Universidade de São Paulo

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Associação entre aterosclerose coronariana com comprometimento cognitivo e doença de Alzheimer: um estudo clinico-patológico

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Programa de Fisiopatologia Experimental

Orientadora: Profa. Dra. Claudia Kimie Suemoto

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Dedico este trabalho

ao meu marido Peterson e à minha filha Julia, que sempre me deram todo suporte para que eu me dedicasse a esta pesquisa, sempre com muito amor e compreensão,

ao meu querido pai Tsutomu Yahagi (*in memorian*),

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RESUMO

Estevam MY. Associação entre aterosclerose coronariana com comprometimento cognitivo e doença de Alzheimer: um estudo clinico-patológico [dissertação]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2023.

Introdução: O envelhecimento populacional tem um profundo impacto no aumento da prevalência de demência, que tem a aterosclerose coronariana como um dos seus fatores de risco. Estudos clínicos mostraram associação entre aterosclerose coronariana e comprometimento cognitivo, porém os estudos baseados em autópsia mostraram resultados controversos. **Objetivos:** Investigar a associação da aterosclerose em artérias coronárias com comprometimento cognitivo e doença de Alzheimer, avaliada por critérios clínicos e neuropatológicos. **Método:** Este estudo observacional transversal foi conduzido em amostras coletadas pelo Biobanco para Estudos em Envelhecimento. Foram avaliadas a associação entre medidas morfométricas de estenose coronária e comprometimento cognitivo definido por critérios clínicos, e a associação entre componentes da placa aterosclerótica e neuropatologia da doença de Alzheimer, caracterizada por placas neuríticas e emaranhados neurofibrilares. **Resultados**: Na publicação "*The potential role of selection bias in the association between coronary atherosclerosis and cognitive impairment*" não houve associação entre estenose coronária e comprometimento cognitivo. Para explorar o papel dos fatores de seleção, dividimos os indivíduos em nascidos antes de 1936 e estratificamos por causa de morte cardiovascular. Em indivíduos que nasceram antes de 1936 e sem doença cardiovascular como causa de morte, maior estenose foi associada a maiores chances de comprometimento cognitivo e pior função cognitiva. Por outro lado, em indivíduos que morreram por causas cardiovasculares, a maior estenose foi relacionada à melhor função cognitiva tanto na amostra total quanto na restrita aos nascidos antes de 1936. O viés de seleção pode ser uma questão importante ao investigar fatores de risco para doenças crônico-degenerativas em indivíduos mais velhos usando amostras de autópsia. No manuscrito "*Association of atherosclerotic plaque components with Alzheimer's disease pathology*" o aumento da calcificação foi associado à diminuição do depósito de placas neuríticas e o aumento de *vasa vasorum* foi associado ao aumento do diagnóstico de Alzheimer. Hipotetizamos que componentes ligados à estabilidade da placa aterosclerótica estariam associados a neuropatologia de Alzheimer, visto que é uma doença de início tardio e decorrente de mudanças crônicas. Porém, estabelecer uma ligação clara entre aterosclerose e a doença de Alzheimer é um desafio, principalmente devido à complexidade da progressão da placa aterosclerótica.

Palavras-chave: Doença de Alzheimer. Demência. Emaranhados neurofibrilares. Placa neurítica. Aterosclerose. Doença da artéria coronariana.

ABSTRACT

Estevam MY. Association between coronary atherosclerosis with cognitive impairment and Alzheimer's disease: a clinicopathological study [dissertation]. São Paulo: "Faculdade de Medicina, Universidade de São Paulo"; 2023.

Introduction: Population aging has a profound impact on the increased prevalence of dementia, which has coronary atherosclerosis as one of its risk factors. Clinical studies have shown an association between coronary atherosclerosis and cognitive impairment, but autopsy-based studies have shown controversial results. **Objectives**: To investigate the association of atherosclerosis in coronary arteries with cognitive impairment and Alzheimer's disease, assessed by clinical and neuropathological criteria. **Method**: This cross-sectional observational study was conducted on samples collected by the Biobank for Studies in Aging. The association between morphometric measurements of coronary stenosis and cognitive impairment defined by clinical criteria and the association between atherosclerotic plaque components and the neuropathology of Alzheimer's disease, characterized by neuritic plaques and neurofibrillary tangles, were evaluated. **Results**: In the publication "*The potential role of selection bias in the association between coronary atherosclerosis and cognitive impairment*" there was no association between coronary stenosis and cognitive impairment. To explore the role of selection factors, we divided individuals into those born before 1936 and stratified by cause of cardiovascular death. In individuals born before 1936 and without cardiovascular disease as a cause of death, greater stenosis was associated with greater odds of cognitive impairment and worse cognitive function. On the other hand, in individuals who died from cardiovascular causes, greater stenosis was related to better cognitive function both in the total sample and in the sample restricted to those born before 1936. Selection bias can be an important issue when investigating risk factors for diseases chronic degenerative diseases in older individuals using autopsy samples. In the manuscript "*Association of atherosclerotic plaque components with Alzheimer's disease pathology*", increased calcification was associated with a decrease in the deposition of neuritic plaques and an increase in *vasa vasorum* was associated with an increase in the diagnosis of Alzheimer's. We hypothesized that components linked to the stability of the atherosclerotic plaque would be associated with Alzheimer's neuropathology, as it is a late-onset disease resulting from chronic changes. However, establishing a clear link between atherosclerosis and Alzheimer's disease is challenging, mainly due to the complexity of atherosclerotic plaque progression.

Keywords: Alzheimer disease. Dementia. Neurofibrillary tangles. Neuritic plaque. Atherosclerosis. Coronary artery disease.

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LISTA DE SIGLAS

IBGE	Instituto Brasileiro de Geografia e Estatística
DA	Doença de Alzheimer
DCV	Doenças cardiovasculares
DAC	Doença arterial coronariana
AVC	Acidente vascular cerebral
CAC	Calcificação na artéria coronária
APOE4	Alelo ε4 da apolipoproteína E
LIM	Laboratório de Investigação Médica
BEE	Biobanco para Estudos em Envelhecimento
TCLE	Termo de consentimento livre e esclarecido
SVOC-USP	Serviço de Verificação de Óbitos da Capital da Universidade de São Paulo
REDCap	Research Electronic Data Capture
IMC	Índice de Massa Corpórea
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating Sum Box
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
APA	Atherosclerotic Plaque Analyser

Esta dissertação ou tese está de acordo com as seguintes normas, em vigor no momento desta publicação: Referências: Diretrizes para apresentação de dissertações e teses da USP, 3ª edição Revisada, Ampliada e Modificada, 2016, Parte IV (Vancouver). DOI: 10.11606/978857314056

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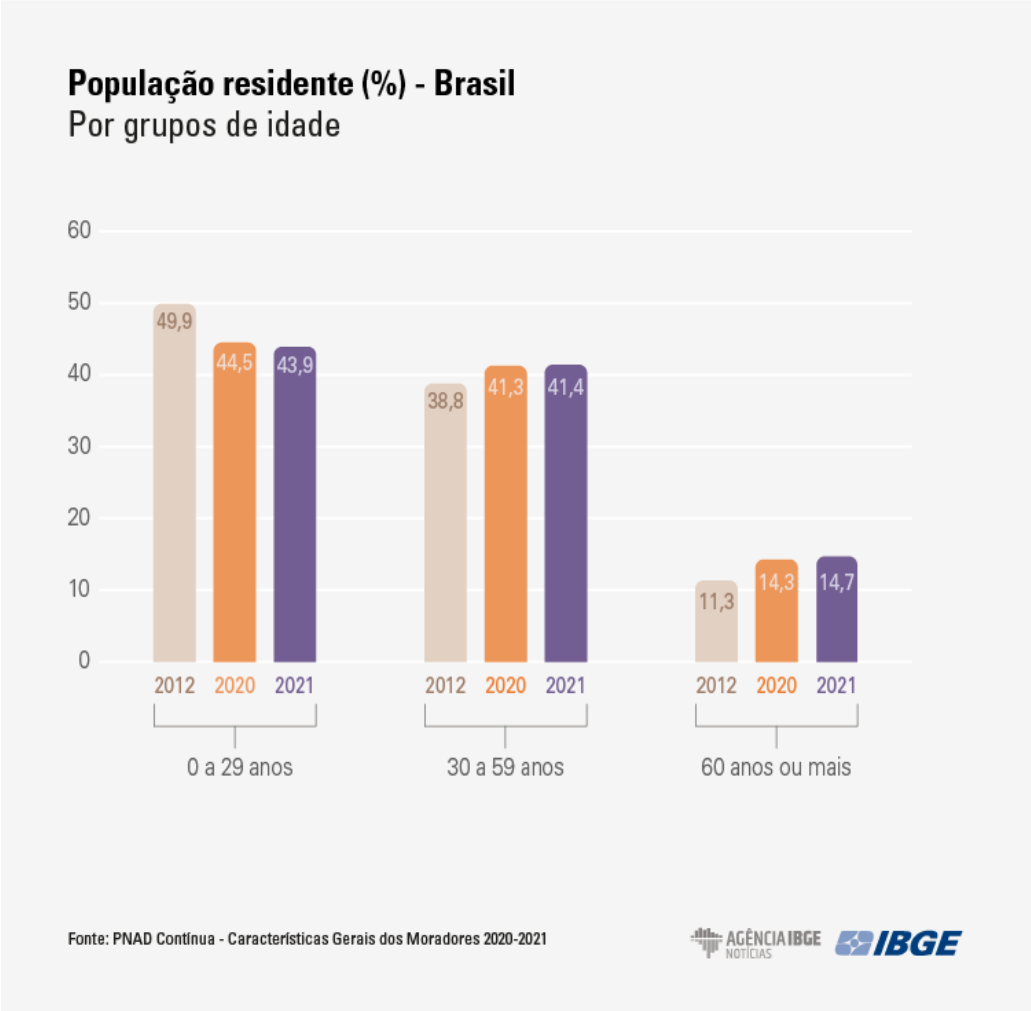
1 INTRODUÇÃO

1.1 Envelhecimento

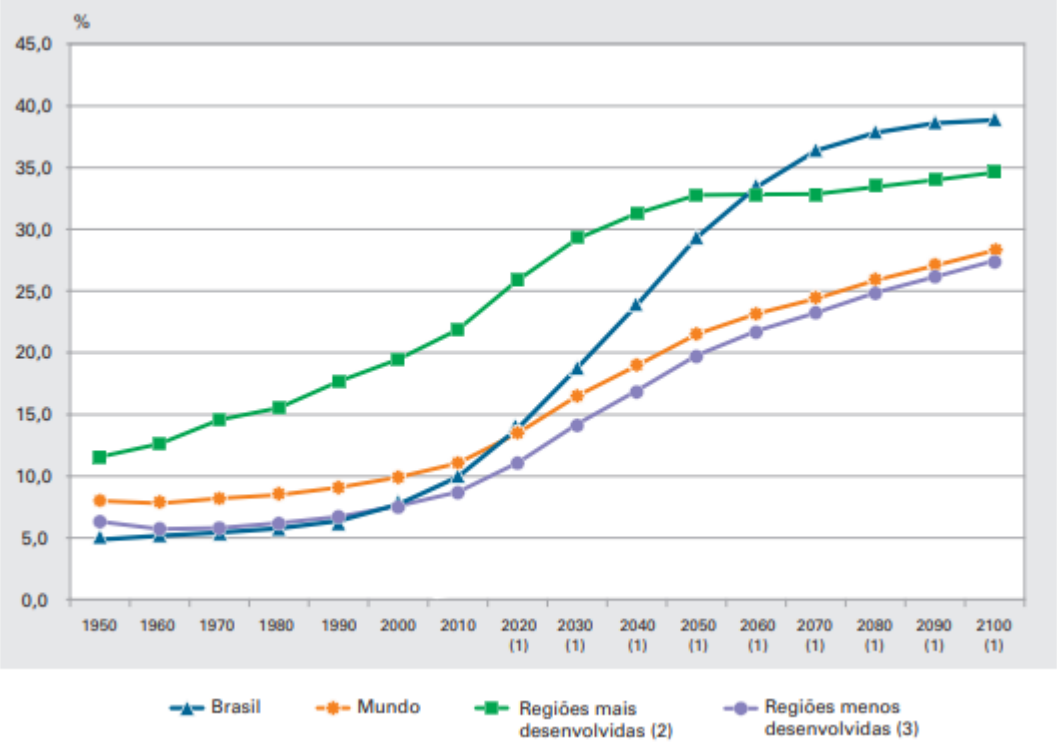
A população idosa mundial está crescendo em função da queda da taxa de fecundidade e aumento da expectativa de vida (1). A população brasileira também tem experimentado este fenômeno. Em 2021, residentes no Brasil com mais de 60 anos correspondiam à 14,7% da população (2) (Figura 1). Nas projeções populacionais realizadas pelas Nações Unidas, a população idosa no Brasil alcançará 23,5% em 24 anos. Esta transição acelerada contrasta com a de países desenvolvidos, onde a transição ocorreu em 62 anos, entre 1952 a 2014, ou mesmo em países menos desenvolvidos, onde esta transição será mais gradual, levando 49,2 anos, entre 2022 e 2071 (3) (Figura 2).

Figura 1. População residente no Brasil por grupos de idade



Proporção de acordo com as faixas etárias (0-29 anos, 30-59 anos e ≥ 60 anos) dos residentes no Brasil em 2012, 2020 e 2021. Fonte: agência de notícias, IBGE, 2022

Figura 2. Proporção de pessoas com idade igual ou superior a 60 anos população mundial, no Brasil, em regiões com mais ou menos desenvolvimento.



Dados de 1950/2100. (1) Dados projetados (variante média). (2) Regiões mais desenvolvidas: compreende Europa, América do Norte, Austrália/Nova Zelândia e Japão. (3) Regiões menos desenvolvidas: compreende todas as regiões da África, Ásia (exceto Japão), América Latina e Caribe mais Melanésia, Micronésia e Polinésia. Fonte: World Population Prospects, 2015

Há uma correlação entre os processos de transição da estrutura etária e epidemiológica. A queda inicial da mortalidade deve-se à diminuição das doenças infecciosas e tende a beneficiar os jovens, os quais passam a conviver com fatores de risco para doenças crônico-degenerativas, à medida que cresce o número de idosos e aumenta a expectativa de vida (4). Porém, há um entendimento de que muitos fatores de risco podem estar relacionados com o aumento da idade, mas não necessariamente, dependem somente da idade. Alguns fatores modificáveis como prevenção de doenças e deficiências, manutenção da função física e cognitiva, engajamento social e atividades produtivas são aspectos do envelhecimento bem-sucedido (5).

1.2 **Doença de Alzheimer (DA)**

O envelhecimento populacional está tendo um profundo impacto no aumento dos casos de demência (6). A quantidade de pessoas vivendo com demência ao redor do mundo era de 47

milhões em 2015, número que deverá aumentar para 75 milhões em 2030 e 132 milhões em 2050 (7).

A demência é uma síndrome clínica, que pode ser causada por diversas doenças e condições, incluindo a neurodegeneração e doenças cerebrovasculares. A demência é caracterizada por perda de autonomia e dependência funcional progressivas, altamente incapacitante e que gera muitos custos para o sistema de saúde e alto impacto familiar (7). A DA é a forma mais frequente de demência caracterizada neuropatologicamente por placas neuríticas, agregados extracelulares de proteína β amilóide, e emaranhados neurofibrilares intraneurais (formados pelo acúmulo de proteína tau hiperfosforilada intracelular (8,9).

1.3 **Doença cardiovascular**

As doenças cardiovasculares (DCV) continuam sendo a principal causa de mortalidade no mundo. Estima-se que 17,7 milhões de pessoas morreram por doenças cardiovasculares em 2015, representando 31% de todas as mortes em nível global (10). Entre as doenças cardiovasculares, a doença arterial coronariana (DAC) é a principal causa de morte (43,8%) nos Estados Unidos, seguida de acidente vascular cerebral (AVC) (16,8%), hipertensão (9,4%), insuficiência cardíaca (9,0%), e outras doenças cardiovasculares (17,9%) (11). Mais de três quartos das mortes por doença cardiovascular ocorrem em países de média e baixa renda (12). No Brasil, o número total de mortes por DCV aumentou, provavelmente como resultado do envelhecimento da população (13).

