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Complementary study design strategies for assessing neurosensory, bone density, and behavioral outcomes.

by
Sepehr Hashemi

DISSERTATION
Submitted in partial satisfaction of the requirements for degree of
DOCTOR OF PHILOSOPHY

in

Epidemiology and Translational Science

in the

GRADUATE DIVISION
of the
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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Dedication and Acknowledgments

My family, my mentors, every human so far is to be acknowledged. Dedicated to every human and ahuman consciousness to follow.

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Epigraph

"When I see your face, the stones start spinning!
You appear; all studying wanders."

Shared by a colleague in UCSF School of Medicine, in our study halls.

Complementary study design strategies for assessing neurosensory, bone density, and behavioral outcomes

Sepehr Hashemi

Abstract

This dissertation uses a flight of analytical approaches to assess the (1) influence of various surgical instruments on post-operative neurosensory deficits (pair-matched double randomized controlled trial); (2) diagnostic determination of osteoporosis using routine dental X-rays (cross-sectional); and (3) association of early life education with lifetime smoking habits across multiple generations from late twentieth century to early twenty-first century (secular trends). Each approach demonstrated its own advantages and challenges, resulting in a range of findings from purely associative to causal. In these three studies, we find that (1) compared to reciprocating saws, ultrasonic surgical instruments result in less inferior alveolar nerve paresthesia in bilateral sagittal split osteotomies, and also that right mandibles are less likely than left mandibles to experience paresthesia in after this surgery; (2) bone mineral density calculated from dental bite-wing X-rays do not determine femoral neck osteoporosis, and are not of clinical or diagnostic use in screening for osteoporosis; and (3) as expected, education has a protective effect on smoking behaviors, however, this effect has been decreasing in magnitude over recent generations, and also, paradoxically, increasing education up to 11 years of education increases the odds of smoking behaviors.

Table of Contents

List of Figures

List of Tables

List of Appendices

List of Abbreviations

Chapter 1:

BSSO: Bilateral Saggital Split Osteotomy

IAN: Inferior Alveolar Nerve

OMFS: Oral and Maxillofacial Surgery

SSO: Saggital Split Osteotomy

TPD: Two Point Discrimination

VFH: Von Frey Hair

Chapter 2:

AUC: Area Under Curve

BMD: Bone Mineral Density

BW: Bite Wing X-Ray

DXA: Dual X-Ray Absorptiometry

MrOS: Osteoporotic Fractures in Men study

QCT: Quantitative Computed Tomography

ROC: Receiver Operator Characteristic

Chapter 3:

(11+): 11 or more

Chapter 1. Does using ultrasonic saw improve IAN neurosensory outcomes after bilateral sagittal split osteotomy compared to traditional reciprocating saw? A split-mouth double-randomized control trial.

Introduction

Given the reported benefit of using ultrasonic saws over conventional methods in other outcomes, such as favorable fracture lines [1] and reduced intraoperative bleeding [2], it is reasonable to expect that they result in improved neruosensory outcomes as well, especially since ultrasonic saws are less invasive to soft tissues compared to traditional reciprocating saws. However, despite the widespread use of ultrasonic saw in oral and maxillofacial surgery, this is still a relatively novel application in this field and there are mixed reports of its impact on the inferior alveolar nerve (IAN) neurosensory outcomes in Bilateral Sagittal Split Osteotomies (BSSO) surgeries.

The few studies that have been completed have mixed findings, with some reporting reduced post-operative IAN neurosensory deficits compared to other conventional techniques [2,3], and others reporting null findings [4,5]. Also, methodological concerns regarding the use of too small of a sample size [5,6] and possible confounding due to nonrandomized designs [2–4] remain in current literature that have studied this question. Another limitation of the current literature is the non-standardization across studies as to the exact definition of neurosensory disturbance and the measurement technique used. Unfortunately this is a common theme across literature assessing sensory outcomes in BSSOs, and is one possible culprit of why the report of neurosensory disturbances after mandibular surgeries ranges from 0%-100% in literature [7].

In this study, we set out to robustly assess if ultrasonic saws result in lower incidence of post-BSSO paresthesias, specifically hypoesthesia, as compared to traditional reciprocating saws. We randomized either side of mandibles within each of 28 patients to whether they undergo BSSO via reciprocating saw or ultrasonic saw, and also whether the attending surgeon or chief resident surgeon is performing the osteotomies. By interim analysis, we found that indeed ultrasonic saws result in lower odds of hypoesthesia post-BSSO compared to reciprocating saws, however exact mechanism of this difference remains unclear.

Materials and Methods

Study Sample

Study enrolled patients under 45 years old enrolling to undergo BSSO +/- Single Piece LF1, Multipiece LF1, +/- genioplasty at University of California, Department of Oral and Maxillofacial Surgery were enrolled prior to undergoing their surgery. A ceiling age inclusion criteria was only planned on for analytical reasons, and not for safety reasons, as patients in this age group regularly undergo BSSO at study institution using both of the osteotomy instruments used in this study. However, during the study accrual, it was determined that restriction by age is not necessary for limiting bias in the study, and any benefit such restriction might provide in terms of generalizability to younger patients would largely be offset by the limitations of a smaller sample size. Patients with self-reported preexisting paresthesia were excluded. All participants were followed up an absolute minimum of three months after their BSSO to complete study.

IRB approval was obtained by hosting institution, with ClinicalTrials.gov ID of NCT05205616. This study did not receive any support nor was sponsored by any industry organizations.

Study Interventions and Instruments

The primary instruments used were 1. Stryker RemB Reciprocating Saw/Drill (herein referred to as "reciprocating saw"), which is a part of Stryker Consolidated Operating Room Equipment (CORE) System, and 2. Stryker Surgical Ultrasonic Aspirator (herein referred to as "ultrasonic saw"), which is a part of Sonopet iQ Aspirator System. Although performance settings may have been adjusted for each surgery intraoperatively, the following were the default settings used for BSSOs: 40,000 RPM when using RemB Reciprocating Saw, and power at 70% with Irrigation at 40 when using Ultrasonic Aspirator. As UCSF is a teaching institution, surgeries are performed by both an attending surgeon, and a chief surgeon resident (in final year of OMFS training program). While multiple chief residents were the performing providers throughout the study, only one attending surgeon was involved in all surgeries. Which provider uses which instrument was randomized as detailed subsequently.

Randomization Protocol and Variables

A factorial randomization was conducted for each person. Each patient underwent randomization for either the left or right mandibular ramus to receive ultrasonic Saw, with the remaining contralateral mandibular ramus receiving reciprocating saw. In addition, each BSSO were randomized as to whether the attending surgeon or the chief resident surgeon uses the ultrasonic saw, with the remaining surgeon using reciprocating saw. This design ensured that among the two mandible sides within each person, both attending surgeon and resident surgeon were assigned to operate, and both ultrasonic and reciprocating saw were assigned to be used

Permuted blocks of size 8 containing 2 separate types of assignments were made with person receiving a combination of following assignments: 1. *Left mandible ramus receives ultrasonic saw*, or *right* *mandible ramus receives ultrasonic saw*, and 2. *Chief resident surgeon uses ultrasonic saw*, or *attending surgeon uses ultrasonic saw.*

Randomization assignments were concealed in an envelope prior to beginning enrollment, sequentially assigned to patients on enrollment, and opened in the operating room immediately prior to beginning patient's surgery. Only the primary study analyst (SH) had access to envelopes during the study. Patients were blinded as to randomization assignments, as were the examiners measuring neurosensory outcomes. However, it was impossible to blind the operating surgeons as to the randomization assignments.

Other Study Variables and Data Collection Methods

Prior to surgery, the following variables were collected: sex, age, and race/ethnicity, and IAN neurosensory measurement (as subsequently described).

The following variables were collected intraoperatively: simultaneous extraction of unilateral lower third molar, unfavorable sagittal split (reference: favorable split ; other categories: unfavorable buccal plate fracture), intraoperative IAN complication (reference: no complication, other categories: IAN directly manipulated intraoperatively, IAN retained in proximal segment post-split, IAN severed during operation).

Neurosensory measurements were collected for each patient at 1, 2, 4, 12 weeks post-operatively. Additionally, measurements were also collected if patient presented at any other time intervals other than the aforementioned postoperative periods, including beyond 12 weeks post-operatively. The following measurements were collected post-operatively: smallest Von Frey Hair (VFH) filament force (reported in grams, g) sensed in the dermatome of IAN on the chin. Both variables were measured at

1.5cm medial and inferior to oral commissure, with participant's eyes closed during measurement. Application of VFH was standardized by pressing each filament on target area with exact force to elicit a 2cm bowing of the filament midpoint.

Interim Analysis

The study planned to enroll 50 patients, which would have allowed for 50% power to detect a difference of 0.2 in the proportion of neurosensory deficit between the ultrasonic and reciprocating saw arm. Power analyses were carried out per conservative calculation methods as outlined in Shiley et al. [8], which take into account the paired nature control-intervention arms within an individual and uses McNemar's test. This calculation was conservative as it ignored the efficiency of repeated measurements within a cluster. A single interim analysis was scheduled to be performed once 25 patients had finished study follow up, with a group sequential of $p < 0.005$. The study passed the critical value and we report here on the results on 28 patients enrolled as of the interim analysis.

Outcome Operationalization

Primary outcome, VFH, was operationalized as an ordinal variable, with following levels: 0.02g, 0.04g, 0.07g, 0.16g, 0.4g, 0.6g, 1g, 1.4g, 2g, 4g, 6g, 8g, 10g, and 15g. Primary predictor was whether ultrasonic saw (experimental intervention) or reciprocating saw (control intervention) was used. Given the randomized trial nature of study accounting for any possible confounding, this primary model was only adjusted for time of followup visit during which each VFH assessment was made. To improve precision, model was additionally adjusted for randomization of provider, baseline VFH value, and mandible side. Lastly, assumption of proportional odds across the range of ordinal outcome's values was assessed.

Primary analyses

Primary analysis was performed using mixed effects ordinal logistic regression, clustered on the individual, with unit of observation being each mandible side. Ordinal logistic regression provides the odds ratio of the experimental intervention (i.e. ultrasonic saw) predicting a qualitatively higher outcome value (i.e. VFH Score) at each level of the ordinal outcome, compared to a control intervention (i.e. reciprocating saw). To do so, it assumes that the relationship of a predictor and an ordinal outcome is similar across the various levels of the ordinal outcome, which is termed as the proportional odds assumption. Given that each side of mandible belongs to the same individual (the level of the cluster), the mixed effects approach accounts for the non-independent correlation among observations, thereby increasing the precision and efficiency of the analysis Proportional odds assumption was assessed using, All analyses are intent to treat, unless otherwise specified.

Sensitivity Analyses

Lastly, a sensitivity analyses was carried out to assess for the effect of missing data in the study results. The VFH score at three months for those who completed study follow up, but did not attend a visit that would fall within the criteria of a 3 month postoperative visit, were imputed. The median VFH score of 50 imputations for each mandible was used (as mean and mode of the 50 imputations were shown to largely overestimate and understimate the VFH measurement relative to healing course observed by other measurements in the same mandible). Then a similar analyses as the primary analyses (the portion of mandibles with normal IAN dermatome sensation at each arm of the study) was completed.

Results

28 patients completed the study **[Figure 1.1]**, including two inadvertent enrollment of two ineligible patients, who were ineligible due to being aged > 45 years old (46 and 53 years of age at time of surgery). Fifteen patients (54%) were female, mean age at surgery was 26 (SD: 9.8, median = 22.5), 46% were Caucasian, 29% were Latinx, and 21% were East Asian / Pacific Islander **[Table 1.1]**.

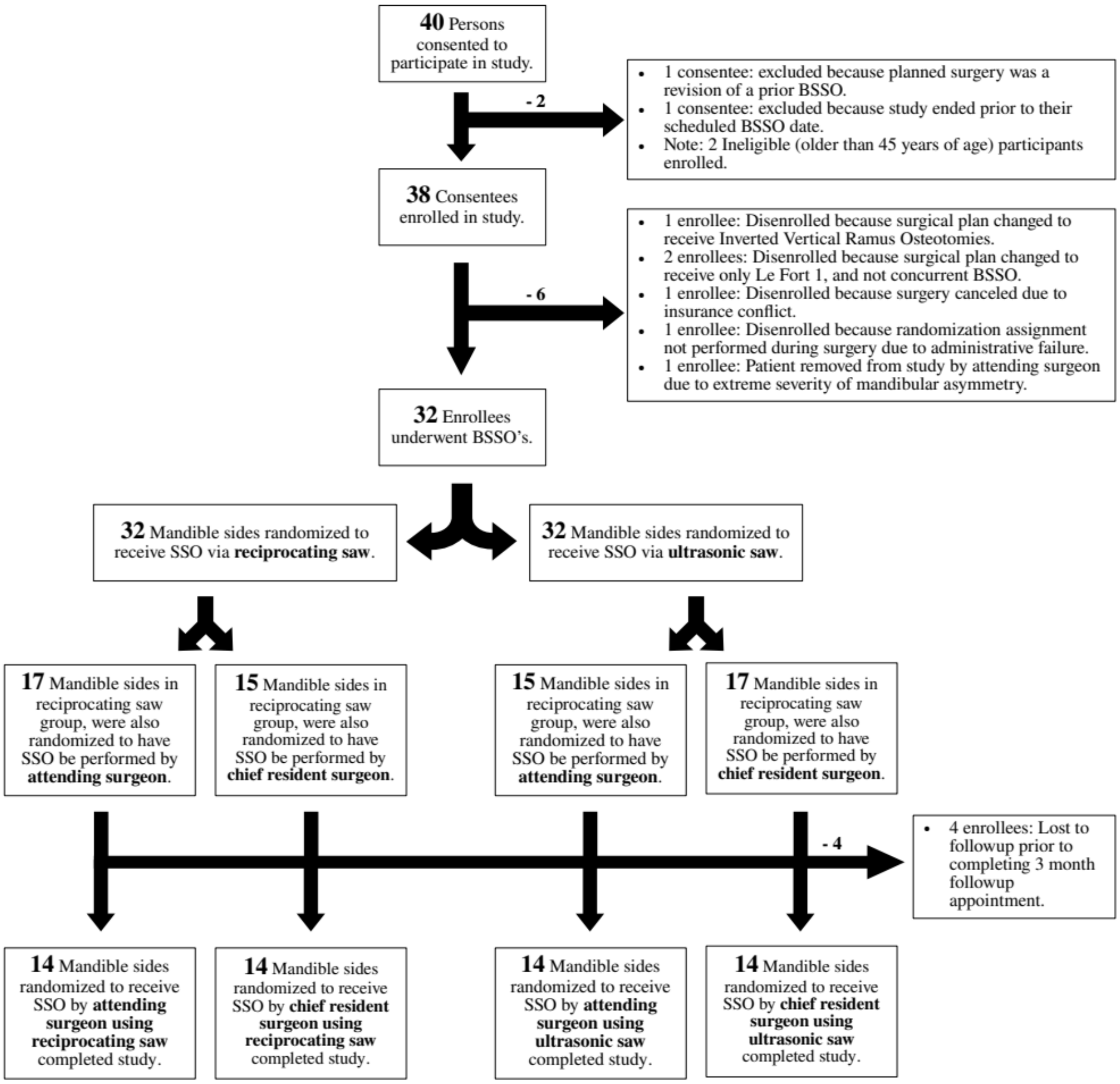

Figure 1.1: Study sample accrual flowchart.

Table 1.1: Participant demographics and randomization assignments

Table 1: Participant Demographics and Randomization Assignments

	RANDOMIZED INSTRUMENT							
	Reciprocating Saw				Ultrasonic Saw			
	RANDOMIZED PROVIDER				RANDOMIZED PROVIDER			
	Attending Surgeon		Chief Resident		Attending Surgeon		Chief Resident	
	Count / Mean	% / (SD)	Count / Mean	% / (SD)	Count / Mean	% / (SD)	Count / Mean	% / (SD)
N	14		14		14		14	
Age at Surgery	27.6	(11.4)	24.3	(8.2)	24.3	(8.2)	27.6	(11.4)
Race								
Caucasian	8	57.1%	5	35.7%	5	35.7%	8	57.1%
African American	0	0.0%	1	7.1%	1	7.1%	0	0.0%
Latino	3	21.4%	5	35.7%	5	35.7%	3	21.4%
Asian	3	21.4%	3	21.4%	3	21.4%	3	21.4%
Gender								
male	7	50.0%	6	42.9%	6	42.9%	7	50.0%
female	7	50.0%	8	57.1%	8	57.1%	7	50.0%
Baseline VFH Force								
0.008g	11	78.6%	12	85.7%	11	78.6%	11	78.6%
0.02g	1	7.1%	1	7.1%	2	14.3%	1	7.1%
0.04g	1	7.1%	0	0.0%	0	0.0%	1	7.1%
0.16g	1	7.1%	1	7.1%	1	7.1%	1	7.1%
Advancement Distance (mm)	4.5	(4.1)	4.2	(4.8)	4.2	(4.8)	4.5	(4.1)
Setback Distance (mm)	1.0	(1.7)	1.4	(1.9)	1.4	(1.9)	1.0	(1.7)
BSSO Rotation								
No rotation	8	57.1%	9	64.3%	9	64.3%	8	57.1%
Clockwise	3	21.4%	3	21.4%	3	21.4%	3	21.4%
CCW	3	21.4%	2	14.3%	2	14.3%	3	21.4%
Concurrent Genioplasty								
No Genioplasty	14	100.0%	13	92.9%	13	92.9%	14	100.0%
Genioplasty	0	0.0%	1	7.1%	1	7.1%	0	0.0%
M3 Extraction								
No Extraction	11	78.6%	14	100.0%	13	92.9%	11	78.6%
Ipsilateral M3 Extraction	3	21.4%	0	0.0%	1	7.1%	3	21.4%
Intraoperative IAN Complication								
No Complication	5	35.7%	4	28.6%	9	64.3%	7	50.0%
IAN Manipulated	1	7.1%	0	0.0%	0	0.0%	2	14.3%
IAN Retained in Proximal Segment	8	57.1%	6	42.9%	5	35.7%	4	28.6%
IAN Severed	0	0.0%	4	28.6%	0	0.0%	1	7.1%
SSO Split Outcome								
Favorable	14	100.0%	12	85.7%	14	100.0%	14	100.0%
Buccal Plate Fracture	0	0.0%	2	14.3%	0	0.0%	0	0.0%

- For each BSSO, both the instrument used and the provider using that instrument were randomized.
- Each observation represents one mandible *side* undergoing a SSO, and not one person undergoing a BSSO.

Baseline preoperative VFH force was > 0.008g among 11/56 (19.6 %) mandible sides Analytic models adjusted for baseline VFH measurement (to improve precision), baseline VFH measurement did not predict VHF scores.

Median follow-up was 206 days (range: 85 to 419 days). Post-BSSO, 284 measurements were collected at various matched followup times **[Figure 1.2]**.Overall, 21 pairs of measurements were made at the predefined study period of 3 months post-operative **[Figure 1.2]**. At 3 months post-BSSO, of all mandible rami randomized to receive SSO using ultrasonic saw, 18/21 (86%) had no hypoesthesia, while of mandible sides randomized to receive SSO using reciprocating saw, 13/21 (62%) had no hypoesthesia **[Figure 1.3]**.

