ou pré-treinos				

Shohet, K. L., & Landrum, R. E. (2001). Caffeine consumption questionnaire: a standardized measure for caffeine consumption in undergraduate students. Psychological reports, 89(3), 521-526; Irons, J.G.; Bassett, D.T.; Prendergast, C.O.; Landrum, R.E.; Heinz, A.J. Development and Initial Validation of the Caffeine Consumption Questionnaire-Revised. J. Caffeine Res. 2016, doi:10.1089/jcr.2015.0012. (instrumento adaptado)