1.3.1 Aterosclerose

A doença cardiovascular aterosclerótica permanece a principal causa de doença vascular no mundo (14). A aterosclerose se refere ao acúmulo de gordura e/ou tecido fibroso na camada íntima das artérias. É um processo dinâmico que engloba desde lesões precoces até placas mais avançadas (15). Em lesões não ateroscleróticas precoces, o espessamento difuso ou adaptativo da camada íntima das artérias é considerado uma resposta fisiológica ao fluxo de sangue, assim como os xantomas intimais compostos primariamente de células musculares lisas com infiltrados macrofágicos (16). Morfologicamente, as células espumosas são abundantes e não apresenta capa fibrosa, necrose ou trombose (17). Nas lesões ateroscleróticas progressivas, o espessamento patológico da camada íntima das artérias é formado por restos de células musculares em uma matriz de colágeno e proteoglicanas com um núcleo lipídico subjacente (18), e também pode apresentar calcificações (19). Fibroateromas, precoce e tardio, são os

estágios progressivos da aterosclerose, caracterizados pela presença de núcleo necrótico, resultado da infiltração macrofágica nos núcleos lipídicos. A área dos núcleos necróticos é cercada pela capa fibrosa, composta principalmente por colágeno, proteoglicanas e músculo liso intercalado. No fibroateroma tardio é maior a presença de fissuras de colesterol, calcificações, hemorragia intraplaca e neoangiogênese, do que no fibroateroma precoce (17). A capa fibrosa fina é precursora da ruptura da placa, principal causa de trombose coronariana, seguida de erosão e, em menor proporção, nódulos calcificados (16). A trombose coronariana pode ocorrer silenciosamente através de rupturas não oclusivas, seguidas de cicatrização com deposição de proteoglicanas e colágeno, formando as lesões fibróticas. As lesões fibrocalcificadas podem conter grandes áreas de calcificação com núcleo necrótico pequeno ou ausente. As lesões fibróticas e fibrocalcificadas apresentam estenose importante e ausência de trombose (17).

A aterosclerose e a demência compartilham fatores de risco cardiovasculares (hipertensão arterial sistêmica (20), dislipidemia (21), tabagismo, diabetes mellitus (22) e a aterosclerose *per se* tem sido associada à demência (23–25).

1.4 **DAC e demência**

A DAC, principal causa de morte entre as doenças cardiovasculares, está associada a um aumento de 45% do risco de desenvolver comprometimento cognitivo ou demência em um estudo de metanálise envolvendo 10 estudos de coorte (26). Outra metanálise associa a DAC a 27% de aumento no risco de desenvolver demência (27). A avaliação clínica da DAC foi baseada em entrevista ou exames clínicos em ambas as metanálises.

A calcificação na artéria coronária (CAC) é uma condição subclínica e é um marcador de carga aterosclerótica (28). Estudos mostraram associação entre CAC medida por tomografia computadorizada e declínio cognitivo (29–31). Vidal *et al.* (29) em um estudo transversal com 4.250 indivíduos mostraram que o aumento da CAC está associado com o aumento do risco de demência e diminuição da velocidade de processamento cognitivo e função executiva, mediado principalmente pela diminuição dos volumes cerebrais, enquanto o estudo transversal de Suemoto *et al.* mostrou que o aumento de CAC estava fracamente associado com pior desempenho em um teste de função executiva em uma amostra de 4104 participantes, do Estudo Longitudinal de Saúde do Adulto (ELSA) (31).

Em estudos baseados em autópsias, a medida morfométrica direta fornece dados mais confiáveis e menos subjetivos do tamanho da placa aterosclerótica comparada com estudos clínicos. Beeri *et al.* (32) em um estudo com 99 indivíduos mostraram associação entre DAC e neuropatologia associada à DA, independentemente de outros fatores de risco tais como idade, sexo, principalmente em portadores do alelo ε4 da apolipoproteína E (*APOE4*). Porém, o estudo longitudinal de Dolan *et al.* com autópsia de 200 indivíduos não encontrou associação entre aterosclerose sistêmica na aorta, artéria coronária e artéria intracraniana com demência (33).

Sendo assim, a associação entre aterosclerose coronária e demência ainda não está totalmente esclarecida em estudos baseados em autópsia. Além disso, o alto risco de mortalidade em indivíduos com DAC pode estar associado a um viés de sobrevivência nos estudos que associam DAC com declínio cognitivo (32,33). Por fim, nenhum estudo de autópsia até o momento estudou a associação entre a composição da placa aterosclerótica em artérias coronárias e a neuropatologia da DA.

2 OBJETIVO

2.1 **Objetivo geral**

Investigar a associação da aterosclerose em artérias coronárias com comprometimento cognitivo e doença de Alzheimer, definidos por critérios clínicos e neuropatológicos.

2.2 **Objetivos específicos**

Avaliar o perfil demográfico e fatores de risco cardiovasculares e sua relação com a demência definida por critérios clínicos.

Avaliar a associação da porcentagem de estenose coronariana com a avaliação clínica de demência.

Avaliar a associação da porcentagem de estenose coronariana e dos componentes da placa aterosclerótica coronariana com lesões neuropatológicas da DA.

3 MÉTODO

3.1 Local do estudo

O presente estudo foi desenvolvido no Laboratório de Investigação Médica (LIM 22) da Faculdade de Medicina da Universidade de São Paulo (FMUSP), que engloba os Laboratórios de Patologia Cardiovascular e Fisiopatologia no Envelhecimento (LFE), onde o Biobanco para Estudos em Envelhecimento (BEE) está localizado.

3.2 Desenho do estudo

Trata-se de um estudo observacional de corte transversal.

3.3 Critérios de elegibilidade

3.3.1 Critérios de Inclusão

- Idade maior de 50 anos na data do óbito;
- Termo de consentimento livre e esclarecido (TCLE) assinado pelo informante;
- Possuir informante (familiar responsável ou responsável legal) que tenha convivido com o falecido diária ou semanalmente, nos seis meses anteriores ao óbito e capaz de prestar informações consistentes a respeito do histórico de saúde do indivíduo;
- Indivíduos que apresentem material completo: entrevista e avaliação clínica de demência; artérias coronárias; amostras do encéfalo que permitam o diagnóstico neuropatológico

3.3.2 Critérios de Exclusão

Consideramos os seguintes critérios de exclusão adotados pelo BEE (34) e os específicos para esse estudo, dos quais são:

- Indivíduos com patologias cerebrais que impossibilitem a avaliação macroscópica cerebral ou amostragem da região de interesse;
- Indivíduos que morreram por causas cerebrais primárias, devido à necessidade de exame imediato durante a autópsia para preenchimento da declaração de óbito;
- Stent coronariano;
- Intervalo *post-mortem* maior ou igual a 24 horas;

- Cadáver em processo de autólise.

3.4 **Coleta de dados**

Os dados analisados foram provenientes das amostras coletadas entre 2011 e 2015 e 2021 e 2022 dos estudos:

- de doutorado, intitulado “Associação entre adiposidade e aterosclerose sistêmica”, de Aline Nishizawa, com aprovação no Comitê de Ética em Pesquisa da Faculdade de Medicina da Universidade de São Paulo, sob protocolo (412/11) (35).
- de mestrado, intitulado “Associação entre inflamação do tecido adiposo epicárdico e doença arterial coronariana: um estudo clinicopatológico” de Daniela Souza Farias, com aprovação no Comitê de Ética em Pesquisa da Faculdade de Medicina da Universidade de São Paulo, sob protocolo (439/12) (36).
- do estudo financiado pela Alzheimer’s Association, aprovado pelo comitê de ética da Faculdade de Medicina da Universidade de São Paulo sob número CAAE: 25213319.4.0000.0065 (Anexo 1).

Os dados coletados nos estudos acima foram obtidos no Serviço de Verificação de Óbitos da Capital da Universidade de São Paulo (SVOC-USP), onde o Laboratório de Fisiopatologia no Envelhecimento mantém uma estrutura organizacional de coleta de dados por meio de entrevista com parente próximo ou responsável legal do falecido, e de materiais biológicos durante a autópsia. Todos os dados coletados foram armazenados na *Research Electronic Data Capture* (REDCap), plataforma para coleta, gerenciamento e disseminação de dados de pesquisa (37).

O SVOC-USP realiza cerca de 13.000 autópsias anuais, com a finalidade de esclarecer *causa mortis* em casos de morte natural causada por moléstias mal definidas antes do óbito ou sem assistência médica ocorridos no município de São Paulo (38).

O BEE surgiu da necessidade de coleta de tecido cerebral para o melhor entendimento sobre os processos relacionados à senescência e à senilidade cerebral, sobretudo quando os dados encontrados na análise anatomopatológica podem ser correlacionados com as condições clínico-funcionais dos indivíduos (34).

3.4.1 Entrevista

Ao se dirigir ao SVOC para solicitar a liberação do corpo e autorizar os procedimentos da autópsia, o familiar foi convidado a participar do estudo pela equipe composta por enfermeiros e gerontólogos. Após a avaliação dos critérios de elegibilidade, o TCLE foi apresentado. Após o aceite e assinatura do TCLE, foi realizada uma entrevista semiestruturada com duração aproximada de 30 minutos. O informante, que pode ser um familiar ou responsável legal, deve ter tido contato próximo ao falecido, pelo menos semanalmente nos seis meses antes da morte, para ser capaz de responder as questões com o rigor de detalhes necessários.

Foram coletados dados demográficos como idade, sexo, cor e escolaridade. Foi questionado ao informante sobre o diagnóstico prévio de hipertensão arterial, DAC, insuficiência cardíaca congestiva, AVC, diabetes mellitus, dislipidemia, sedentarismo, tabagismo e etilismo. O índice de massa corporal (IMC) foi calculado através das medidas de peso realizada através de uma balança com tara para o peso da maca e altura realizada através de um estadiômetro previamente ao exame de autópsia com o cadáver em posição supina sem roupas ou sapatos.

3.4.1.1 *Clinical Dementia Rating (CDR)*

Para avaliar cognição foi utilizada a escala CDR, desenvolvida por Hughes *et al.* (39), adaptada por Morris (40) e validada em português por Montãno e Ramos (41). A avaliação de cognição através de informantes foi previamente validada para aplicação *post mortem* (42). Esta escala está dividida em seis domínios: memória, orientação, julgamento e resolução de problemas, assuntos comunitários, atividades do lar e lazer e cuidados pessoais. Todos esses domínios podem ser pontuados de 0 a 3 de acordo com as informações coletadas no questionário. A classificação final do estadiamento da demência foi baseada na análise dos domínios tendo a memória como domínio primário e os demais como secundários (Anexo 2):

- CDR 0 = sem demência
- CDR 0,5 = demência questionável
- CDR 1 = demência leve
- CDR 2 = demência moderada
- CDR 3 = demência grave

3.4.1.2 *Clinical Dementia Rating Sum Box (CDR-SB)*

A pontuação da CDR-SB foi calculada pela soma da pontuação dos domínios avaliados pelos domínios do CDR descritos acima, com variação de 0 a 18 pontos. Isso permite melhor

avaliação das fases iniciais da demência e aumenta a acurácia da medida de evolução da doença (43,44).

3.4.1.3 *Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)*

Para complementar a avaliação cognitiva foi utilizado o IQCODE, um questionário baseado nas respostas fornecidas pelo informante (45) e validado para a população brasileira (46). O desempenho cognitivo e funcional de três meses antes do óbito foi comparado ao apresentado há 10 anos. A versão completa consiste em 26 perguntas que foram respondidas baseadas numa escala Likert, com 5 opções: 1 – melhorou muito; 2 – melhorou um pouco; 3 – não teve mudanças; 4 – um pouco pior; 5 – muito pior. O cálculo final foi através da média ponderada: soma do peso médio da escala Likert dividido pelo número de questões respondidas. A variação da escala é de 1 a 5, onde as maiores pontuações indicam maior declínio cognitivo (Anexo 3).

3.4.2 Materiais biológicos

A coleta dos materiais biológicos foi realizada durante a autópsia e cedida pelo médico plantonista, respeitando o intervalo *post-mortem* inferior a 24 horas.

Foram coletados o encéfalo e o coração.

3.4.2.1 *Encéfalo*

O cérebro foi coletado e fixado em paraformaldeído tamponado a 4% por 14 a 21 dias. Após a fixação, 13 áreas cerebrais foram representadas e incluídas em parafina:

- Giro frontal médio e inferior
- Giro temporal superior e médio
- Giro do cíngulo anterior e frontal superior
- Lobo occipital
- Lobo parietal inferior
- Hipocampo, no nível do corpo geniculado lateral (córtex entorrinal)
- Amígdala
- Tálamo
- Núcleos da base, incluindo o núcleo basal de Meynert, na altura da comissura anterior
- Mesencéfalo, incluindo a substância negra
- Ponte, incluindo *locus coeruleus*

- Bulbo
- Cerebelo

O estudo neuropatológico foi realizado segundo os critérios aceitos internacionalmente para o diagnóstico de DA (47). Áreas selecionadas foram submetidas à imunohistoquímica utilizando anticorpos contra proteína ß-amilóide (4G8, 1:10.000; BioLegend #800701) e tau hiperfosforilada (AT8, 1:400; Invitrogen MN1020) (Tabela 1).

Tabela 1 – Áreas amostradas, coloração e imuno-histoquímica realizadas na rotina do BEE

Área	Beta amilóide	Tau hiperfosforilada
Giro frontal médio e inferior	x	x
Giro temporal médio e superior	x	x
Cíngulo anterior e frontal superior		
Lobo occipital		
Lobo parietal inferior		
Hipocampo	x	x
Amígdala		x
núcleos da base	x	
Tálamo		
Mesencéfalo	x	
Ponte		
Bulbo		
Cerebelo		

Fonte: Biobanco para Estudos em Envelhecimento

3.4.2.1.1 *Diagnóstico neuropatológico*

A neuropatologia característica da doença de Alzheimer baseia-se na presença e quantidade de placas neuríticas segundo a classificação de *Consortium to Establish a Registry for Alzheimer's Disease* (CERAD) (48) e emaranhados neurofibrilares segundo a classificação de Braak e Braak (49), conforme a seguir (Figura 3).

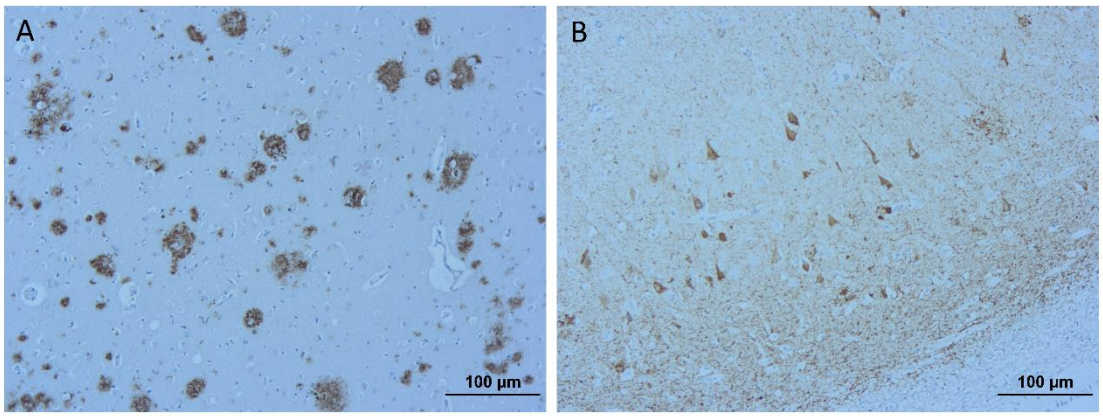
Classificação das placas neuríticas quanto à quantidade, segundo critérios de CERAD (48):

- CERAD 0 – ausência de placas neuríticas no tecido cerebral analisado
- CERAD A – leve (1-5 placas neuríticas por campo, aumento 100X)
- CERAD B – moderado (6-15 placas neuríticas por campo, aumento 100X)
- CERAD C – frequente (>15 placas neuríticas por campo, aumento 100X)

A classificação dos emaranhados neurofibrilares foi baseada na quantidade e distribuição, segundo os critérios de Braak e Braak (49), em seis estágios:

- I: número reduzido de emaranhados neurofibrilares restritos ao córtex transentorrinal;
- II: moderado número de emaranhados neurofibrilares no córtex transentorrinal e poucos no hipocampo;
- III: emaranhados neurofibrilares frequentes no córtex transentorrinal e moderado no hipocampo;
- IV: acometimento grave do hipocampo e discreto no isocórtex temporal;
- V: emaranhados neurofibrilares no isocórtex temporal, frontal e parietal;
- VI: emaranhados neurofibrilares no córtex sensorial primário ou em neurônios piramidais da fáscia dentata no hipocampo.

