Supplementary Online Content

Shiffman S, Kurland BF, Scholl SM, Mao JM. Nondaily smokers' changes in cigarette consumption with very low-nicotine-content cigarettes: a randomized double-blind clinical trial. *JAMA Psychiatry*. Published online June 14, 2018. doi:10.1001/jamapsychiatry.2018.1831

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Age ≥18 (was ≥21 for part of the study period) Smoking for ≥3 years Non-daily smoking for ≥ 1 year Smoking 4-27 days/month Able to read and write English Available for period of study Willingness to try novel research cigarettes	Plans to quit smoking in next 3 months Cost identified as primary reason for non-daily smoking Carbon monoxide >15 ppm at screening Roll-your-own cigarettes used on ≥ 1/3 of smoking days E-cigarette use > 50% of smoking days Use other nicotine products > 4 days per month Current use of varenicline or bupropion Past-month myocardial infarction Past-month new cardiovascular condition Buerger's disease Females: Pregnant (by urine test), or plan to become pregnant in the next 3 months Females: Breastfeeding Severe psychiatric episode in the past month Night and/or 'swing' shift work Member of the same household as a study subject Participation in >3 research studies, or any smoking study, in past 6 months, or any studies that used medication in past month

eTable 2. Missing data patterns

	N (% missing)					
	Baseline	**Weeks 1-2**	**Weeks 3-4**	**Weeks 5-6**	**Weeks 7-8**	**Weeks 9-10**
NNCC	120	118 (2%)	109 (9%)	105 (12%)	100 (17%)	99 (18%)
VLNCC	118	114 (3%)	105 (11%)	99 (16%)	94 (20%)	91 (23%)

NNCC normal-nicotine-content cigarettes; VLNCC very-low-nicotine-content cigarettes

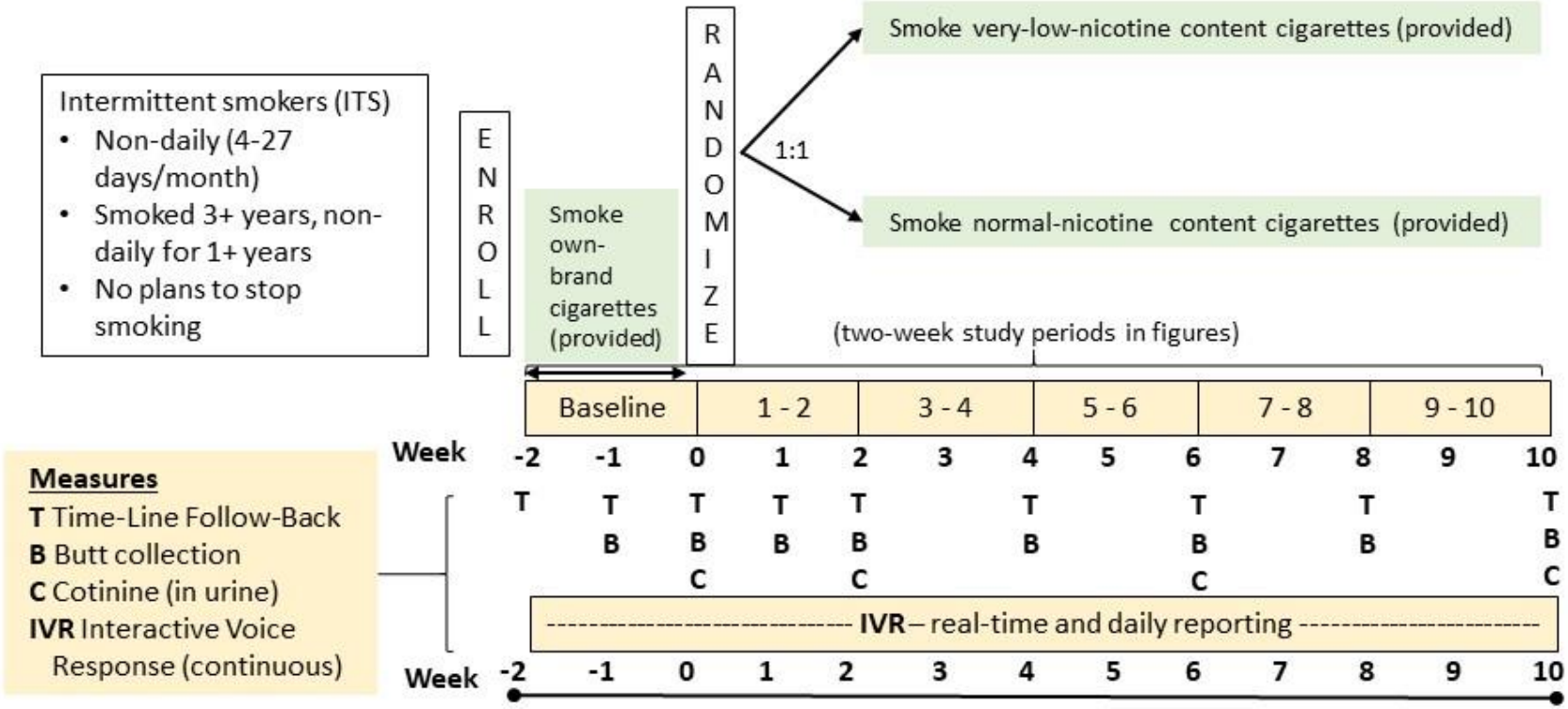
Of 1428 (6*238) expected biweekly CPD summaries, 156 (11%) were missing due to loss to observation. All missing outcome data were monotone (if missing data at one interval, missing at subsequent intervals), reflecting loss to study, rather than missing reports mid-study

eTable 3. Cigarettes per day (CPD) and primary outcome model imputation variance information

