Background and Rationale

Alzheimer's Disease (AD) is a global challenge of escalating magnitude. Alarmingly, in the United States alone, a new case of AD is diagnosed every 35 seconds -- a rate that is accelerating in parallel with the proportion of adults aged over 65[1]. Traditionally defined by its distinctive cognitive, behavioral, and functional deficits, recent advancements have profoundly shifted our understanding of AD and expanded the disease continuum. This paradigm shift reframes AD as a biological disease defined by regionally specific neurodegeneration and the accumulation of pathological proteins - β-amyloid (Aβ) and phosphorylated Tau (pTau) - often decades before the advanced-stage cognitive deterioration[2].

This reconceptualization emphasizes the primary and secondary prevention of AD in asymptomatic individuals, which aims to alter the disease trajectory before the disease reaches a medically intractable phase[3]. Despite the increased allocation of resources towards the development of potentially disease-modifying pharmaceuticals, mounting evidence suggests that up to 40% of AD dementia cases can be prevented or substantively delayed by addressing modifiable risk factors[4]. ***This proposal highlights obstructive sleep apnea (OSA) as a pervasive yet underrecognized modifiable risk factor for AD and emphasizes its detection and management as keys to promoting cognitive healthspan (Fig 1).***

OSA is a sleep disorder characterized by recurrent episodes of pharyngeal (i.e., upper airway) collapse, which repeatedly induce intermittent reduction (hypopnea) or total cessations (apnea) of airflow[5,6]. The severity of OSA is classified by apneic/hypopneic index (AHI), which quantifies the number of hypoxic events per hour (Mild = >5, Moderate = >15, Severe >30)[7]. Cessation of airflow gives rise to hypoxia, which has its own deleterious effects that are compounded by the ensuing arousal response, further fragmenting and degrading time spent in restorative sleep[8].

While it was once considered a relatively rare syndrome primarily afflicting obese patients, recent reports estimate that 54 million adults in the United States alone have OSA (1 billion worldwide)[9-11]. Notably, the risk of OSA varies by age and sex, with estimates suggesting that half of all men aged 50-70 in the United States have OSA[10]. **Critically, upwards of 90% of all OSA cases remain undiagnosed and, thus, unmanaged[12].**

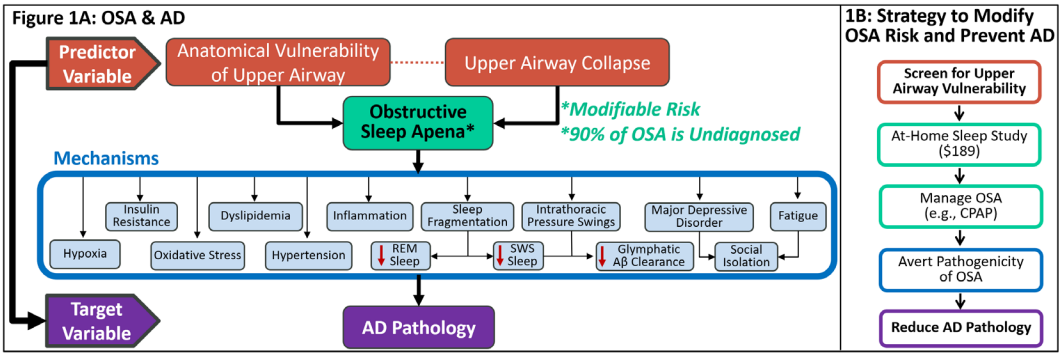
The precipitous rise in prevalence, coupled with the staggering rate of clinical omission, has created a silent epidemic of OSA[13]. This development is alarming, especially given the extensive array of adverse health consequences that stem from untreated OSA, a risk that is efficiently addressable with relatively cheap therapeutic interventions like continuous positive airway pressure (CPAP)[8,14]. The causal links between OSA and comorbidities like insulin resistance, hypertension, atherosclerosis, dyslipidemia, depression, and stroke are well recognized[8]. Neurocognitive dysfunction is another well-described consequence of OSA in young and middle-aged adults that can be effectively mitigated by low-cost, accessible therapies[15-19]. **Recently, however, mounting evidence implicates OSA as a modifiable risk factor for Alzheimer's Disease[5,20-25].**

Hypoxia, a recurrent consequence of OSA, is a neurotoxic factor that is known to promote neural injury and accelerate the accumulation of AD pathology[26]. As AD biomarkers have become more widely available, the last decade has produced a wealth of evidence demonstrating the causal role of OSA-induced hypoxia in accelerating Aβ and pTau pathology, often in asymptomatic populations[27-47]. In cognitively normal samples, studies report:

1. The pathological burden of amyloid and tau significantly correlates with the severity of OSA[28-30,33,36,39,42,45];
2. AD pathology in individuals with OSA is significantly reduced following CPAP and other interventions (e.g., surgical) that restore nocturnal breathing[42-46];

3. Reductions in AD pathology following CPAP intervention are significantly correlated with improvements in cognitive function[40,44];
4. Strikingly, this link is observed across the lifespan as multiple studies have reported significantly elevated Aβ in children as young as four years old relative to age-matched controls[42,43].