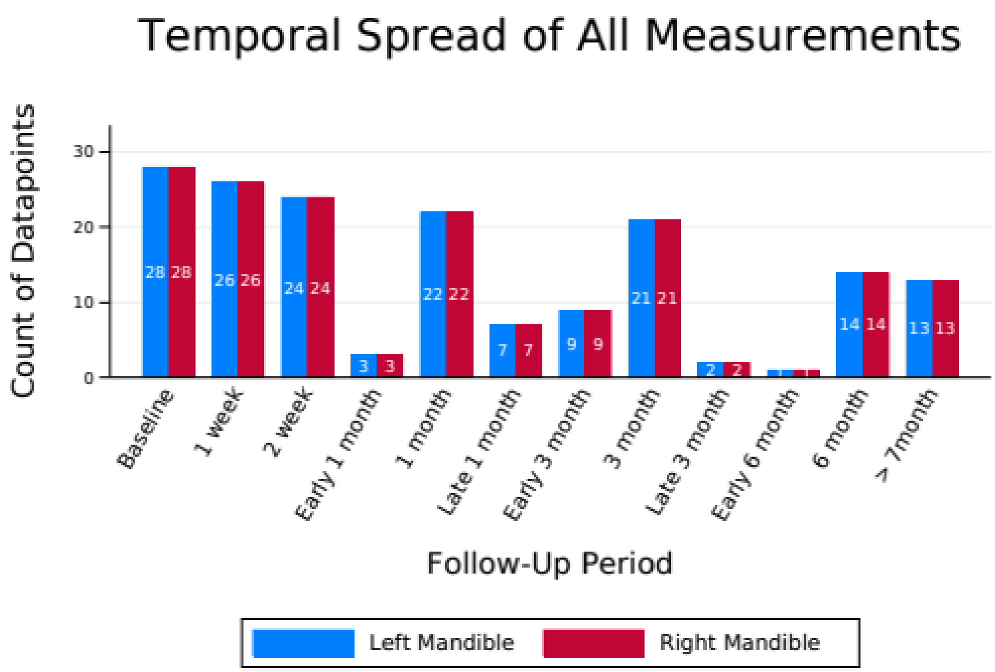

Figure 1.2: Temporal spread of all measurements

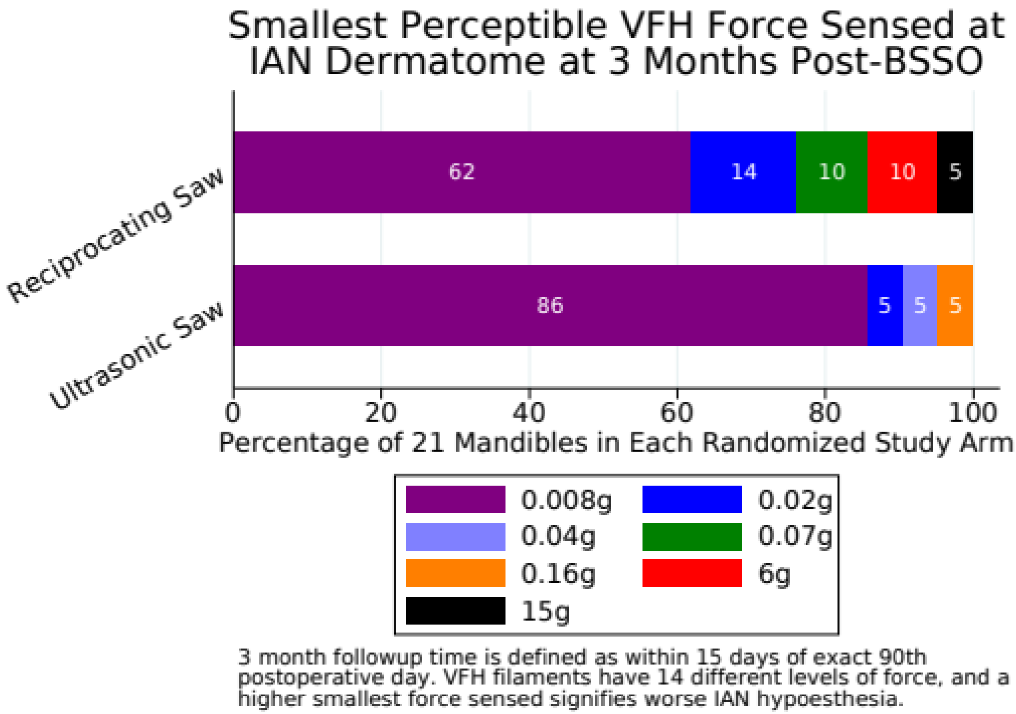

Figure 1.3: Smallest perceptible VFH force sensed at 3 months post-BSSO.

An analysis of all post-surgery mandible shows that of those that underwent SSO using ultrasonic saws have .49 (95% CI: 1.3-3.2, p=0.002) times the odds of having worse IAN hypoesthesia at all levels of VFH filament force, compared to those undergoing SSO using reciprocating saws **[Table 1.2]**. Similarly, right mandibles undergoing SSO had 0.57 (95% CI: 0.36-0.90) times the odds of having worse hypoesthesia at all levels of VFH filament force, compared to left mandibles **[Table 1.2]**. No violation of the proportional odds were detected **[Appendix Table 1.1]**.

Table 1.2: Primary results.

	Intent-to-Treat Analysis (Full Sample)	Per-Protocol Analysis (Full Sample)	Intent-to-Treat Analysis (Sub-Sample with Intact IAN)
Randomized Instrument			
Ultrasonic Saw	0.49***		0.75
	(0.31 - 0.77)		(0.44 - 1.27)
Randomized Provider			
Chief Resident Surgeon	1.24		0.78
	(0.79 - 1.97)		(0.45 - 1.33)
Instrument Used			
Ultrasonic Saw		0.43***	
		(0.26 - 0.70)	
Performing Provider			
Resident		1.68**	
		(1.03 - 2.72)	
Side of Mandible			
Right Mandible	0.57**	0.61**	0.39***
	(0.36 - 0.90)	(0.38 - 0.98)	(0.23 - 0.68)

*** p<.01, ** p<.05, * p<.1
- The 14 ordinal regression cut-point coefficients were excluded from table to simplify results.
- The full sample included 28 persons (56 mandible rami) undergoing SSO, while the Sub-Sample with Intact IAN included 23 persons (46 mandible rami) undergoing SSO's that did not experience a severed IAN on either rami.

Of the 56 mandible rami undergoing BSSO, 5 IAN's were severed: 4 (7.1%)_ in the reciprocating saw randomized arm, and 1 (1.7%) in the ultrasonic saw randomized arm **[Table 1.1]**. The chief resident was the randomized operating provider in all 5 incidences of severed IAN, while 4/5 resected IANs were on the right mandible. Additionally, 2 buccal plate fractures were noted, both in the *reciprocating saw by chief resident* randomized group. Subgroup analysis using measurements from 23 patients who did not experience any IAN resection **[Table 1.2]** revealed an even stronger relationship of mandible side and post-BSSO neurosensory disturbance: right mandibles undergoing SSO had 0.39 (95% CI: 0.23-0.68) times the odds of having worse hypoesthesia at all levels of VFH filament force, compared to left mandibles. In the Sub-Group analysis of mandibular rami with non-resected IAN, ultrasonic saw randomization failed to show a relationship with worsening VFH scores post-operatively (OR: 0.75 ; 95%CI: 0.44-1.27) **[Table 1.2]**.

Individual addition of female sex (ordinal OR: 0.99, 95% CI: 0.41 – 2.39) and concurrent intraoperative ipsilateral M3 extraction (ordinal OR: 0.94, 95% CI: 0.32 – 2.74) to he primary model did not predict different odds of hypoesthesia across all levels of measured VFH filament force. However, each year increase in age predicted 1.05 (95% CI: 1.01-1.09) times the odds increased hypoesthesia.

Fourteen (14/56) mandibles followed longitudinally did not have a VFH measurement at 3 months post-operative period, as the participant arrive at a time that would fall outside of predefined range for 3 months post-operative follow-up. Sensitivity analyses of using imputed VFH scores for missing 3-month post-operative period for those missing this score did not show qualitative difference in the results, with 64% of mandibles in the ultrasonic ar, and 46% of the mandibles in the reciprocating saw group showing normal VFH score at 3 months post-operatively **[Figure 1.4]**.

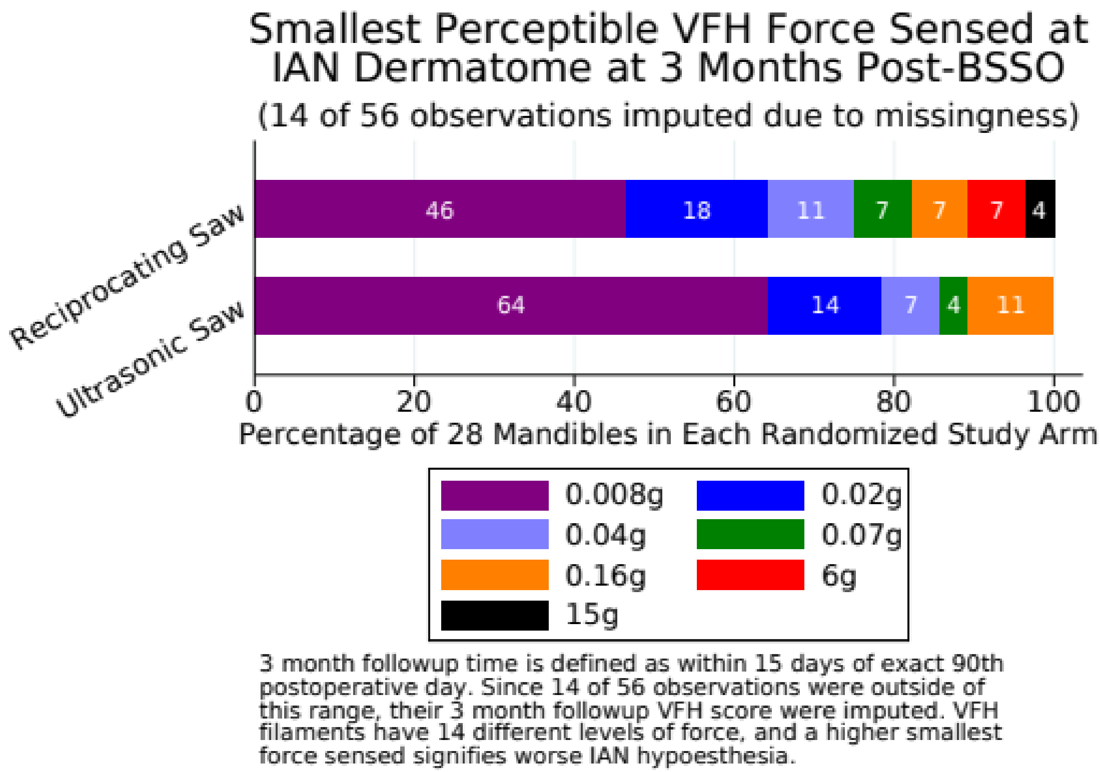

Figure 1.4: Smallest perceptible VFH force sensed at 3 months post-BSSO, in a data set with imputed 3month post-operative VFH for those missing values.

Discussion

While not completely harmless to soft tissues [9], the advent of ultrasonic saws allows osteotomies to be performed while being relatively less invasive to soft tissues. Given the ubiquitous rate of IAN paresthesia and hypoesthesia post-BSSO, the use of ultrasonic instrumentation may improve post-operative neurosensory outcomes via lower intraoperative disturbance of IAN. In this split-mouth four arm randomized controlled trial, we randomized left and right mandibles of 28 patients to either undergo BSSO via traditional reciprocating saw, or via ultrasonic saw. Given that the study was performed in an academic institution where orthognathic surgeries are performed by both an attending surgeon and a chief resident, we also randomized whether the attending surgeon or the chief resident performs the SSO on each mandible side. Study was halted on its first interim analysis once the statistical threshold for stoppage was reached. We found across all levels of minimum perceptible VFH force sensed by patients, those who received BSSO using ultrasonic saw had 0.49 (95% CI: 0.31-0.77) times the odds of having greater IAN hypoesthesia, compared to patients who underwent the BSSO using reciprocating saws.

Despite our finding of lower post-BSSO IAN neurosensory disturbance when using ultrasonic device compared to reciprocating saw, there is not a strong consensus in the greater literature on this question, likely due to the very large heterogeneity with which this relationship has been studied. For example, while a 2017 systematic review of 12 studies reports lower neurosensory disturbance at 6 months post-BSSO in the ultrasonic saw group compared to reciprocating saw group [10], a different 2019 meta-analysis of 5 studies failed to produce a pooled estimate due to the large heterogeneity among the included studies [11]. Yet a third meta-analysis of 6 studies was published in 2022, which reported a null relationship between the surgical instrument used and neurosensory outcomes at 3 months [12]. Such mixed findings likely reflect the numerous variables implicated in studying neurosensory outcomes, and the importance of methods standardization. Different measures of neurosensory function (e.g. light-touch sensation, moving/non-moving two point discrimination test, pin-prick sensation, graduate nylon filament/Von Frey Hairs, thermal/mechanical/pain detection, 1-10 hypoesthesia Likert scale self-report, and etc) [11–13] are a major contributor to the heterogeneity of the results. Also some of these methods may be less reliable than others; for instance, midway in our study we halted the use of two point discrimination (TPD) tests as it was unreliable and unreproducible even in the same visit. Another contributor to the observed heterogeneity is the length of follow up (ranging 2 - 12 months post-BSSO [11–13]), wherein variable healing due to the instruments may mask or result in neurosensory difference between the two instruments. Lastly, many studies were not randomized, allowing for residual confounding even if adjustment was performed in analysis and/or a splitmouth design was used.

Of note, 5 of 56 IAN examined in this study were intraoperatively severed, with 4 IAN severs occurring in the *reciprocating saw-resident randomized arm*, while 1 IAN sever occurring in the *ultrasonic saw-resident randomized arm*. Furthermore, sub-group analysis that excludes patients who experienced an IAN sever nullified the protective relationship of ultrasonic saw and IAN Hypoesthesia, compared to reciprocating saw. Therefore it is possible that mechanism by which ultrasonic saws result in lower post-BSSO hypoesthesia is by causing fewer severed IANs compared to reciprocating saws. However, the aforementioned sub-group analysis may not have the statistical power to support this claim. Furthermore this mechanism may be negligible with increased provider experience, as all IAN severs were performed by chief resident surgeon. Consequently, anecdotal experience of operating surgeons in our study suggest drastically slower operation time of ultrasonic saws, which may perhaps allow for greater prudence in protection of IAN compared to traditional reciprocating saws, which perform similar osteotomies at much greater speeds. However, this difference in speed is only partly supported in the greater literature: while a 2017 metaanalysis of 12 studies reported longer ultrasonic saw operating time [10], a different 2017 metaanalysis of 8 studies reported no difference in orthognathic operating time between ultrasonic saws and reciprocating saws [13], and yet, some studies even report shorter operating time in the ultrasonic groups [14]. Given the relatively low absolute count of IAN severs (n = 5) in our study, it was not reasonable to perform formal mediation analysis of this proposed mechanism. Despite of this subgroup analysis, the exact mechanism by which ultrasonic saws resulted in less hypoesthesia in this study can not be concluded with certainty, which should be elucidated in future studies.

An additional finding was that right mandibles had 0.57 (95% CI: 0.36-0.90) times the odds of experiencing greater hypoesthesia at all levels of VFH filament force, compared to left mandibles. Of note, this relationship became even stronger (OR 0.39, 95% CI: 0.23-0.68) in the subgroup analysis that excluded all IAN severs, as 4/5 IAN severs were in the right mandibular rami. This may be reflective of easier view and access of right mandibular ramus for a "right handed" provider, compared to left mandibular ramus for the same provider. The sole attending of the study is right-hand dominant, as were all but one chief resident who operated in the surgeries involved in this study. We were only able to find one study that compared post-BSSO neruosensory outcomes between left and right mandible sides, which similarly reported lower paresthesia in the right side [15].

Additionally, as already reported in literature [9,16–19], increasing age was associated with higher odds of hypoesthesia. However, female sex did not predict any difference in odds of hypoesthesia (OR: 0.99, 95% CI: 0.41 – 2.39), which is a mixed finding in the greater literature [16,17,20,21].

There are several strengths in this study design. Firstly, a randomized control trial is the current gold standard of experimental analysis. Further, randomizing not only the intervention, but also the provider who is delivering the intervention is a powerful, but seldom used approach in the field of Oral and Maxillofacial Surgery. This approach should be replicated in all OMFS academic institutions, as many research contributions in our field occur in similar academic institutions where surgeries are simultaneously performed by both an attending surgeon and a chief resident in training. Consequently, in the per-protocol analysis of our study, chief resident providers did indeed result in different odds of post-BSSO paresthesia compared to attending surgeon (OR: 1.68, 95% CI: 1.03-2.72) **[Table 1.2]**. Another strength of this study is that split-mouth design, where a left and right mandible are matched together as to control-experimental intervention delivery, thereby significantly increasing the power of the study. This is another unique opportunity in the OMFS research involving bilateral mandibular rami that should be used more frequently. Lastly, the use of VFH filament force measurement as proxy for IAN neurosensory outcome is a strength of this study, as it is a relatively reliable, reproducible, and well-calibrated in application.

Despite the clear study findings, median followup time for the study sample was 197 days, which is considered short term in the context of post-BSSO paresthesia outcomes. Median followup of at least 9 months or longer is more suitable for assessing post-BSSO paresthesia outcomes, as transient post-BSSO paresthesia frequently does not translate to long-term paresthesia. Second, while adverse events such as IAN severs (n=5, of 56 mandibles) and buccal plate fractures (n = 2, of 56 mandibles) were observed, their low absolute counts do not allow for meaningful analysis given resultant erratic sampling error. Lastly, all surgeries were performed under the supervision of one attending surgeon, which limits generalizability of study findings to other providers whose techniques may be different compared to this study's main provider. Similarly, the influence of the surgical experience of chief-resident surgeons involved in this study may render the results not generalizable to more experienced surgeons.

Future directions may include elucidation of farther exploration of the mechanism by which ultrasonic saws result in lower odds of hypoesthesia, compared to reciprocating saw, and if those mechanisms can be employed to reciprocating saws (e.g. slower completion of osteotomy). Furthermore, studies with longer overall followup of patients under BSSO may elucidate if the observed transient difference in this study remains long-term, or if the hypoesthsia differences between ultrasonic saws and reciprocating saws equalize after typical expected recovery period.