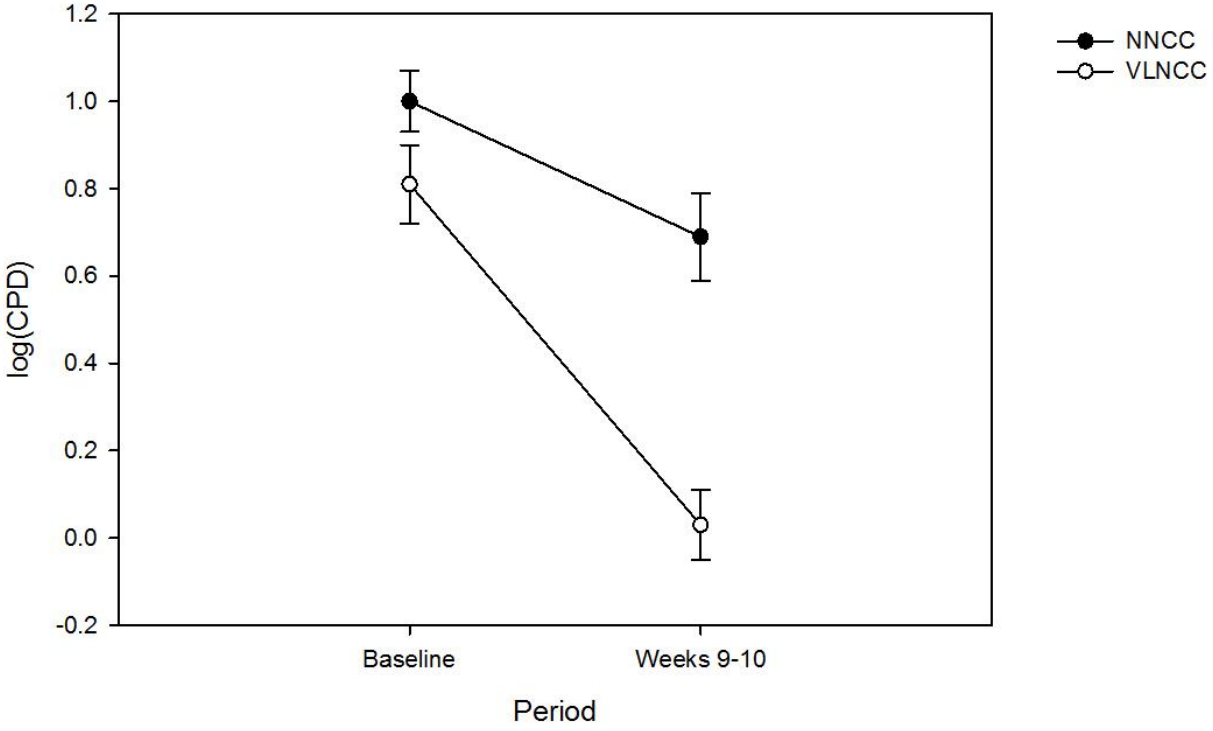
CPD Imputation Variance Information							
	Imputation Variance			Degrees of Freedom	Relative Increase in Variance	Fraction Missing Information	Relative Efficiency
CPD	Between	Within	Total				
Week 1-2	0.0002	0.0455	0.0457	233.96	0.0044	0.0044	0.9998
Week 3-4	0.0005	0.0441	0.0446	231.78	0.0125	0.0124	0.9995
Week 5-6	0.0011	0.0464	0.0475	228.13	0.0246	0.0240	0.9990
Week 7-8	0.0026	0.0492	0.0519	217.48	0.0545	0.0519	0.9979
Week 9-10	0.0022	0.0454	0.0477	218.9	0.0508	0.0485	0.9981
Baseline-to-End CPD Change Model Variance Information							
	Imputation Variance			Degrees of Freedom	Relative Increase in Variance	Fraction Missing Information	Relative Efficiency
Parameter	Between	Within	Total				
Intercept	0.0028	0.0551	0.0579	9776.8	0.0521	0.0497	0.9980
Baseline CPD	0.0004	0.0030	0.0034	1845.5	0.1287	0.1150	0.9954
Nicotine (VLNCC)	0.0019	0.0261	0.0281	4839.7	0.0758	0.0708	0.9972

The relative increase in variance and fraction missing information indicate small amounts of missing data in the CPD data grouped into two-week blocks. Rubin[83] suggests 3-5 imputations are generally sufficient for analyses; we analyzed 25 imputations, yielding greater than 99% relative efficiency in our imputed datasets. This method ensured that any loss of statistical power due to missing data becomes negligible in our model parameter inferences.[102]

eFigure 1. Study schema



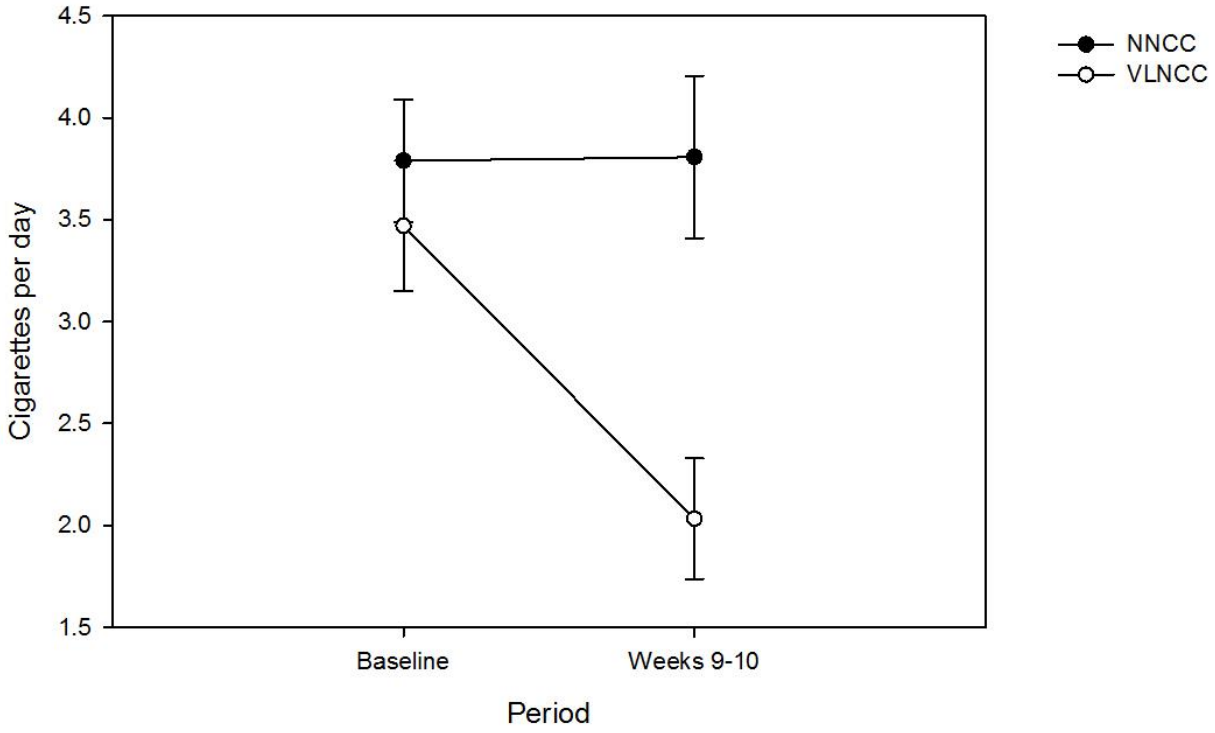
eFigure 2. Log-transformed cigarettes smoked per day at baseline vs end of study



CPD Cigarettes per day; NNCC normal-nicotine-content cigarettes; VLNCC very-low-nicotine-content cigarettes

Data are log-transformed cigarettes per day during the baseline and week 9-10 two-week time blocks by treatment group. A 0.5 offset was included prior to log-transforming the data to account for subjects with a CPD of zero. Observed data plotted (mean ± standard error). Analysis indicated that, while controlling for baseline log(CPD), the VLNCC group (n = 91) reduced their log(CPD) significantly more than the NNCC group (n = 99) over the 10 week post-randomization period ($p < 0.001$). Mean decrease among VLNCC subjects was 0.53 log(CPD) (95% CI, 0.32, 0.73) more than NNCC subjects.