Figura 3. Neuropatologia da Doença de Alzheimer



(A) Placa neurítica em córtex frontal. Imuno-histoquímica com anticorpo contra proteína ß-amilóide. Objetiva de 10x, escala de 100 µm. (B) Emaranhados neurofibrilares em hipocampo. Imuno-histoquímica com anticorpo contra proteína tau hiperfosforilada. Objetiva de 10x, escala de 100 µm. Fonte: Biobanco para Estudos em Envelhecimento

Utilizamos o critério neuropatológico baseado no consenso do *National Institute of Aging – Reagan Institute*, para o diagnóstico de DA (9), que classifica a probabilidade de DA em:

- Baixa probabilidade para DA – CERAD A e Braak e Braak estágio I ou II;
- Moderada probabilidade para DA – CERAD B e Braak e Braak estágio III ou IV;
- Alta probabilidade para DA – CERAD C e Braak e Braak estágio V ou VI.

Neste estudo, moderada e alta probabilidade foram consideradas como diagnóstico de DA.

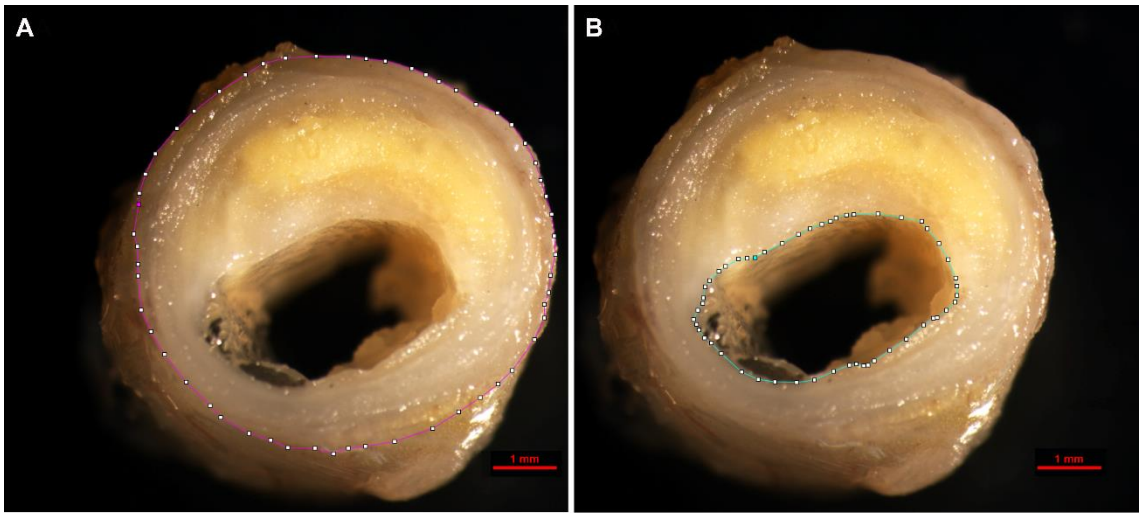
3.4.2.2 *Coração*

O coração foi coletado e lavado em água corrente para retirada de sangue e coágulos. As artérias coronárias direita, tronco da coronária esquerda, descendente anterior e circunflexa foram dissecadas e fixadas em formol diluído a 10% no estudo de Nishizawa (50) e em paraformoldeído tamponado diluído a 4% no estudo de Farias (36). Após fixadas, as artérias coronárias foram cortadas transversalmente a cada 5mm ao longo de todo o trajeto. O fragmento com maior obstrução da luz ou suspeita de placa instável foi amostrado (17)

Os fragmentos das artérias coronárias foram fotografados com o auxílio do estereomicroscópio (Nikon® SMZ 1000) (Figura 4). Para avaliar a estenose coronariana foi utilizado o software de imagem ImageJ®, onde as áreas delimitadas pela borda externa da artéria e pelo lúmen foram mensuradas. A estenose arterial foi calculada utilizando a seguinte fórmula (51):

$$\text{Porcentagem de Estenose} = \frac{\text{Área interna à borda externa} - \text{Área do Lúmen}}{\text{Área interna à borda externa}} \text{x}100$$

Figura 4. Avaliação da estenose coronariana



Vista transversal da artéria coronária descendente anterior. (A) Linha de cor magenta delimita a borda externa da artéria. (B) Linha de cor ciano delimita o lúmen da artéria. Escala de 1mm. Fonte: Biobanco para Estudos em Envelhecimento

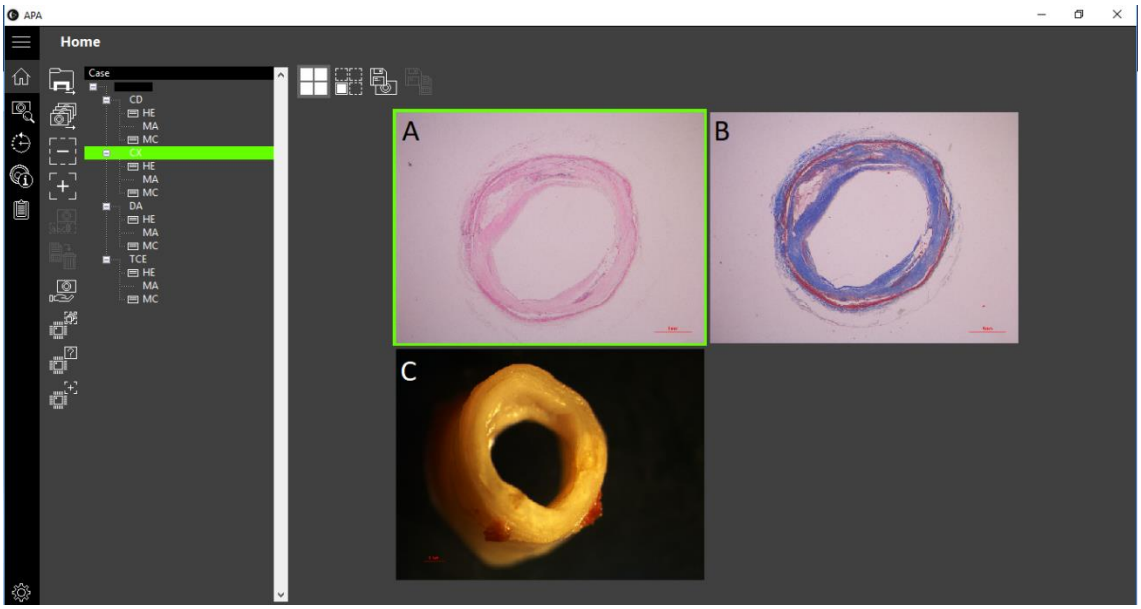
Os fragmentos das artérias amostradas foram encaminhados para o Laboratório de Histotécnica do Departamento de Patologia da Faculdade de Medicina da Universidade de São Paulo para a realização das colorações. Primeiramente as amostras passaram pelo processo de

desidratação, diafanização e emblocamento em parafina. Com auxílio de um micrótomo, foram realizados cortes com 4µm de espessura para confecção das lâminas, e posteriormente cada fragmento foi corado com hemotoxilina-eosina, e tricômico de Masson.

3.4.2.2.1 *Atherosclerotic Plaque Analyzer (APA)*

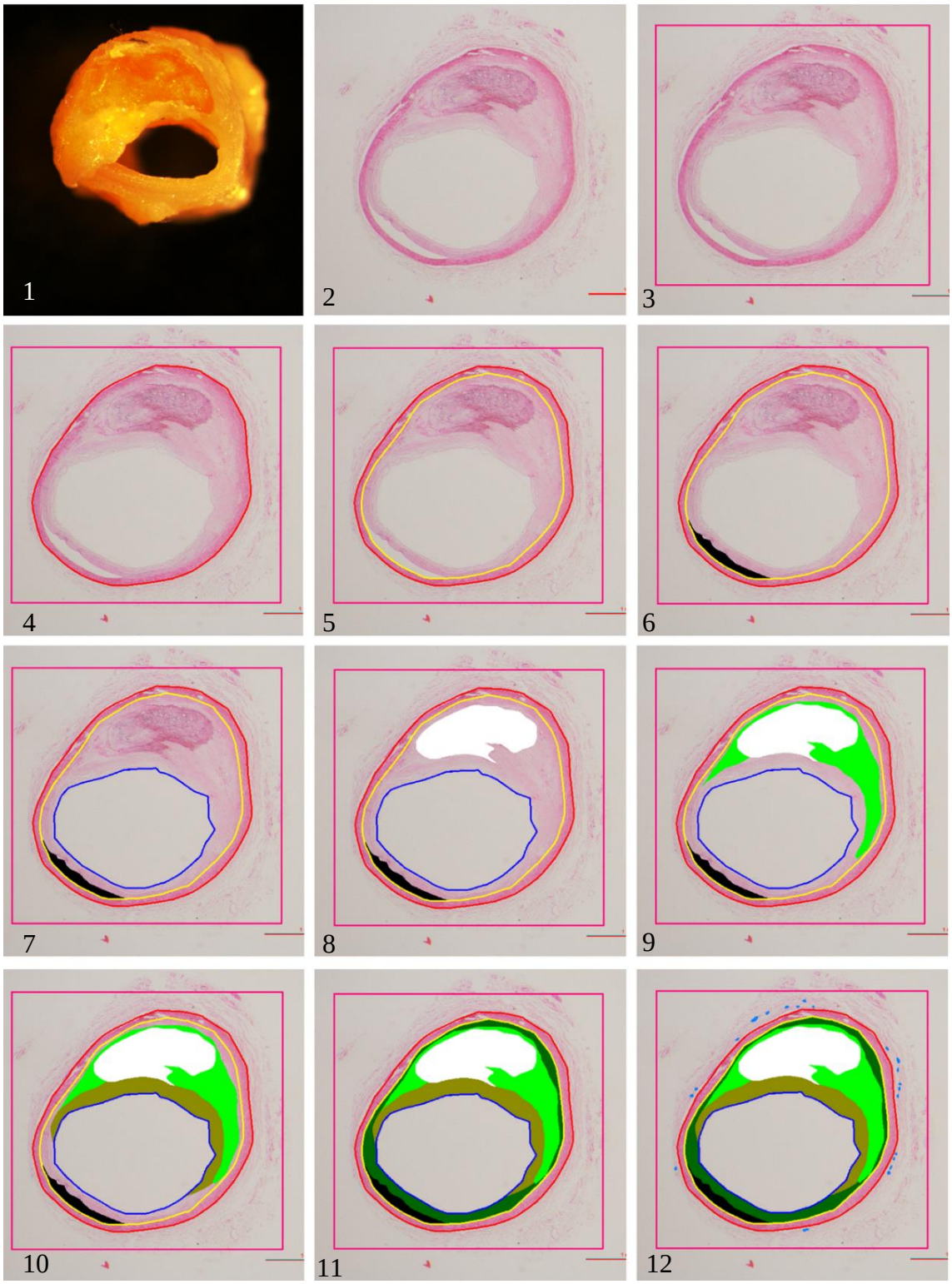
Para realizar a análise morfométrica dos componentes da placa aterosclerótica, um software denominado *Atherosclerotic Plaque Analyser (APA)* foi desenvolvido utilizando o ambiente LabView (Laboratory Virtual Instrumentation Engineering Workbench; National Instruments, Austin, TX)(52) (Figura 5). O APA tem a capacidade de corrigir o fundo da imagem, identificar a artéria e a barra de escala e contornar o lúmen, a lâmina elástica externa e interna, de forma automática ou manual. A identificação da artéria permite a transferência de medidas para outras colorações. Além disso, os componentes da placa aterosclerótica, que incluem núcleo lipídico, núcleo necrótico, calcificações, trombo cicatrizado, hemorragia intraplaca, colágeno/célula muscular lisa, foram delimitados manualmente (Figuras 6 e 7). O APA calculou então a percentagem de cada componente dentro da placa aterosclerótica.

Figura 5. Interface do software *Atherosclerotic Plaque Analyzer (APA)*



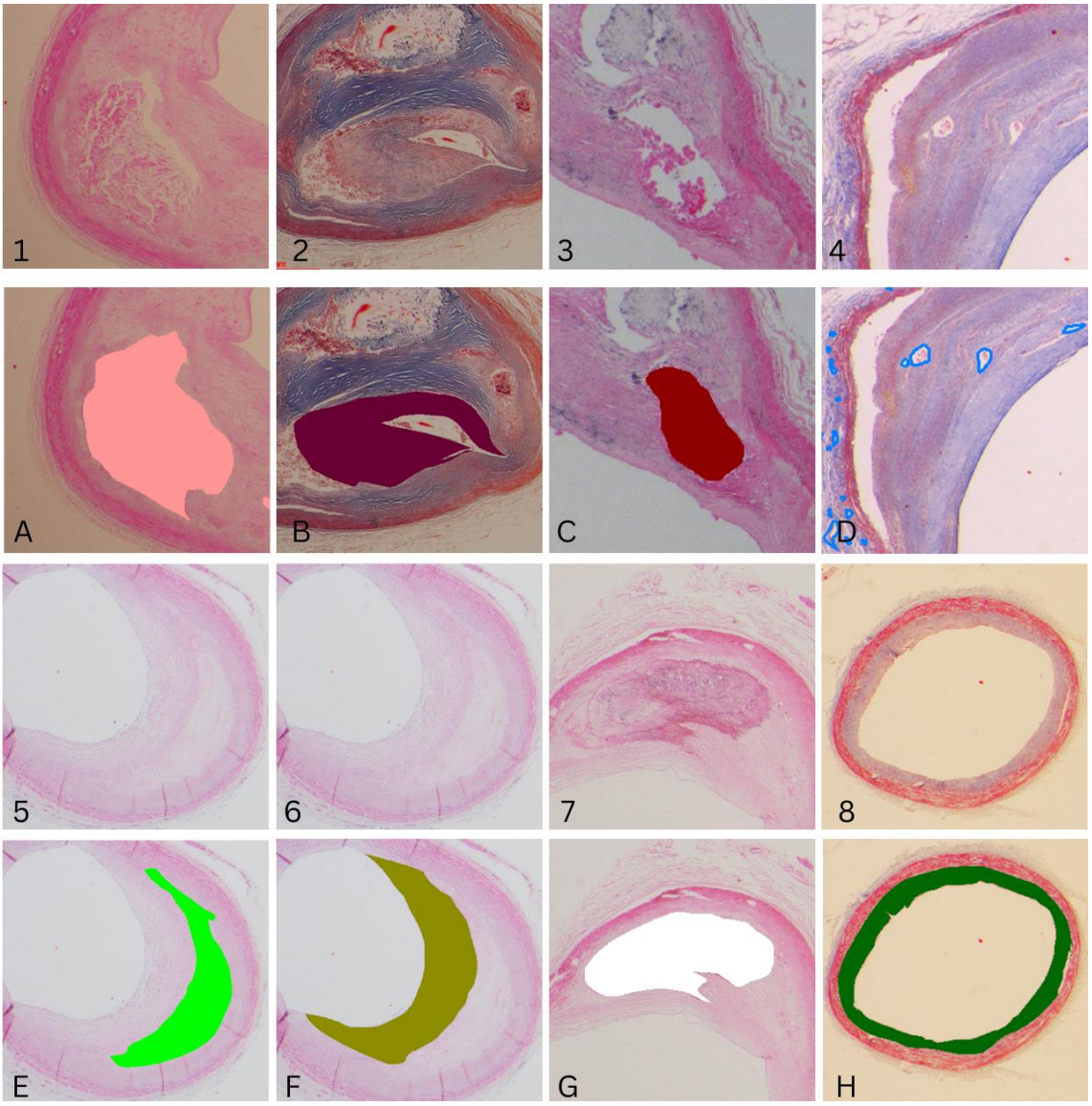
Vista transversal da artéria coronária esquerda circunflexa corada em (A) hematoxilina-eosina (B) tricômico de Masson e (C) vista macroscópia da artéria. Escala de 1mm. Fonte: Biobanco para Estudos em Envelhecimento

Figura 6. Sequência da análise pelo APA



Coronária descendente anterior, corada com hemotoxilina-eosina. 1. Visão macroscópica 2. Vista microscópica 3. Identificação da artéria em quadrado pink 4. Lâmina limitante externa em vermelho 5. Lâmina limitante interna em amarelo 6. Artefato em preto 7. Lumem em azul 8. Calcificação em branco 9. Núcleo lipídico em verde claro 10. Capa fibrosa em marrom 11. Colágeno em verde escuro 12. *Vasa vasorum* em azul claro. Fonte: Biobanco para Estudos em Envelhecimento

Figura 7. Contorno dos componentes no APA



1A. contorno de necrose 2B. contorno de trombo cicatrizado 3C. contorno de hemorragia 4D. contorno de *vasa vasorum* 5E. contorno de núcleo lipídico 6F. contorno da capa fibrosa 7G. contorno de calcificação 8H. contorno de colágeno/célula muscular lisa. Fonte: Biobanco para Estudos em Envelhecimento

A identificação dos componentes da placa aterosclerótica foi realizada com base na descrição morfológica que abrange os processos fisiopatológicos da aterosclerose e o papel de cada componente em cada fase (17,18) (Tabela 2).