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Appendices

Appendix Table 1.1: Prediction of binary VFH hypoesthesia at each specific force value of VFH by randomized instrument

	VFH Cut at 0.02g	VFH Cut at 0.04g	VFH Cut at 0.07g	VFH Cut at 0.16g	VFH Cut at 0.4g	VFH Cut at 0.6g	VFH Cut at 1g	VFH Cut at 1.4g	VFH Cut at 2g	VFH Cut at 4g	VFH Cut at 6g	VFH Cut at 8g	VFH Cut at 10g	VFH Cut at 15g
Instrument Randomization														
Sonopet	0.62*	0.59*	0.52**	0.34***	0.37***	0.31***	0.21***	0.21***	0.32***	0.22***	0.18***	0.25**	0.18***	0.11***
	(0.35 - 1.08)	(0.34 - 1.04)	(0.28 - 0.95)	(0.17 - 0.68)	(0.18 - 0.76)	(0.14 - 0.70)	(0.09 - 0.50)	(0.09 - 0.51)	(0.13 - 0.74)	(0.08 - 0.58)	(0.06 - 0.53)	(0.09 - 0.73)	(0.06 - 0.56)	(0.02 - 0.51)
Follow-Up Period														
intraoperative	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1 week	5.10***	3.11**	2.63*	2.84*	2.57	4.16**	3.35*	2.89	4.22*	5.81**	9.90**	6.76**	16.00**	15.28**
	(1.80 - 14.49)	(1.22 - 7.93)	(0.99 - 7.02)	(0.96 - 8.47)	(0.81 - 8.18)	(1.12 - 15.44)	(0.88 - 12.81)	(0.76 - 10.92)	(1.00 - 17.84)	(1.18 - 28.55)	(1.57 - 62.31)	(1.15 - 39.67)	(1.58 -162.38)	(1.25 -186.87)
2 week	2.41*	1.24	1.51	2.45	3.57**	7.04***	6.47***	5.15**	8.04***	7.87**	10.06**	6.86**	12.94**	7.19
	(0.92 - 6.33)	(0.49 - 3.15)	(0.55 - 4.15)	(0.79 - 7.57)	(1.07 - 11.88)	(1.77 - 28.05)	(1.58 - 26.53)	(1.29 - 20.50)	(1.82 - 35.43)	(1.56 - 39.67)	(1.55 - 65.14)	(1.13 - 41.50)	(1.25 -133.95)	(0.57 - 91.52)
1 month	1.46	1.06	1.43	1.61	1.84	3.47*	2.35	2.25	2.51	3.13	4.09	3.54	7.59*	8.41
	(0.56 - 3.76)	(0.41 - 2.77)	(0.51 - 4.03)	(0.50 - 5.21)	(0.52 - 6.51)	(0.83 - 14.46)	(0.54 - 10.26)	(0.53 - 9.63)	(0.53 - 11.96)	(0.57 - 17.23)	(0.58 - 28.74)	(0.53 - 23.49)	(0.69 - 82.97)	(0.63 -112.55)
3 month	0.21***	0.18***	0.19***	0.17**	0.18**	0.26	0.25	0.26	0.50	0.79	1.32	0.32	0.69	0.59
	(0.07 - 0.58)	(0.06 - 0.56)	(0.06 - 0.65)	(0.04 - 0.69)	(0.04 - 0.89)	(0.05 - 1.44)	(0.04 - 1.42)	(0.05 - 1.47)	(0.08 - 2.95)	(0.12 - 5.24)	(0.17 - 10.57)	(0.02 - 4.44)	(0.03 - 13.67)	(0.03 - 13.58)
6 month	0.49	0.41	0.30*	0.36	0.30	0.42	0.21	0.21	0.17	0.28	0.44	0.44	0.96	1.00
	(0.16 - 1.43)	(0.13 - 1.26)	(0.09 - 1.08)	(0.09 - 1.49)	(0.06 - 1.57)	(0.07 - 2.42)	(0.03 - 1.57)	(0.03 - 1.49)	(0.01 - 2.03)	(0.02 - 3.51)	(0.03 - 6.41)	(0.03 - 6.28)	(0.05 - 19.68)	
> 7month	0.15***	0.10***	0.10**	0.16**	0.13*	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	(0.04 - 0.53)	(0.02 - 0.45)	(0.02 - 0.59)	(0.03 - 1.00)	(0.01 - 1.34)									
OTHER (< 5 month)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Provider Randomization														
Resident	1.33	0.98	1.30	1.60	1.60	2.43**	2.08*	2.04*	1.91	3.42**	3.64**	3.06**	2.68*	3.67*
	(0.76 - 2.33)	(0.56 - 1.71)	(0.71 - 2.37)	(0.82 - 3.14)	(0.78 - 3.28)	(1.08 - 5.45)	(0.89 - 4.87)	(0.88 - 4.73)	(0.82 - 4.47)	(1.28 - 9.16)	(1.25 - 10.60)	(1.08 - 8.69)	(0.90 - 7.96)	(0.87 - 15.40)
Side of Mandible														
Right Mandible	0.65	0.52**	0.59*	0.43**	0.44**	0.42**	0.66	0.67	0.61	0.57	0.66	0.66	0.88	0.56
	(0.37 - 1.14)	(0.30 - 0.91)	(0.33 - 1.09)	(0.22 - 0.86)	(0.21 - 0.90)	(0.19 - 0.91)	(0.29 - 1.49)	(0.30 - 1.50)	(0.27 - 1.39)	(0.23 - 1.42)	(0.25 - 1.73)	(0.25 - 1.72)	(0.32 - 2.43)	(0.17 - 1.86)
Baseline VFH Force														
0.02g	0.76	0.39	0.57	0.34	0.32	0.49	0.25	0.27	0.36	0.50	0.21	0.23	0.23	0.24
	(0.21 - 2.73)	(0.10 - 1.50)	(0.14 - 2.41)	(0.07 - 1.75)	(0.05 - 1.82)	(0.07 - 3.26)	(0.03 - 2.36)	(0.03 - 2.39)	(0.04 - 3.16)	(0.06 - 4.57)	(0.01 - 3.11)	(0.02 - 3.07)	(0.02 - 3.37)	(0.01 - 4.68)
0.04g	0.52	0.41	0.34	0.15	0.22	0.29	0.36	0.39	0.49	0.77	1.00	1.00	1.00	1.00
	(0.06 - 4.49)	(0.04 - 4.48)	(0.02 - 6.50)	(0.00 - 5.28)	(0.01 - 7.46)	(0.00 - 16.76)	(0.00 - 25.74)	(0.01 - 23.47)	(0.01 - 25.53)	(0.02 - 36.46)				
0.16g	0.55	1.24	1.01	0.10	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	(0.11 - 2.84)	(0.22 - 7.05)	(0.12 - 8.46)	(0.01 - 2.10)										

*** p<.01, ** p<.05, * p<.1

- Reference values are as follows: Instrument randomization (Reciprocating Saw), provider randomization (attending), mandible side (left), baseline VFH force (0.008g).

Chapter 2. MrOS Cohort Study: Does jaw bone mineral density measured using routine dental bite-wing X-rays determine changes in femoral bone density among older men?

Introduction

Globally, osteoporosis prevalence is reported to be 23.1% in women and 11.7% in men [1], often not diagnosed until pathological fractures that have great quality of life [2,3] and economic impact [4,5]. Yet, osteoporosis is asymptomatic and often underdiagnosed until pathological fractures occur [6]. While Osteoporosis is diagnosed via Dual-Energy X-ray Absorptiometry (DXA) scans of the hip, one study reported that only 25% of women 65+ in the United States underwent DXA scans over a study period [7]. More accessible means of osteoporosis screening may help alleviate this underdiagnosis; given that 63.7% of United States adults 65+ reported having seen a dentist in the last 12 months [8], dental X-rays should be explored for capacity as a relatively affordable, low radiation method of screening for osteoporosis.

Accordingly, early as 1993 [9] numerous approaches to measure mandibular bone mineral density (BMD) have been proposed and used to associate mandibular density with femur bone mineral density. One approach has used Mandibular Cortex Score (MCI), which subjectively grades the quality of mandibular bone using a dental panoramic radiograph (panograph), and has shown positive correlation with skeletal BMD measured by DXA scans [10] specifically among post-menopausal women. However this technique may have high inter-examiner variability as the panograph is subjectively visually scored by a dentist. Also other reports suggest a less successful correlation, with MCI having a sensitivity of 0.35 and specificity of 0.88 in diagnosing osteoporosis [11] . A different approach has been the use of mandibular cortical width, which showed a sensitivity of 0.57 and specificity of 0.83 in diagnosing osteoporosis [11] . A more sensitive approach has been to assess for presence of any mandibular cortical erosion at all, which showed a sensitivity of 0.81 and specificity of 0.64 in detecting osteoporosis [12].

Lastly, quantitative computed tomoraphy has been used (QCT) to quantitatively correlate BMD of various regions in mandible to predict osteoporosis, but to mixed or moderate success [9,13,14]. Regardless, a CT may not have major advantages over DXA scans, since it has higher radiation than other forms of dental radiographs, and is not routinely used to be ideal as it is not routinely used in care provided by general dentists. Despite the exploration of these several approaches, studies have largely focused on post-menopausal women, and there is less data as to their utilization in older men.

A different approach to measuring mandibular bone density is to use dental bite-wing (BW) X-rays, which are affordable, pose minimal radiation, and are routinely performed every 1-2 years in regular dental care of patients. We are only aware of one study that assessed mandibular BMD using BW X-rays, and it found a statistically significant association between crestal/subcrestal mandibular BMD measured from BW X-rays and a composite outcome of osteopenia/osteoporosis, among 28 post-menopausal women [15]. Further study of this association is needed for implementation of BW X-rays as a screening adjunct in detecting osteoporosis. Therefore, in the current study we explored this association between mandibular BMD and femur BMD using BW X-rays and femoral DXA and femoral CT scans in a cohort of 1,034 older men.

Materials and Method

Study Sample

Participants in this study were a subgroup of men from the Osteoporotic Fractures in Men (MrOS) Study [16], a multi-center longitudinal cohort study that began initial recruitment from March 2000 to April 2002, from six clinical sites - Birmingham (AL) Minneapolis (MN) Palo Alto (CA) Pittsburgh (PA) Portland (OR) and San Diego (CA). Recruitment population consisted of community dwelling, ambulatory men aged 65 years or older, who were intended to be representative of the broad population men in this age group. The recruitment inclusion criteria were: (1) ability to walk without the assistance of another, (2) absence of bilateral hip replacements, (3) ability to provide self-reported data, (4) residence near a clinical site for the duration of the study, (5) absence of a medical condition that (in the judgment of the investigator) would result in imminent death, and (6) ability to understand and sign an informed consent. This analysis included only men enrolled in the MrOS cohort who also completed an additional dental visit (from September 2002 to May 2003), which were only performed in the Portland and Birmingham sites [17].

Approval of MrOS study was obtained from the institutional review boards of the participating clinics, and informed consent was obtained from all study participants.

Study Variables: Overview

Analysis include variables from both the baseline visit performed from March 2000 to April 2002, and also variables from the dental visit performed from September 2002 to May 2003. The variables in the baseline visit included proximal femur strength, proximal femur average BMD, race, highest education level (High school, some college, college, some graduate school, graduate school), history of diabetes, bisphosphonate use, inhaled/nasal corticosteroid use. The variables from the dental visit included variables from the dental visit performed from September 2002 to May 2003 (specifically: mandibular BMD, femoral neck BMD, age, BMI, smoking status, alcohol use, gingivitis status, periodontitis status). All variables were obtained via self-report, except for mandibular BMD (obtained via dental 'bite-wing' X-rays), femoral neck BMD (via Dual X-ray Absorptiometry scans), proximal femur average BMD and proximal femur strength (both via computed via Computed Tomography scans), and BMI (measured).

Study Variables: Exposure

Mandibular BMD was calculated using dental bite-wing X-rays of patients who were randomized to receive bite-wing X-rays of either to area of teeth #29 and #30 (patient's right mandible), or teeth #19 and #20 (patient's left mandible). From each bite-wing X-ray, 3 regions of interest near the apex of roots of the teeth were chosen, and their density was averaged to calculated to represent the final mandibular bone density measure. To measure the density of each of the three regions of interest, a calibration phantom with a known density was used. The final mandibular density is reported as equivalent thickness of aluminum (in millimeters, mm) that has the same density as observed from the average of the density of the three sites of interest in each person's dental bite-wing X-ray.

Study Variables: Outcome

Osteoporosis status of each persons was calculated using T-Scores obtained from femoral neck BMD from DXA scans during the participant's dental visit.

The secondary outcomes of proximal femur average BMD and proximal femur strength were obtained from CT's of proximal femur. The former variable is the average BMD of the entire proximal femur (including both cortical and trabecular bone), expressed in gm/cm^3, often referred to as the integral in literature. The latter variable is the strength of proximal femur under a lateral loading (fall conditions), expressed in Newtons (N). Proximal femur strength < 3,500 Newton is considered a fragile bone in men, and indicative of higher fracture risk. These variables were only available for participants enrolled at the Portland site.

Statistical Analyses

The primary outcome of femoral neck BMD (g/cm^2), and the two secondary outcomes of proximal femur average BMD (mg/cm^3) and proximal femur strength (Newton) were each separately regressed on standardized mandibular BMD (Z-score) using linear regression, and all three models were additionally adjusted for age categories, BMI categories, racial categories, and highest obtained education level. Aforementioned covariates were operationalized as categorical variables. Those with missing mandibular BMD were excluded from the analysis. Stata 17.0 was used for Statistical analysis.

Receiver Operator Curve Analysis

Additionally, Area Under Curve (AUC) from Receiver Operator Characteristic (ROC) curves were used to assess diagnostic impact of mandibular BMD in correctly determining the dichotomous outcome of *Osteoporosis vs normal femoral neck BMD*. To do so, first AUC was calculated for a logistic regression model already adjusted for age, BMI, race, and education level (herein referred to as the *demographics-only* model). Mandibular BMD was subsequently added to this model (herein referred to as the *full* model), a second AUC for this full model was calculated, and the statistical significance of the difference between the two AUC from the models with and without mandibular BMD were calculated using methods outlined by DeLong et al. [18]. Given that rarity of osteoporosis in MrOS data makes osteoporosis a highly unbalanced outcome, this analysis was also repeated for the composite dichotomous composite outcome of *Osteoporosis or Osteopenia vs normal femoral neck BMD* was also calculated.

Age Difference Needed for Equivalent Effect on Each Outcome

Lastly, to demonstrate the relative effect of a Z-score change in manidbular BMD on each of the three outcomes, and equivalent age difference that would have the same equivalent effect was calculated for each of the three outcomes. This was calculated by computing the ratio of standardized mandibular BMD coefficient over age coefficient, in each regression.

Results

Of the greater MrOS cohort (5,994 persons), 1,261 men attended the dental visit. Of these, 1,034 persons obtained dental bite-wings, allowing for computation of mandibular BMD, and thus the primary analytical sample of N = 1,034 men **[Table 2.1]**. Of this group, 196 men had obtained CT's at their baseline visit, allowing for computation of the secondary outcomes of proximal femur average BMD and proximal femur strength, and thus the secondary analytical sub-sample of N = 196 men.

Table 2.1: Participant demographics and covariates

	Osteoporosis (per Femoral Neck BMD T-Score)						P-Value
	Normal BMD (n = 625)		Osteopenia (n = 386)		Osteoporosis (n = 23)		
	Count / Mean	% / (SD)	Count / Mean	% / (SD)	Count / Mean	% / (SD)	
Mandibular BMD (mm)	3.23	(1.84)	2.99	(1.76)	2.43	(1.43)	.014*
Gingivitis							
No	483	60%	311	38%	17	2%	.6
Yes	93	65%	46	32%	3	2%	
Don't know	49	60%	29	36%	3	4%	
Periodontitis							
No	457	59%	304	39%	16	2%	.16
Yes	108	63%	57	33%	6	4%	
Don't know	60	70%	25	29%	1	1%	
Diabetes History							
No	538	58%	361	39%	21	2%	.0011**
Yes	87	76%	25	22%	2	2%	
Age	74	(5)	76	(6)	78	(7)	<.0001***
Body Mass Index	28.3	(3.8)	26.3	(3.4)	24.9	(4.0)	<.0001***
Race/Ethnicity							
White	546	60%	348	38%	20	2%	.00015***
African American	56	86%	9	14%	0	0%	
Asian	16	46%	17	49%	2	6%	
Hispanic	2	25%	6	75%	0	0%	
Other	5	42%	6	50%	1	8%	
Highest Education Level							
Some high school or less	40	57%	27	39%	3	4%	.37
High school	77	55%	60	43%	2	1%	
Some college	145	58%	100	40%	7	3%	
College	126	61%	75	36%	6	3%	
Some graduate school	68	61%	41	37%	3	3%	
Graduate school	169	67%	83	33%	2	1%	
Smoking Status							
Nonsmoker	236	65%	121	33%	7	2%	.016*
Ex-Smoker	370	58%	250	39%	13	2%	
Current Smoker	15	45%	15	45%	3	9%	
Missing	4	100%	0	0%	0	0%	
Weekly Alcohol Use							
None	227	56%	167	41%	9	2%	.09
< 1 / week	73	61%	40	34%	6	5%	
1-2 / week	62	56%	45	41%	3	3%	
Don't know	109	64%	60	36%	0	0%	
6-13 / week	111	66%	53	32%	3	2%	
> 13 / week	43	65%	21	32%	2	3%	
Bisphosphonate Use							
No	603	60%	373	37%	21	2%	.04*
Yes	3	30%	7	70%	0	0%	
Missing	19	70%	6	22%	2	7%	
Inhaled/Nasal Corticosteroids Use							
No	570	61%	349	37%	20	2%	.26
Yes	39	53%	33	45%	2	3%	
Missing	16	76%	4	19%	1	5%	

*** p<.01, ** p<.05, * p<.1

- The following variables were collected at baseline visit: demographic variables (Race/Ethnicity, Education Level), health variables (Diabetes History), and medication variables (Bisphosphonate Use, Inhaled/Nasal Corticosteroids Use). The following variables were collected at Dental Visit: demographic variables(Age, BMI, Smoking Status, Alcohol Use), oral health variables (Gingivitis, Periodontitis), and bone mineral density variables (Osteoporosis Status, Mandibular BMD).
- Osteoporosis is defined via Femoral Neck BMD T-Score.

Among the 1,034 participants, 23 (2.2%) had osteoporosis and 386 (37%) had osteopenia, while 914 (88.4%) were White, 633 (61.2%) were ex-smokers 33 (3.1%) were current smokers, and 254 (24.6%) had obtained graduate level education. Mean age was 74.7 (SD 5.5), and mean BMI was 27.5 (SD 3.84). Mean mandibular BMD was 3.1 mm (SD 1.8), while mean femoral neck BMD was 0.78 g/cm^2

(SD 0.13). Furthermore, 142 (13.7%) men reported gingivitis, and 171 (16.5%) reported periodontitis. As for relevant medication use, 10 (1%) reported bisphosphonate use, 74 (7.2%) reported inhaled/nasal corticosteroid use, and 114 (11%) reported a history of diabetes.

In the secondary analysis subsample of 196 men, mean total proximal femur average BMD was 238.2 mg/cm^3 (SD 39.8), while the mean proximal femur strength , was 5,139 Newtons (SD 1,358).

Standardized mandibular BMD statistically associated with changes in all three outcomes of femoral neck BMD (0.01 g/cm^2, 95% CI: 0.0047 – 0.02), total proximal femur average BMD (8.21 mg/cm^3, 95% CI: 2.41 – 14), and proximal femur strength (221 Newtons, 95% CI: 30 – 411) **[Table 2.2]**.

Table 2.2: Determination of femoral $_{bone}$ vairables by Standardized Mandibular BMD.

	Femoral Neck BMD (g/cm2, n = 1,034)	Proximal Femur Integral vBMD (mg/cm3, n = 196)	Proximal Femur Strength (Newtons, n = 196)
Standardized Mandibular BMD	0.01*** (0.00 -0.02)	9*** (4 - 14)	261*** (78 - 445)
Age	-0.00*** (-0.00 --0.00)	-1*** (-2 - -0)	-48*** (-82 - -15)
Body Mass Index	0.01*** (0.01 -0.01)	2** (1 - 4)	90*** (26 - 154)
Race/Ethnicity			
African American	0.10*** (0.07 -0.13)	52*** (17 - 87)	2507*** (1513 -3501)
Asian	-0.04** (-0.07 --0.01)	0 (-14 - 14)	-368 (-862 - 126)
Hispanic	-0.07 (-0.18 -0.03)	-17 (-66 - 32)	-459 (-1629 - 711)
Other	-0.05 (-0.14 -0.05)	-43*** (-69 - -16)	-1218*** (-2085 --352)
Highest Education Level			
High school	-0.03 (-0.06 -0.01)	-22** (-42 - -1)	-679** (-1341 - -17)
Some college	-0.01 (-0.05 -0.02)	-14 (-32 - 3)	-401 (-984 - 183)
College	-0.01 (-0.04 -0.03)	-6 (-24 - 12)	-151 (-717 - 414)
Some graduate school	0.00 (-0.03 -0.04)	-9 (-28 - 11)	-342 (-968 - 285)
Graduate school	0.01 (-0.03 -0.04)	-9 (-26 - 9)	-190 (-757 - 377)

*** p<.01, ** p<.05, * p<.1
All models were adjusted for age, BMI, race/ethnicity (reference = Caucasian), education (reference: Did not complete high school).

For the outcome of *osteoporosis*, AUC for the demographics-only model was 0.78 (95% CI: 0.66 - 0.9), while the AUC for the full model was 0.8 (95% CI: 0.68 – 0.91) **[Figure 2.1]**. The two AUC were statistically insignificant, at a p-value = 0.26 . For the composite outcome of *osteoporosis or osteopenia*, AUC for the demographics-only model was 0.6994 (95% CI: 0.67 - 0.73), while the AUC for the full model was 0.7054 (95% CI: 0.67 - 0.74) **[Figure 2.2]**. The two AUC were again statistically insignificant, at a p-value = 0.17 .