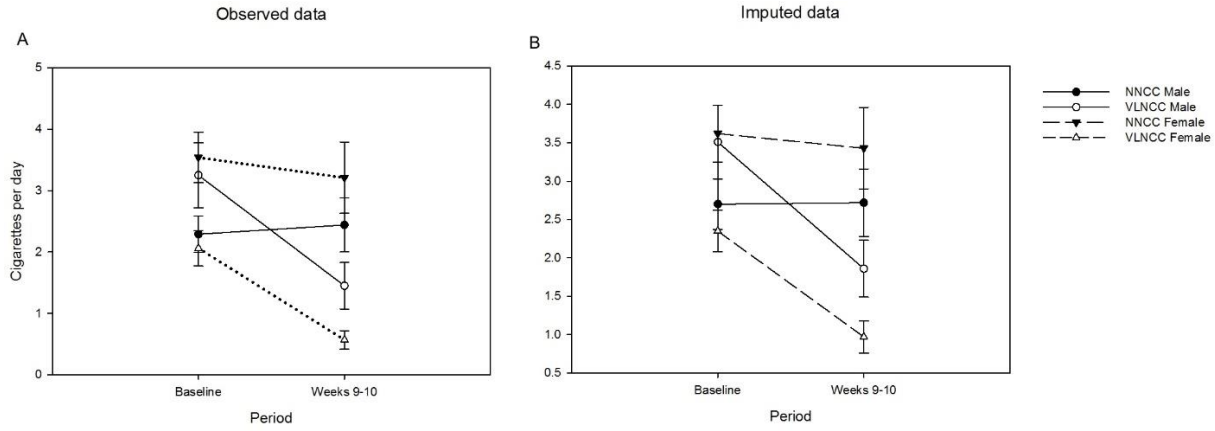
eFigure 3. Cigarettes smoked per day on days smoked, at baseline vs end of study



NNCC normal-nicotine-content cigarettes; VLNCC very-low-nicotine-content cigarettes

Cigarette consumption during the baseline and week 9-10 two-week time blocks by treatment group, based on CPD on days subjects smoked. Observed data plotted (mean ± standard error). Analysis indicated that, while controlling for baseline CPD, the VLNCC group (n = 91) reduced their cigarette consumption significantly more than the NNCC group (n = 99) over the 10 week post-randomization period ($p < 0.001$). Mean decrease among VLNCC subjects was 1.57 CPD (95% CI, 0.74, 2.39) more than NNCC subjects.

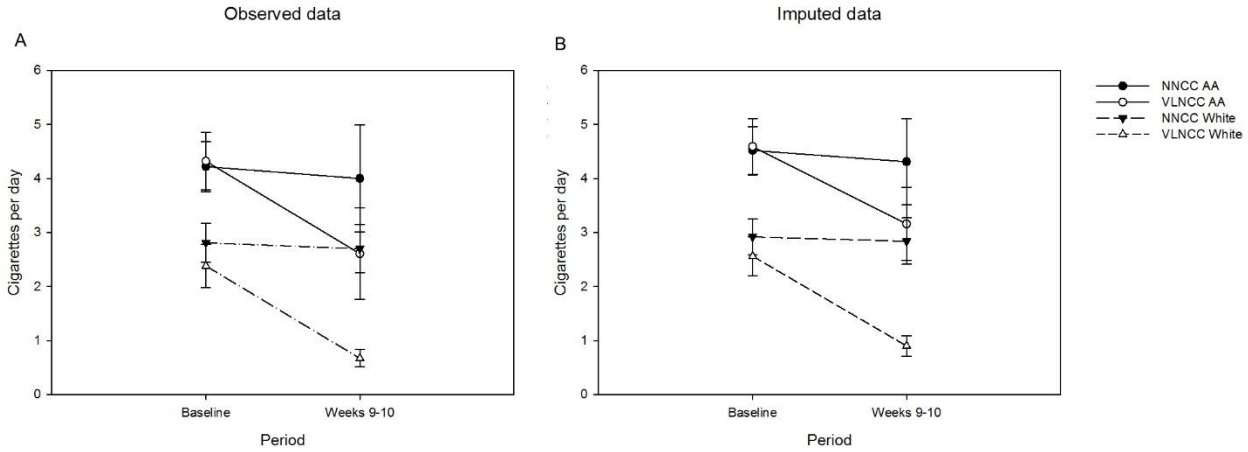
eFigure 4. Cigarette consumption, at baseline vs end of study, for male and female subjects



CPD cigarettes per day; NNCC normal-nicotine-content cigarettes; VLNCC very-low-nicotine-content cigarettes

Cigarette consumption during the baseline and week 9-10 two-week time blocks by treatment group, contrasting male and female subjects. Data are displayed by two different estimation methods: observed data (A), and multiple imputation (B) (mean ± standard error). Analysis of observed data indicated that, while controlling for baseline CPD, gender did not significantly moderate the treatment effect (p = 0.96). Mean decrease in CPD among male VLNCC subjects (n = 46) was 1.49 CPD (95% CI, 0.52, 2.46) greater than male NNCC subjects (n = 41). Similarly, among female VLNCC subjects (n = 45) mean CPD decreased 1.45 (0.37, 2.52) more than female NNCC subjects (n = 58). Analysis of imputed data showed substantively the same result; gender was not shown to moderate the treatment effect (p = 0.77). Mean decrease in CPD among male VLNCC subjects (n = 46) was 1.49 CPD (95% CI, 0.52, 2.46) greater than male NNCC subjects (n = 41). Similarly, among female VLNCC subjects (n = 45) mean CPD decreased 1.45 (0.37, 2.52) more than female NNCC subjects (n = 58).

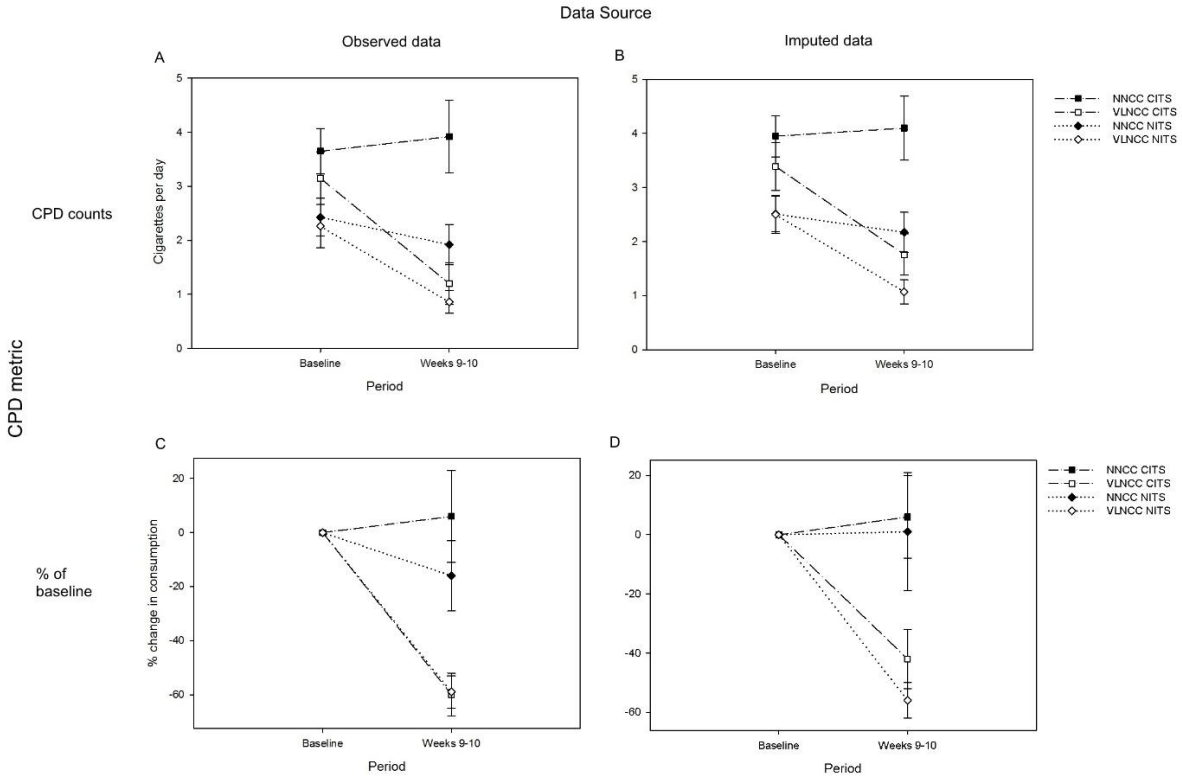
eFigure 5. Cigarette consumption, at baseline and end of study, for African American and White Subjects