Tabela 2 – Classificação das lesões ateroscleróticas baseada na morfologia (17)

Tipo de lesão	Subtipo de lesão	Descrição morfológica
Lesão intimal não aterosclerótica	Espessamento intimal	Acúmulo natural de células musculares espumosas, ausência de lipídios, células espumosas macrofágicas e trombose
	Xantoma intimal	Acúmulo superficial de células espumosas sem um núcleo necrótico, capa fibrosa ou trombose
Lesão aterosclerótica progressiva	Espessamento intimal patológico	Placa rica em células musculares espumosas, com matriz hialina e proteoglicana e acúmulo focal de lipídio extracelular. Ausência de trombose
	Fibroateroma	Durante necrose precoce: infiltração focal de macrófagos em áreas de núcleos lipídicos sobrepondo a capa fibrosa. Durante necrose tardia: perda da matriz e fragmentos celulares extensivos com uma sobreposição da capa fibrosa. Com ou sem calcificação. Ausência de trombose
	Hemorragia intraplaca ou fissura da placa	Grande núcleo necrótico (tamanho >10% da área da placa) com hemorragia, e a área da placa mostra presença de angiogênese. Núcleo necrótico comunica com o lúmen através de uma fissura. Mínimo rompimento sem trombo evidente
	Fina capa de fibroateroma	Uma fina, fibrosa capa (<65μm) infiltrado por macrófagos e linfócitos, com células musculares espumosas raras ou ausentes e sobreposição relativamente grande do núcleo necrótico (>10% da área da placa). Hemorragia intraplaca e/ou fibrina pode estar presente. Ausência de trombose
Lesão com trombose aguda	Ruptura da placa	Fina capa de fibroateroma com rompimento da capa. Trombose está presente e pode ou não ser oclusiva. O trombo luminal comunica com o núcleo necrótico sobreposto
	Erosão da placa	Pode ocorrer no espessamento intimal patológico ou no fibroateroma. Trombose é presente e deve ou não ser oclusiva. Não há comunicação do trombo com o núcleo necrótico
	Nódulo calcificado	Erupção (derramamento) do nódulo calcificado com uma placa fibrocalcificada sobreposta com necrose mínima ou ausente. Trombose é normalmente não oclusiva
Lesão cicatrizada	Ruptura da placa cicatrizada, erosão ou nódulo calcificado	Lesão cicatrizada composta de células musculares espumosas, proteoglicanos, e colágeno tipo III com ou sem sobreposição de capa fibrose rompida, núcleo necrótico, ou calcificação nodular. Lesões podem conter grandes áreas de calcificação com poucas células inflamatórias e ter um núcleo necrótico pequeno ou ausente. A placa fibrótica ou fibrocalcificada rica em colágeno é associada com significante estenose luminar. Ausência de trombose.

Fonte: Adaptado e traduzido de Yahagi *et al.* (2016)

A espessura da camada íntima média foi calculada como a distância entre o lúmen e a lâmina elástica externa. A espessura da capa fibrosa foi delineada manualmente e medida na seção mais fina ao longo da capa. Também foi contabilizado o número de vasa vasorum na camada íntima (53). A porcentagem de obstrução arterial foi calculada usando a seguinte fórmula (51):

$$\text{Porcentagem de Obstrução} = \frac{\text{Área interna à Lâmina Limitante Elástica Interna} - \text{Área do Lúmen}}{\text{Área interna à Lâmina Limitante Elástica Interna}} \text{x}100$$

4 RESULTADOS

O presente estudo gerou o artigo nomeado “The potential role of selection bias in the association between coronary atherosclerosis and cognitive impairment” que foi publicado no Journal of Alzheimer's Disease, vol. 93, no. 4, pp. 1307-1316, 2023 93 (2023) 1307–1316, DOI 10.3233/JAD-220820; e o artigo nomeado “Association of atherosclerotic plaque components with Alzheimer's disease pathology”, sob submissão, que serão apresentados a seguir.

4.1 **Artigo 1**

O manuscrito "*The potential role of selection bias in the association between coronary atherosclerosis and cognitive impairment*" foi publicado no Journal of Alzheimer's Disease, vol. 93, no. 4, pp. 1307-1316, 2023. DOI: 10.3233/JAD-220820.

Neste estudo baseado em autópsia, foi avaliada a associação entre estenose coronariana e comprometimento cognitivo, determinado por escalas CDR, CDR-SB e IQCODE. Além disso, foi investigada a possibilidade de viés de seleção em um estudo de autópsia.

A estenose aterosclerótica coronariana não foi associada ao comprometimento cognitivo e à função cognitiva relacionado a amostra total. No entanto, em indivíduos que nasceram em 1935 ou antes, na ausência de doença cardiovascular como causa de morte, a estenose mais elevada foi associada a maiores probabilidades de comprometimento cognitivo e pior função cognitiva. Por outro lado, em indivíduos que morreram por causas cardiovasculares, a maior estenose foi relacionada à melhor função cognitiva tanto na amostra total quanto quando restrita aos nascidos em 1935 ou antes.

Estudos baseados em autópsia têm uma pressão de seleção sobre quem entra na amostra de autópsia que pode alterar significativamente os resultados, e o resultado pode ser tendencioso em relação à população-alvo de interesse. A doença cardiovascular como causa da morte é um fator importante relacionado ao viés de seleção, pois esses participantes têm maior probabilidade de morrer antes de desenvolver comprometimento cognitivo.

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The Potential Role of Selection Bias in the Association Between Coronary Atherosclerosis and Cognitive Impairment

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Abstract.
Background: Coronary atherosclerosis assessed *in vivo* was associated with cognitive impairment; however, conflicting findings have been reported in autopsy samples.
Objective: Our aims were to assess the association between atherosclerotic stenosis in the coronary arteries and cognitive impairment and to investigate the possibility of selection bias in an autopsy study.
Methods: Coronary arteries were collected, and the largest luminal stenosis was measured. Sociodemographic, clinical, and cognitive information were reported by a reliable next-of-kin. The association was tested using logistic and linear regressions adjusted for sociodemographic and clinical variables. We restricted the sample to individuals that were born in 1935 or earlier and stratified the analysis by cause of death to investigate the role of selection bias.
Results: In 253 participants (mean age = 78.0 ± 8.5 years old, 48% male), stenosis was not associated with cognitive impairment (OR = 0.85, 95%CI = 0.69; 1.06, $p = 0.15$). In individuals who were born before 1936 in the absence of cardiovascular disease as the cause of death, greater stenosis was associated with cognitive impairment (OR = 4.02, 95%CI = 1.39; 11.6, $p = 0.01$). On the other hand, this association was not present among those born in 1935 or earlier who died of cardiovascular diseases (OR = 0.83, 95%CI = 0.60; 1.16, $p = 0.28$).
Conclusion: We found that higher coronary stenosis was associated with cognitive impairment only in individuals born in 1935 or earlier and who had not died from cardiovascular diseases. Selection bias may be an important issue when investigating risk factors for chronic degenerative diseases in older individuals using autopsy samples.

Keywords: Aging, Alzheimer's disease, atherosclerosis, bias, cognitive impairment, dementia

INTRODUCTION

Coronary heart disease (CHD) is the leading cause of mortality worldwide [1], and it is most commonly due to coronary artery atherosclerosis [2]. At the same time, around 50 million people are living with

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dementia, and we anticipate about 10 million new cases every year [3]. Dementia is also among the ten most common causes of mortality [4], and it is one of the main causes of disability in older people [5]. Atherosclerosis and dementia share common risk factors, as hypertension [6], dyslipidemia [7], smoking, and diabetes mellitus [8].

Most previous studies have suggested a link between CHD and cognitive impairment. A meta-analysis of cross-sectional, case-control, and cohort studies showed an association of CHD with mild cognitive impairment and dementia only in prospective cohort studies. In these studies, CHD was defined by a combination of a previous diagnosis of myocardial infarction and/or angina pectoris and alterations of laboratory tests and electrocardiogram [9]. On the other hand, coronary artery calcium (CAC) measured by computerized tomography is a quantitative method to evaluate indirectly the subclinical atherosclerosis. CAC was associated with an increased risk of incident dementia, cognitive impairment, and poor performance in cognitive tests [10–12]. However, CAC captures the presence of calcium in the atherosclerotic plaque, which is related to stable and advanced atherosclerotic plaque, and does not necessarily evaluate the artery narrowing [10, 11, 13, 14].

A previous autopsy study with 99 participants showed an association between CHD with AD pathology, mainly in apolipoprotein allele E4 (*APOE4*) genotype carriers that was independent of other risk factors, such as age and sex [15]. On the other hand, another study found no association between systemic atherosclerosis in the aorta, coronary artery, and intracranial artery with AD pathology. Only cerebral atherosclerosis was associated with an increased dementia risk [16]. Autopsy studies could provide a reliable and less subjective assessment of atherosclerosis due to the possibility of direct arterial measurements when compared to clinical studies. However, previous autopsy studies did not measure coronary atherosclerosis by morphometric methods. One study performed a visual inspection of the artery with the categorization of atherosclerotic plaques into three grades [16] and the stenosis of the coronary artery was not measured in another study [15].

The discrepancy between studies in living persons with autopsy samples could be attributed to issues of measurement or selection biases. Autopsy studies are, by their nature, selected samples. Selection bias could be caused by oversampling of persons with premature mortality due to other mortality causes that compete with the cognitive impairment outcome [17]. Premature deaths due to cardiovascular diseases are a potential selection confounding factor could lead to a false protective effect or absence of association between cardiovascular exposures and cognitive impairment [18]. Analytical strategies are needed to decrease bias. Although some strategies have already been implemented in previous cohort studies, additional strategies should be conducted in cross-sectional studies [12]. Therefore, we aimed to assess the association between morphometric measures of atherosclerosis in coronary arteries and cognitive impairment in an autopsy study and explore the potential impact of selection bias acting on this association.

METHODS

Participants

This study was conducted at the Laboratory of Cardiovascular Pathology and is part of the Biobank for Aging Studies (BAS) collection [19]. Data were collected from 2011 to 2015 at the Sao Paulo Autopsy Service (SPAS), which performs the autopsy on participants who died in Sao Paulo city from non-traumatic and undefined causes of death [20]. The next-of-kin (NOK) signed an informed consent form before the sample collection and the refusal rate in our sample was 14%. The inclusion criteria for this study were individuals aged 65 years or older, postmortem interval less than 24 hours, availability of a NOK who had at least weekly contact with the deceased in the last six months before death, complete cognitive assessment completed by the next-of-kin, and the collection of heart. Exclusion criteria were participants with injuries that occurred close to death that could influence cognitive function (e.g., anoxic encephalopathy) and inconsistent data provided by the NOK during the clinical interview (e.g., inability to answer appropriately) [19]. This study was approved by the local ethics committee and followed the ethical guidelines of the Declaration of Helsinki.

Clinical evaluation

Trained gerontologists administered a semi-structured interview to the NOK. This interview obtained data on the deceased, including sociodemographic information, such as date of birth collected from official governmental document, sex, and race, which was categorized as White and No-White. Education was measured as the number of years of formal

education. The clinical information was investigated through previous diagnoses of hypertension, diabetes mellitus, CHD, heart failure, stroke, and dyslipidemia. We investigated the lifestyle factors as binary variables: physical activity was defined as performing domestic, occupational activities, or formal physical exercises at least 3 times per week; current alcohol consumption (yes or no); and smoking (current or previous/never smokers). Body mass index (BMI) was calculated using the direct measures from weight in kilograms and height in meters measured in a supine position, while the deceased have no clothes or shoes before the autopsy exam [21].

Cognitive evaluation

The NOK completed semi-structured questionnaires previously validated for postmortem application [22] to assess cognitive impairment in the deceased, including the Clinical Dementia Rating Scale (CDR) [23, 24] and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [25], validated for the Brazilian population [26].

The CDR is a scale used to obtain information on six domains: memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. The CDR assesses the presence and the stage of dementia, using a point scale distributed as follows: CDR 0 - cognitively normal individuals, CDR 0.5 - questionable dementia, CDR 1, 2, and 3 - mild, moderate, and severe cognitive impairment, respectively [23, 24]. NOK was instructed to answer the CDR and IQCODE questionnaires based on the deceased's cognitive abilities three months before death to avoid the cognitive impact of the disease that led the individual to death.

In this study, just the informant section of CDR was applied, and cognitive impairment was used as a categorical variable determined by the presence of CDR $\geq$ 0.5. We also used the CDR scale sum of the boxes (CDR-SB). The CDR-SB score is obtained by summing the score in each of the CDR domains, with the total score ranging from 0 to 18 with higher scores meaning poorer cognitive function [27].

We used the informant-based version of the IQCODE to retrospectively ascertain the change in cognitive and functional performance over a 10-year time period [25, 28]. The full version consists of 26 questions. The questions were answered based on the Likert scale, with five options: 1 – much improved; 2 – a bit improved; 3 – not much change; 4 – a bit worse, 5 – much worse). The IQCODE has 26 questions that have five possible answers on a Likert scale ranging from 1.00 to 5.00. The final IQCODE score was calculated by summing the points for each question and dividing them by the total number of questions that were answered. Higher scores corresponded to greater cognitive impairment.

Coronary artery atherosclerosis evaluation

The heart was collected and washed to remove clots, and then the right coronary artery, left main coronary or left anterior descending artery, and left circumflex arteries were dissected, filled with gelatin solution to prevent arterial collapse, and then fixed in formalin [29, 30]. The arteries were cut transversally at 5 mm-thickness sections, and each segment was evaluated for the presence of atherosclerotic plaques. The segment with the largest obstruction in each coronary was photographed using a camera (Nikon® SMZ 1000) attached to a stereomicroscope (Leica® DMR). The contour of the lumen area and the outer area was determined using the software Image J®. The stenosis of the coronary arteries was calculated by dividing the difference between the outer area and the lumen area by the outer area and multiplied by 100 to obtain the percentage (Fig. 1) [31].

Statistical analysis

The characteristics of study participants were described using the mean and standard deviation (SD) or the median and interquartile range (IQR) for continuous variables, and absolute and relative frequencies for categorical variables. The sociodemographic and cardiovascular risk factors were compared across individuals with (CDR $\geq$ 0.5) and without (CDR = 0) cognitive impairment using unpaired *t*-test for continuous variables with normal distribution and non-parametric Mann-Whitney test when we had a non-normal distribution. The categorical variables were compared using chi-squared test.

The independent variable was the percentage of stenosis categorized in 10 groups: category 1 = 0 | 10%; category 2 = 10 | 20%; category 3 = 20 | 30%; category 4 = 30 | 40%; category 5 = 40 | 50%; category 6 = 50 | 60%; category 7 = 60 | 70%; category 8 = 70 | 80%; category 9 = 80 | 90%; and category 10 = 90 | 100%. The dependent variables were cognitive impairment as a binary variable (CDR) and cognitive function as a continuous variable (CDR-SB and IQCODE). We used logistic (cognitive impair-

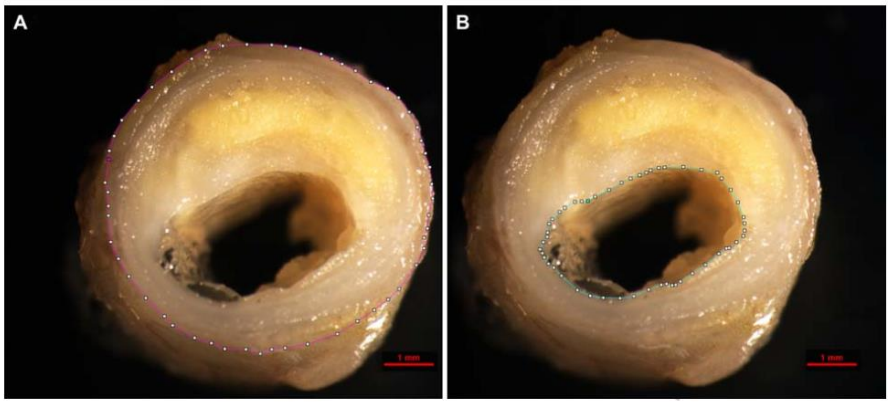

Fig. 1. Cross-sectional view of the anterior descending artery. A) Delimitation of the outer border of the artery. B) Delimitation of the lumen of the artery. Source: Laboratory of Cardiovascular Pathology.

ment outcome) and linear regression (CDR-SB and IQCODE outcomes) models with robust standard error to account for repeated measures in the same individual (i.e., three coronary artery measurements per person). Regression models were adjusted for age at death, sex, race, education, alcohol use, smoking, physical activity, hypertension, diabetes mellitus, and BMI.