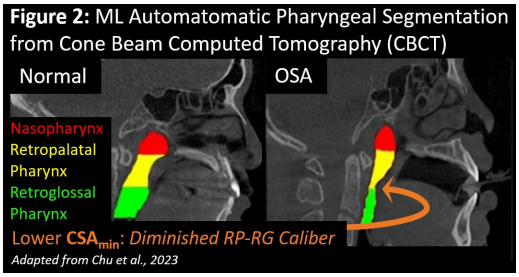
Beyond AD-specific pathology, multimodal neuroimaging data indicates that cognitively normal adults with OSA have deficits a) in grey matter volume[15,17,48-51], b) white matter integrity[52-54], c) hippocampal functional connectivity[17,55-57], d) task-related activation patterns[19], and e) cerebral metabolism[35,51,58]. Similarly, these structural and functional neural deficits correlate with OSA severity[48,51,52,58], and can be ameliorated by CPAP[15,17,19,35,49,52,54-56]. Epidemiological studies further support the elevated risk of developing AD dementia among individuals with OSA while also highlighting its modifiable nature (e.g., via CPAP adherence)[23,24].



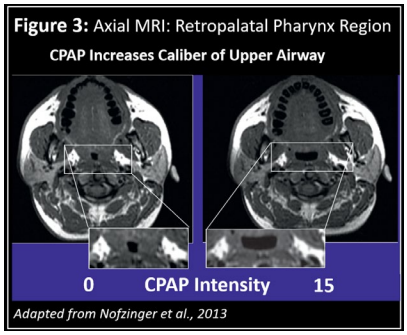
Tens of millions of Americans are, often unknowingly, chronically exposed to hypoxic conditions while they sleep, unnecessarily elevating their risk for AD. Since this risk is readily modifiable when OSA is diagnosed and managed, the staggering rate of clinical omission represents a highly leveraged opportunity to enhance the primary and secondary prevention of AD. **Addressing this urgent need, this proposal seeks to examine airway volume by leveraging the radiographs routinely acquired at dental screenings and machine-learning (ML) to better detect OSA and mitigate the risk of AD.**

Utility and Rigor

Strong evidence for two causal associations currently exist in isolation: 1) upper airway anatomy is a significant predictor of OSA[6,59-72], and 2) OSA is a significant predictor of AD pathology[27-47]. This proposal seeks to bridge this gap by directly examining the predictive utility of upper airway caliber (***predictor variable***) for an individual's risk of AD, as assessed by the pathological load of plasma-derived AD biomarkers (***target variable***) in cognitively normal individuals.



Predictor Variable: The primary predictor variable for our analyses will be the minimum cross-sectional area ($CSA_{min;}$ i.e., area at the narrowest point) at the retropalatal-retroglossal (RP-RG) region of the pharynx.



Airway collapse is both necessary and sufficient for the development of OSA[64]. Thus, a narrow airway, more prone to collapse, is a major risk factor for OSA (Fig 2)[65,67]. CPAP and related therapies are effective, in part, because they increase the caliber of the upper airway (Fig 3). A wide array of

anatomical features can contribute to narrowing the pharynx (i.e., airway). These include obesity, increased neck size, heritable features of craniofacial structure, and enlargement of the upper airway soft tissue[67]. In 1995, Schwab and colleagues first reported that structural magnetic resonance imaging (MRI) can be used to examine anatomical features associated with the risk of OSA[6]. Examining the upper airway, they identified anatomical features like minimum cross-sectional area, tongue volume, and lateral pharyngeal wall volume independently associated with a 6-fold increased risk of OSA[69]. Other groups have replicated this work with MRI[59-62,68,69,71] and other imaging modalities[63,66,70,72].

Developed in the late 1990s, CBCT has become the accepted standard for three-dimensional (3D) imaging in dentomaxillofacial radiography over the last two decades[73]. Due to lower costs and radiation exposure than conventional CT, CBCT has grown in popularity and is increasingly utilized in dental offices across the United States[74,75]. As the adoption of CBCT has continued, this 3D imaging device offers a more accessible modality to examine upper airway volume at a fraction of the cost and time (20-40s) of an MRI[76]. Using CBCT, anatomical features of the upper airway have been significant predictors of OSA and tightly correlate with OSA severity[63,66,70,72,77]. For example, Momany et al. reported a significant negative correlation between minimum cross-sectional area and OSA severity ($r = -0.653$, $P < 0.001$)[77].