CPD cigarettes per day; NNCC normal-nicotine-content cigarettes; VLNCC very-low-nicotine-content cigarettes; AA African American

Cigarette consumption during the baseline and week 9-10 two-week time blocks by treatment group, presented separately for African-American (AA) and White subjects. Data are displayed by two different estimation methods: observed data (A), and multiple imputation (B) (mean ± standard error). Analysis of observed data indicated that, while controlling for baseline CPD, race does not significantly moderate the effect of the treatment group (p = 0.75). Mean change among African American VLNCC subjects (n = 17) was -1.47 CPD (95% CI, -4.04, 1.10) compared to mean change among AA NNCC subjects (n = 23). Mean change among White VLNCC subjects (n = 63) was -1.77 (95% CI, -2.58, - 1.06) compared to mean change among White NNCC subjects (n = 68) Analysis of imputed data showed substantively the same results; race was not shown to significantly moderate the treatment effect (p = 0.56). Mean change among AA VLNCC subjects (n = 27) was -1.20 CPD (95% CI, -3.12, 0.73) compared to mean change among AA NNCC subjects (n = 34). Mean change among White VLNCC subjects (n = 76) was -1.70 (95% CI, -2.40, - 1.01) compared to mean change among White NNCC subjects (n = 76).

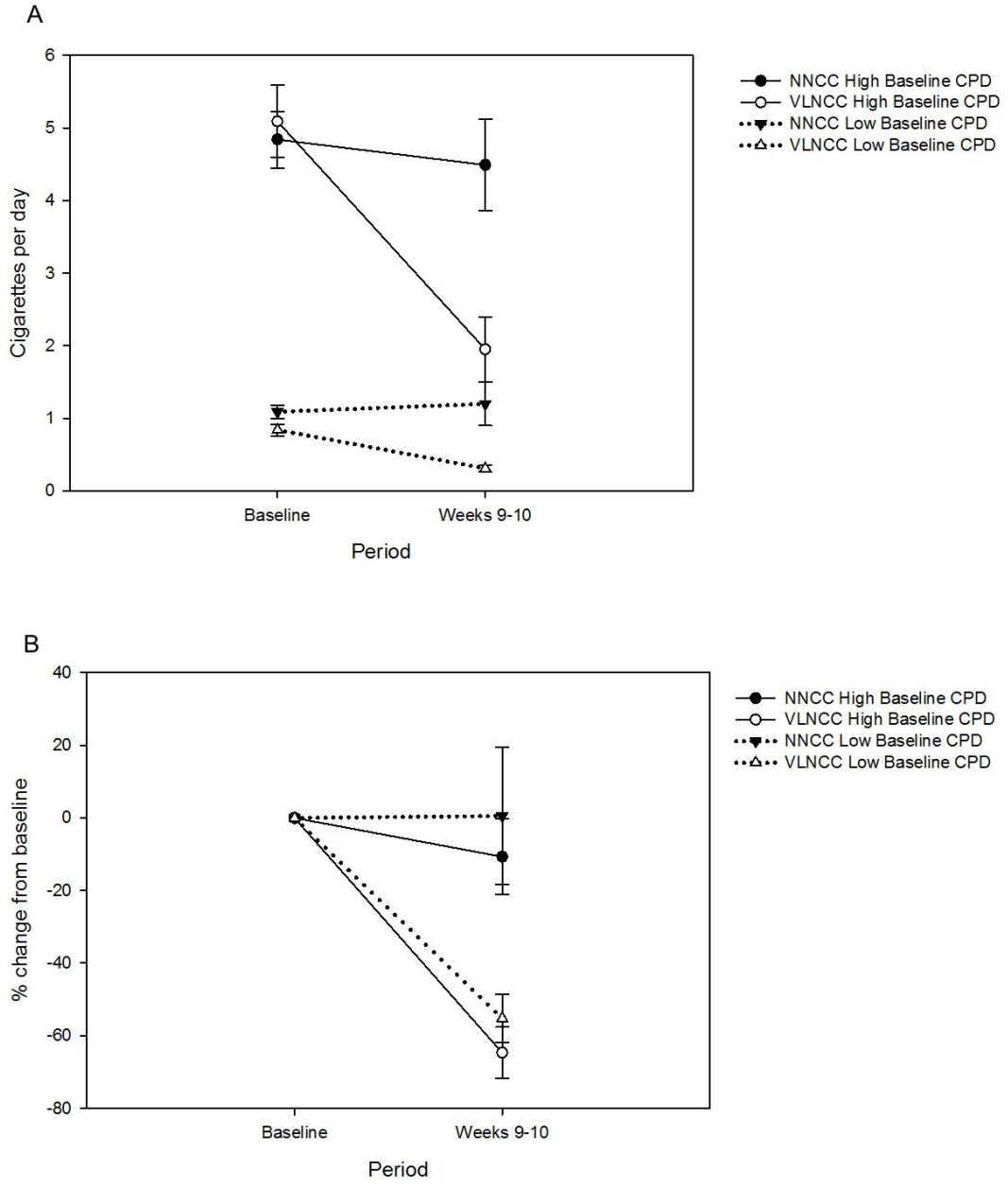
eFigure 6. Cigarette consumption, at baseline vs end of study, for CITS and NITS



NNCC normal-nicotine-content cigarettes; VLNCC very-low-nicotine-content cigarettes; CITS “converted” non-daily, intermittent smokers with a prior history of daily smoking; NITS “native” non-daily, intermittent smokers