To explore the role of selection factors, we restricted the sample to individuals that were born in 1935 or earlier and stratified all analyses by whether the deceased had a cardiovascular cause of death. Restriction to those born in 1935 or earlier allowed us to consider a sample that was not enriched in those with premature death (and associated risk factors), and which was composed of older adults who experienced similar environmental risk factors in a similar time period [32]. Stratified analysis by cardiovascular disease as the cause of death allowed us to consider whether selection into the autopsy sample based on cardiovascular death could have biased study results [33]. We considered a 5% level of significance in two-tailed tests. All analyses were performed using STATA 13 (StataCorp., College Station, TX, USA).

RESULTS

The final sample consisted of 253 participants with a mean age was 78.0 (SD 8.5) years old; 48% were male, 65% were white, and 77% had 0 to 4 years of education. Cognitive impairment, defined as CDR $\geq$ 0.5 was present in 31%. Compared to participants without cognitive impairment, participants with cognitive impairment were older and more likely to be women, were more physically inactive, and had lower values of BMI. Individuals without cognitive impairment presented more hypertension, previous history of CAD, and current smoking (Table 1). Among 128 participants who were born in 1935 or earlier, the mean age was 85 (SD 5.2) years old, 46% presented cognitive impairment, hypertension was less prevalent, BMI was lower, and physical inactivity was more frequent among participants with cognitive impairment (Supplementary Table 1).

In adjusted models, stenosis was not associated with cognitive impairment in either the total sample (OR = 0.85 per 10% increase in stenosis, 95% CI = 0.69; 1.06, $p = 0.15$) or in individuals who were born in 1935 or earlier (OR = 0.95, 95% CI = 0.73; 1.24, $p = 0.73$). Coronary stenosis was not associated with CDR-SB in the total sample (β=–0.39, 95% CI=–0.89; 0.09, $p = 0.11$) and among individuals born in 1935 or earlier (β=–0.26, 95% CI = –1.01; 0.48, $p = 0.48$). Similarly, there was no association between stenosis and IQCODE in the total sample (β=–0.04, 95% CI = –0.09; 0.01, $p = 0.11$) and among individuals born in 1935 or earlier (β=–0.03, 95% CI = –0.11; 0.04, $p = 0.38$) (Table 2).

Although the average age at death was similar between cardiovascular and other causes of death in the whole sample ($p = 0.19$) and both birth cohorts (1935 or earlier: $p = 0.54$ and before 1935: $p = 0.41$) (Supplementary Table 2), there was an excess of deaths by CVD, which is three times more frequent (75%) than death by other causes (25%). Deaths by CVD were also highly correlated with coronary stenosis (Supplementary Table 3) and with cognitive impairment, especially in those born after 1935 ($p = 0.03$). After selecting only participants who were born in 1935 or earlier because they survived pre-

Table 1
Description of the clinical variables of the study participants ($n = 253$ participants)

Variable	Total	CDR = 0 ($n = 174$)	CDR ≥ 0.5 ($n = 79$)	p^*
Age (y), mean (SD)[a]	78 (8.6)	76 (8.1)	82 (7.8)	< 0.0001
Sex, n (%)[b]				0.01
Male	121 (47.8)	100 (57.5)	32 (40.5)	
Female	132 (52.2)	74 (42.5)	47 (59.5)	
White, n (%)[b]	164 (64.8)	112 (64.4)	52 (65.8)	0.69
Schooling (y), median (IQR)[c]	4 (2; 4)	4 (2;5)	4 (0; 4)	0.004
Hypertension, n (%)[b]	187 (74.5)	138 (80.2)	49 (62.0)	0.002
Diabetes mellitus, n (%)[b]	94 (37.4)	69 (40.1)	25 (31.6)	0.19
CAD, n (%)[b]	51 (20.3)	43 (25.0)	8 (10.1)	0.007
Heart failure, n (%)[b]	60 (23.9)	46 (26.7)	14 (17.7)	0.12
Stroke, n (%)[b]	47 (17.1)	22 (12.8)	21 (26.6)	0.007
Dyslipidemia, n (%)[b]	48 (19.1)	35 (20.3)	13 (16.5)	0.46
BMI, mean (SD) [a]	23.2 (5.8)	24.7 (5.6)	19.6 (4.8)	< 0.0001
Physical inactivity, n (%)[b]	177 (71.1)	113 (65.0)	64 (85.2)	0.001
Current smoking, n (%)[b]	141 (55.7)	105 (60.3)	36 (45.6)	0.02
Current alcohol use, n (%)[b]	121 (48.0)	89 (51.1)	32 (41.0)	0.13
Stenosis, median (IQR) [c]				
Right Coronary Artery	79.4 (67.7; 91.3)	82.2 (71.6; 91.7)	72.3 (64.6; 86.1)	0.003
Left Anterior Descending Artery/Left Main Coronary	82.7 (73.9; 91.2)	84.5 (74.4; 90.9)	81.4 (70.8; 91.9)	0.16
Left Circumflex Artery	79.8 (68.2; 89.3)	82.0 (69.6; 91.0)	74.7 (62.1; 84.8)	0.002
IQCODE, mean (SD) [a]	3.4 (0.7)	3.0 (0.04)	4.3 (0.7)	< 0.0001
CDR Sum box, mean (SD) [a]	4.0 (6.9)	0.008 (0.06)	13.4 (5.6)	< 0.0001
Cause of death by CVD, n (%)[b]	188 (74.3)	135 (77.6)	53 (67.1)	0.07
CAD by report autopsy exam, n (%)[b]	109 (43.1)	77 (44.2)	32 (40.5)	0.57

CDR, Clinical Dementia Rating scale; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; CVD, cardiovascular disease; CAD, coronary artery disease; SD, standard deviation; IQR, interquartile range; BMI, body mass index. *Comparison of social and clinical variables between groups: CDR = 0 and CDR ≥ 0.5; [a]*t*-test; [b]chi-squared; [c]Mann-Whitney test.

Table 2
Association between dementia, CDR Box Sum, IQCODE, and stenosis in coronary arteries

Stenosis	Cognitive impairment OR (95% CI) p^*	CDR Box sum β (95% CI) p^{**}	IQCODE β (95% CI) p^{**}
Total sample ($n = 759$ coronary arteries)			
Univariate Model	0.80 (0.68; 0.94) 0.009	–0.075 (–1.27; –0.22) 0.005	–0.08 (–0.13; –0.02) 0.003
Adjusted Model[a]	0.85 (0.69; 1.06) 0.15	–0.39 (–0.89; 0.09) 0.11	–0.04 (–0.09; 0.01) 0.11
Born in 1935 or earlier ($n = 384$ coronary arteries)			
Univariate Model	0.95 (0.77; 1.16) 0.63	–0.31 (–1.12; 0.49) 0.44	–0.03 (–0.11; 0.05) 0.45
Adjusted Model[a]	0.95 (0.73; 1.24) 0.73	–0.26 (–1.01; 0.48) 0.48	–0.03 (–0.11; 0.04) 0.38

CDR, Clinical Dementia Rating scale; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; OR, odds ratio; CI, confidence interval. *Logistic regression with robust SEs to account for repeated measures in the same individual through cluster adjustment. **Linear regression with robust SEs to account for repeated measures in the same individual through cluster adjustment. [a]Adjusted for age, sex, race, education in years, alcohol use, smoking, physical inactivity, hypertension, diabetes mellitus, and body mass index.

mature deaths due to cardiovascular diseases, we observed the loss of significance between death from cardiovascular disease and the cognitive impairment ($p = 0.46$, Supplementary Table 4). Therefore, the excess of death by CVD is a potential source of selection bias. After stratifying the sample by cause of death, we found that among participants that died from cardiovascular causes, a higher stenosis was related to a better cognitive function defined by lower scores in the CDR-SB (β=–0.67, 95% CI = –1.28; –0.06, $p = 0.03$) and IQCODE (β=–0.07, 95% CI = –0.13; –0.005, $p = 0.03$), while we did not find any association among those who did not die from cardiovascular disease and in stratified analysis by the presence of cognitive impairment (Table 3). After restricting to individuals born in 1935 or ear-

Table 3
Association between dementia, CDR Box Sum, IQCODE, and stenosis in coronary arteries stratified by cardiovascular disease as the cause of death

Stenosis	Cognitive Impairment		CDR Box sum		IQCODE	
	CVD (-) OR (95%CI) p^*	CVD (+) OR (95%CI) p^*	CVD (-) β (95%CI) p^{**}	CVD (+) β (95%CI) p^{**}	CVD (-) β (95%CI) p^{**}	CVD (+) β (95%CI) p^{**}
Total sample	$n = 195$ coronary arteries	$n = 564$ coronary arteries	$n = 195$ coronary arteries	$n = 564$ coronary arteries	$n = 195$ coronary arteries	$n = 564$ coronary arteries
Univariate Model	0.89 (0.67; 1.80) 0.42	0.79 (0.65; 0.97) 0.03	–0.18 (–1.13; 0.76) 0.69	–0.94 (–1.60; –0.28) 0.005	–0.01 (–0.12; 0.08) 0.71	–0.10 (–0.16; –0.03) 0.003
Adjusted Model [a]	1.01 (0.67; 0.49) 0.96	0.86 (0.67; 1.11) 0.26	0.42 (–0.36; 1.21) 0.28	–0.67 (–1.28; –0.06) 0.03	0.03 (–0.04; 0.11) 0.38	–0.07 (–0.13; –0.005) 0.03
Born in 1935 or earlier	$n = 99$ coronary arteries	$n = 285$ coronary arteries	$n = 99$ coronary arteries	$n = 285$ coronary arteries	$n = 99$ coronary arteries	$n = 285$ coronary arteries
Univariate Model	1.12 (0.77; 1.63) 0.53	0.90 (0.70; 1.15) 0.42	0.68 (–0.77; 2.14) 0.34	–0.68 (–1.66; 0.29) 0.17	0.08 (–0.06; 0.23) 0.24	–0.07 (–0.17; 0.02) 0.14
Adjusted Model [a]	4.02 (1.39; 11.6) 0.01	0.83 (0.60; 1.16) 0.28	1.19 (0.09; 2.29) 0.03	–0.83 (–1.76; 0.09) 0.07	0.09 (–0.02; 0.21) 0.12	–0.09 (–0.19; 0.01) 0.07

CDR, Clinical Dementia Rating Scale; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; OR, odds ratio; CI, confidence interval; CVD (+), presence of cardiovascular disease; CVD (-), absence of cardiovascular disease. *Logistic regression with robust SEs to account for repeated measures in the same individual through cluster adjustment. **Linear regression with robust SEs to account for repeated measures in the same individual through cluster adjustment. [a]Adjusted for age, sex, race, education in years, alcohol use, smoking, physical inactivity, hypertension, diabetes mellitus, and body mass index.

lier that died from cardiovascular disease, we found a borderline protective association between stenosis and CDR-SB (β=–0.83, 95% CI = –1.76; 0.09, $p = 0.07$) and IQCODE (β=–0.09, 95% CI = –0.19; 0.01, $p = 0.07$). On the other hand, in individuals who were born in 1935 or earlier in the absence of cardiovascular disease as the cause of death, higher stenosis was associated with 4-fold increased risk of cognitive impairment (OR = 4.02, 95% CI = 1.39; 11.6, $p = 0.01$), and poorer cognitive function defined by higher CDR-SB scores (β=1.19, 95% CI = 0.09; 2.29, $p = 0.03$) while no association was observed with IQCODE scores (β = 0.09, 95% CI=–0.02; 0.21, $p = 0.12$) (Table 3).

DISCUSSION

In this autopsy study, coronary atherosclerotic stenosis was not associated with cognitive impairment and related daily functioning in the whole sample. However, in individuals who were born in 1935 or earlier, in the absence of cardiovascular disease as the cause of death, higher stenosis was associated with higher odds of cognitive impairment and poorer cognitive function. On the other hand, in individuals who died from cardiovascular causes, higher stenosis was related to better cognitive function in both the total sample and when restricted to those born in 1935 or earlier.

We hypothesized that a higher coronary atherosclerotic stenosis would be associated with cognitive impairment as shown in a previous meta-analysis from cohort studies [9, 34] and in an autopsy-based study that showed an association between with AD-associated neuropathology, mostly in *APOE4* genotype carriers [15]. However, our findings were in line with Dolan et al. [16] that found no association of the degree of atherosclerosis in coronary, carotid, and cerebral arteries with the degree of Alzheimer's type pathology.

However, the results of autopsy analyses are dependent on the autopsy sample. Autopsied participants may not be representative of the target population and can yield biased results. Beeri et al. [15] found an association between CAD with Alzheimer's disease pathology; however, the studied sample had only 99 brains. Of those 42 were *APOE4* carriers and the majority were institutionalized women (82%) that are known risk factors for cognitive impairment. *APOE4* carriers probably had more chances to develop cognitive impairment before death, counteracting the effect of selection bias in this study [35]. On other hand, Dolan et al. [16] did not find associations between atherosclerosis with Alzheimer's disease in a well-educated sample (mean education of 17.1 ± 3.9 years), which is considered a protective factor [3]. Our sample was more balanced concerning sex and education distribution, avoiding these possible biases. The lack of association in our first result, even after careful statistical analysis and accurate direct morphometric measurements of atherosclerosis could be explained by selection bias, which was frequent in investigations about the association between cardiovascular and neurodegenerative diseases [17, 18]. The excess of CVD deaths in younger participants led to selection bias in our study. However, stratifying the sample by cardiovascular and non-cardiovascular cause of death without the birth cohort restriction would lead to a spurious protective association. We found that higher coronary stenoses were associated with a better cognitive function in those that died from cardiovascular disease. This finding could be related to the fact that participants who died from cardiovascular causes died at a younger age than those who die from other causes is lower than other death causes and they were too young for having a high risk to have cognitive impairment. The arbitrary cutoff of age at 80 years old at 2015, which was the last year of our sample collection, was done to restrict the sample to older adults that survived premature death by cardiovascular disease. In the group that was born in 1935 or earlier and did not die from cardiovascular disease, an increase in coronary stenosis was related to cognitive impairment and worse cognitive function, as expected. These findings are probably related to survival bias since participants with high atherosclerotic stenosis are more likely to die before they can develop cognitive impairment, as shown previously in studies related to cancer and dementia [36, 37]. Death from cardiovascular disease may be acting as a collider since dementia [38] and higher coronary stenosis may both lead to death [33, 39]. The association between coronary stenosis with poor cognitive function was found for CDR-SB, but not for the IQCODE. Differences in the pattern of associations may be due to the differences in range and scale in the two questionnaires, the CDR-SB ranges from 0 to 18, while the IQCODE ranges from 1.00 to 5.00, which gives more power to analyses that have the CDR-SB as the outcome. Moreover, the two questionnaires measure different constructs related to cognitive impairment. The CDR is used to determine the presence and severity of dementia, while

IQCODE evaluates cognitive decline when comparing current cognitive abilities related to 10 years ago [40, 41]. The linear regression coefficients represent the average increase or decrease in the CDR-SB or IQCODE scores for each 10% increase of stenosis.

The full-body autopsy allows the determination of the accurate cause of death. Furthermore, the autopsy is an important tool to study risk factors for cognitive change since a full-body autopsy exam allows for direct and reliable measurements of tissue damage [42, 43]. For example, the assessment of atherosclerosis *in vivo* is based on calcification measured by computerized tomography. However, calcification assessed by CAC is useful to detect stable and advanced atherosclerotic plaque and does not necessarily evaluate the arterial narrowing, because other atherosclerotic plaque components were not evaluated by this imaging method [44]. On the other hand, the autopsy exam allows studying other components of the atherosclerotic plaque.

The association between coronary artery atherosclerosis and cognitive impairment could be explained by different mechanisms [10, 12]. Coronary atherosclerosis could be a marker of intracranial cerebral atherosclerosis [45], which could be the cause of vascular dementia and may also be related to amyloid pathology as a result of amyloid-β accumulation and impaired amyloid-β clearance [46]. Another mechanism could be chronic cerebral hypoperfusion due to a narrowing of the coronary arteries, leading to reduced cardiac output, and consequently lower brain blood flow, leading to impaired cognitive function [47].