Target Variable: To assess the utility of our novel predictor variable (CSA_{min}), we will assess blood plasma for the hallmark pathological biomarkers of AD. Specifically, our target variables of interest will be 1) $A\beta_{42}/A\beta_{40}$ ratio[78,79], 2) $pTau_{217}$[80-86], and 3) $pTau_{181}$[87-89].

Generalizability and Validation Studies: As a submission for the "Ideas for Data Collection" Challenge, we propose collecting data from CBCT scans routinely acquired at private dental clinics (to extract morphological features of the pharynx) alongside blood plasma (to extract AD biomarkers). However, in parallel, we also intend to conduct a validation study that utilizes the rich Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. To enable this validation study, we are preparing a distinct grant submission for the PAR-23-179 funding opportunity sponsored by the *National Institute of Aging*. In this separate validation study, we plan to leverage ADNI's longitudinal dataset to examine the predictive utility of pharyngeal anatomical features (extracted from T1 MRI) in forecasting the risk of AD. Though the ADNI data exquisitely enables a validation study of the work proposed herein, observing the same signal from data collected from CBCT scans at dental offices would afford a new tier of scalability and generalizability.

Basic Information

The study team will partner with private dental clinic(s) in the local area surrounding the University of Arizona (Tucson, AZ). These clinics will serve as the primary point of recruitment, where potential participants can consent to data sharing of their routine CBCT scans and one additional study visit at UArizona. This additional study visit will comprise a brief cognitive screen (Montreal Cognitive Assessment; MoCA), an OSA screening questionnaire (STOP-Bang)[90], and a blood draw. The blood draw will be conducted by trained phlebotomists at UArizona's Clinical and Translational Sciences (CATS) Research Center. The blood plasma will be processed and stored at UArizona's Biorepository and later shipped to the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD) for analysis.

To improve the scalability and practicality of using pharyngeal morphology as a predictive variable, we will employ machine learning (ML) algorithms to automatically segment upper airway anatomical features. Several high-performing ML algorithms for pharyngeal morphology segmentation from MRI[91-94] and CBCT[95-100] images have demonstrated high accuracy (Dice Similarity Coefficient = 0.95) and efficiency (<60 seconds for processing) in comparison to manual segmentation[100]. We will utilize *nnU-Net*[101], an open-source, deep learning-based tool known for its 'out of the box' functionality and self-configuring features, to train our model using a publicly available dataset of 389 dental CBCTs[102,103]. Our model's performance will be

evaluated against manual segmentations by our team's orthodontal experts. Upon successful training, the model will autonomously segment and extract pharyngeal morphological features from the data collected in our study, which will then be used as a predictor for AD pathology.

We estimate it will take roughly six months to develop, train, implement, and evaluate the nnU-Net automatic segmentation model. We will begin data collection in parallel, which we estimate will take 12-18 months to reach our target sample size of 40 individuals for this preliminary study, which is in line with the effect sizes reported for the influence of OSA on AD pathology in cognitively normal samples. See the "*Feasibility"* section for discussion on expected challenges.

Innovation and Disproportionate Impact

Our proposal reflects a high degree of innovation in both conceptual and practical terms. ***Conceptually***, we are illuminating an evidence-based throughline to connect disparate areas of scientific knowledge currently siloed (i.e., upper airway vulnerability → OSA → AD risk; Fig 1A). ***Practically***, our proposal seeks to leverage a low-cost and widespread tool (CBCT) that has rapid acquisition time (20-40s) and existing infrastructure (dental offices) to enhance screening of a highly modifiable risk factor for AD (OSA; Fig 1B).

Additionally, multiple aspects of OSA synergize to create a unique, highly levered opportunity for disproportionate impact as a preventative target for AD: 1) OSA is highly prevalent (>50 million Americans), 2) there is an alarming rate of clinical omission (>90% cases remain undiagnosed), 3) strong empirical evidence links OSA and AD alongside numerous, intertwined theoretical mechanisms of action (Fig 1A), and 4) existing evidence demonstrates that OSA can be cost-effectively managed (e.g., CPAP) to ameliorate the pathological burden of Aβ and pTau. This is a rare instance where the puzzle pieces all seem to align with one critically missing piece: improved OSA screening methodology to address the rate of clinical omission. Our proposal addresses this urgent need with a scalable, low-cost, and widely accessible tool.