Cigarette consumption by study time point and group, and by history of daily smoking, contrasting CITS (observed n=89, imputed n= 118 MI), who have previously been daily smokers, with NITS (observed n=101, imputed n = 120), who have never smoked daily for 6 months or more. Data are displayed in two different metrics: CPD counts (A and B) and % of baseline CPD (C and D), and by two different estimation methods: observed data (A and C), and multiple imputation (B and D). (mean ± standard error). In analysis of imputed data, mean decrease among CITS was 1.89 CPD (95% CI, 0.80, 2.97) more with VLNCC than NNCC, while mean decrease among “native” ITS (NITS) without a history of daily smoking was 1.07 CPD (95% CI, 0.35, 1.79) more. With observed data, mean decrease among CITS was 2.32 CPD (95% CI, 1.07, 3.57) more with VLNCC than NNCC, while mean decrease among NITS was 0.99 CPD (95% CI, 0.28, 1.70) more. When CPD was expressed as a percentage of baseline, with observed and imputed data, CITS and NITS showed very similar two-thirds decrease in CPD.

eFigure 7. Cigarette consumption, at baseline vs end of study, for subjects stratified by baseline CPD

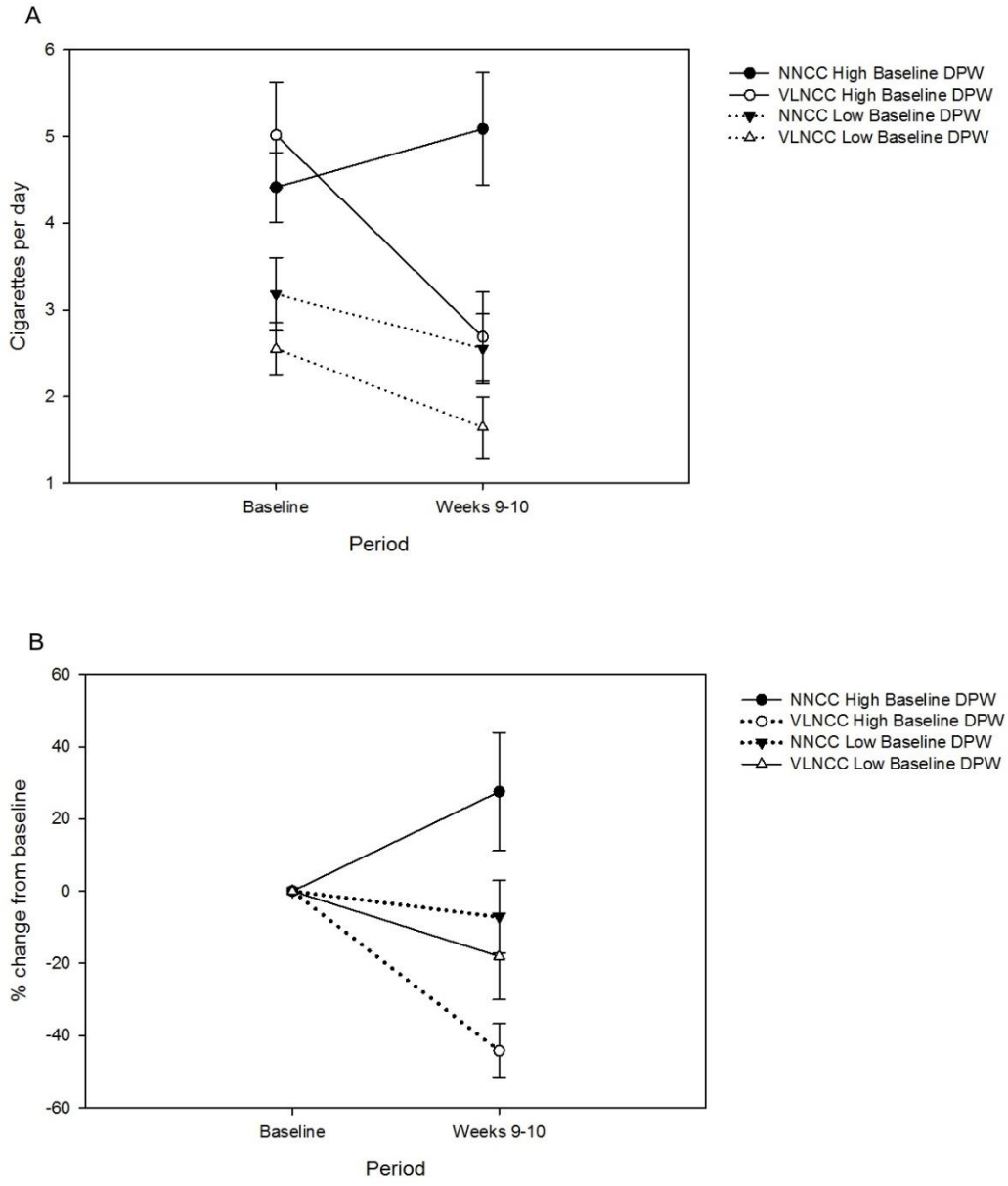


CPD Cigarettes per day; NNCC normal-nicotine-content cigarettes; VLNCC very-low-nicotine-content cigarettes

Cigarette consumption during the baseline and week 9-10 two-week time blocks by treatment group, contrasting subjects above (high) and below (low) the median baseline

CPD (2.15 CPD). Data are displayed in two different metrics: CPD counts (A) and % of baseline CPD (B). Observed data plotted (mean ± standard error). Analysis indicated a significant interaction between the baseline CPD strata and treatment group ($p = 0.004$). In the low baseline CPD stratum, mean decrease among VLNCC subjects ($n = 52$) was 0.64 CPD (95% CI, 0.08, 1.19) more than NNCC subjects ($n = 48$). In the high baseline CPD stratum, mean decrease among VLNCC subjects ($n = 39$) was 2.79 CPD (95% CI, 1.38, 4.20) more than NNCC subjects ($n = 51$). This effect did not hold when CPD change was expressed as a percentage of baseline CPD. When expressed as % of baseline CPD, analysis indicated that the interaction between baseline CPD strata and treatment group is not significant ($p = 0.94$). In both baseline CPD strata, the VLNCC group decreased cigarette consumption by approximately 55% more than the NNCC group.

eFigure 8. Cigarette consumption, at baseline vs end of study, for subjects stratified by baseline number of days per week smoking