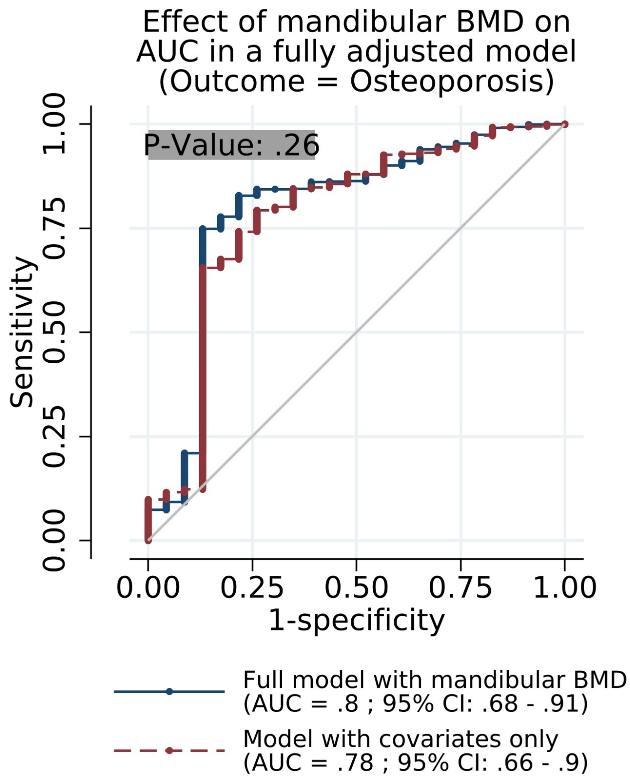

Figure 2.1: Receiver Operator Characteristic curve determination of osteoporosis by mandibular BMD.

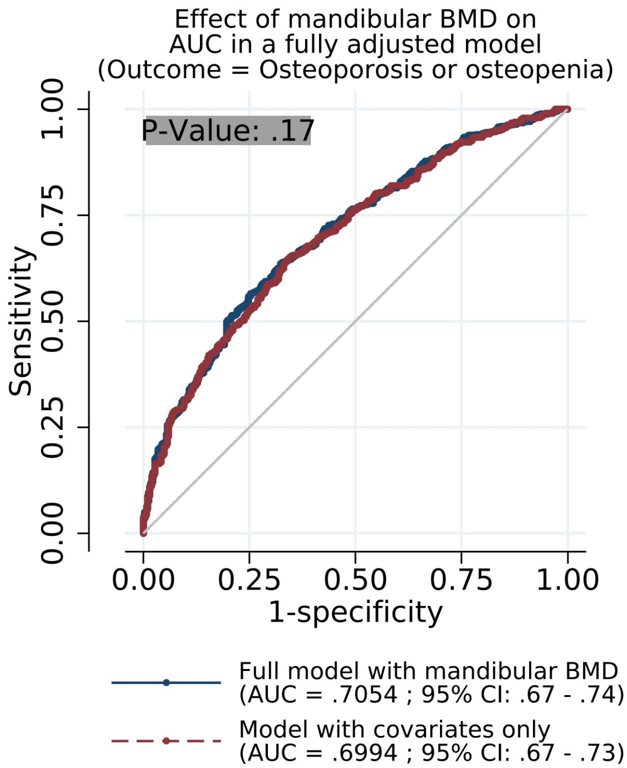

*Figure 2.2: Receiver Operator Characteristic curve determination of osteoporosis *or* osteopenia by mandibular BMD.*

Lastly, a similar effect size on the three outcomes as 1 Z-score increase in mandibular BMD was observed when age was changed by -4.39 years (95% CI: -7.79 - -0.98) for femoral neck BMD, -7 years (95% CI: -14 – 0) for proximal femur integral vBMD, and -5 years (95% CI: -11 – 1) for proximal femur strength **[Table 2.3]**.

Table 2.3: Age difference (years) needed to experience an outcome effect size equivalent to 1 Z-Score increase in Standardized Mandibular BMD

	Femoral Neck BMD (g/cm2, n = 1,034)	Proximal Femur Integral vBMD (mg/cm3, n = 196)	Proximal Femur Strength (Newtons, n = 196)
Change in age (Years)	-4.39** (-7.79 --0.98)	-7* (-14 - 0)	-5* (-11 - 1)

*** p<.01, ** p<.05, * p<.1

- All models were adjusted for age, BMI, race/ethnicity (reference = White), education (reference: Did not complete high school).

Discussion

Using a large cohort of older men, this study analyzed the association between mandibular BMD, as measured from dental bite-wing (BW) X-rays, to femoral neck bone density as measured via DXA scans, and found no clinically meaningful association. Similarly, no clinically meaningful relationship was found between mandibular BMD and the secondary outcomes of total proximal femur average BMD or proximal femur strength. This is the first study of this scale, with a sample of 1,034 men, to assess this association between BW X-rays and femoral DXA and femoral CT scans. Although this null association does not preclude the possibility of using mandibular BMD in predicting femoral BMD, it is strong evidence against using the specific method used in this study for measuring mandibular BMD from BW X-rays as screening utility for osteoporosis.

Numerous methods have been proposed in the greater literature for assessing mandibular BMD, in determination of osteoporosis. These include mandibular cortex index (MCI) [10,11], mandibular cortical width [11], mandibular cortical erosion [12], quantitative computer tomography (OCT) [9,13,14] , and BW X-rays [15]. However, associations from these methods have largely been mixed, or at best, of moderate diagnostic utility. Although statistically significant, our approach of using a single X-ray BW for assessing femoral BMD was also of limited utility, given the minimal clinical correlation between the two measures. This may reflect that the mandibular BMD may be driven by different physiological and behavioral factors than femoral BMD. One such factor may be the continued loading of mandible from eating at older age, while loading of femurs may decrease as physical activity decreases. There is a moderate body of evidence linking diet consistency [19–21] and parafunctional habits [22–25] to mandibular and cranial growth and morphology, whereas these factors may not affect femoral BMD. Although various studies have measured BMD of different locations in the mandible, most of the accessible locations of mandible are participants to osteogenic loading forces of oral function. Such differential drivers of growth may explain the lack of association between mandibular and femoral BMD.

In light of its null findings, this study has several strengths and limitations that must be considered. Firstly, to our knowledge this is the largest single study assessing the relationship between mandibular BMD and skeletal BMD, particularly using BWs. Furthermore, the novel approach of measuring mandibular BMD we used is less subjective than most measures, thereby reducing possibility of inter-examiner error, and given that it's a continuous exposure, it even farther increases the power of the analysis. Lastly, sample consists of older men, whereas most literature on this research question has largely only analyzed post-menopausal women. However, there are also several shortcomings to this study, mainly those that limit the null finding's generalizability. The study sample, while among the largest studies, consists of relatively fewer men with osteoporosis (2.2%) compared to greater population of United States. Also, the sample is largely White and highly educated men, farther limiting external validity of the findings. Lastly, while mandibular BMD and most other non-static variables in this study that are relevant to the analysis were collected during the dental visits (September 2002 to May 2003), the secondary outcomes of total proximal femur average BMD and proximal femur strength were collected during the baseline visits (March 2000 to April 2002). This offset of possibly 3 years between the exposure and outcome may bias the correlations measured in the analysis. However, this would most likely be a bias away from null.

In light of the findings in this study, we recommend use of other approaches of accessible and non-invasive osteoporosis screening than assessing mandibular BMD. However, certain modifications in measuring mandibular BMD may nonetheless increase diagnostic capacity of this approach. Firstly, taking into account masseter size or volume (as a proxy for mandibular mechanical loading) in prediction models may improve correlation of mandibular and femoral BMD. Similarly, analysis of this association among patients who are edentulous, and therefore experience less loading of their cranial skeleton, may similarly a show stronger correlation. Lastly, an approach similar to current DXA scans, where two X-rays of varying penetrative energy are used, may allow for drastic improvement in accuracy of measurement of mandibular BMD using BWs, without significantly increasing radiation exposure. Regardless of the approach, osteoporosis in older adults is largely underdiagnosed, and any method of improving diagnosis rates will have important impact in prevention of pathological fractures and quality of life of susceptible patients.

Although standardized mandibular BMD statistically associated with femoral neck BMD, proximal femur integral vBMD, and proximal femur strength, the magnitude of this association was modest. The use of mandibular BMD to determine osteoporosis status may be efficacious via dental BW X-rays.

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Chapter 3. The protective relationship between education and smoking in middle age strengthened between 1992 and 2004, then stabilized.

Introduction

Smoking is a leading preventable cause of death, accounting for 18% of total US deaths in 2000 [1], and also the single most preventable cause of cardiovascular death, accounting for about 17 million deaths globally [2]. Although still a major contributor to our national mortality and healthcare burden, smoking prevalence in the US has decreased in recent decades. For instance, the prevalence of current smoking decreased from 2005 (21%) to 2016 (16%). Much of this decline was achieved via smoking cessation: the percentage of ever smokers who no longer smoked, which increased from 51% to 59% during that period. However, the decline in smoking prevalence among adults has been stagnant since 2015 [3].

Higher educational attainment is a consistent predictor of better smoking behaviors [4–7]. It is associated with decreased smoking prevalence [7–10] and duration [11–13], and increased smoking cessation [14–16]. Substantial reductions in the overall prevalence of smoking in recent decades may have altered the relationship between education and smoking behaviors. Importantly, secular trends in education attainment have been noted among those born 1909 - 1982, with both later cohorts enjoying steady increases in education attainment compared to those born earlier [17]. Other reports also demonstrate increase in education attainment over a more narrow period, such as those having attended "some college" steadily increasing from the 1930 to 1950 birth cohorts, and stabilizing afterwards until 1970 birth cohort [18]. Documenting trends in educational inequalities in smoking will help anticipate future inequalities in smoking-related outcomes and help prioritize smoking prevention and cessation strategies.

One such trend may be that the relationship between education and smoking may not be linear [19]. Accordingly, inflection points in the education-health association are sometimes used at the completion of high school or college (e.g. inflection points at 12 for a high school diploma, or 16 years for a college diploma) based on social theory of education [20,21]. However, few studies have assessed the education-smoking gradient with greater granularity [19] via assessing relationships with inflections points set at other attainment levels than these social milestones of education completion. In this study, we analyzed the education-smoking relationship using inflection points that are informed by the data. We examined secular trends in smoking behaviors (current smoking, ever smoking, and smoking cessation) over time by evaluating HRS respondents aged 50-56 over 30 years (interviews completed from 1992 to 2016).

Methods

Sample

Data came from the nationally representative United States Health and Retirement Survey (HRS) [22], a longitudinal sample of non-institutionalized Americans aged 50 and older, and their spouses. New cohorts of respondents were enrolled to HRS every 6 years including 1992, 1998, 2004, 2010, and 2016 to maintain a steady state population). To compare similar populations across the five cohorts and evaluate secular trends, we limited analysis to respondents aged 50 – 56 at enrollment (n = 18,929 eligible for analysis). We excluded respondents who were missing data on smoking outcomes (n = 2 excluded), had a sampling weight of zero (Excluded n = 771; a weight of zero is typically assigned to spouses who have not yet aged into eligibility, or to those who live in facilities), and those with missing data on covariates (n = 2 excluded; we used missing indicators to retain those with missing parents education and missing data on race / ethnicity, as detailed below); we retained n = 72 respondents who were missing data on the exposure, educational attainment, as detailed below. The resulting final analytic sample of n=18,154 (95.9% of the eligible sample) included n = 5,851 from the 1992 enrollment cohort, n = 2,013 from the 1998 enrollment cohort, n = 2,708 from 2004, n = 4,075 from 2010, and n = 3,507 from 2016 **[Table 3.1]**, which were used to assess the outcomes of ever-smokers and current smokers. Since the analytic sample for the smoking cessation outcome consisted of ever-smokers only, this second analytic sample was smaller, with total n = 10,568 (n = 3,717 from the 1992 enrollment cohort, n = 1,244 from the 1998 enrollment cohort, n = 1,483 from 2004, n = 2,328 from 2010, and n = 1,796 from 2016) **[Appendix Table 3.1]**.

Exposure

Years of education were self-reported (0 – 17+ years) in HRS. In our analytic sample, there were n = 642 persons with 0-5 years of education. Due to data sparseness, we collapsed education less than 5 years as 5 years to reduce the possibility that these outliers could bias estimates. Education level was also missing for 72 respondents. We assumed that those with missing education levels are among the most marginalized persons, and therefore coded them to have 5 years of education, the lowest educational category in our analysis. We also conducted sensitivity analyses of the impact of excluding these persons with missing education levels from the main analysis.

To determine how to best operationalize the relationship between years of education and smoking behaviors, we plotted the prevalence of smoking behaviors (ever smoking, current smoking, smoking cessation) for each year of education **[Appendix Figure 3.1]**. These graphs showed that the relationship between education and all three smoking behaviors was relatively flat before 11 years of schooling, followed by a linear decline after 11 years. We therefore modeled education as a linear spline with discontinuous knot at 11 years (i.e. a binary discontinuity indicator). This operationalization allowed for the relationship between years of education and smoking to be different between those with less than 11 years of education, compared to those with 11 or more (11+) years of education. We call this the "data-driven" operationalization of education, which we present in the main paper.

As a sensitivity analyses, we also repeated the entire analyses using a more traditional "theory driven" operationalization with a knot and discontinuity knot at 12 years of education, since a high school diploma is typically attained after 12 years of schooling.

Outcomes

Outcomes were ever smoking, current smoking and smoking cessation. Participants self-reported ever smoking as a yes response to "have you smoked more than 100 cigarettes?", and current smoking as a yes response to "Do you smoke cigarettes now?". From these two variables, we created a smoking cessation variable as *ever smokers who were not current smokers at the time of their interview*. The smoking-cessation outcome was only analyzed among N = 10,568 respondents who were ever smokers **[Appendix Table 3.1]**.

Covariates

All models were adjusted for gender (dichotomous, reference: male), race/ethnicity, maternal and paternal education level, place of birth, and birth year. The most socially advantaged groups were considered the reference in each categorical covariate.

Race/ethnicity was categorized as White (reference), Black, Latino, Other race/missing. Other race/missing was included to improve precision and include a more complete dataset, however, due to small numbers and ambiguous interpretation, results for the Other race/missing category are neither presented nor discussed.

Maternal and paternal education were both operationalized linearly, from 0-17 years [23]. We did not exclude parent's with missing education, as it is an important marker of childhood socioeconomic status (cSES), and prior work in the HRS cohort suggests that excluding people with missing cSES disproportionately excludes the most vulnerable and may bias estimates [23]. Missing maternal and paternal education values came from previous imputations when available (for the 1992, 1998 and 2004 entry cohorts), and were otherwise modeled with a missing indicator when imputation were not available (for the 2010 and 2016 entry cohorts; for missing mothers education, n = 689 values were modeled with a missing indicator; for missing father's education, n = 1547 values were modeled with a missing indicator). In analytic models, mothers' and father's education was a linear term with a missing indicator for the years when imputations were not available (2010 and 2016 HRS cohorts). In sensitivity analyses, we evaluated if treating parental education the same way across cohorts (using missing indicator for all, without imputations) impacted estimates.

Place of birth was categorized as born in Non-Southern United States [24], born in Southern United States, and born outside of United States (immigrants). Southern United States was defined as South Atlantic (WV, MD, DE, DC, VA, NC, SC, GA, FL), East South Central (KY, TN, MS, AL), and West South Central (TX, OK, AR, LA).

Analysis

We estimated five separate sets of logistic regression models for each entry cohort (1992, 1998, 2004, 2010, 2016), using sampling weights for that cohort (e.g. the 1992 HRS sampling weights were applied to the 1992 entry cohort). Within each entry cohort, we used the operationalizations of the exposure and covariates described above to predict our three smoking outcomes (ever smoking, current smoking, smoking cessation).

Additionally, to empirically evaluate changes in secular trends in the relationship between educational attainment and smoking over time, we fit an unweighted, pooled logistic regression model that included persons from all five birth cohorts. We included interactions terms between education (3 variables to model the spline) and entry cohort indicators. Statistical significance of the interaction terms indicated meaningful changes in secular trends in the relationship between education and smoking over time. We evaluated secular trends in this manner for each of our three smoking outcomes. To better evaluate the secular trends across cohorts, we assessed whether the estimates achieved by each cohort were statistically different from one another (performed separately for each of the three outcomes). Since each HRS cohort consisted of a 6 year span, we also adjusted for birthyear as a covariate, to account for variability in age within each HRS cohort. However, we also conducted a sensitivity analysis of including birthyear vs. not including birthyear in the analysis.

All data cleaning and analyses were performed in Stata 17. These analyses were considered exempt by the University of California, San Francisco International Review Board. Survey weights were applied using the *svy* command suite in Stata so that each cohort was nationally representative of the US population aged 50 – 56 at its enrollment time. All data cleaning and analysis code was written by the first author, and reviewed by the second author [25].

Results

In each HRS entry cohort, the higher education group (with 11 or more years of schooling) was more advantaged: their parents had more education, there was a high proportion of White respondents, a higher proportion were born outside the South, and there was less missing data on parent's education (for the 2010 and 2016 cohorts) **[Table 3.1] [Appendix Table 3.1]**.

Table 3.1: Demographics of final HRS sample.

Table 1. Demographics of Final HRS Analytic Sample.

	HRS Cohort																			
	1992 HRS Cohort (n = 5,851) Education Category				1998 HRS Cohort (n = 2,013) Education Category				2004 HRS Cohort (n = 2,708) Education Category				2010 HRS Cohort (n = 4,075) Education Category				2016 HRS Cohort (n = 3,507) Education Category			
	< 11 years of education		11 or more years of education		< 11 years of education		11 or more years of education		< 11 years of education		11 or more years of education		< 11 years of education		11 or more years of education		< 11 years of education		11 or more years of education	
	Count / Mean	% / (SD)	Count / Mean	% / (SD)	Count / Mean	% / (SD)	Count / Mean	% / (SD)	Count / Mean	% / (SD)	Count / Mean	% / (SD)	Count / Mean	% / (SD)	Count / Mean	% / (SD)	Count / Mean	% / (SD)	Count / Mean	% / (SD)
Year of Birth	1938	(1.8)	1938	(1.8)	1944	(1.7)	1945	(1.7)	1951	(1.6)	1951	(1.7)	1957	(1.7)	1957	(1.7)	1963	(1.6)	1963	(1.6)
Total Education (Years)	8.6	(2.1)	13.6	(1.9)	8.8	(2.0)	14.0	(2.0)	8.0	(2.3)	14.2	(1.9)	8.2	(2.4)	14.0	(1.8)	8.5	(2.3)	14.1	(1.9)
Maternal Education (Years)	6.9	(3.6)	10.1	(3.1)	6.8	(4.1)	10.9	(3.1)	6.5	(4.5)	11.1	(3.3)	5.5	(5.1)	10.4	(4.4)	6.4	(5.1)	10.6	(4.5)
Maternal Education Missingness																				
Missing	0	0	0	0	0	0	0	0	0	0	0	0	159	19.89987	217	6.623932	106	17.37705	207	7.145323
Paternal Education (Years)	6.6	(3.6)	9.8	(3.6)	6.3	(3.9)	10.4	(3.5)	6.4	(4.2)	10.7	(3.6)	4.0	(5.0)	9.4	(5.4)	4.6	(5.1)	9.3	(5.7)
Paternal Education Missingness																				
Missing	0	0	0	0	0	0	0	0	0	0	0	0	291	36.42053	526	16.05617	199	32.62295	531	18.32931
Smoking History																				
Never Smoker	489	31.28599	1645	38.36287	100	30.67485	669	39.65619	139	34.15233	1086	47.19687	303	37.9224	1444	44.07814	194	31.80328	1517	52.36452
Ever Smoker	485	31.03007	1541	35.9375	98	30.06135	638	37.81861	120	29.48403	730	31.72534	208	26.03254	1063	32.44811	161	26.39344	749	25.85433
Current Smoker	589	37.68394	1102	25.69963	128	39.2638	380	22.52519	148	36.36364	485	21.07779	288	36.04506	769	23.47375	255	41.80328	631	21.78115
Race / Ethnicity																				
Caucasian	784	50.15995	3368	78.54478	150	46.01227	1346	79.7866	115	28.25553	1618	70.31725	159	19.89987	1733	52.89988	157	25.7377	1237	42.69934
African American	381	24.3762	619	14.43563	91	27.91411	223	13.21873	82	20.14742	389	16.90569	223	27.90989	955	29.1514	153	25.08197	825	28.47774
Latinx	288	18.4261	170	3.964552	48	14.72393	58	3.438056	97	23.83292	97	4.215558	184	23.02879	217	6.623932	108	17.70492	230	7.939247
Other / missing	110	7.037748	131	3.055037	37	11.34969	60	3.556609	113	27.76413	197	8.561495	233	29.16145	371	11.32479	192	31.47541	605	20.88367
Birth Place																				
Non-Southern USA	493	31.54191	2483	57.90578	79	24.23313	1035	61.35151	126	30.95823	1477	64.18948	218	27.28411	1632	49.81685	215	35.2459	1567	54.09044
Southern USA	776	49.64811	1490	34.74813	187	57.36196	567	33.60996	128	31.44963	600	26.07562	243	30.41302	1179	35.98901	165	27.04918	862	29.75492
Immigrant	294	18.80998	315	7.346082	60	18.40491	85	5.03853	153	37.59214	224	9.734898	338	42.30288	465	14.19414	230	37.70492	468	16.15464
Gender																				
Female	858	54.89443	2260	52.70522	156	47.85276	787	46.65086	196	48.15725	1128	49.02216	411	51.4393	1722	52.5641	299	49.01639	1547	53.40007

Among those with less than 11 years of education, we found each additional year of education was associated with higher odds of ever smoking in the 2004, 2010 and 2016 cohorts (e.g. OR for 2016 cohort ever smoking: 1.17, 95% CI 1.03-1.33) **[Figure 3.1; Appendix Table 3.2]**. Similarly, each additional year of education under 11 years was associated with higher odds of being a current smoker in the 2010 and 2016 cohorts (Figure 2A), and lower odds of smoking cessation in the 2016 cohort (Figure 3A). However, in all five cohorts, among those with 11+ years of education, each additional year of education was associated with lower odds of ever smoking (OR for 1992 cohort: 0.90, 95% CI 0.87-0.94) **[Figure 3.1]**, current smoking (OR for 1992 cohort: 0.84, 95% CI 0.81-0.87) **[Figure 3.3]**, and higher odds of smoking cessation among ever smokers (OR for 1992 cohort: 1.18, 95% CI 1.13-1.23) **[Figure 3.5]**. Statistically significant spline knot discontinuity (at 11 years of education) was consistently observed across cohorts with ever-smoking (OR for 2016 cohort: 0.28, 95% CI: 0.16 – 0.49) **[Figure 3.2; Appendix Table 3.2]**, however, was not consistent for current smoking and smoking cessation outcomes **[Figure 3.4, Figure 3.6 ; Appendix Table 3.3, Appendix Table 3.4]**.