Enhancing Sample Representation

Access and coverage disparities for dental care remain, but notable progress is ongoing. The percentage of Americans covered by dental insurance grew from 55% in 2009 to 80% in 2019, largely thanks to the expansion of social programs like CHIPS and Medicaid[104]. Similarly, from 2000 to 2022, the number of active dentists in the United States increased by 23%[104]. Though participation is less than ideal, roughly 40% of adults visit the dentist in a given year, ~20% of whom have not seen a physician in the preceding year[105]. This discrepancy suggests that oral health professionals have an outsized ability to reduce the burden of chronic diseases with preventative screenings[105]. We will exploit this advantage by recruiting participants at their dental exams and improve enrollment by monetarily compensating participation in our study.

Additionally, this recruitment channel facilitates the identification of dentistry clinics serving patient populations more likely to be underrepresented in clinical trials. For example, the study team will be able to identify dentistry clinics in geolocations with a higher density of traditionally underserved communities (e.g., www.mapszipcode.com reveals the demographic statistics of a specific geolocation) and meet those patients where they are.

Feasibility

A major confounding factor in CBCT studies that evaluate the airway is the head, body, and jaw position during the scan[106]. We will work with the dentistry professionals on our study team (L.H. & N.M.) to develop protocols that homogenize these and related confounding factors. Another limiting factor may be data sharing of CBCT scans acquired in dental offices; we will develop protocols (e.g., anonymization of DICOM images) and work closely with dental professionals to mitigate these concerns. Another considerable challenge will be developing and validating our automatic segmentation tool with nnU-Net. If our model is not satisfactory, high-performing commercial products (e.g., Cephx, Dentocat) are available for turn-key use at a higher cost[107].

Team Introduction

Dr. Mark Sundman is a postdoctoral research scientist in the Brain Imaging and TMS laboratory at the University of Arizona. Holding degrees in Exercise Science (BS), Integrative Medicine (MS), and Cognition & Neural Systems (PhD), Dr. Sundman has developed a unique multidisciplinary approach to studying the aging brain. His research probes the complex etiology of neurodegenerative disease by holistically characterizing the factors conferring risk and resilience for the aging brain. His technical expertise extends to neuroimaging and brain stimulation technologies. At this early stage of his career, he has demonstrated high productivity ***(h-index: 14)*** and has extensive experience working with participants on the Alzheimer's continuum.

Primary Relevant Expertise: Alzheimer's Disease and Integrative Medicine

Dr. Ying-hui Chou is an Associate Professor in the Department of Psychology, the Evelyn F. McKnight Brain Institute, and the Neuroscience and Cognitive Science Graduate Programs of UArizona. As the Director of the Brain Imaging and TMS Laboratory, she has been a PI or Co-Investigator on multiple NIH-, DoD-, and university-funded grants. Dr. Chou's expertise lies in the cognitive and clinical neuroscience of aging and neurodegenerative disorders, focusing on advanced neuroimaging and brain stimulation technologies ***(h-index: 20).***

Primary Relevant Expertise: Alzheimer's Disease and Neuroimaging

Dr. Chidi Ugonna, a Senior Research Specialist in the Biomedical Engineering Department at the University of Arizona, brings a wide array of technical skills to the team. He successfully spearheaded the institution-wide implementation of XNAT (open-source imaging informatics software) at UArizona for the Precision Aging Network (PAN) study (n=1200 participants). He currently leads the development of robust and replicable neuroimaging pipelines for the PAN study, which integrates data collected on the XNAT with computational nodes on UArizona's High-Performance Cluster (HPC). His expertise extends to designing and implementing Machine Learning applications on XNAT using Jupyter Notebooks and the MONAI Label ecosystem for novel research-driven neuroimaging applications.

Primary Relevant Expertise: Machine Learning, Data Informatics, and Neuroimaging

Yilin Liu is a Ph.D. candidate at the University of Arizona pursuing a doctoral degree in Cognition and Neural Systems, where she is a member of the Brain Imaging and TMS laboratory. She has led the design and implementation of Machine Learning pipelines for streamlining data purification, feature extraction, and model comparisons. She has designed and implemented customized deep learning models on large datasets (n=90,000), where she leveraged recurrent neural networks (RNNs) to adeptly handle sequential data for precise and dynamic clinical trial forecasting. Her expertise in using custom Docker images on UArizona's HPC for streamlined image processing and analyses greatly enhances the team's capabilities.

Primary Relevant Expertise: Machine Learning; Image Processing and Analysis

Dr. Nick Miller (DDS) is a general dentist at the Davis Monthan clinic in Tucson, Arizona. He regularly conducts and interprets CBCT scans.

Primary Relevant Expertise: Dental Professional; CBCT acquisition and interpretation

Dr. Leah Stetzel (DDS) is an Orthodontist at the Leber Ortho clinic in Tucson, Arizona. She regularly conducts and interprets CBCT scans.

Primary Relevant Expertise: Dental Professional; CBCT acquisition and interpretation

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