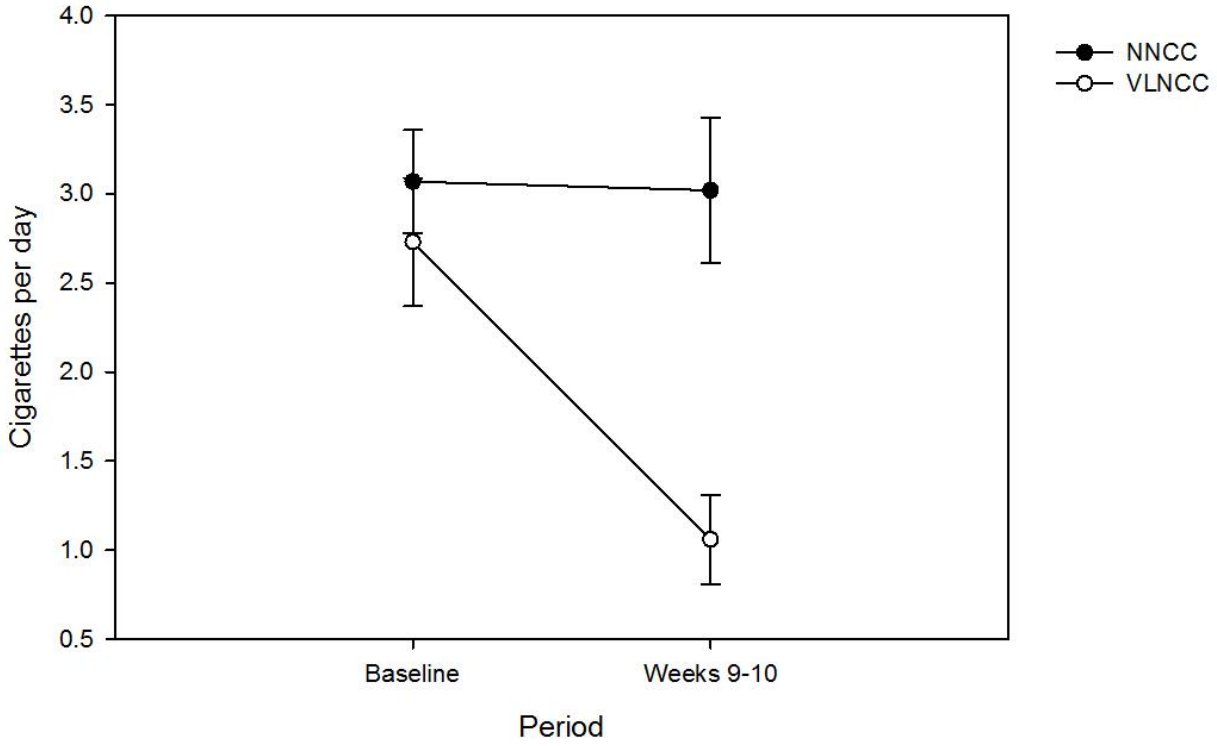
CPD cigarettes per day; NNCC normal-nicotine-content cigarettes; VLNCC very-low-nicotine-content cigarettes; DPW=days per week

Panel A. Cigarette consumption during the baseline and week 9-10 two-week time blocks by treatment group, contrasting subjects above (high) and below (low) the median baseline number of days smoking per week (DPW) (median = 5.5 days). Cigarettes consumption was based on CPD on days subjects smoked. Otherwise, low DPW

subjects would have low CPD by definition. Data are displayed in two different metrics: CPD counts (A) and % of baseline CPD (B) Observed data plotted (mean ± standard error). Analysis indicated that, while controlling for baseline CPD, there is a significant interaction between the baseline DPW strata and treatment group (p = -0.007). In the low baseline DPW stratum, mean decrease among VLNCC subjects (n = 34) was 0.53 CPD (95% CI, 0.34, 1.41) more than NNCC subjects (n = 49). In the high baseline CPD stratum, mean decrease among VLNCC subjects (n = 34) was 2.80 (95% CI, 1.28, 4.32) more than NNCC subjects (n = 49).

Panel B. Analysis of change as % of baseline CPD indicated there is a significant interaction between the baseline DPW strata and treatment group (p = 0.033). In the low baseline DPW stratum, mean change among VLNCC subjects (n = 34) was -14.86% (95% CI, -46.16%, 16.45%) more than NNCC subjects (n = 49). In the high baseline CPD stratum, mean change among VLNCC subjects (n = 34) was -69.46% (95% CI, -100%, -28.36%) more than NNCC subjects (n = 49). The figure shows that the interaction is due to the fact that the more frequent smokers (high-baseline-DPW) assigned to NNCCs actually increased their smoking over time, whereas those assigned to VLNCCs decreased smoking, regardless of their baseline frequency.

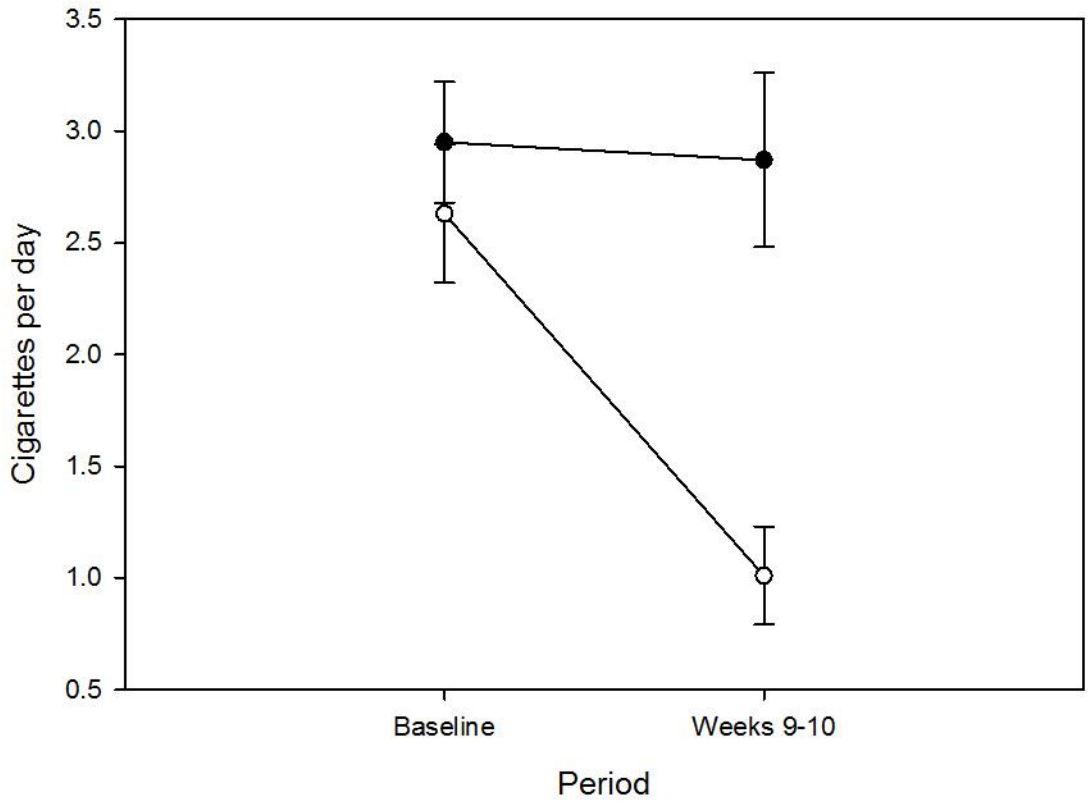
eFigure 9. Cigarette consumption at baseline vs end of study among subjects with low self-reported smoking conventional cigarettes



CPD Cigarettes per day; NNCC normal-nicotine-content cigarettes; VLNCC very-low-nicotine-content cigarettes

Cigarette consumption during the baseline and week 9-10 two-week time blocks by treatment group, excluding 21 subjects who reported ≥10% use of non-research conventional cigarettes. Observed data plotted (mean ± standard error). Analysis indicated that, while controlling for baseline CPD, the VLNCC group (n = 76) reduced their cigarette consumption significantly more than the NNCC group (n = 93) over the 10 week post-randomization period ($p < 0.001$). Mean decrease among VLNCC subjects was 1.73 CPD (95% CI, 0.94, 2.52) more than NNCC subjects.