Our study has some limitations. This cross-sectional study does not allow establishing causal inference. Moreover, the cognitive assessment was based on postmortem information collected from the next-of-kin. Although this approach has been validated [22] and applied in several studies [48, 49], a pre-morbid assessment would be preferable. Furthermore, as neuropathological assessment was not performed at this time, we were not able to analyze the association of coronary atherosclerosis with the neuropathology of Alzheimer's disease or vascular dementia. Although we included education in our adjusted analyses, other measures of socioeconomic status were not collected in our study and residual confounding may be present in our study. Additionally, we were unable to collect clinical and sociodemographic data from those who refused to participate in the study, which did not allow us to compare excluded individuals with study participants. The main strengths of this study are the direct anatomic measurement of the atherosclerotic plaque, instead of symptoms-based diagnosis, and the determination of causes of death by full-body autopsy.

In conclusion, this study showed no association between coronary stenosis and cognitive impairment. Larger coronary atherosclerosis was associated with cognitive impairment only in individuals born in 1935 or earlier without cardiovascular disease as cause of death. In the presence of cardiovascular disease as cause of death, the association tends to be protective. Autopsy-based studies have a selection pressure about who gets into autopsy sample that can change the results significantly, and the result may be biased concerning the target population of interest. Cardiovascular disease as the cause of death is an important factor related to selection bias since these participants are more likely to die before developing cognitive impairment. Aging research is a challenge, and it is important to be aware of methodological problems in studies about chronic degenerative diseases. Further longitudinal studies with longer follow-up and methodological approaches to control for selection bias will be important to assess whether coronary atherosclerosis is a risk factor for cognitive impairment.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-220820.

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4.2 **Artigo 2**

O manuscrito intitulado "*Association of atherosclerotic plaque components with Alzheimer's disease pathology*" está em fase de submissão.

Os resultados preliminares foram apresentados na Alzheimer's Association International Conference (AAIC), com apresentação do poster nomeado "Association between coronary artery atherosclerosis and Alzheimer's disease pathology: preliminary results"

Neste estudo, avaliamos a associação entre os componentes da placa aterosclerótica e a neuropatologia da doença de Alzheimer.

Nesta amostra com 321 adultos, foram observadas diversas associações. A calcificação coronária foi associada a uma menor chance de deposição de placas neuríticas, enquanto a necrose foi associada a uma menor chance de emaranhados neurofibrilares. Além disso, um aumento na contagem de vasa vasorum na camada íntima foi associado a uma maior probabilidade de deposição de placas neuríticas e diagnóstico de DA. Quando as análises foram estratificadas por idade, entre os participantes com menos de 75 anos, o conteúdo lipídico na placa aterosclerótica foi associado a uma maior probabilidade de PN e uma capa fibrosa mais espessa foi associada a uma menor probabilidade de diagnóstico de DA. Entre os participantes com 75 anos ou mais, o trombo cicatrizado foi associado ao diagnóstico de DA.

Hipotetizamos que os componentes da placa aterosclerótica ligados à estabilidade da placa estariam associados à neuropatologia da doença de Alzheimer, por ser uma doença de início tardio e decorrente de mudanças crônicas. No entanto, dada a complexidade da progressão da placa aterosclerótica, os componentes desempenham diferentes papéis no processo de ruptura e cicatrização.

Este manuscrito encontra-se em fase de revisão em revista internacional.

Association of atherosclerotic plaque components with Alzheimer's disease pathology

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ABSTRACT

Globally, approximately 50 million people live with dementia, and Alzheimer's disease (AD) stands as the most prevalent type of dementia, characterized by the deposition of neuritic plaques (NP) and neurofibrillary tangles (NFT). Although coronary atherosclerosis has been associated with dementia, the association of coronary plaque components with AD pathology is unclear. We aimed to investigate the association of coronary atherosclerotic plaque components and morphometric measures with neuropathological markers of AD in an autopsy study. We performed morphometric measures of atherosclerotic plaque burden and composition in coronary arteries, and NP and NFT were evaluated following standard criteria. The sample comprised 321 participants, with an average age of 77±11 years old. Coronary calcification was associated with lower odds of NP deposition (OR=0.88 per 10% increase in calcification, CI=0.79; 0.97, p=0.008), while a higher number of vasa vasorum in the intimal layer was associated with higher odds of NP (OR=1.02 CI=1.00; 1.04, p=0.045) and AD diagnosis (OR=1.04, CI=1.01; 1.08, p=0.014). An increase in necrosis burden was associated with lower odds of NFT (OR=0.84 per 10% increase in necrosis, CI=0.71; 0.99, p=0.040). Among participants <75 years old, greater lipid deposition was associated with an increased odds of NP (OR=1.19 per 10% increase lipids, 95% CI=1.01; 1.39, p=0.032), and greater thickening of the fibrous cap was associated with a decreased likelihood of AD diagnosis (OR=0.98, 95% CI=0.96; 1.00, p=0.023). Among participants aged 75 years and older, healed thrombus was associated with AD diagnosis (OR=1.84 per 10% in healed thrombus area, 95% CI=1.10; 3.06, p=0.020). We hypothesized that atherosclerotic plaque components linked to plaque stability would be associated with the neuropathology of AD. However, the association of atherosclerotic plaque components with AD pathology may change throughout atherosclerotic plaque progression.

Keywords: atherosclerosis, neuritic plaque, neurofibrillary tangle, Alzheimer’s disease

INTRODUCTION

Globally, approximately 50 million individuals live with dementia, and nearly 10 million new cases arising annually. About two-thirds reside in low-middle-income countries (1). Alzheimer's disease (AD) stands as the most prevalent type of dementia and is characterized by the deposition of neuritic plaques (NP) and neurofibrillary tangles (NFT) (2). It has been suggested that cardiovascular disease (CVD) may play etiological role on AD pathology (3).

Coronary heart disease (CHD) remains the leading cause of mortality worldwide, typically arising from luminal thrombosis, most commonly due to atherosclerotic disease of the coronary arteries (4,5). Atherosclerosis is a chronic disease that results in the progressive wall thickening of major arteries, which can lead to acute events or persist in an asymptomatic state for decades (5). Many clinical studies have established a link between CHD and dementia (6,7). Coronary artery calcification (CAC), considered a marker of coronary atherosclerosis, was linked with cognitive function (8,9). In an autopsy-based study involving 99 participants, CHD was associated with AD pathology, particularly in individuals carrying the apolipoprotein E allele ε4 (APOE4) (10). Conversely, another autopsy study did not find any association of systemic atherosclerosis in the aorta, and coronary and intracranial arteries with AD pathology. Only intracranial atherosclerosis was associated with an elevated risk of clinical dementia (11,12). The atherosclerotic plaque includes deposition of lipids, calcification, necrosis, hemorrhage, fibrous cap, collagen, smooth muscle cells, healed thrombus, and vasa vasorum. Although the presence of certain atherosclerosis plaque components was related to a greater risk of stroke (13–15), the association of plaque components and AD pathology has not been investigated previously. Therefore, we aimed to investigate the association of coronary atherosclerotic plaque components and morphometric measures with neuropathological markers of AD in an autopsy study.

METHODS

Participants

This study utilized materials from the Biobank for Aging Studies (BAS) at the University of Sao Paulo. In Brazil, autopsies are mandatory for determining the cause of death in

individuals who died of natural causes when the death etiology is not clear. In this study, the materials were collected from the Sao Paulo Autopsy Service, where the BAS maintains a structure of trained professionals to interview, collect and process the materials for research purposes (16). Eligible participants were selected between 2011 to 2022.

The inclusion criteria for this study were individuals aged 50 years or older, a *post-mortem* interval of less than 24 hours, and having a next of kin (NOK) who had maintained at least weekly contact with the deceased during the six months preceding death to provide accurate clinical information. Exclusions were made if clinical data were inconsistent or if the brain tissue was unsuitable for neuropathological analyses (e.g., cerebrospinal fluid pH<6.5 or significant acute brain lesions, including hemorrhages) (16). An informed consent form, authorizing the donation of the heart and brain of the deceased, was signed by the NOK, and a semi-structured interview was conducted by trained gerontologists (16). This study was approved by the local ethics committee and adhered to the ethical guidelines of the Declaration of Helsinki. Data were stored using the REDCap electronic data capture tool (17).

Clinical assessment

The NOK was interviewed to determine the deceased's clinical status. The interview followed a semi-structured format, which was previously validated for *post-mortem* use and has shown evidence of validity in detecting cognitive impairment (18). The interview included information on sociodemographic data (age, sex, education, race); past medical history (hypertension, diabetes, coronary artery disease, heart failure, arrhythmia, and stroke), and lifestyle variables as smoking (never, current and previous), alcohol use (never, current and previous), and physical activity (at least 3 times a week of domestic, work, or leisure physical activities). Upon autopsy, the deceased's weight and height were measured without clothes in the supine position, using an electronic scale and a stadiometer. The body mass index was calculated by dividing the weight in kilos by the square of the height in meters (16).

Coronary arteries assessment

The heart was collected, and the right coronary artery, left main coronary artery, left anterior descending artery, and left circumflex artery were dissected. Subsequently, they were fixed in formalin. The arteries were transversally cut into 5 mm thickness sections, and the largest obstruction in each coronary was sampled. These samples were then photographed using a camera (Nikon® SMZ 1000) attached to a stereomicroscope (Leica® DMR). The segments were embedded in paraffin, cut into 4-µm slices, and stained with hematoxylin-eosin and Masson's trichrome. Each stained slide was photographed (19,20).

To evaluate the coronary arteries, a software toll named Atherosclerotic Plaque Analyser (APA) was developed using the LabView environment (Laboratory Virtual Instrumentation Engineering Workbench; National Instruments, Austin, TX) (Fig.1 and 2). APA corrects the image background, identifies the artery and the scale bar, and contours the lumen, and external and internal elastic lamina automatically. Identification of the artery enables the transfer of measurements to other staining. Additionally, the components of the atherosclerotic plaque, which include the lipid core, necrotic core, calcifications, healed thrombus, intraplaque hemorrhage, collagen, and smooth muscle cells, were manually delimited. APA then calculated the percentage of the area of each component within the atherosclerotic plaque area (Fig.2).

The intima-media thickness (IMT) was calculated as the distance between the lumen and the external elastic lamina. The fibrous cap thickness (FCT) was manually delineated and measured at the thinnest section along the cap. The number of vasa vasorum in the intimal layer was also counted (21). The percentage of arterial obstruction was calculated using the following formula (22):

$$\text{arterial obstruction} = \frac{\text{area delimited by the internal elastic lamina} - \text{area delimited by the lumen}}{\text{area delimited by the internal elastic lamina}} \text{x100}$$

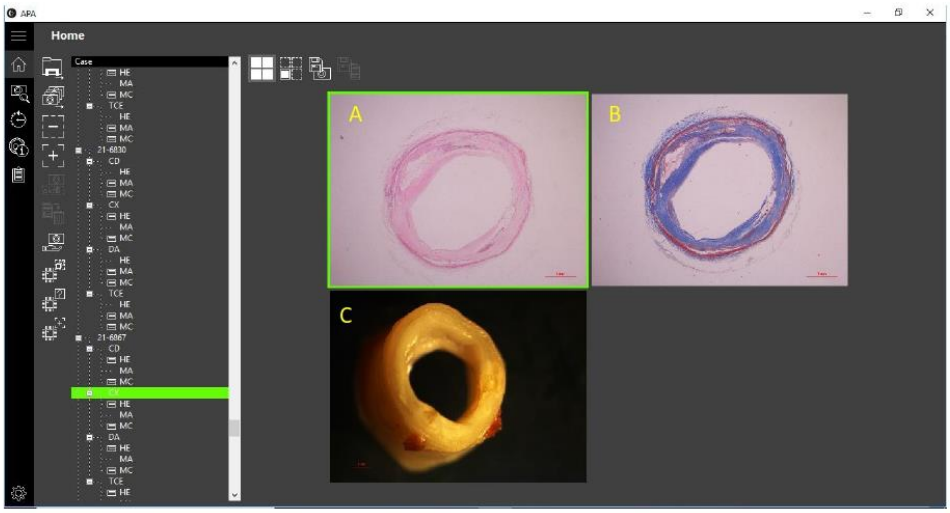

Figure 1. Interface of the Atherosclerotic Plaque Analyzer (APA) software with cross-sectional views of the left circumflex artery coronary artery stained with (A) hematoxylin-eosin and (B) Masson's trichrome, and the (C) macroscopic view of the artery. 1mm scale bar. Source: Biobank for Aging Studies.

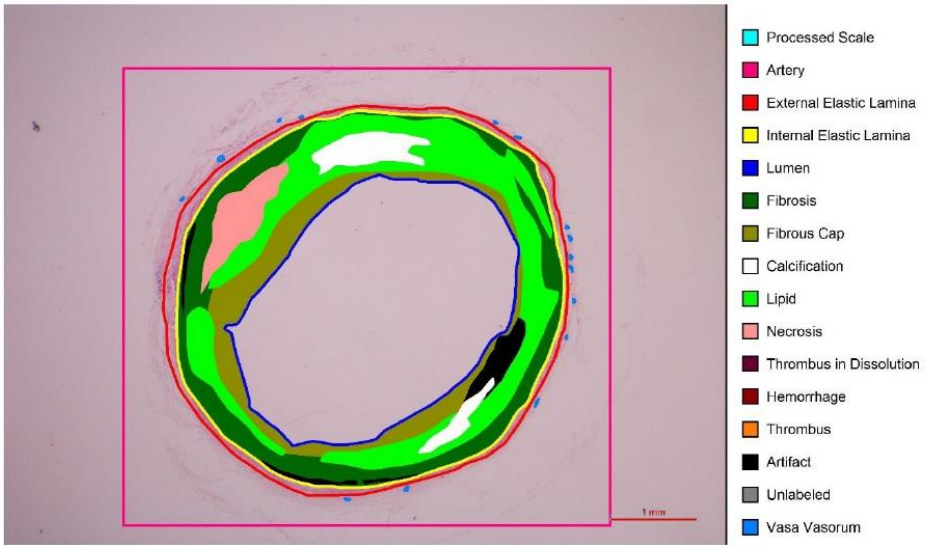

Figure 2. Plaque composition analysis using the Atherosclerotic Plaque Analyzer (APA) program. In the lower right corner, a 1mm scale bar is provided. On the right, the components of the atherosclerotic plaque are labeled. The square pink line identifies the artery, which enables the transfer of measurements to other staining. Source: Biobank for Aging Studies.

Neuropathological assessment

Brains were collected and the selected areas of one hemisphere were frozen at −80 ℃. The other hemisphere was fixed in 4% buffered paraformaldehyde and, after 15 days, the 14 selected areas (middle frontal gyrus, middle and superior temporal gyri, angular gyrus, superior frontal and anterior cingulate gyrus, visual cortex, hippocampal formation at the level of the lateral geniculate body, amygdala, basal ganglia at the level of the anterior commissure, thalamus, midbrain, pons, medulla oblongata, and cerebellum) were sampled and embedded in paraffin, cut into 5-µm slices, and stained with hematoxylin and eosin. Immunohistochemistry with antibodies against β-amyloid (4G8,1:10.000; Signet Pathology Systems, Dedham, Massachusetts), phosphorylated tau (PHF-1, 1:2.000;), were executed in selected sections (23).

Neuropathological assessment was performed using internationally accepted criteria for staging and diagnosing AD pathology (24,25). NFT were evaluated following the Braak and Braak staging system. This system begins in the transentorhinal area (Stage I), spread to the entorhinal region (II), extend to the hippocampus proper (III), increase in number there (IV), and involve the neocortex (V) and finally the primary cortex (VI) (24). NP were assessed according to the Consortium to Establish a Registry for AD (CERAD) criteria, which is based on the density of NP observed under a light microscope at 100X magnification. The classification included CERAD 0 (no plaques), CERAD A (sparse plaques), CERAD B (moderate plaques), and CERAD C (frequent plaques) (25) (Fig. 3). The neuropathological diagnosis of AD was ascertained when the Braak stage was III or higher and CERAD was classified as B or C (23). These neuropathological assessments were conducted without knowledge of the clinical status of the deceased individuals.