In our analysis for secular trends, among those with 11+ years of education, the magnitude of the protective estimate for each additional year of education for ever smoking increased across cohorts (1992 vs. 2004 cohort: p<0.0001 ; 1998 vs 2004 cohort: p=0.0019 **[Appendix Table 3.5])**, with the OR of 0.90 (95% CI 0.87-0.94) in the 1992 cohort to an OR of 0.79 (95% CI 0.74-0.83) in the 2004 cohort, and stabilizing from 2010 onwards at OR 0.78 (95% CI 0.73-0.83) **[Figure 3.1 ; Appendix Table 3.2]**. There was a similar but weaker secular trend for current-smoking, (1992 vs. 2010 cohorts, p<0.0001 **[Appendix Table 3.6]**) with OR of 0.84 (95% CI 0.81-0.87) in 1992 cohort, and OR of 0.74 (95% CI 0.70-0.78) in the 2010 cohort **[Figure 3.3, Appendix Table 3.3]**. No Statistically significant secular trends were observed in the relationship between increased education attainment and smoking cessation **[Appendix Table 3.7]**.

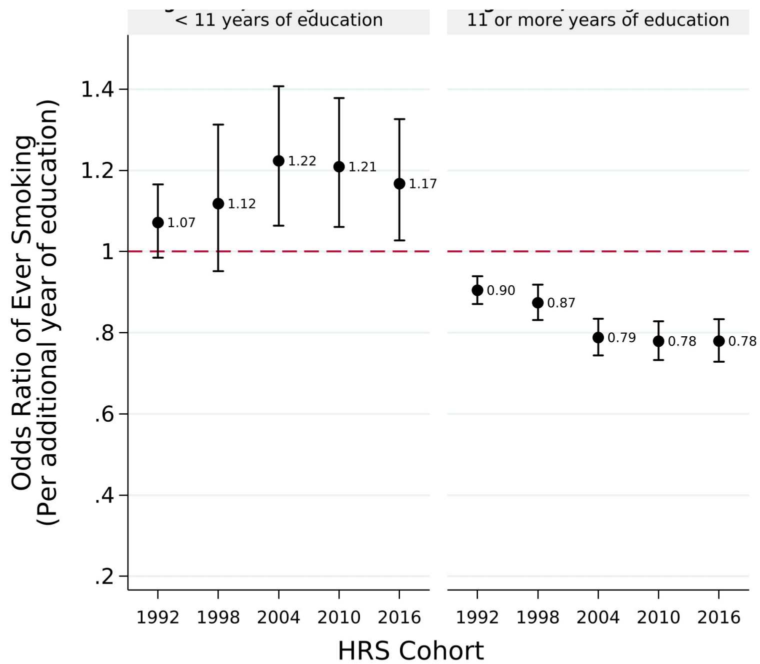

Figure 3.1: Eversmoking outcome

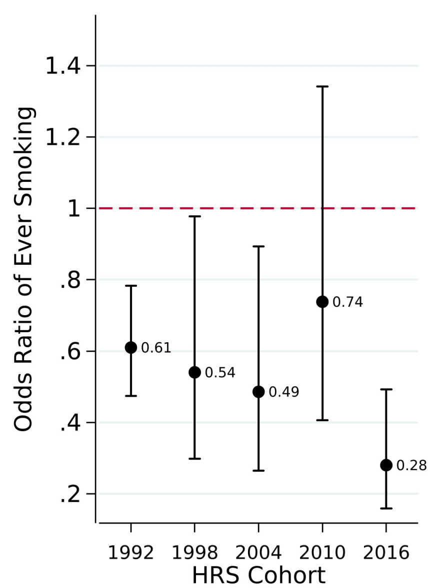

Figure 3.2: Eversmoker outcome discontinuity.

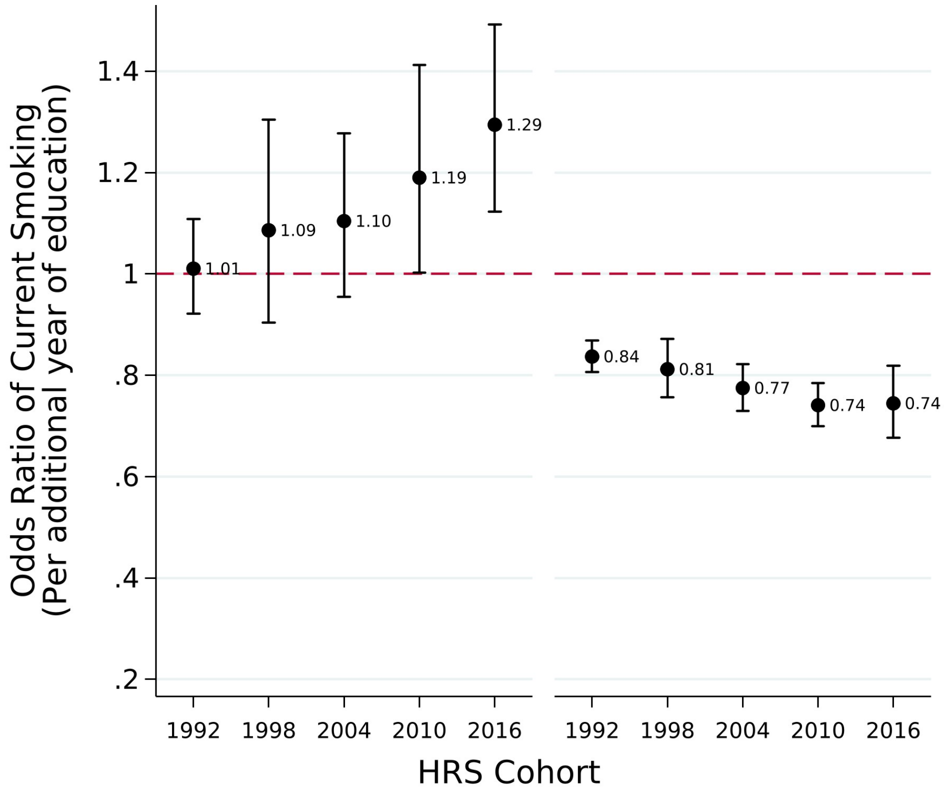

Figure 3.3: Current smoking outcome

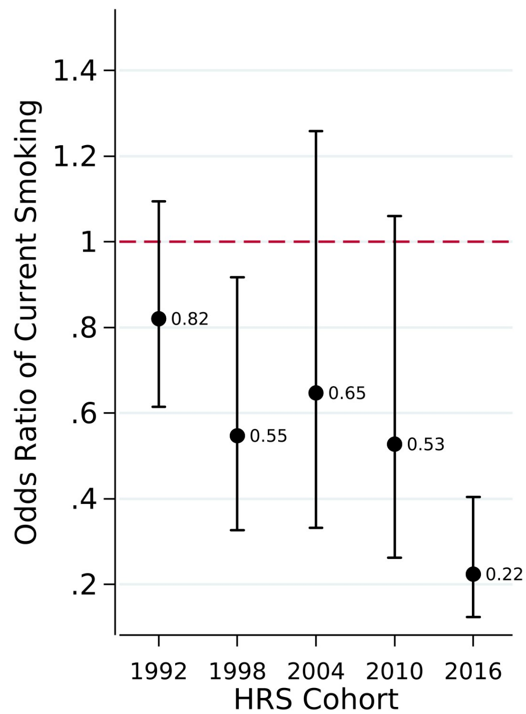

Figure 3.4: Current smoking outcome discontinuity.

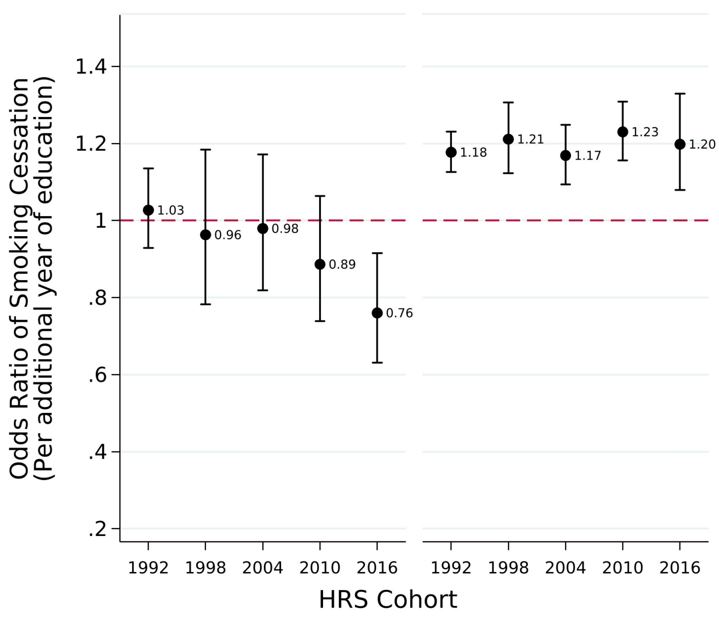

Figure 3.5: Smoking cessation outcome.

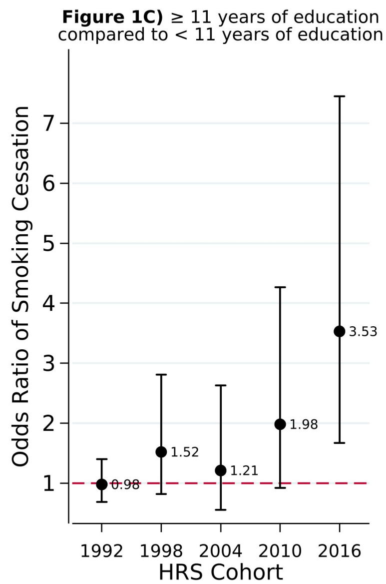

Figure 3.6: Smoking cessation outcome discontinuity.

Robustness checks

As a robustness check, we repeated these analyses using the "theory driven approach" to specify the spline (that is, with a knot at 12 years of education rather than 11 years). Although point estimates and precisions differed very slightly **[Appendix Tables 3.8, 3.9, 3.10]**, the results were substantively similar, and our main findings and conclusions were unchanged. Sensitivity analyses that excluding the 72 persons with missing education level **[Appendix Table 3.11, 3.12, 3.13]**, using non-imputed maternal/paternal education levels **[Appendix Table 3.14, 3.15, 3.16]**, or not including birthyear in analyses **[Appendix Table 3.17, 3.18, 3.19]**, demonstrated no difference in our results.

Discussion

In this nationally representative sample of adults 50-56 years old from 1992-2016 (born between 1936-1966), we found a deleterious relationship between each additional year of education and being an ever smoker for those with less than 11 years of education; however, for those with 11 or more (11+) years of education, each additional year of education predicted lower odds of ever smoking and current smoking, and was associated with higher odds of smoking cessation among ever smokers. We additionally found the protective relationship between education and smoking, for those with 11(+) years of schooling, got stronger for those aged 50-56 years in the 1992-2004 cohorts, and then stabilized in peers of the same age in the subsequent cohorts.

Our findings that additional education after 11 years predicts better smoking behaviors is supported by previous literature finding that more education predicts lower smoking prevalence [8–10], shortened smoking duration [11–13], lowered odds of ever or current smoking [26], and more quit attempts [21,27,28]. However, we also found a less expected deleterious relationship between each additional year of education and being an ever smoker smoking among those with less than 11 years of education, emphasizing the importance of a more nuanced approach to operationalizing education to assess education-smoking relationships. Although not consistently statistically significant, results also trended towards a similar relationship among those with <11 years of education, with the current smoking outcome. This unexpected finding supports an earlier finding using a different nationally representative data (sampled 1978-1988) showing that smoking prevalence decreased across generations among those with a high school or more education, but not in those with less than a high school education [20]. Another nationally representative cross-sectional study (using the 1983 to 1991 National Health Interview Survey (NHIS) samples) also recommended operationalizing education as categories of 0-8, 9-11, 11, 12, 13-15, and 16 or more years of education [19]. These reports along with our findings suggest that the traditional operationalization of education as monotonic and linear (i.e. 0 to 17+), or simple binary categories of <high school vs. high school or greater, masks more granular but significant heterogeneities in the education-smoking gradient.

This surprising deleterious education-smoking relationship, where additional years of education years was associated with higher odds of being an ever smoker in some cohorts among those with less than 11 years of education, may be due to multitude of reasons. Firstly, this may represent an increase in the opportunity to smoke at social gatherings facilitated via high school relationships made up to 11 years of education. Since HRS interviewers defined study participants as an “ever smoker” if they had smoked “more than 100 cigarettes”, a portion of this group may be those who were occasional social smokers and not necessary long-term smokers. In our analysis, this may be supported by the null relationship between more education and being a current smoker among the same group of those with <11 years of education. More research is needed to see if these results are robust to different operationalizations of ever smoking and are true in other populations.

Our findings of a secular trend in the magnitude of the relationship between education and smoking showed that these relationships became stronger across successive birth cohorts from 1992 to 2010, then stabilized. This adds important farther nuance to the wider literature on secular trends in smoking. Prior work has noted cross-generational secular trends of decreased smoking uptake [8,29], decreased prevalence [30], and increased cessation [9] within the United States. Secular trends in specifically the education-smoking gradient have also been noted. For instance, generational decrease in current smoking prevalence from 1965-1991 was greater among those with more education [8], with the largest percentage change being among those with 16 or more years of education. An increase in magnitude of education-smoking relationship was also seen more recently using in the NHIS Adult Sample of 2010 [31]. However, while we saw a similar secular trend in the education-smoking relationship, we also found that the secular trends stabilized in adults experiencing middle-age in 2010 and forward. Understanding the reasons for this stagnation in further strengthening of the protective education-smoking gradient will help continual efforts to tame the smoking epidemic.

There are limitations with our approach and available data that should be acknowledged. First, although we adjusted for a range of demographic covariates, residual confounding is still possible in this observational study; for this reason, we consider these analyses associational. Second, almost all variables were a result of self-report, leaving possible measurement bias. Lastly, while there were relatively fewer persons with <11 years compared to 11(+) years of education, using sampling weights should again have resulted in a representative analysis of the United States, therefore this may not be a limitation.

Since HRS data are nationally representative of older adults in the United states, our findings cannot generalize to younger populations. In particular, future analyses should evaluate secular trends in current youth who have dramatically different smoking behaviors due to the well-documented rise in use of e-cigarettes [32,33] and the legalization of cannabis in many jurisdictions within the US [34], all of which may lower barriers to smoking cigarettes.

Conclusion

In this analysis of middle-aged adults born from 1992-2016, we found that among those with 11(+) years of education, each additional year of education was associated with decreased odds of ever smoking and current smoking, and increased odds of smoking cessation among ever-smokers. We also found the protective relationship between increasing education and smoking behaviors became stronger across successive HRS cohorts from 1992-2010, but was stable for those experiencing middle ages afterwards. Among those with less than 11 years of education, we found a surprising increase in the odds of being an ever smoker associated with each additional year of education, only among those experiencing middle-ages between 2004-2016. Our results suggest the relationship between years of education and smoking is more nuanced than previously believed. More research is needed to determine if these findings are robust to changes in place and population.

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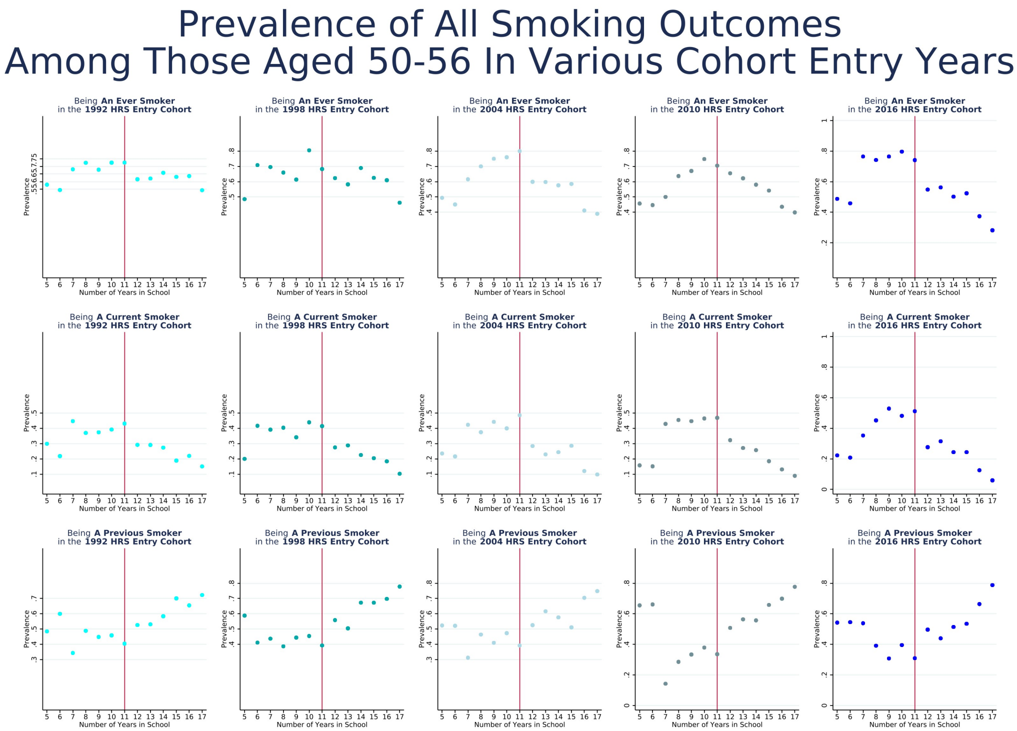
Appendices



Appendix Figure 3.1: Proportion of current smokers, ever smoker, and not currently smoking ever-smokers, across cohorts by years of education attained.

Appendix Table 3.1: Demographics of the ever-smoker subsample.