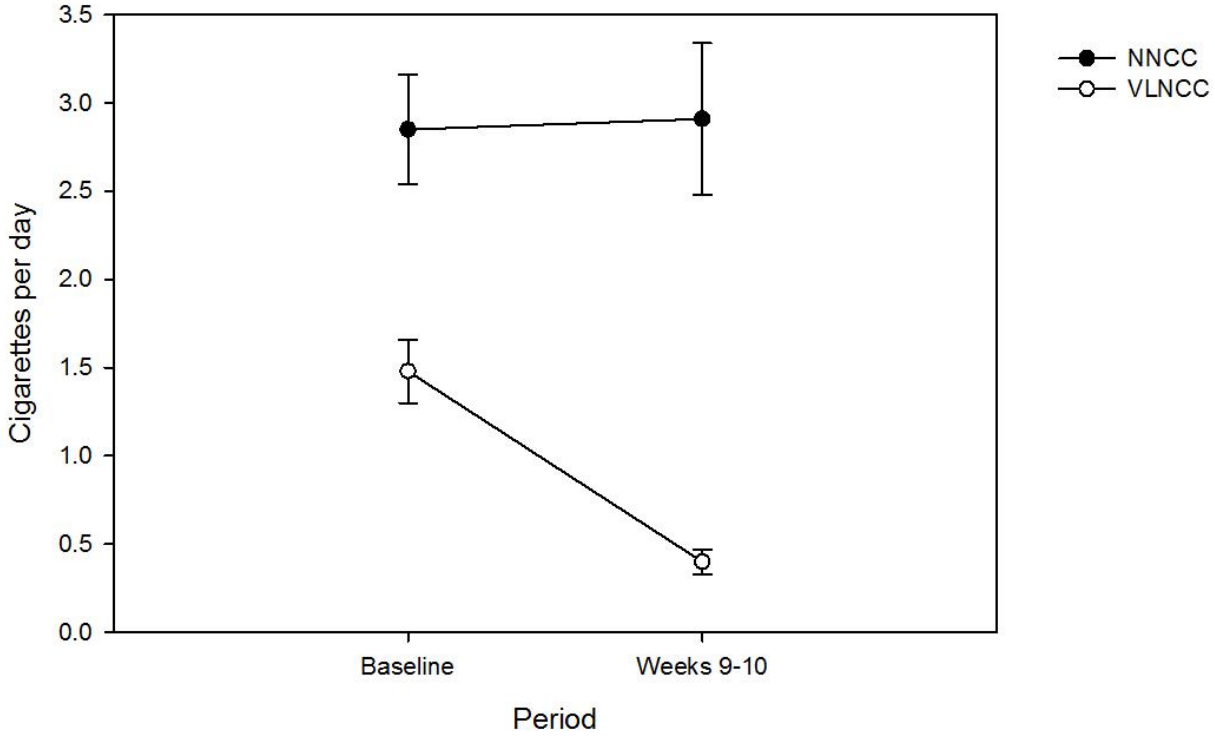
eFigure 10. Cigarettes smoked per day (Research Cigarettes Only), at baseline (2 weeks prior to randomization) vs end of study (weeks 9-10)



CPD Cigarettes per day; NNCC normal-nicotine-content cigarettes; VLNCC very-low-nicotine-content cigarettes

Cigarette consumption during the baseline and week 9-10 two-week time blocks by treatment group, based on research cigarettes (i.e., excluding conventional cigarettes reported or butts submitted). Observed data plotted (mean ± standard error). Controlling for baseline CPD, the VLNCC group (n = 91) reduced their cigarette consumption significantly more than the NNCC group (n = 99) over the 10 week post-randomization period (1.64 CPD, 95% CI 0.94-2.34, $p < 0.001$), similar to the primary analysis.

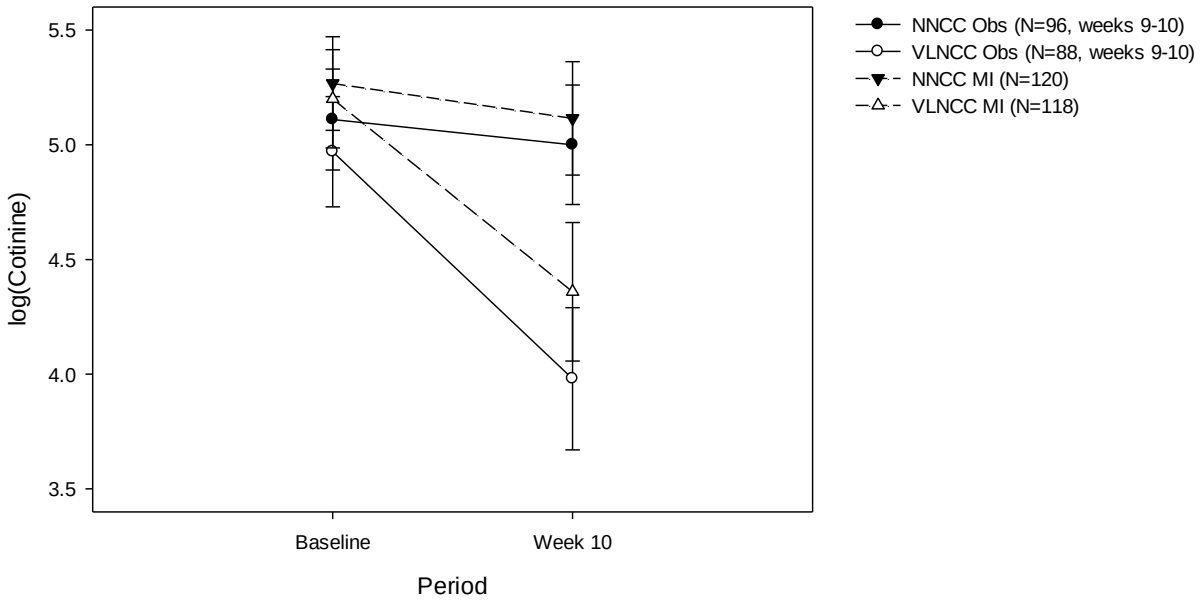
eFigure 11. Cigarette consumption at baseline vs end of study, excluding subjects inferred to have cheated with conventional cigarettes, based on urinary cotinine values



CPD Cigarettes per day; NNCC normal-nicotine-content cigarettes; VLNCC very-low-nicotine-content cigarettes

Cigarette consumption during the baseline and week 9-10 two-week time blocks by treatment group, excluding subjects who were inferred to have “cheated” by smoking conventional cigarettes, based on their urinary cotinine concentrations (see supplementary Methods section 2.4 for algorithm). Observed data plotted (mean ± standard error). Analysis indicated that, while controlling for baseline CPD, the VLNCC group (n = 61) reduced their cigarette consumption significantly more than the NNCC group (n = 83) over the 10 week post-randomization period (p = 0.001). Mean decrease among VLNCC subjects was 1.29 CPD (95% CI, 0.53, 2.05) more than NNCC subjects.