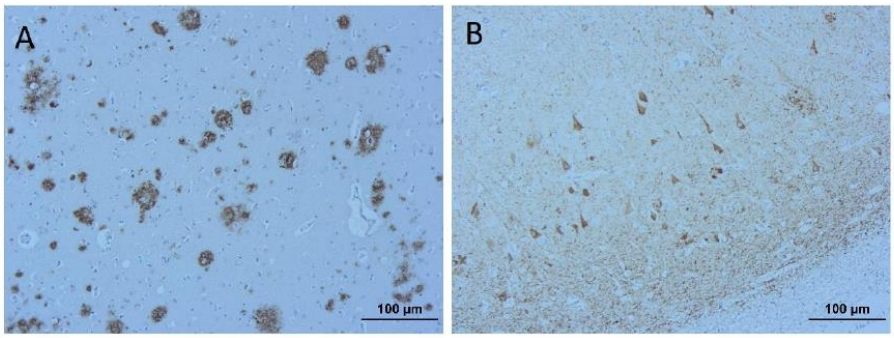

Figure 3. (A) Amyloid pathology with NP in the frontal cortex. Immunohistochemistry with

antibody against ß-amyloid protein. 10x magnification, scale bar of 100 µm. (B)Neurofibrillary pathology in hippocampus Immunohistochemistry with antibody against hyperphosphorylated tau protein. 10x magnification, scale bar of 100 µm. Source: Biobank for Aging Studies

Statistical Analysis

Clinical and sociodemographic data were presented as mean and standard deviation for continuous variables, and as absolute and relative frequencies for categorical variables. The independent variables consisted of the components of the atherosclerotic plaque and morphometric measures, which were expressed as a percentage (per 10%), count, or micrometers. The dependent ordinal variables included the scores of CERAD, Braak, and the categorical diagnosis of AD. The associations of atherosclerosis plaque components with the morphometric measures with CERAD and Braak were assessed using ordinal logistic regression with robust standard errors (SE) for repeated measures in the same individual (four arterial segments per person). When the outcome variable was AD, the association was assessed using logistic regression with robust SE. The models were adjusted for age, sex, race, education, hypertension, diabetes, smoking, alcohol use, physical activity, and body mass index.

To better understand the impact of selection bias in a sample that likely contains a proportion of individuals with premature mortality due to cardiovascular disease, we also tested the association of atherosclerotic plaque components and morphometric measurements with CERAD, Braak and AD stratified by age (< 75 years old and age ≥ 75 years old). We considered a 5% level of significance in two-tailed tests. Analyses were performed using STATA 13 (Stata Corp., College Station, TX, USA).

RESULTS

The final sample comprised 321 participants with an average age of 77±11 years. Among these participants, 56% were male, 64% were white, and education had a mean of 5±4 years. Additionally, 71% had arterial hypertension, 35% had diabetes mellitus, and 27% had history of coronary disease. On average, the participants had a body mass index of 23±6 kg/m². Among them, 46% had never smoked, 68% had either no alcohol use or only social use, and 67% were physically inactive (Table 1).

Regarding coronary measurements, the lumen obstruction averaged 59±15%. In terms of atherosclerosis plaque composition, collagen was the most prevalent component, occupying on average 28±13% of the atherosclerosis plaque area, followed by lipids (26±12%), smooth muscle cells (21±26%), and calcification (10±11%). The vasa vasorum count in the intimal layer was on average of 0.9±2.3. Additionally, the mean intimal media thickness was 533±185 μm, and the minimum fibrous cap thickness was 21±17 μm (Table 1).

Table 1. Descriptive analyses of the sociodemographic, clinical and atherosclerosis plaque component variables (n=321)

Variables	Total
Age (years), mean (SD)	76.9 (11.0)
Men, n (%)	179 (55.8)
Race, n (%)	
. *White*	207 (64.5)
. *Black*	104 (32.4)
. *Asian*	10 (3.1)
Education (Years), mean (SD)	5.1 (4.2)
Hypertension, n (%)	229 (71.3)
Diabetes, n (%)	111 (34.6)
Coronary artery disease, n (%)	88 (27.4)
Cardiac failure, n (%)	85 (26.5)
Dyslipidemia, n (%)	82 (25.5)
Stroke, n (%)	43 (13.4)
Body mass index (kg/m^2), mean (SD)	22.8 (5.6)
Smoking, n (%)	
. *never*	147 (45.8)
. *current*	56 (17.4)
. *previous*	118 (36.8)
Alcohol use, n (%)	
. *never/Social use*	218 (67.9)
. *current*	31 (9.6)
. *previous*	72 (22.4)
Physical inactivity, n (%)	216 (67.3)
Atherosclerosis plaque components, mean (SD)	
. *% of Lumen obstruction*	58.9 (15.3)
. *% of Collagen*	27.8 (12.7)
. *% of Smooth Muscle Cell*	21.1 (26.2)
. *% of Calcification*	9.7 (11.5)
. *% of Lipids*	25.9 (11.8)
. *% of Necrosis*	2.2 (4.6)
. *% of Healed thrombus*	0.5 (2.1)
. *% of Hemorrhage*	0.6 (1.7)
. *vasa vasorum intimal layer (n)*	0.9 (2.3)
. *intima media thickness (µm)*	532.9 (185.3)
. *fibrous cap thickness (µm)*	20.7 (16.8)

SD standard deviation

In adjusted models, increase in the percentage of coronary calcification was associated with lower odds of NP deposition (OR=0.88 per 10% increase in calcification, CI=0.79; 0.97, p=0.008) and increase in the count of vasa vasorum in the intimal layer was associated with higher odds of NP (OR=1.02 CI=1.00; 1.04, p=0.045) (Table 2). Lumen obstruction was not associated with NP (OR=1.02, 95% CI=0.93; 1.11, p=0.673), as well as other plaque components (Table 2). Increase in the percentage of necrosis was

associated with lower odds of NFT (OR=0.84 per 10% increase in necrosis, CI=0.71; 0.99, p=0.040). NFT deposition was not associated with lumen obstruction or other atherosclerosis plaque components (Table 2). Higher number of the vasa vasorum in the intima layer was associated with a higher likelihood of AD diagnosis (OR=1.04, CI=1.01; 1.08, p=0.014) (Table 2).

Table 2. Association of atherosclerosis plaque components with NP, NFT, and AD diagnosis (n=1,284 arterial segments)

Atherosclerosis plaque components	Unadjusted model			Adjusted model*		
	OR	95% CI	*p*	OR	95% CI	*p*
			Neuritic Plaques†			
Lumen obstruction	0.92	0.84; 0.99	0.036	1.02	0.93; 1.11	0.673
Collagen	1.01	0.95; 1.07	0.757	1.01	0.95; 1.08	0.755
Smooth Muscle Cell	1.00	0.97; 1.04	0.818	1.00	0.96; 1.04	0.938
Calcification	0.92	0.84; 1.01	0.086	0.88	0.79; 0.97	0.008
Lipids	1.04	0.97; 1.13	0.277	1.08	0.99; 1.18	0.061
Necrosis	0.90	0.77; 1.06	0.231	0.86	0.72; 1.04	0.121
Healed thrombus	0.76	0.50; 1.16	0.202	1.15	0.84; 1.58	0.371
Hemorrhage	0.63	0.29; 1.36	0.241	0.63	0.30; 1.31	0.217
Vasa vasorum intimal layer	0.99	0.96; 1.03	0.900	1.02	1.00; 1.04	0.045
Intima-media thickness	1.00	1.00; 1.00	0.090	1.00	1.00; 1.00	0.735
Fibrous cap thickness	0.99	0.99; 1.00	0.098	1.00	0.99; 1.00	0.411
			Neurofibrillary tangles†			
Lumen obstruction	0.86	0.79; 0.93	<0.001	0.98	0.90; 1.07	0.644
Collagen	0.98	0.92; 1.05	0.652	0.97	0.91; 1.04	0.405
Smooth Muscle Cell	1.01	0.97; 1.04	0.716	1.00	0.96; 1.04	0.877
Calcification	1.00	0.92; 1.09	0.934	0.99	0.91; 1.07	0.801
Lipids	1.02	0.95; 1.09	0.564	1.04	0.97; 1.13	0.216
Necrosis	0.86	0.72; 1.04	0.117	0.84	0.71; 0.99	0.040
Healed thrombus	0.64	0.49; 0.83	0.001	0.97	0.76; 1.22	0.776
Hemorrhage	0.79	0.54; 1.14	0.217	0.81	0.61; 1.06	0.132
Vasa vasorum intimal layer	0.98	0.96; 1.01	0.229	1.02	0.99; 1.04	0.117
Intima-media thickness	1.00	1.00; 1.00	0.023	1.00	1.00; 1.00	0.564
Fibrous cap thickness	0.99	0.99; 1.00	0.025	1.00	0.99; 1.00	0.475
			AD‡			
Lumen obstruction	0.91	0.83; 1.00	0.055	1.03	0.92; 1.15	0.562
Collagen	1.02	0.95; 1.10	0.532	1.02	0.94; 1.09	0.610
Smooth Muscle Cell	1.00	0.96; 1.04	0.964	0.99	0.95; 1.03	0.747
Calcification	0.96	0.86; 1.07	0.437	0.92	0.82; 1.05	0.217
Lipids	1.03	0.94; 1.13	0.549	1.07	0.96; 1.20	0.220
Necrosis	0.78	0.60; 1.00	0.058	0.73	0.53; 1.01	0.063
Healed thrombus	0.64	0.29; 1.44	0.288	1.09	0.58; 2.06	0.777
Hemorrhage	0.55	0.22; 1.37	0.201	0.49	0.20; 1.17	0.110
Vasa vasorum intimal layer	1.00	0.97; 1.05	0.708	1.04	1.01; 1.08	0.014
Intima-media thickness	1.00	1.00; 1.00	0.132	1.00	1.00; 1.00	0.899
Fibrous cap thickness	0.99	0.99; 1.00	0.279	1.00	0.99; 1.00	0.804

OR: odds ratio; CI: confidence Interval
*Adjusted model for age, sex, race, education, hypertension, diabetes, body mass index, physical inactivity, alcohol use, and smoking
†Ordinal logistic regression with SE adjusted for repeated measures in the same individual.
‡Logistic regression with SE adjusted for repeated measures in the same individual.

When we stratified the analyses by age, among participants younger than 75 years old, greater lipid depositions were associated with an increased likelihood of NP (OR=1.19 per 10% increase lipids, 95% CI=1.01; 1.39, p=0.032), while increased calcification was linked to reduced odds of NP (OR=0.75 per 10% increase in calcification, 95% CI=0.59; 0.96, p=0.023). In the same age group, greater thickening of the fibrous cap was associated with a decreased likelihood of AD diagnosis (OR=0.98, 95% CI=0.96; 1.00, p=0.023) (Table 3).

Among participants aged 75 years and older, an increase in vasa vasorum count in the intimal layer was associated with higher odds of NP (OR=1.03, 95% CI=1.00; 1.07, p=0.027) as well as a greater likelihood of AD diagnosis (OR=1.07, 95% CI=1.00; 1.16, p=0.045). Furthermore, necrosis was associated with reduced odds of NFT (OR=0.77 per 10% increase in necrosis area, 95% CI=0.64; 0.92, p=0.005), and healed thrombus was associated with AD diagnosis (OR=1.84 per 10% in healed thrombus area, 95% CI=1.10; 3.06, p=0.020) (Table 3).

Table 3. Association between atherosclerosis plaque components with NP, NFT, and AD diagnosis, stratified by age (n= 1,284 arterial segments)

Atherosclerosis plaque components	Age < 75 (n=137)			Age ≥ 75 (n= 184)		
	OR	95% CI	*p*	OR	95% CI	*p*
			Neuritic Plaques†*			
Lumen obstruction	1.05	0.90; 1.22	0.535	1.02	0.92; 1.14	0.641
Collagen	1.05	0.94; 1.17	0.382	0.99	0.90; 1.07	0.749
Smooth Muscle Cell	0.96	0.89; 1.03	0.276	1.00	0.96; 1.05	0.752
Calcification	0.75	0.59; 0.96	0.023	0.92	0.82; 1.03	0.147
Lipids	1.19	1.01; 1.39	0.032	1.05	0.94; 1.17	0.393
Necrosis	0.97	0.63; 1.49	0.893	0.87	0.70; 1.09	0.225
Healed thrombus	1.12	0.76; 1.65	0.569	1.26	0.91; 1.76	0.165
Hemorrhage	0.75	0.24; 2.29	0.612	0.64	0.26; 1.57	0.335
Vasa vasorum intimal layer	1.00	0.96; 1.05	0.794	1.03	1.00; 1.07	0.027
Intima-media thickness	1.00	1.00; 1.00	0.561	1.00	1.00; 1.00	0.581
Fibrous cap thickness	0.99	0.98; 1.00	0.543	1.00	0.99; 1.00	0.966
			Neurofibrillary tangles†*			
Lumen obstruction	1.01	0.89; 1.15	0.787	0.95	084; 1.07	0.410
Collagen	0.99	0.89; 1.09	0.814	0.94	0.86; 1.03	0.185

Smooth Muscle Cell	0.98	0.92; 1.04	0.462	1.02	0.97; 1.08	0.328
Calcification	0.98	0.86; 1.12	0.807	1.02	0.93; 1.11	0.727
Lipids	1.10	098; 1.25	0.099	0.98	0.89; 1.09	0.760
Necrosis	1.01	0.75; 1.37	0.940	0.77	0.64; 0.92	0.005
Healed thrombus	0.96	0.71; 1.29	0.781	1.14	0.88; 1.47	0.300
Hemorrhage	0.59	0.28; 1.24	0.166	0.98	0.66; 1.47	0.941
Vasa vasorum intimal layer	1.03	0.99; 1.06	0.112	1.00	0.98; 1.04	0.597
Intima-media thickness	1.00	1.00; 1.00	0.405	1.00	1.00; 1.00	0.140
Fibrous cap thickness	1.00	0.99; 1.00	0.773	1.00	0.99; 1.00	0.601
			AD[‡*]			
Lumen obstruction	1.05	0.87; 1.27	0.588	1.05	0.92; 1.20	0.488
Collagen	1.07	0.96; 1.19	0.220	0.99	0.90; 1.09	0.903
Smooth Muscle Cell	0.97	0.90; 1.04	0.401	0.99	0.94; 1.05	0.823
Calcification	0.84	0.63; 1.12	0.237	0.94	0.82; 1.09	0.441
Lipids	1.05	0.81; 1.36	0.700	1.08	0.94; 1.24	0.300
Necrosis	1.07	0.56; 2.03	0.835	0.69	0.44; 1.08	0.106
Healed thrombus	1			1.84	1.10; 3.06	0.020
Hemorrhage	0.66	0.90; 4.90	0.690	0.47	0.17; 1.30	0.147
Vasa vasorum intimal layer	1.04	0.96; 1.12	0.323	1.07	1.00; 1.16	0.045
Intima-media thickness	1.00	1.00; 1.00	0.600	1.00	1.00; 1.00	0.790
Fibrous cap thickness	0.98	0.96; 1.00	0.023	1.00	0.99; 1.01	0.493

OR: odds ratio; CI: confidence Interval
AD: Alzheimer's Disease
[*]Adjusted model for age, sex, race, education, hypertension, diabetes, body mass index, physical inactivity, alcohol use, and smoking
[†]Ordinal logistic regression with SE adjusted for repeated measures in the same individual.
[‡]Logistic regression with SE adjusted for repeated measures in the same individual.

DISCUSSION

In this study with 321 adults, several associations were observed. Coronary calcification was associated with a decreased chance of NP deposition, while necrosis was associated with decreased odds of NFT. Additionally, an increase in the count of vasa vasorum in the intimal layer was associated with a higher likelihood of NP deposition and AD diagnosis. When the analyses were stratified by age, among participants under 75 years old, lipid content in the atherosclerotic plaque was associated with an increased likelihood of NP and a thicker fibrous cap was associated to a lower likelihood of AD diagnosis. Among participants aged 75 years and older, healed thrombus was associated with AD diagnosis.