Appendix Table 1. Demographics of the ever-smoker subsample.

	1992 HRS Cohort (n = 3,717) Education Category				1998 HRS Cohort (n = 1,244) Education Category				HRS Cohort 2004 HRS Cohort (n = 1,483) Education Category				2010 HRS Cohort (n = 2,328) Education Category				2016 HRS Cohort (n = 1,796) Education Category			
	< 11 years of education		11 or more years of education		< 11 years of education		11 or more years of education		< 11 years of education		11 or more years of education		< 11 years of education		11 or more years of education		< 11 years of education		11 or more years of education	
	Count / Mean	% / (SD)	Count / Mean	% / (SD)	Count / Mean	% / (SD)	Count / Mean	% / (SD)	Count / Mean	% / (SD)	Count / Mean	% / (SD)	Count / Mean	% / (SD)	Count / Mean	% / (SD)	Count / Mean	% / (SD)	Count / Mean	% / (SD)
Year of Birth	1938	(1.8)	1938	(1.8)	1944	(1.6)	1945	(1.7)	1951	(1.6)	1951	(1.7)	1957	(1.7)	1957	(1.7)	1962	(1.6)	1963	(1.6)
Total Education (Years)	8.8	(2.0)	13.5	(1.9)	9.0	(1.9)	13.8	(1.9)	8.4	(2.2)	13.9	(1.8)	8.6	(2.3)	13.7	(1.8)	8.8	(2.1)	13.7	(1.7)
Maternal Education (Years)	7.2	(3.5)	10.2	(3.1)	7.0	(3.9)	11.0	(3.0)	7.2	(4.4)	11.0	(3.1)	6.2	(5.2)	10.3	(4.4)	7.2	(5.1)	10.7	(4.4)
Maternal Education Missingness																				
Missing	0	0	0	0	0	0	0	0	0	0	0	0	100	20.16129	141	7.696507	71	17.06731	111	8.043478
Paternal Education (Years)	6.8	(3.5)	9.9	(3.6)	6.4	(3.8)	10.4	(3.6)	6.9	(4.2)	10.6	(3.4)	4.4	(5.2)	9.0	(5.5)	5.0	(5.2)	9.0	(5.8)
Paternal Education Missingness																				
Missing	0	0	0	0	0	0	0	0	0	0	0	0	186	37.5	326	17.79476	142	34.13462	294	21.30435
Smoking Cessation																				
Currently Smoking	589	54.84171	1102	41.69504	128	56.63717	380	37.32809	148	55.22388	485	39.9177	288	58.06452	769	41.97598	255	61.29808	631	45.72464
Stopped Smoking	485	45.15829	1541	58.30496	98	43.36283	638	62.67191	120	44.77612	730	60.0823	208	41.93548	1063	58.02402	161	38.70192	749	54.27536
Race / Ethnicity																				
Caucasian	596	55.49348	2113	79.94703	110	48.67257	817	80.2554	97	36.19403	854	70.28807	117	23.58871	970	52.9476	134	32.21154	632	45.7971
African American	248	23.09125	372	14.07491	68	30.0885	137	13.45776	59	22.01493	209	17.20165	167	33.66935	548	29.91266	112	26.92308	362	26.23188
Latinx	159	14.80447	89	3.367386	23	10.17699	27	2.652259	47	17.53731	49	4.032922	90	18.14516	119	6.495633	57	13.70192	92	6.666667
Other / missing	71	6.610801	69	2.61067	25	11.06195	37	3.634578	65	24.25373	103	8.477366	122	24.59677	195	10.6441	113	27.16346	294	21.30435
Birth Place																				
Non-Southern USA	382	35.56797	1607	60.80212	54	23.89381	643	63.16306	98	36.56716	793	65.26749	172	34.67742	953	52.01965	182	43.75	799	57.89855
Southern USA	550	51.21043	870	32.91714	143	63.27434	334	32.80943	97	36.19403	330	27.16049	178	35.8871	653	35.6441	129	31.00962	412	29.85507
Immigrant	142	13.2216	166	6.280742	29	12.83186	41	4.027505	73	27.23881	92	7.572016	146	29.43548	226	12.33624	105	25.24038	169	12.24638
Gender																				
Female	497	46.27561	1194	45.17594	90	39.82301	424	41.65029	97	36.19403	509	41.893	220	44.35484	926	50.54585	186	44.71154	736	53.33333

Appendix Table 3.2: Complete primary analysis results, with spline knot at 11 years of education. Outcome: Ever smoking status, among those 50-56 years of age at cohort entry.

	1992 HRS Cohort (n = 5,851)	1998 HRS Cohort (n = 2,013)	2004 HRS Cohort (n = 2,708)	2010 HRS Cohort (n = 4,075)	2016 HRS Cohort (n = 3,507)
Intercept	4.93***	4.59***	14.67***	3.90**	16.20***
	(3.59 - 6.78)	(2.03 - 10.39)	(6.07 - 35.44)	(1.31 - 11.64)	(3.35 - 78.34)
Discontinuity Indicator (at 11 years of education)					
11 or more years of education	0.61***	0.54**	0.49**	0.74	0.28***
	(0.47 - 0.78)	(0.30 - 0.98)	(0.26 - 0.89)	(0.41 - 1.34)	(0.16 - 0.49)
Low-education (0-10 years)	1.07	1.12	1.22***	1.21***	1.17**
	(0.99 - 1.17)	(0.95 - 1.31)	(1.06 - 1.41)	(1.06 - 1.38)	(1.03 - 1.33)
High-education (11-17 years)	0.90***	0.87***	0.79***	0.78***	0.78***
	(0.87 - 0.94)	(0.83 - 0.92)	(0.74 - 0.83)	(0.73 - 0.83)	(0.73 - 0.83)
Gender					
Female	0.40***	0.52***	0.45***	0.97	0.99
	(0.36 - 0.45)	(0.40 - 0.66)	(0.39 - 0.52)	(0.80 - 1.17)	(0.82 - 1.19)
Race / Ethnicity					
African American	0.97	1.25	0.88	1.08	0.80
	(0.78 - 1.19)	(0.90 - 1.74)	(0.66 - 1.16)	(0.85 - 1.37)	(0.59 - 1.09)
Latinx	0.79*	0.66	0.90	1.17	0.92
	(0.63 - 1.00)	(0.36 - 1.21)	(0.57 - 1.42)	(0.87 - 1.57)	(0.60 - 1.42)
Other / missing	0.88	1.29	1.18	0.89	1.33*
	(0.61 - 1.26)	(0.79 - 2.10)	(0.86 - 1.63)	(0.61 - 1.30)	(0.98 - 1.79)
Birth Place					
Southern USA	0.84*	0.93	1.12	0.94	0.90
	(0.69 - 1.01)	(0.71 - 1.21)	(0.90 - 1.40)	(0.79 - 1.13)	(0.71 - 1.14)
Immigrant	0.62***	0.64	0.55***	0.78	0.50***
	(0.48 - 0.78)	(0.37 - 1.12)	(0.36 - 0.82)	(0.57 - 1.06)	(0.36 - 0.70)
Birth Year	1.00	0.97	0.94**	0.99	0.94*
	(0.97 - 1.03)	(0.92 - 1.03)	(0.89 - 0.99)	(0.95 - 1.04)	(0.88 - 1.01)
Maternal Education (Years)	1.02**	1.03	1.01	1.01	1.04
	(1.00 - 1.05)	(0.99 - 1.07)	(0.98 - 1.05)	(0.98 - 1.05)	(0.99 - 1.09)
Maternal Education Missingness					
Missing				1.45	1.10
				(0.84 - 2.49)	(0.54 - 2.25)
Paternal Education (Years)	1.00	1.01	0.99	1.00	1.01
	(0.98 - 1.03)	(0.97 - 1.05)	(0.96 - 1.02)	(0.97 - 1.04)	(0.97 - 1.05)
Paternal Education Missingness					
Missing				1.02	1.93***
				(0.69 - 1.52)	(1.24 - 3.01)

*** p<.01, ** p<.05, * p<.1

Appendix Table 3.3: Complete primary analysis results, with spline knot at 11 years of education. Outcome: Current smoking status, among those 50-56 years of age at cohort entry

	1992 HRS Cohort (n = 5,851)	1998 HRS Cohort (n = 2,013)	2004 HRS Cohort (n = 2,708)	2010 HRS Cohort (n = 4,075)	2016 HRS Cohort (n = 3,507)
Intercept	0.83	1.00	1.50	0.86	0.93
	(0.57 - 1.21)	(0.48 - 2.09)	(0.49 - 4.55)	(0.17 - 4.39)	(0.08 - 11.51)
Discontinuity Indicator (at 11 years of education)					
11 or more years of education	0.82	0.55**	0.65	0.53*	0.22***
	(0.61 - 1.09)	(0.33 - 0.92)	(0.33 - 1.26)	(0.26 - 1.06)	(0.12 - 0.40)
Low-education (0-10 years)	1.01	1.09	1.10	1.19**	1.29***
	(0.92 - 1.11)	(0.90 - 1.30)	(0.95 - 1.28)	(1.00 - 1.41)	(1.12 - 1.49)
High-education (11-17 years)	0.84***	0.81***	0.77***	0.74***	0.74***
	(0.81 - 0.87)	(0.76 - 0.87)	(0.73 - 0.82)	(0.70 - 0.78)	(0.68 - 0.82)
Gender					
Female	0.80***	0.86	0.62***	0.93	0.94
	(0.71 - 0.90)	(0.70 - 1.05)	(0.49 - 0.77)	(0.77 - 1.12)	(0.72 - 1.23)
Race / Ethnicity					
African American	1.03	1.62***	1.19	1.21	1.11
	(0.86 - 1.24)	(1.15 - 2.28)	(0.85 - 1.67)	(0.95 - 1.55)	(0.79 - 1.55)
Latinx	0.86	0.60*	0.79	0.89	0.88
	(0.61 - 1.22)	(0.36 - 1.00)	(0.52 - 1.18)	(0.55 - 1.41)	(0.46 - 1.67)
Other / missing	1.09	0.88	1.28	0.94	1.04
	(0.78 - 1.53)	(0.51 - 1.51)	(0.78 - 2.09)	(0.54 - 1.63)	(0.76 - 1.44)
Birth Place					
Southern USA	1.03	0.78	1.26*	0.95	1.00
	(0.85 - 1.25)	(0.57 - 1.06)	(0.96 - 1.65)	(0.78 - 1.15)	(0.76 - 1.31)
Immigrant	0.57***	0.76	0.56**	0.35***	0.40***
	(0.40 - 0.80)	(0.42 - 1.37)	(0.35 - 0.88)	(0.22 - 0.58)	(0.24 - 0.68)
Birth Year	1.06***	0.98	0.97	1.05	1.02
	(1.02 - 1.09)	(0.92 - 1.04)	(0.90 - 1.05)	(0.99 - 1.12)	(0.92 - 1.14)
Maternal Education (Years)	1.01	1.01	1.02	0.99	1.04
	(0.98 - 1.04)	(0.96 - 1.06)	(0.98 - 1.06)	(0.95 - 1.03)	(0.99 - 1.10)
Maternal Education Missingness					
Missing				0.85	1.30
				(0.44 - 1.63)	(0.65 - 2.58)
Paternal Education (Years)	0.99	1.01	0.97	0.97	1.00
	(0.97 - 1.01)	(0.97 - 1.06)	(0.95 - 1.01)	(0.93 - 1.02)	(0.95 - 1.04)
Paternal Education Missingness					
Missing				0.87	1.72**
				(0.52 - 1.47)	(1.04 - 2.85)

*** p<.01, ** p<.05, * p<.1

Appendix Table 3.4: Complete primary analysis results, with spline knot at 11 years of education. Outcome: Smoking cessation, among those 50-56 years of age at cohort entry.

	1992 HRS Cohort (n = 3,717)	1998 HRS Cohort (n = 1,244)	2004 HRS Cohort (n = 1,483)	2010 HRS Cohort (n = 2,328)	2016 HRS Cohort (n = 1,796)
Intercept	0.88 (0.57 - 1.34)	0.72 (0.32 - 1.64)	0.82 (0.24 - 2.84)	0.73 (0.14 - 3.97)	2.74 (0.14 - 53.15)
Discontinuity Indicator (at 11 years of education)					
11 or more years of education	0.98 (0.69 - 1.40)	1.52 (0.82 - 2.81)	1.21 (0.56 - 2.63)	1.98* (0.92 - 4.27)	3.53*** (1.67 - 7.45)
Low-education (0-10 years)	1.03 (0.93 - 1.14)	0.96 (0.78 - 1.18)	0.98 (0.82 - 1.17)	0.89 (0.74 - 1.06)	0.76*** (0.63 - 0.91)
High-education (11-17 years)	1.18*** (1.13 - 1.23)	1.21*** (1.12 - 1.31)	1.17*** (1.09 - 1.25)	1.23*** (1.16 - 1.31)	1.20*** (1.08 - 1.33)
Gender					
Female	0.74*** (0.65 - 0.84)	0.78** (0.62 - 0.99)	1.00 (0.76 - 1.32)	1.04 (0.86 - 1.28)	1.10 (0.79 - 1.55)
Race / Ethnicity					
African American	0.93 (0.73 - 1.17)	0.60** (0.40 - 0.89)	0.72* (0.51 - 1.03)	0.79 (0.59 - 1.06)	0.68* (0.44 - 1.05)
Latinx	1.07 (0.76 - 1.51)	1.36 (0.68 - 2.74)	1.24 (0.78 - 1.98)	1.37 (0.78 - 2.41)	1.11 (0.49 - 2.52)
Other / missing	0.89 (0.62 - 1.29)	1.41 (0.73 - 2.72)	0.81 (0.47 - 1.39)	1.03 (0.56 - 1.87)	1.12 (0.76 - 1.65)
Birth Place					
Southern USA	0.85 (0.69 - 1.05)	1.32 (0.94 - 1.85)	0.79 (0.58 - 1.08)	0.98 (0.79 - 1.23)	0.95 (0.67 - 1.34)
Immigrant	1.35 (0.91 - 2.00)	0.94 (0.52 - 1.72)	1.31 (0.79 - 2.18)	2.60*** (1.46 - 4.64)	1.66* (0.98 - 2.82)
Birth Year	0.93*** (0.89 - 0.97)	1.00 (0.94 - 1.07)	0.99 (0.92 - 1.08)	0.93* (0.87 - 1.00)	0.91 (0.80 - 1.03)
Maternal Education (Years)	1.00 (0.97 - 1.04)	1.00 (0.95 - 1.06)	0.99 (0.95 - 1.03)	1.02 (0.97 - 1.07)	0.98 (0.91 - 1.05)
Maternal Education Missingness					
Missing				1.60 (0.77 - 3.32)	0.73 (0.31 - 1.70)
Paternal Education (Years)	1.01 (0.99 - 1.03)	0.99 (0.94 - 1.03)	1.03 (0.99 - 1.07)	1.03 (0.98 - 1.07)	1.00 (0.94 - 1.07)
Paternal Education Missingness					
Missing				1.17 (0.71 - 1.92)	0.73 (0.36 - 1.49)

*** p<.01, ** p<.05, * p<.1

Appendix Table 3.5: P-values showing statistical difference in the effect of increasing education on each smoking outcome, when comparing each HRS cohort to all others. Outcome: Eversmoking

.	1992 HRS Cohort	1998 HRS Cohort	2004 HRS Cohort	2010 HRS Cohort	2016 HRS Cohort
1992 HRS Cohort	.	0.0934	0.0000	0.0000	0.0000
1998 HRS Cohort	.	.	0.0019	0.0015	0.0006
2004 HRS Cohort	.	.	.	0.8749	0.8584
2010 HRS Cohort	.	.	.	.	0.7165
2016 HRS Cohort	.	.	.	.	.

Appendix Table 3.6: P-values showing statistical difference in the effect of increasing education on each smoking outcome, when comparing each HRS cohort to all others. Outcome: Current smoking

.	1992 HRS Cohort	1998 HRS Cohort	2004 HRS Cohort	2010 HRS Cohort	2016 HRS Cohort
1992 HRS Cohort	.	0.2118	0.0067	0.0000	0.0000
1998 HRS Cohort	.	.	0.2666	0.0421	0.0253
2004 HRS Cohort	.	.	.	0.3736	0.2539
2010 HRS Cohort	.	.	.	.	0.7566
2016 HRS Cohort	.	.	.	.	.

Appendix Table 3.7: P-values showing statistical difference in the effect of increasing education on each smoking outcome, when comparing each HRS cohort to all others. Outcome: Smoking cessation

.	1992 HRS Cohort	1998 HRS Cohort	2004 HRS Cohort	2010 HRS Cohort	2016 HRS Cohort
1992 HRS Cohort	.	0.4413	0.8375	0.0717	0.2114
1998 HRS Cohort	.	.	0.6216	0.4927	0.7472
2004 HRS Cohort	.	.	.	0.2010	0.3870
2010 HRS Cohort	.	.	.	.	0.7049
2016 HRS Cohort	.	.	.	.	.

Appendix Table 3.8: Complete secondary analysis results, with the spline knot at 12 years of education. Outcome: Eversmoking

	1992 HRS Cohort (n = 5,851)	1998 HRS Cohort (n = 2,013)	2004 HRS Cohort (n = 2,708)	2010 HRS Cohort (n = 4,075)	2016 HRS Cohort (n = 3,507)
Intercept	5.13***	3.53***	15.95***	3.54**	10.24***
	(3.71 - 7.09)	(1.74 - 7.18)	(7.47 - 34.06)	(1.21 - 10.34)	(1.99 - 52.69)
Discontinuity Indicator (at 12 years of education)					
12 or more years of education	0.50***	0.61*	0.34***	0.64*	0.32***
	(0.37 - 0.68)	(0.37 - 1.01)	(0.19 - 0.60)	(0.39 - 1.04)	(0.19 - 0.55)
Low-education (0-11 years)	1.06	1.04	1.20***	1.15***	1.05
	(0.99 - 1.14)	(0.92 - 1.17)	(1.08 - 1.33)	(1.05 - 1.26)	(0.94 - 1.17)
High-education (12-17 years)	0.92***	0.87***	0.79***	0.78***	0.79***
	(0.88 - 0.96)	(0.83 - 0.92)	(0.75 - 0.84)	(0.73 - 0.83)	(0.74 - 0.85)
Gender					
Female	0.40***	0.51***	0.45***	0.97	0.98
	(0.36 - 0.44)	(0.40 - 0.65)	(0.39 - 0.53)	(0.80 - 1.17)	(0.82 - 1.18)
Race / Ethnicity					
African American	0.94	1.23	0.87	1.08	0.79
	(0.76 - 1.17)	(0.89 - 1.70)	(0.67 - 1.14)	(0.85 - 1.37)	(0.58 - 1.07)
Latinx	0.78**	0.65	0.89	1.17	0.92
	(0.62 - 0.99)	(0.35 - 1.20)	(0.56 - 1.41)	(0.87 - 1.57)	(0.59 - 1.42)
Other / missing	0.86	1.31	1.17	0.89	1.32*
	(0.60 - 1.23)	(0.81 - 2.13)	(0.84 - 1.62)	(0.62 - 1.30)	(0.98 - 1.79)
Birth Place					
Southern USA	0.83*	0.94	1.12	0.95	0.90
	(0.69 - 1.00)	(0.71 - 1.22)	(0.90 - 1.40)	(0.79 - 1.13)	(0.71 - 1.14)
Immigrant	0.61***	0.64	0.55***	0.77*	0.49***
	(0.48 - 0.78)	(0.37 - 1.10)	(0.36 - 0.83)	(0.57 - 1.05)	(0.35 - 0.68)
Birth Year	1.00	0.97	0.94**	0.99	0.94
	(0.97 - 1.03)	(0.92 - 1.03)	(0.89 - 0.99)	(0.95 - 1.04)	(0.88 - 1.01)
Maternal Education (Years)	1.03**	1.03	1.01	1.01	1.03
	(1.00 - 1.05)	(0.99 - 1.07)	(0.98 - 1.05)	(0.98 - 1.05)	(0.98 - 1.09)
Maternal Education Missingness					
Missing				1.45	1.04
				(0.84 - 2.52)	(0.50 - 2.19)
Paternal Education (Years)	1.00	1.01	0.99	1.00	1.01
	(0.98 - 1.03)	(0.97 - 1.05)	(0.96 - 1.02)	(0.97 - 1.04)	(0.97 - 1.05)
Paternal Education Missingness					
Missing				1.02	1.96***
				(0.69 - 1.52)	(1.22 - 3.13)

*** p<.01, ** p<.05, * p<.1

Appendix Table 3.9: Complete secondary analysis results, with the spline knot at 12 years of education. Outcome: Current smoking.

	1992 HRS Cohort (n = 5,851)	1998 HRS Cohort (n = 2,013)	2004 HRS Cohort (n = 2,708)	2010 HRS Cohort (n = 4,075)	2016 HRS Cohort (n = 3,507)
Intercept	0.97	0.87	1.60	0.66	0.61
	(0.68 - 1.40)	(0.39 - 1.94)	(0.63 - 4.08)	(0.16 - 2.78)	(0.05 - 7.56)
Discontinuity Indicator (at 12 years of education)					
12 or more years of education	0.55***	0.49***	0.45***	0.51***	0.22***
	(0.43 - 0.70)	(0.29 - 0.81)	(0.27 - 0.76)	(0.32 - 0.84)	(0.14 - 0.36)
Low-education (0-11 years)	1.04	1.04	1.10*	1.09*	1.15**
	(0.97 - 1.11)	(0.90 - 1.20)	(0.98 - 1.23)	(0.98 - 1.21)	(1.03 - 1.28)
High-education (12-17 years)	0.86***	0.82***	0.78***	0.74***	0.77***
	(0.83 - 0.89)	(0.77 - 0.88)	(0.73 - 0.84)	(0.70 - 0.79)	(0.70 - 0.84)
Gender					
Female	0.79***	0.85	0.62***	0.93	0.93
	(0.71 - 0.89)	(0.70 - 1.05)	(0.50 - 0.77)	(0.78 - 1.12)	(0.71 - 1.21)
Race / Ethnicity					
African American	1.01	1.57**	1.18	1.21	1.07
	(0.84 - 1.22)	(1.11 - 2.22)	(0.85 - 1.65)	(0.95 - 1.53)	(0.76 - 1.51)
Latinx	0.86	0.60**	0.78	0.88	0.86
	(0.61 - 1.21)	(0.36 - 0.99)	(0.52 - 1.16)	(0.55 - 1.40)	(0.45 - 1.65)
Other / missing	1.08	0.89	1.26	0.93	1.03
	(0.77 - 1.50)	(0.52 - 1.53)	(0.77 - 2.08)	(0.54 - 1.61)	(0.75 - 1.42)
Birth Place					
Southern USA	1.02	0.78	1.26*	0.95	1.01
	(0.84 - 1.24)	(0.56 - 1.07)	(0.96 - 1.65)	(0.77 - 1.15)	(0.76 - 1.34)
Immigrant	0.57***	0.76	0.56**	0.35***	0.38***
	(0.40 - 0.80)	(0.43 - 1.35)	(0.36 - 0.89)	(0.21 - 0.57)	(0.23 - 0.64)
Birth Year	1.06***	0.98	0.97	1.05*	1.03
	(1.02 - 1.09)	(0.92 - 1.04)	(0.90 - 1.05)	(0.99 - 1.12)	(0.93 - 1.14)
Maternal Education (Years)	1.01	1.01	1.02	0.99	1.04
	(0.98 - 1.04)	(0.96 - 1.06)	(0.98 - 1.06)	(0.95 - 1.03)	(0.98 - 1.10)
Maternal Education Missingness					
Missing				0.84	1.17
				(0.44 - 1.61)	(0.57 - 2.38)
Paternal Education (Years)	0.99	1.01	0.97	0.98	1.00
	(0.97 - 1.01)	(0.97 - 1.06)	(0.94 - 1.01)	(0.94 - 1.02)	(0.95 - 1.05)
Paternal Education Missingness					
Missing				0.87	1.77**
				(0.52 - 1.47)	(1.06 - 2.96)

*** p<.01, ** p<.05, * p<.1

Appendix Table 3.10: Complete secondary analysis results, with the spline knot at 12 years of education. Outcome: Smoking cessation.

	1992 HRS Cohort (n = 3,717)	1998 HRS Cohort (n = 1,244)	2004 HRS Cohort (n = 1,483)	2010 HRS Cohort (n = 2,328)	2016 HRS Cohort (n = 1,796)
Intercept	0.74	0.73	0.78	0.94	3.33
	(0.49 - 1.10)	(0.29 - 1.83)	(0.26 - 2.34)	(0.21 - 4.27)	(0.17 - 64.80)
Discontinuity Indicator (at 12 years of education)					
12 or more years of education	1.44**	1.93**	1.53	1.91**	3.71***
	(1.06 - 1.96)	(1.09 - 3.43)	(0.82 - 2.86)	(1.12 - 3.27)	(2.26 - 6.10)
Low-education (0-11 years)	0.99	0.97	0.97	0.95	0.83***
	(0.91 - 1.06)	(0.82 - 1.16)	(0.85 - 1.11)	(0.85 - 1.06)	(0.74 - 0.94)
High-education (12-17 years)	1.16***	1.20***	1.16***	1.22***	1.16***
	(1.10 - 1.21)	(1.11 - 1.29)	(1.08 - 1.25)	(1.14 - 1.30)	(1.04 - 1.29)
Gender					
Female	0.74***	0.78**	1.00	1.04	1.12
	(0.65 - 0.84)	(0.62 - 0.98)	(0.76 - 1.31)	(0.86 - 1.27)	(0.80 - 1.57)
Race / Ethnicity					
African American	0.93	0.61**	0.73*	0.81	0.71
	(0.74 - 1.18)	(0.41 - 0.93)	(0.51 - 1.04)	(0.60 - 1.09)	(0.45 - 1.11)
Latinx	1.07	1.37	1.25	1.39	1.08
	(0.76 - 1.51)	(0.69 - 2.71)	(0.78 - 1.98)	(0.79 - 2.43)	(0.48 - 2.47)
Other / missing	0.89	1.40	0.82	1.05	1.13
	(0.62 - 1.28)	(0.73 - 2.69)	(0.48 - 1.40)	(0.57 - 1.93)	(0.77 - 1.68)
Birth Place					
Southern USA	0.85	1.32	0.79	0.99	0.94
	(0.69 - 1.06)	(0.93 - 1.88)	(0.58 - 1.08)	(0.79 - 1.23)	(0.65 - 1.35)
Immigrant	1.33	0.96	1.30	2.65***	1.71**
	(0.90 - 1.97)	(0.53 - 1.76)	(0.79 - 2.15)	(1.48 - 4.74)	(1.01 - 2.88)
Birth Year	0.93***	1.00	0.99	0.93*	0.91
	(0.89 - 0.97)	(0.94 - 1.07)	(0.92 - 1.08)	(0.87 - 1.00)	(0.80 - 1.03)
Maternal Education (Years)	1.00	1.00	0.99	1.02	0.98
	(0.97 - 1.04)	(0.95 - 1.06)	(0.95 - 1.03)	(0.98 - 1.08)	(0.91 - 1.05)
Maternal Education Missingness					
Missing				1.63	0.76
				(0.79 - 3.36)	(0.33 - 1.74)
Paternal Education (Years)	1.01	0.99	1.03	1.03	1.00
	(0.99 - 1.03)	(0.94 - 1.03)	(0.99 - 1.07)	(0.98 - 1.07)	(0.94 - 1.06)
Paternal Education Missingness					
Missing				1.17	0.71
				(0.71 - 1.92)	(0.35 - 1.44)

*** p<.01, ** p<.05, * p<.1

Appendix Table 3.11: Sensitivity analyses of excluding from analysis the 72 persons who had missing education levels. Outcome: Eversmoking.

	1992 HRS Cohort (n = 5,851)	1998 HRS Cohort (n = 2,013)	2004 HRS Cohort (n = 2,689)	2010 HRS Cohort (n = 4,023)	2016 HRS Cohort (n = 3,506)
Intercept	4.93*** (3.59 - 6.78)	4.59*** (2.03 - 10.39)	14.62*** (5.83 - 36.67)	4.05** (1.33 - 12.35)	16.18*** (3.35 - 78.27)
Discontinuity Indicator (at 11 years of education)					
11 or more years of education	0.61*** (0.47 - 0.78)	0.54** (0.30 - 0.98)	0.49** (0.26 - 0.92)	0.71 (0.40 - 1.29)	0.28*** (0.16 - 0.49)
Low-education (0-10 years)	1.07 (0.99 - 1.17)	1.12 (0.95 - 1.31)	1.22** (1.04 - 1.43)	1.23*** (1.07 - 1.41)	1.17** (1.03 - 1.33)
High-education (11-17 years)	0.90*** (0.87 - 0.94)	0.87*** (0.83 - 0.92)	0.79*** (0.74 - 0.83)	0.78*** (0.73 - 0.83)	0.78*** (0.73 - 0.83)
Gender					
Female	0.40*** (0.36 - 0.45)	0.52*** (0.40 - 0.66)	0.45*** (0.38 - 0.52)	0.98 (0.81 - 1.19)	0.99 (0.82 - 1.19)
Race / Ethnicity					
African American	0.97 (0.78 - 1.19)	1.25 (0.90 - 1.74)	0.88 (0.67 - 1.16)	1.05 (0.82 - 1.33)	0.80 (0.59 - 1.09)
Latinx	0.79* (0.63 - 1.00)	0.66 (0.36 - 1.21)	0.91 (0.57 - 1.46)	1.15 (0.85 - 1.54)	0.92 (0.60 - 1.43)
Other / missing	0.88 (0.61 - 1.26)	1.29 (0.79 - 2.10)	1.20 (0.86 - 1.66)	0.87 (0.59 - 1.28)	1.33* (0.98 - 1.79)
Birth Place					
Southern USA	0.84* (0.69 - 1.01)	0.93 (0.71 - 1.21)	1.12 (0.89 - 1.39)	0.95 (0.78 - 1.14)	0.90 (0.71 - 1.14)
Immigrant	0.62*** (0.48 - 0.78)	0.64 (0.37 - 1.12)	0.54*** (0.36 - 0.80)	0.81 (0.59 - 1.11)	0.50*** (0.36 - 0.70)
Birth Year	1.00 (0.97 - 1.03)	0.97 (0.92 - 1.03)	0.94** (0.89 - 0.99)	0.99 (0.95 - 1.04)	0.94* (0.88 - 1.01)
Maternal Education (Years)	1.02** (1.00 - 1.05)	1.03 (0.99 - 1.07)	1.01 (0.98 - 1.05)	1.01 (0.98 - 1.05)	1.04 (0.99 - 1.09)
Maternal Education Missingness					
Missing				1.46 (0.84 - 2.53)	1.11 (0.54 - 2.25)
Paternal Education (Years)	1.00 (0.98 - 1.03)	1.01 (0.97 - 1.05)	0.99 (0.96 - 1.02)	1.00 (0.97 - 1.04)	1.01 (0.97 - 1.05)
Paternal Education Missingness					
Missing				1.03 (0.69 - 1.53)	1.92*** (1.23 - 3.00)

*** p<.01, ** p<.05, * p<.1

Appendix Table 3.12: Sensitivity analyses of excluding from analysis the 72 persons who had missing education levels. Outcome: Current smoking.

	1992 HRS Cohort (n = 5,851)	1998 HRS Cohort (n = 2,013)	2004 HRS Cohort (n = 2,689)	2010 HRS Cohort (n = 4,023)	2016 HRS Cohort (n = 3,506)
Intercept	0.83	1.00	1.42	0.89	0.92
	(0.57 - 1.21)	(0.48 - 2.09)	(0.45 - 4.49)	(0.18 - 4.55)	(0.07 - 11.41)
Discontinuity Indicator (at 11 years of education)					
11 or more years of education	0.82	0.55**	0.69	0.52**	0.22***
	(0.61 - 1.09)	(0.33 - 0.92)	(0.35 - 1.36)	(0.27 - 0.99)	(0.12 - 0.40)
Low-education (0-10 years)	1.01	1.09	1.06	1.20**	1.31***
	(0.92 - 1.11)	(0.90 - 1.30)	(0.90 - 1.25)	(1.03 - 1.41)	(1.13 - 1.51)
High-education (11-17 years)	0.84***	0.81***	0.77***	0.74***	0.74***
	(0.81 - 0.87)	(0.76 - 0.87)	(0.73 - 0.82)	(0.70 - 0.79)	(0.68 - 0.82)
Gender					
Female	0.80***	0.86	0.61***	0.95	0.94
	(0.71 - 0.90)	(0.70 - 1.05)	(0.49 - 0.76)	(0.78 - 1.14)	(0.71 - 1.23)
Race / Ethnicity					
African American	1.03	1.62***	1.18	1.17	1.11
	(0.86 - 1.24)	(1.15 - 2.28)	(0.84 - 1.66)	(0.91 - 1.51)	(0.80 - 1.55)
Latinx	0.86	0.60*	0.78	0.82	0.88
	(0.61 - 1.22)	(0.36 - 1.00)	(0.52 - 1.16)	(0.52 - 1.31)	(0.46 - 1.67)
Other / missing	1.09	0.88	1.28	0.90	1.05
	(0.78 - 1.53)	(0.51 - 1.51)	(0.78 - 2.10)	(0.51 - 1.57)	(0.76 - 1.44)
Birth Place					
Southern USA	1.03	0.78	1.27*	0.93	1.00
	(0.85 - 1.25)	(0.57 - 1.06)	(0.97 - 1.66)	(0.77 - 1.14)	(0.76 - 1.32)
Immigrant	0.57***	0.76	0.52***	0.36***	0.41***
	(0.40 - 0.80)	(0.42 - 1.37)	(0.33 - 0.83)	(0.22 - 0.59)	(0.24 - 0.69)
Birth Year	1.06***	0.98	0.97	1.06*	1.03
	(1.02 - 1.09)	(0.92 - 1.04)	(0.90 - 1.04)	(0.99 - 1.13)	(0.92 - 1.14)
Maternal Education (Years)	1.01	1.01	1.02	0.99	1.04
	(0.98 - 1.04)	(0.96 - 1.06)	(0.98 - 1.06)	(0.95 - 1.03)	(0.99 - 1.10)
Maternal Education Missingness					
Missing				0.85	1.32
				(0.44 - 1.63)	(0.66 - 2.63)
Paternal Education (Years)	0.99	1.01	0.98	0.97	1.00
	(0.97 - 1.01)	(0.97 - 1.06)	(0.95 - 1.01)	(0.93 - 1.01)	(0.95 - 1.04)
Paternal Education Missingness					
Missing				0.85	1.69**
				(0.50 - 1.43)	(1.02 - 2.80)

*** p<.01, ** p<.05, * p<.1

Appendix Table 3.13: Sensitivity analyses of excluding from analysis the 72 persons who had missing education levels. Outcome: Smoking cessation.

	1992 HRS Cohort (n = 3,717)	1998 HRS Cohort (n = 1,244)	2004 HRS Cohort (n = 1,472)	2010 HRS Cohort (n = 2,294)	2016 HRS Cohort (n = 1,795)
Intercept	0.88	0.72	0.86	0.72	2.77
	(0.57 - 1.34)	(0.32 - 1.64)	(0.24 - 3.13)	(0.13 - 3.96)	(0.14 - 54.26)
Discontinuity Indicator (at 11 years of education)					
11 or more years of education	0.98	1.52	1.13	2.01*	3.61***
	(0.69 - 1.40)	(0.82 - 2.81)	(0.51 - 2.53)	(0.97 - 4.15)	(1.71 - 7.62)
Low-education (0-10 years)	1.03	0.96	1.02	0.88	0.75***
	(0.93 - 1.14)	(0.78 - 1.18)	(0.83 - 1.25)	(0.75 - 1.04)	(0.62 - 0.90)
High-education (11-17 years)	1.18***	1.21***	1.17***	1.23***	1.20***
	(1.13 - 1.23)	(1.12 - 1.31)	(1.09 - 1.25)	(1.15 - 1.31)	(1.08 - 1.33)
Gender					
Female	0.74***	0.78**	1.00	1.03	1.11
	(0.65 - 0.84)	(0.62 - 0.99)	(0.76 - 1.31)	(0.84 - 1.26)	(0.79 - 1.55)
Race / Ethnicity					
African American	0.93	0.60**	0.73*	0.80	0.68*
	(0.73 - 1.17)	(0.40 - 0.89)	(0.52 - 1.04)	(0.59 - 1.09)	(0.44 - 1.05)
Latinx	1.07	1.36	1.25	1.46	1.10
	(0.76 - 1.51)	(0.68 - 2.74)	(0.79 - 2.00)	(0.83 - 2.57)	(0.48 - 2.50)
Other / missing	0.89	1.41	0.82	1.06	1.12
	(0.62 - 1.29)	(0.73 - 2.72)	(0.48 - 1.40)	(0.58 - 1.95)	(0.76 - 1.65)
Birth Place					
Southern USA	0.85	1.32	0.78	1.00	0.94
	(0.69 - 1.05)	(0.94 - 1.85)	(0.57 - 1.06)	(0.80 - 1.26)	(0.67 - 1.33)
Immigrant	1.35	0.94	1.40	2.59***	1.65*
	(0.91 - 2.00)	(0.52 - 1.72)	(0.84 - 2.34)	(1.45 - 4.64)	(0.97 - 2.79)
Birth Year	0.93***	1.00	1.00	0.93**	0.91
	(0.89 - 0.97)	(0.94 - 1.07)	(0.92 - 1.08)	(0.86 - 1.00)	(0.80 - 1.03)
Maternal Education (Years)	1.00	1.00	0.99	1.03	0.97
	(0.97 - 1.04)	(0.95 - 1.06)	(0.95 - 1.03)	(0.98 - 1.08)	(0.91 - 1.05)
Maternal Education Missingness					
Missing				1.61	0.71
				(0.77 - 3.33)	(0.30 - 1.67)
Paternal Education (Years)	1.01	0.99	1.03	1.03	1.00
	(0.99 - 1.03)	(0.94 - 1.03)	(0.99 - 1.07)	(0.99 - 1.08)	(0.94 - 1.07)
Paternal Education Missingness					
Missing				1.21	0.74
				(0.73 - 2.02)	(0.36 - 1.52)

*** p<.01, ** p<.05, * p<.1

Appendix Table 3.14: Sensitivity analyses of not replacing missing maternal and paternal education levels with imputed values. Outcome: Eversmoking

	1992 HRS Cohort (n = 5,851)	1998 HRS Cohort (n = 2,013)	2004 HRS Cohort (n = 2,708)	2010 HRS Cohort (n = 4,075)	2016 HRS Cohort (n = 3,507)
Intercept	4.78***	4.27***	13.59***	3.89**	16.20***
	(3.46 - 6.61)	(1.93 - 9.46)	(5.64 - 32.71)	(1.30 - 11.62)	(3.35 - 78.34)
Discontinuity Indicator (at 11 years of education)					
11 or more years of education	0.62***	0.57*	0.50**	0.74	0.28***
	(0.48 - 0.80)	(0.31 - 1.02)	(0.28 - 0.92)	(0.41 - 1.34)	(0.16 - 0.49)
Low-education (0-10 years)	1.07	1.11	1.22***	1.21***	1.17**
	(0.99 - 1.17)	(0.95 - 1.31)	(1.07 - 1.39)	(1.06 - 1.38)	(1.03 - 1.33)
High-education (11-17 years)	0.91***	0.88***	0.79***	0.78***	0.78***
	(0.88 - 0.95)	(0.84 - 0.92)	(0.75 - 0.84)	(0.73 - 0.83)	(0.73 - 0.83)
Gender					
Female	0.40***	0.51***	0.45***	0.97	0.99
	(0.36 - 0.44)	(0.40 - 0.65)	(0.39 - 0.53)	(0.80 - 1.17)	(0.82 - 1.19)
Race / Ethnicity					
African American	0.94	1.18	0.84	1.08	0.80
	(0.76 - 1.16)	(0.84 - 1.65)	(0.62 - 1.12)	(0.85 - 1.37)	(0.59 - 1.09)
Latinx	0.79**	0.61	0.89	1.17	0.92
	(0.62 - 1.00)	(0.33 - 1.13)	(0.56 - 1.42)	(0.87 - 1.57)	(0.60 - 1.42)
Other / missing	0.86	1.26	1.16	0.89	1.33*
	(0.61 - 1.23)	(0.77 - 2.07)	(0.84 - 1.60)	(0.61 - 1.30)	(0.98 - 1.79)
Birth Place					
Southern USA	0.83*	0.92	1.11	0.94	0.90
	(0.69 - 1.01)	(0.70 - 1.21)	(0.89 - 1.39)	(0.79 - 1.13)	(0.71 - 1.14)
Immigrant	0.62***	0.62*	0.54***	0.78	0.50***
	(0.49 - 0.78)	(0.36 - 1.07)	(0.36 - 0.80)	(0.57 - 1.06)	(0.36 - 0.70)
Birth Year	1.00	0.98	0.94**	0.99	0.94*
	(0.97 - 1.03)	(0.92 - 1.03)	(0.89 - 0.99)	(0.95 - 1.04)	(0.88 - 1.01)
Nonimputed Maternal Education (Years)	1.03**	1.03	1.01	1.01	1.04
	(1.00 - 1.05)	(0.99 - 1.07)	(0.98 - 1.05)	(0.98 - 1.05)	(0.99 - 1.09)
Nonimputed Maternal Education Missingness					
Missing	1.20	1.45	0.97	1.45	1.10
	(0.82 - 1.76)	(0.87 - 2.42)	(0.58 - 1.62)	(0.84 - 2.50)	(0.54 - 2.25)
Nonimputed Paternal Education (Years)	1.00	1.00	0.99	1.00	1.01
	(0.98 - 1.02)	(0.97 - 1.04)	(0.96 - 1.01)	(0.97 - 1.04)	(0.97 - 1.05)
Nonimputed Paternal Education Missingness					
Missing	1.35*	1.27	1.23	1.03	1.93***
	(0.99 - 1.82)	(0.86 - 1.87)	(0.88 - 1.71)	(0.69 - 1.52)	(1.24 - 3.01)

*** p<.01, ** p<.05, * p<.1

Appendix Table 3.15: Sensitivity analyses of not replacing missing maternal and paternal education levels with imputed values. Outcome: current smoking.