We hypothesized that atherosclerotic plaque components linked to plaque stability would be associated with the neuropathology of AD, given that AD is neurodegenerative disease that develops over 2-3 decades before the cognitive symptoms (26). However, in this study, more calcification was associated with fewer NP deposition in contrast to the

previous studies that showed the association of CAC with cognitive status (8,9). Although calcification is a hallmark of stable plaques, the role of calcification in plaque stability may change as plaque progresses. Initially, coronary calcification may manifest as microcalcifications in the pathological intimal thickening during the early stages of atherosclerotic lesion development. As the atherosclerotic plaque advances, it progresses to nodular calcification. Microcalcification and nodular calcification are associated with plaque instability and stability, respectively (27,28). Atherosclerosis, primarily with accumulation of lipids core, involves the gradual thickening of the intima, resulting in lumen narrowing, and subsequently triggers hypoxia, a significant driver of neovascularization. The presence of vasa vasorum is a response to hypoxia, which is a result of low cardiac output. Low cardiac output can lead to changes in cerebral blood flow, reducing β-amyloid clearance and, consequently, contributing to the NP deposition (29,30). This cascade of events highlights the role of atherosclerotic plaque components and corroborates the findings of this study, an increase of lipid core was associated with NP deposition in the group under 75 years old and vasa vasorum count was associated with both NP and AD diagnosis. On the other hand, although the vasa vasorum expansion throughout the development of the atherosclerotic plaque occurs due to chronic process aimed at maintaining perfusion, it can potentially lead to an acute event with intraplaque hemorrhage, which is highly linked to CHD instability (31,32). A crucial component in the stability of the atherosclerotic plaque is the fibrous cap. In this study, a thicker fibrous cap reduces the likelihood of developing AD in the group under 75 years old. This finding is contrary to the hypothesis that a thicker fibrous cap is more stable and may signalize that chronic CHD is related to AD etiology (33). On the other hand, the fibrous cap serves as the primary structural component that contains the atheromatous hemorrhagic material within the necrotic core. It is susceptible to thinning and potential rupture. Plaque ruptures happen when a necrotic core is located under a thin fibrous cap that has ruptured. Such plaque instability can lead to fatal outcomes. This scenario may explain the presence of a necrotic nucleus with fewer NFT depositions in this study. These necrotic cores can continue to develop and expand, sometimes rapidly, particularly through intraplaque hemorrhage caused by leaky vasa vasorum (32). Furthermore, thin fibrous cap is more susceptible to silent events of thrombosis and healing (31,34). This process of healing, known as healed thrombus, was associated with AD in the group 75 years or older in this study(34). Although healed thrombus is usually associated with a more stable lesion, healed thrombus proved to be the predictor of rapid plaque progression (34,35).

Establishing a clear link between atherosclerosis and AD is challenging, mainly due to the complexity of atherosclerotic plaque progression. Coronary atherosclerosis can manifest as chronic or acute conditions in a dynamic process that progresses from early lesions to advanced lesions. The components have different characteristics throughout the plaque progression. Furthermore, observing the combination between them may be more relevant than evaluating each one separately. For example, evaluating the combination of lipids with a thin fibrous cap is more important to determine plaque rupture than the isolated components (28). We must also consider the survival bias, as atherosclerosis can progress to an acute event resulting in premature death before AD can manifest, or to a chronic advanced lesion that older people can experience by facing risk factors (36).

Several studies have indicated an association between CHD and cognitive decline or AD (6,10,37,38) while others have not found any association (11,39). While the precise cause of cognitive changes in individuals with atherosclerosis remains uncertain, this relationship seems to be associated with either embolic strokes or chronic cerebral hypoperfusion (40,41). Coronary atherosclerosis may also indicate the presence of atherosclerosis in other beds, including intracranial atherosclerosis, which can directly lead to small vessel disease, reducing cerebral blood flow in the brain (40), affecting in the reduction in the amyloid-β clearance, consequently increasing amyloid-β deposition (42). Lastly, reduced cardiac output itself caused by CHD can lead to cerebral hypoperfusion, causing cognitive impairment (30).

Our findings must be understood within specific constraints. Due to the nature of this cross-sectional observational study, we are unable to establish causal relationships. We did not conduct follow-ups on participants during their lifetime, and clinical variables were assessed postmortem through informant interviews. To enhance the reliability of these data, we restricted our analysis to individuals who maintained at least weekly contact with the informant and excluded cases where conflicting information was provided during the clinical interview (18). It is important to note that our sample may not accurately represent all deaths that occurred in Sao Paulo during the study period. Sao Paulo Autopsy Service (SPAS) primarily handles cases of natural deaths and given the prevalence of cardiac arrests in this population, we may have a higher proportion of individuals with cardiovascular diseases, potentially leading to an overrepresentation of CHD in our sample. Furthermore, atherosclerotic plaque and neuropathological changes involve multiple factors that mediate their complex progression, which were not

evaluated in this study, as inflammation and genetic factors, among others. On the other hand, our study has advantages. Firstly, the components of the atherosclerotic plaque and its association with AD pathology were evaluated, not just the lumen obstruction and calcification evaluated in previous clinical and autopsy-based studies (9–11,43). We presented clinical and neuropathological data from individuals with a low educational level (most only had 0 to 4 years of education) and diverse racial backgrounds. It is worth noting that previous larger studies predominantly included white or Asian participants with higher levels of education (10,11).

In summary, we found associations between atherosclerotic plaque components and AD pathology. Components linked to stability like calcification and thicker fibrous cap were associated with lower NP deposition and a lower chance to having AD diagnosis, respectively. Components linked to the attempt to maintain perfusion, vasa vasorum was associated with NP deposition and AD diagnosis and healed thrombus was associated with AD diagnosis. Given the complexity of atherosclerotic plaque progression, the components play different roles in the rupture and healing process. New studies are needed to evaluate the association of AD pathology with the combination of atherosclerotic plaque components.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The data associated with the paper are not publicly available but can be obtained from the senior author on reasonable request.

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5 DISCUSSÃO

Nós hipotetizamos que os componentes da placa aterosclerótica, principalmente os ligados à estabilidade, assim como a maior estenose coronariana estariam associados ao comprometimento cognitivo e à neuropatologia da doença de Alzheimer.

No primeiro artigo, a estenose aterosclerótica coronariana não foi associada ao comprometimento cognitivo na amostra total. No entanto, em indivíduos que nasceram em 1935 ou antes, na ausência de doença cardiovascular como causa de morte, uma estenose mais elevada foi associada a maiores probabilidades de comprometimento cognitivo e pior habilidade cognitiva. Por outro lado, em indivíduos que morreram por causas cardiovasculares, a maior estenose foi relacionada à melhor função cognitiva tanto na amostra total quanto quando restrita aos nascidos em 1935 ou antes. Esses achados provavelmente estão relacionados ao viés de sobrevida, uma vez que os participantes com estenose aterosclerótica elevada têm maior probabilidade de morrer antes de desenvolverem comprometimento cognitivo, como mostrado anteriormente em estudos relacionados ao câncer e à demência (54,55). A morte por doença cardiovascular pode estar agindo como um acelerador, uma vez que estenose coronária grave pode levar à morte (56).

No segundo artigo, o aumento na porcentagem de calcificação coronariana foi associado à diminuição da chance de deposição de placas neuríticas, enquanto um aumento na necrose foi associado à diminuição dos emaranhados neurofibrilares. Além disso, um aumento na contagem de vasa vasorum na camada íntima foi associado a uma maior probabilidade de deposição de placas neuríticas e diagnóstico de DA. Quando as análises foram estratificadas por idade, um aumento no trombo cicatrizado mostrou uma associação com o diagnóstico de DA. Entre os participantes com menos de 75 anos, maiores depósitos de lipídeos foram associados a uma maior probabilidade de placas neuríticas e uma capa fibrosa mais espessa foi associada a uma menor probabilidade de diagnóstico de DA. Os componentes apresentam características diferentes ao longo da progressão da placa, podendo desempenhar papéis distintos na estabilidade da placa (17). Além disso, observar a combinação entre eles pode ser mais relevante do que avaliar cada um separadamente. Por exemplo, avaliar a combinação de lipídios com uma capa fibrosa fina é mais importante para determinar a ruptura da placa do que os componentes isolados (57).

Vários estudos indicaram uma associação entre doença coronariana e declínio cognitivo ou DA (26,27,32,58), enquanto outros não encontraram qualquer associação (33,59). Embora a causa precisa das alterações cognitivas em indivíduos com aterosclerose permaneça incerta, esta relação parece estar associada a acidentes vasculares cerebrais embólicos ou a hipoperfusão cerebral crônica (60,61). A aterosclerose coronariana indica aterosclerose em outros leitos, incluindo aterosclerose intracraniana, que pode levar diretamente à doença de pequenos vasos, reduzindo o fluxo sanguíneo cerebral no cérebro (60), afetando na redução do clearance, consequentemente aumento dos níveis de β-amiloide (62). Por último, a própria redução do débito cardíaco pode levar à hipoperfusão cerebral, causando comprometimento cognitivo (63).

Estabelecer uma ligação clara entre aterosclerose e DA é um desafio, principalmente devido à complexidade da progressão da placa aterosclerótica. A aterosclerose coronariana pode se manifestar como condições crônicas ou agudas em um processo dinâmico que progride de lesões iniciais para lesões avançadas. Além disso, os componentes podem desempenhar diferentes papéis no processo de ruptura e cicatrização da placa aterosclerótica. Devemos considerar ainda o viés de sobrevivência, pois a aterosclerose pode evoluir para um evento agudo resultando em morte precoce, ou para uma lesão crônica avançada que os idosos podem vivenciar ao enfrentarem fatores de risco. Novos estudos são necessários para avaliar a associação da patologia da DA com a combinação dos componentes da placa aterosclerótica.

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7 ANEXOS

Anexo 1. Parecer substanciado do CEP do presente estudo

USP - HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO - HCFMUSP

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: ASSOCIAÇÃO DE ATEROSCLEROSE SISTÊMICA COM DOENÇA NEURODEGENERATIVA E CEREBROVASCULAR:UM ESTUDO

Pesquisador: Claudia Kimie Suemoto

Área Temática:

Versão: 2

CAAE: 25213319.4.0000.0065

Instituição Proponente: Faculdade de Medicina da Universidade de São Paulo

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 5.025.381

Apresentação do Projeto:

Trata-se de informação do pesquisador principal informando que o projeto não pode ser iniciado pela interrupção de necropsias devido a pandemia COVID e informando que foram retomadas no momento, permitindo a ativação formal do projeto.

Objetivo da Pesquisa:

ASSOCIAÇÃO DE ATEROSCLEROSE SISTÊMICA COM DOENÇA NEURODEGENERATIVA E CEREBROVASCULAR:UM ESTUDO CLINICOPATOLÓGICO

Avaliação dos Riscos e Benefícios:

Inalterados

Comentários e Considerações sobre a Pesquisa:

Adequada e a proposta é meritória

Considerações sobre os Termos de apresentação obrigatória:

Inalterados

Recomendações:

Aprovação da emenda e prorrogação de prazos do projeto.

Conclusões ou Pendências e Lista de Inadequações:

Nenhuma

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Bairro: Cerqueira Cesar **CEP:** 05.403-010
UF: SP **Município:** SAO PAULO
Telefone: (11)2661-7585 **Fax:** (11)2661-7585 **E-mail:** cappesq.adm@hc.fm.usp.br

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_1815176_E1.pdf	21/09/2021 11:12:26		Aceito
Outros	andamento_Projeto.pdf	21/09/2021 11:11:50	Claudia Kimie Suemoto	Aceito
Outros	FORMULARIO_PARA_SUBMISSAO_DE_EMENDAS_E_BROCHURAS.pdf	21/09/2021 11:06:18	Claudia Kimie Suemoto	Aceito
Outros	CEPFMUSP_atualizado.pdf	30/10/2019 15:58:43	Maristella Yahagi Estevam	Aceito
Parecer Anterior	resposta_181019.docx	18/10/2019 17:36:45	Claudia Kimie Suemoto	Aceito
Folha de Rosto	folha_rosto.pdf	09/10/2019 14:46:00	Claudia Kimie Suemoto	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_DE_PESQUISA_20092019.pdf	20/09/2019 17:13:33	Maristella Yahagi Estevam	Aceito
Outros	carta_ao_cep.pdf	20/09/2019 16:58:14	Maristella Yahagi Estevam	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	CEP_Nishizawa.pdf	20/09/2019 16:15:01	Maristella Yahagi Estevam	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	CEP_Farias.pdf	20/09/2019 16:14:48	Maristella Yahagi Estevam	Aceito
Declaração de Manuseio Material Biológico / Biorepositório / Biobanco	PB_PARECER_CONSUBSTANCIADO_CEP_458272.pdf	20/09/2019 16:14:16	Maristella Yahagi Estevam	Aceito
Outros	cart_anu_bee.pdf	20/09/2019 15:31:16	Maristella Yahagi Estevam	Aceito
Outros	Carta_de_anu_card.pdf	20/09/2019 14:10:40	Maristella Yahagi Estevam	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 07 de Outubro de 2021

Assinado por:
ALFREDO JOSE MANSUR
(Coordenador(a))

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Anexo 2. Clinical Dementia Rating (CDR)

	Saudável CDR 0	Demência questionável CDR 0,5	Demência leve CDR 1	Demência moderada CDR 2	Demência grave CDR 3
MEMÓRIA	Sem perda de memória, ou apenas esquecimento discreto e inconsistente	Esquecimento leve e consistente; lembrança parcial de eventos; "esquecimento benigno"	Perda de memória moderada, mais acentuada para fatos recentes; o déficit interfere com atividades do dia a dia	Perda de memória grave; apenas material *muito* aprendido é retido; materiais novos são rapidamente perdidos	Perda de memória grave; apenas fragmentos permanecem
ORIENTAÇÃO	Plenamente orientado	Plenamente orientado	Dificuldade moderada com as relações de tempo; orientado no espaço no exame, mas pode ter desorientação geográfica em outros locais	Geralmente desorientado	Orientação pessoal apenas
JULGAMENTO E SOLUÇÃO DE PROBLEMAS	Resolve bem problemas do dia a dia, juízo crítico é bom em relação ao desempenho passado	Leve comprometimento na solução de problemas, semelhanças e diferenças	Dificuldade moderada na solução de problemas, semelhanças e diferenças; julgamento social geralmente mantido	Gravemente comprometido para solução de problemas, semelhanças e diferenças. Juízo social geralmente comprometido	Incapaz de resolver problemas ou de ter qualquer juízo crítico
ASSUNTOS NA COMUNIDADE	Função independente na função habitual de trabalho, compras, negócios, finanças, e grupos sociais	Leve dificuldade nestas atividades	Incapaz de funcionar independentement e nestas atividades embora ainda possa desempenhar algumas; pode parecer normal à avaliação superficial	Sem possibilidade de desempenho fora de casa. Parece suficientemente bem para ser levado a atividades fora de casa	Sem possibilidade de desempenho fora de casa. Parece muito doente para ser levado a atividades fora de casa
LAR E PASSATEMPOS	Vida em casa, passatempos, e interesses intelectuais mantidos	Vida em casa, passatempos, e interesses intelectuais levemente afetados	Comprometimento leve, mas evidente em casa; abandono das tarefas mais difíceis; passatempos e interesses mais complicados são também abandonados	Realiza as tarefas mais simples. Interesses muito limitados e pouco mantidos	Sem qualquer atividade significativa em casa
CUIDADOS PESSOAIS	Plenamente capaz	Plenamente capaz	Necessita assistência ocasional	Requer assistência no vestir e na higiene	Requer muito auxílio nos cuidados pessoais. Geralmente incontinente

Anexo 3. Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)

Informant questionnaire on cognitive decline in the elderly

(IQCODE – Versão retrospectiva)

Gostaríamos que você se lembrasse de como era seu amigo ou familiar há 10 anos atrás e compare com o estado em que ele estava há 3 meses antes de sua morte.
Comparada com há 10 anos atrás, como estava a pessoa antes de sua morte:

	Muito melhor (1)	**Um pouco melhor (2)**	**Não muito alterado (3)**	**Um pouco pior (4)**	**Muito pior (5)**
1. Reconhecer a face das pessoas amigas e da família					
2. Lembrar do nome de parentes e amigos					
3. Lembrar de coisas sobre a família e amigos (aniversários, ocupações, endereços...)					
4. Lembrar de coisas que aconteceram recentemente					
5. Lembrar de conversas que teve nos últimos dias					
6. Esquecia o que queria dizer no meio de uma conversa					
7. lembrar-se de seu próprio endereço e telefone					
8. lembrar (saber) que dia e mês era					
9. Lembrar onde as coisas são usualmente guardadas					
10. Lembrar-se de onde encontrar as coisas que foram colocadas em lugares fora do comum					
11. Adaptar-se a qualquer mudança na sua rotina diária					
12. Saber como funcionam os eletrodomésticos					
13. Aprender a usar novos eletrodomésticos/ utensílios domésticos					
14. Aprender coisas novas em geral					
15. Lembrar-se de coisas que aconteceram em sua vida quando era jovem					
16. Lembrar-se de coisas que aprendeu quando era jovem					
17. Entender o significado de palavras não comuns					
18. Entender o significado do que está escrito em jornais e revistas					
19. Acompanhar uma estória em um livro ou pela TV					
20. Escrever uma carta para um amigo ou com fins de trabalho					
21. Saber sobre eventos históricos importantes do passado					
22. Tomar decisões com problemas do dia a dia					
23. Manusear dinheiro para compras					
24. Lidar com problemas financeiros (ex: pensão, conta bancária)					
25. Lidar com outros problemas matemáticos, por exemplo: saber quanto comprar de comida, saber quanto tempo se passou entre as visitas dos familiares/ amigos.					
26. Usar sua inteligência para entender o que está acontecendo e o motivo pelo qual está acontecendo.					

Total: _____