	1992 HRS Cohort (n = 5,851)	1998 HRS Cohort (n = 2,013)	2004 HRS Cohort (n = 2,708)	2010 HRS Cohort (n = 4,075)	2016 HRS Cohort (n = 3,507)
Intercept	0.84	0.97	1.47	0.86	0.93
	(0.57 - 1.24)	(0.44 - 2.17)	(0.47 - 4.59)	(0.17 - 4.38)	(0.08 - 11.51)
Discontinuity Indicator (at 11 years of education)					
11 or more years of education	0.83	0.58**	0.68	0.53*	0.22***
	(0.63 - 1.11)	(0.34 - 0.99)	(0.34 - 1.33)	(0.26 - 1.06)	(0.12 - 0.40)
Low-education (0-10 years)	1.01	1.08	1.10	1.19**	1.29***
	(0.92 - 1.11)	(0.90 - 1.31)	(0.95 - 1.27)	(1.00 - 1.41)	(1.12 - 1.49)
High-education (11-17 years)	0.84***	0.83***	0.78***	0.74***	0.74***
	(0.81 - 0.88)	(0.77 - 0.88)	(0.73 - 0.83)	(0.70 - 0.78)	(0.68 - 0.82)
Gender					
Female	0.80***	0.85	0.62***	0.93	0.94
	(0.71 - 0.90)	(0.69 - 1.05)	(0.49 - 0.77)	(0.77 - 1.12)	(0.72 - 1.23)
Race / Ethnicity					
African American	1.01	1.45**	1.14	1.21	1.11
	(0.83 - 1.21)	(1.03 - 2.04)	(0.82 - 1.59)	(0.95 - 1.55)	(0.79 - 1.55)
Latinx	0.85	0.55**	0.77	0.88	0.88
	(0.60 - 1.20)	(0.33 - 0.89)	(0.52 - 1.15)	(0.55 - 1.41)	(0.46 - 1.67)
Other / missing	1.07	0.84	1.24	0.94	1.04
	(0.77 - 1.49)	(0.49 - 1.45)	(0.76 - 2.05)	(0.54 - 1.63)	(0.76 - 1.44)
Birth Place					
Southern USA	1.02	0.75*	1.25*	0.95	1.00
	(0.84 - 1.24)	(0.54 - 1.05)	(0.96 - 1.64)	(0.78 - 1.15)	(0.76 - 1.31)
Immigrant	0.56***	0.76	0.54***	0.35***	0.40***
	(0.40 - 0.80)	(0.43 - 1.35)	(0.35 - 0.85)	(0.22 - 0.58)	(0.24 - 0.68)
Birth Year	1.06***	0.98	0.97	1.05	1.02
	(1.02 - 1.09)	(0.93 - 1.04)	(0.90 - 1.05)	(0.99 - 1.12)	(0.92 - 1.14)
Nonimputed Maternal Education (Years)	1.00	1.02	1.01	0.99	1.04
	(0.98 - 1.03)	(0.97 - 1.07)	(0.97 - 1.05)	(0.95 - 1.03)	(0.99 - 1.10)
Nonimputed Maternal Education Missingness					
Missing	1.04	1.04	0.87	0.85	1.30
	(0.75 - 1.46)	(0.56 - 1.92)	(0.54 - 1.40)	(0.44 - 1.63)	(0.65 - 2.58)
Nonimputed Paternal Education (Years)	0.99	0.98	0.97	0.97	1.00
	(0.97 - 1.01)	(0.95 - 1.02)	(0.94 - 1.01)	(0.93 - 1.02)	(0.95 - 1.04)
Nonimputed Paternal Education Missingness					
Missing	1.15	1.36	1.08	0.87	1.72**
	(0.91 - 1.46)	(0.85 - 2.19)	(0.68 - 1.72)	(0.52 - 1.48)	(1.04 - 2.85)

*** p<.01, ** p<.05, * p<.1

Appendix Table 3.16: Sensitivity analyses of not replacing missing maternal and paternal education levels with imputed values. Outcome: Smoking cessation.

	1992 HRS Cohort (n = 3,717)	1998 HRS Cohort (n = 1,244)	2004 HRS Cohort (n = 1,483)	2010 HRS Cohort (n = 2,328)	2016 HRS Cohort (n = 1,796)
Intercept	0.85	0.72	0.80	0.73	2.74
	(0.55 - 1.30)	(0.29 - 1.76)	(0.22 - 2.89)	(0.14 - 3.97)	(0.14 - 53.15)
Discontinuity Indicator (at 11 years of education)					
11 or more years of education	0.97	1.42	1.17	1.98*	3.53***
	(0.69 - 1.37)	(0.75 - 2.71)	(0.53 - 2.55)	(0.92 - 4.27)	(1.67 - 7.45)
Low-education (0-10 years)	1.02	0.97	0.99	0.89	0.76***
	(0.93 - 1.14)	(0.78 - 1.20)	(0.82 - 1.18)	(0.74 - 1.06)	(0.63 - 0.91)
High-education (11-17 years)	1.17***	1.19***	1.16***	1.23***	1.20***
	(1.12 - 1.23)	(1.11 - 1.28)	(1.09 - 1.25)	(1.16 - 1.31)	(1.08 - 1.33)
Gender					
Female	0.74***	0.79**	1.00	1.05	1.10
	(0.65 - 0.84)	(0.62 - 1.00)	(0.76 - 1.31)	(0.86 - 1.28)	(0.79 - 1.55)
Race / Ethnicity					
African American	0.94	0.65**	0.74*	0.79	0.68*
	(0.74 - 1.19)	(0.44 - 0.98)	(0.52 - 1.05)	(0.59 - 1.06)	(0.44 - 1.05)
Latinx	1.08	1.43	1.24	1.37	1.11
	(0.77 - 1.52)	(0.72 - 2.86)	(0.78 - 1.96)	(0.78 - 2.41)	(0.49 - 2.52)
Other / missing	0.90	1.45	0.83	1.03	1.12
	(0.63 - 1.31)	(0.74 - 2.82)	(0.48 - 1.42)	(0.57 - 1.87)	(0.76 - 1.65)
Birth Place					
Southern USA	0.85	1.35*	0.79	0.98	0.95
	(0.69 - 1.05)	(0.96 - 1.90)	(0.58 - 1.08)	(0.79 - 1.23)	(0.67 - 1.34)
Immigrant	1.36	0.95	1.34	2.60***	1.66*
	(0.92 - 2.01)	(0.52 - 1.72)	(0.80 - 2.23)	(1.45 - 4.64)	(0.98 - 2.82)
Birth Year	0.93***	1.01	0.99	0.93*	0.91
	(0.89 - 0.97)	(0.94 - 1.07)	(0.91 - 1.08)	(0.87 - 1.00)	(0.80 - 1.03)
Nonimputed Maternal Education (Years)	1.01	0.99	1.00	1.02	0.98
	(0.98 - 1.04)	(0.93 - 1.04)	(0.96 - 1.04)	(0.97 - 1.07)	(0.91 - 1.05)
Nonimputed Maternal Education Missingness					
Missing	1.08	1.16	1.21	1.60	0.73
	(0.70 - 1.66)	(0.58 - 2.32)	(0.76 - 1.92)	(0.77 - 3.31)	(0.31 - 1.70)
Nonimputed Paternal Education (Years)	1.01	1.02	1.03	1.03	1.00
	(0.99 - 1.03)	(0.98 - 1.06)	(0.98 - 1.07)	(0.98 - 1.07)	(0.94 - 1.07)
Nonimputed Paternal Education Missingness					
Missing	0.97	0.76	1.04	1.17	0.73
	(0.74 - 1.27)	(0.46 - 1.25)	(0.59 - 1.82)	(0.71 - 1.92)	(0.36 - 1.49)

*** p<.01, ** p<.05, * p<.1

Appendix Table 3.17: Sensitivity analyses of not including birthyear as a covariate in the analyses. Outcome: eversmoking.

	1992 HRS Cohort (n = 5,851)	1998 HRS Cohort (n = 2,013)	2004 HRS Cohort (n = 2,708)	2010 HRS Cohort (n = 4,075)	2016 HRS Cohort (n = 3,507)
Intercept	4.91***	4.18***	7.52***	3.36***	4.24***
	(3.62 - 6.66)	(1.96 - 8.94)	(3.42 - 16.55)	(1.62 - 6.96)	(2.16 - 8.33)
Discontinuity Indicator (at 11 years of education)					
11 or more years of education	0.61***	0.53**	0.49**	0.74	0.28***
	(0.47 - 0.78)	(0.29 - 0.97)	(0.26 - 0.90)	(0.41 - 1.34)	(0.16 - 0.49)
Low-education (0-10 years)	1.07	1.12	1.22***	1.21***	1.17**
	(0.99 - 1.17)	(0.95 - 1.32)	(1.06 - 1.41)	(1.06 - 1.38)	(1.03 - 1.32)
High-education (11-17 years)	0.90***	0.87***	0.79***	0.78***	0.78***
	(0.87 - 0.94)	(0.83 - 0.92)	(0.75 - 0.84)	(0.73 - 0.83)	(0.73 - 0.84)
Gender					
Female	0.40***	0.51***	0.45***	0.97	0.98
	(0.36 - 0.45)	(0.40 - 0.65)	(0.39 - 0.52)	(0.80 - 1.17)	(0.82 - 1.17)
Race / Ethnicity					
African American	0.97	1.25	0.88	1.08	0.80
	(0.78 - 1.19)	(0.90 - 1.74)	(0.67 - 1.16)	(0.85 - 1.37)	(0.59 - 1.09)
Latinx	0.80*	0.65	0.91	1.17	0.92
	(0.63 - 1.00)	(0.35 - 1.20)	(0.57 - 1.44)	(0.87 - 1.57)	(0.60 - 1.42)
Other / missing	0.88	1.28	1.17	0.89	1.33*
	(0.62 - 1.26)	(0.79 - 2.09)	(0.85 - 1.61)	(0.61 - 1.30)	(0.99 - 1.80)
Birth Place					
Southern USA	0.84*	0.93	1.12	0.94	0.90
	(0.69 - 1.01)	(0.71 - 1.21)	(0.90 - 1.40)	(0.79 - 1.13)	(0.71 - 1.14)
Immigrant	0.62***	0.65	0.55***	0.78	0.49***
	(0.48 - 0.78)	(0.37 - 1.13)	(0.36 - 0.82)	(0.57 - 1.06)	(0.35 - 0.68)
Maternal Education (Years)	1.02**	1.03	1.01	1.01	1.03
	(1.00 - 1.05)	(0.99 - 1.07)	(0.98 - 1.05)	(0.98 - 1.05)	(0.98 - 1.09)
Maternal Education Missingness					
Missing				1.45	1.08
				(0.84 - 2.50)	(0.54 - 2.19)
Paternal Education (Years)	1.00	1.01	0.99	1.00	1.01
	(0.98 - 1.03)	(0.97 - 1.05)	(0.96 - 1.01)	(0.97 - 1.04)	(0.97 - 1.05)
Paternal Education Missingness					
Missing				1.03	1.94***
				(0.69 - 1.52)	(1.25 - 3.00)

*** p<.01, ** p<.05, * p<.1

Appendix Table 3.18: Sensitivity analyses of not including birthyear as a covariate in the analyses. Outcome: Current smoking.

	1992 HRS Cohort (n = 5,851)	1998 HRS Cohort (n = 2,013)	2004 HRS Cohort (n = 2,708)	2010 HRS Cohort (n = 4,075)	2016 HRS Cohort (n = 3,507)
Intercept	0.74	0.93	1.10	2.02	1.60
	(0.50 - 1.08)	(0.47 - 1.82)	(0.52 - 2.34)	(0.79 - 5.21)	(0.67 - 3.82)
Discontinuity Indicator (at 11 years of education)					
11 or more years of education	0.83	0.54**	0.65	0.53*	0.22***
	(0.62 - 1.10)	(0.32 - 0.91)	(0.33 - 1.26)	(0.26 - 1.06)	(0.12 - 0.40)
Low-education (0-10 years)	1.01	1.09	1.10	1.19**	1.29***
	(0.92 - 1.11)	(0.90 - 1.31)	(0.95 - 1.28)	(1.00 - 1.41)	(1.12 - 1.49)
High-education (11-17 years)	0.84***	0.81***	0.78***	0.74***	0.74***
	(0.81 - 0.87)	(0.76 - 0.87)	(0.73 - 0.82)	(0.70 - 0.78)	(0.68 - 0.82)
Gender					
Female	0.80***	0.85	0.61***	0.94	0.94
	(0.71 - 0.90)	(0.69 - 1.05)	(0.49 - 0.77)	(0.78 - 1.12)	(0.72 - 1.23)
Race / Ethnicity					
African American	1.03	1.62***	1.19	1.21	1.11
	(0.86 - 1.24)	(1.15 - 2.28)	(0.85 - 1.67)	(0.95 - 1.55)	(0.80 - 1.55)
Latinx	0.88	0.60**	0.78	0.89	0.88
	(0.62 - 1.24)	(0.36 - 1.00)	(0.52 - 1.18)	(0.56 - 1.43)	(0.46 - 1.67)
Other / missing	1.10	0.87	1.27	0.94	1.04
	(0.79 - 1.55)	(0.51 - 1.50)	(0.78 - 2.05)	(0.54 - 1.64)	(0.76 - 1.43)
Birth Place					
Southern USA	1.03	0.77	1.26*	0.94	1.00
	(0.85 - 1.25)	(0.56 - 1.06)	(0.96 - 1.65)	(0.78 - 1.15)	(0.76 - 1.31)
Immigrant	0.57***	0.77	0.56**	0.36***	0.41***
	(0.40 - 0.81)	(0.42 - 1.38)	(0.35 - 0.88)	(0.22 - 0.58)	(0.24 - 0.68)
Maternal Education (Years)	1.01	1.01	1.02	0.99	1.04
	(0.98 - 1.04)	(0.96 - 1.06)	(0.98 - 1.06)	(0.95 - 1.04)	(0.98 - 1.10)
Maternal Education Missingness					
Missing				0.84	1.31
				(0.44 - 1.62)	(0.65 - 2.61)
Paternal Education (Years)	0.99	1.01	0.97*	0.98	1.00
	(0.97 - 1.02)	(0.97 - 1.06)	(0.95 - 1.01)	(0.94 - 1.02)	(0.95 - 1.04)
Paternal Education Missingness					
Missing				0.87	1.72**
				(0.52 - 1.46)	(1.04 - 2.86)

*** p<.01, ** p<.05, * p<.1

Appendix Table 3.19: Sensitivity analyses of not including birthyear as a covariate in the analyses. Outcome: Smoking cessation.

	1992 HRS Cohort (n = 3,717)	1998 HRS Cohort (n = 1,244)	2004 HRS Cohort (n = 1,483)	2010 HRS Cohort (n = 2,328)	2016 HRS Cohort (n = 1,796)
Intercept	1.03	0.73	0.76	0.24***	0.33**
	(0.68 - 1.56)	(0.34 - 1.56)	(0.33 - 1.77)	(0.09 - 0.66)	(0.12 - 0.95)
Discontinuity Indicator (at 11 years of education)					
11 or more years of education	0.97	1.52	1.21	1.94*	3.60***
	(0.67 - 1.39)	(0.82 - 2.83)	(0.56 - 2.63)	(0.90 - 4.20)	(1.73 - 7.49)
Low-education (0-10 years)	1.03	0.96	0.98	0.89	0.76***
	(0.93 - 1.14)	(0.78 - 1.19)	(0.82 - 1.17)	(0.74 - 1.07)	(0.63 - 0.91)
High-education (11-17 years)	1.18***	1.21***	1.17***	1.24***	1.19***
	(1.12 - 1.23)	(1.12 - 1.31)	(1.09 - 1.25)	(1.16 - 1.31)	(1.08 - 1.33)
Gender					
Female	0.74***	0.78**	1.00	1.03	1.10
	(0.65 - 0.85)	(0.62 - 0.99)	(0.76 - 1.31)	(0.85 - 1.25)	(0.79 - 1.54)
Race / Ethnicity					
African American	0.93	0.60**	0.72*	0.80	0.68*
	(0.74 - 1.18)	(0.40 - 0.89)	(0.51 - 1.03)	(0.59 - 1.07)	(0.44 - 1.05)
Latinx	1.05	1.36	1.24	1.34	1.07
	(0.75 - 1.47)	(0.68 - 2.73)	(0.78 - 1.97)	(0.76 - 2.35)	(0.47 - 2.41)
Other / missing	0.87	1.41	0.81	1.02	1.13
	(0.60 - 1.26)	(0.73 - 2.72)	(0.48 - 1.38)	(0.56 - 1.87)	(0.76 - 1.67)
Birth Place					
Southern USA	0.84	1.32	0.79	0.99	0.95
	(0.68 - 1.05)	(0.94 - 1.85)	(0.58 - 1.08)	(0.79 - 1.24)	(0.67 - 1.35)
Immigrant	1.34	0.94	1.31	2.59***	1.61*
	(0.90 - 1.99)	(0.52 - 1.72)	(0.79 - 2.18)	(1.46 - 4.58)	(0.96 - 2.70)
Maternal Education (Years)	1.00	1.00	0.99	1.02	0.97
	(0.97 - 1.04)	(0.95 - 1.06)	(0.95 - 1.03)	(0.97 - 1.07)	(0.90 - 1.04)
Maternal Education Missingness					
Missing				1.62	0.70
				(0.78 - 3.35)	(0.30 - 1.64)
Paternal Education (Years)	1.01	0.99	1.03	1.03	1.00
	(0.98 - 1.03)	(0.94 - 1.03)	(0.99 - 1.07)	(0.98 - 1.07)	(0.94 - 1.07)
Paternal Education Missingness					
Missing				1.17	0.73
				(0.71 - 1.92)	(0.36 - 1.48)

*** p<.01, ** p<.05, * p<.1

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