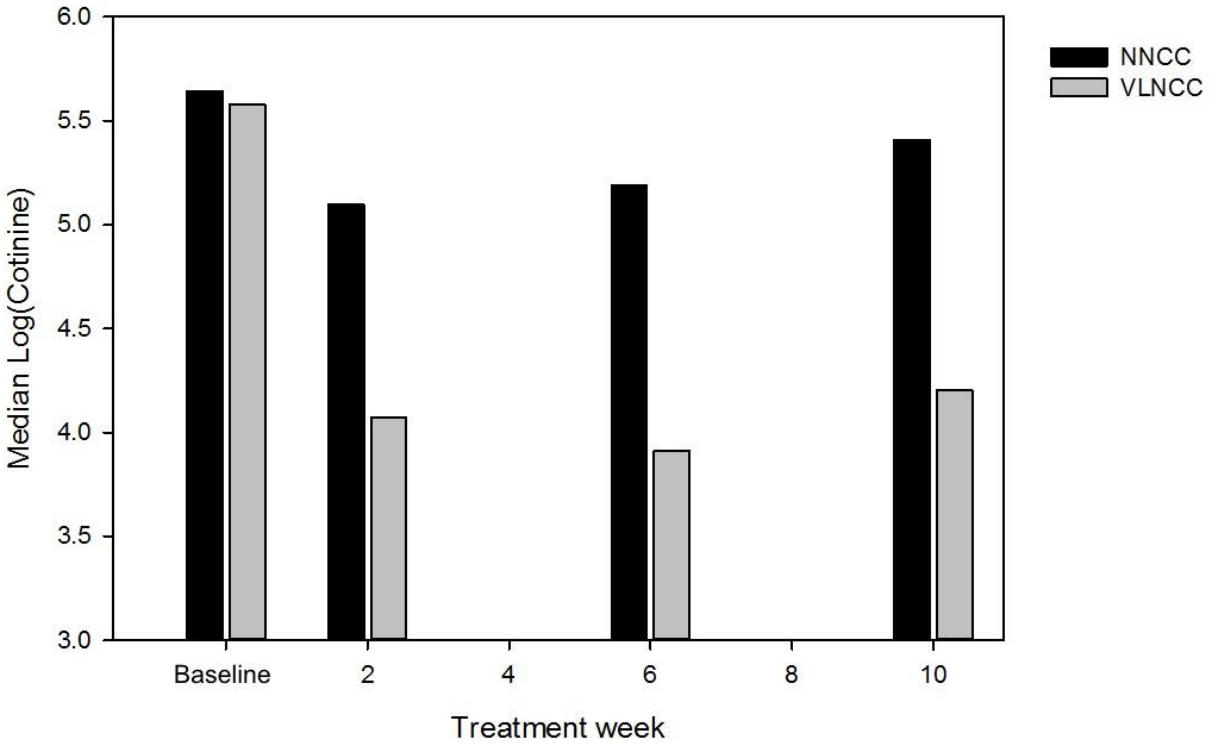
eFigure 12. Mean total urinary cotinine concentrations, at baseline and end of study



NNCC normal-nicotine-content cigarettes; VLNCC very-low-nicotine-content cigarettes; Obs observed; MI multiple imputation; CPD cigarettes per day

Data are log-transformed mean (± standard error) total (free + glucuronidated) urinary cotinine concentrations (ng/mL) in urine. Baseline data are based on observed data. Week 10 data are based either on observed data (subjects not lost to observation) (_____) or a monotone multiple imputation model of baseline variables (same as listed in Figure 2) and all longitudinal cotinine values (- - - -). Controlling for baseline cotinine, in the multiple-imputation analyses, there was a treatment group difference in modeled cotinine decrease (50.1% greater decrease in VLNCC than NNCC, 95% CI, 12.2% to 71.7%, P=0.016). The treatment group effect was greater in the complete case analysis, with a 58.9% (95% CI, 28.6% to 76.4%) greater cotinine decrease in the VLNCC group (P=.002).

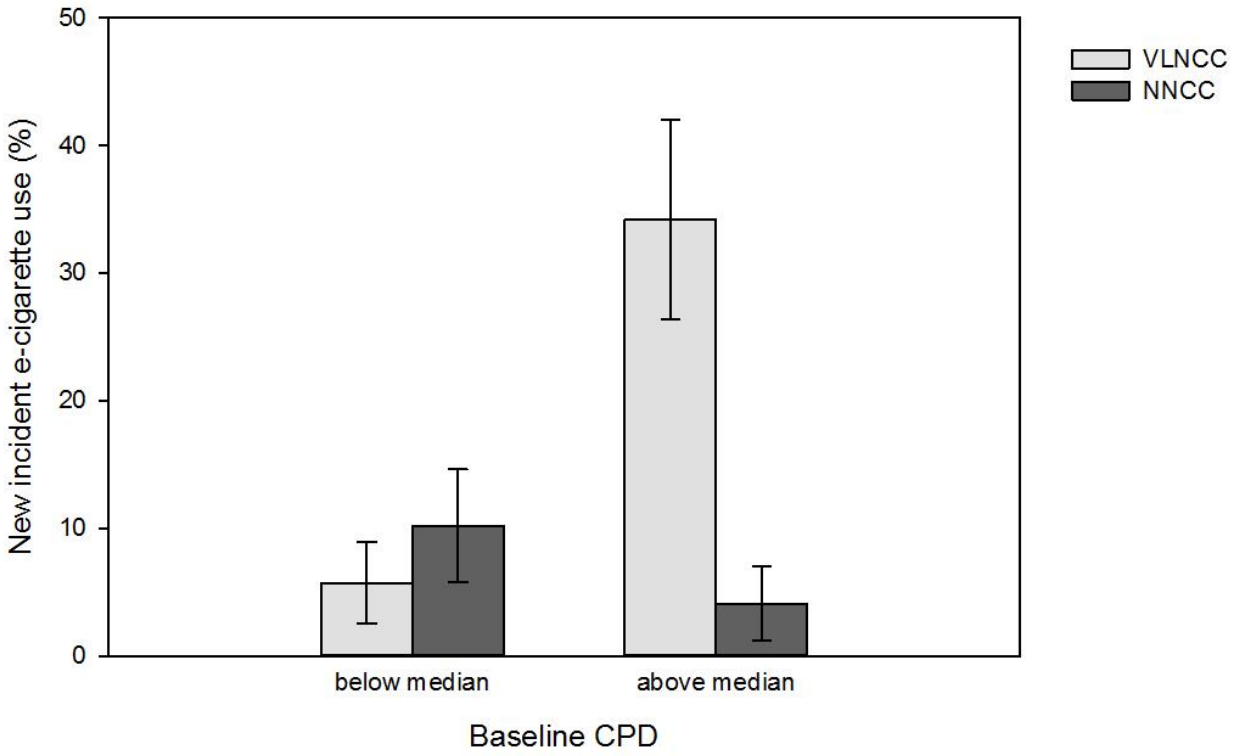
eFigure 13. Urinary total cotinine concentrations by time and treatment group



NNCC normal-nicotine-content cigarettes; VLNCC very-low-nicotine-content cigarettes

Values are medians of logged concentrations (ng/mL) of total (glucuronidated + free) cotinine in urine samples collected at the indicated time-points. (Per protocol, urine samples were not collected at weeks 4 or 8.) Observed data medians.

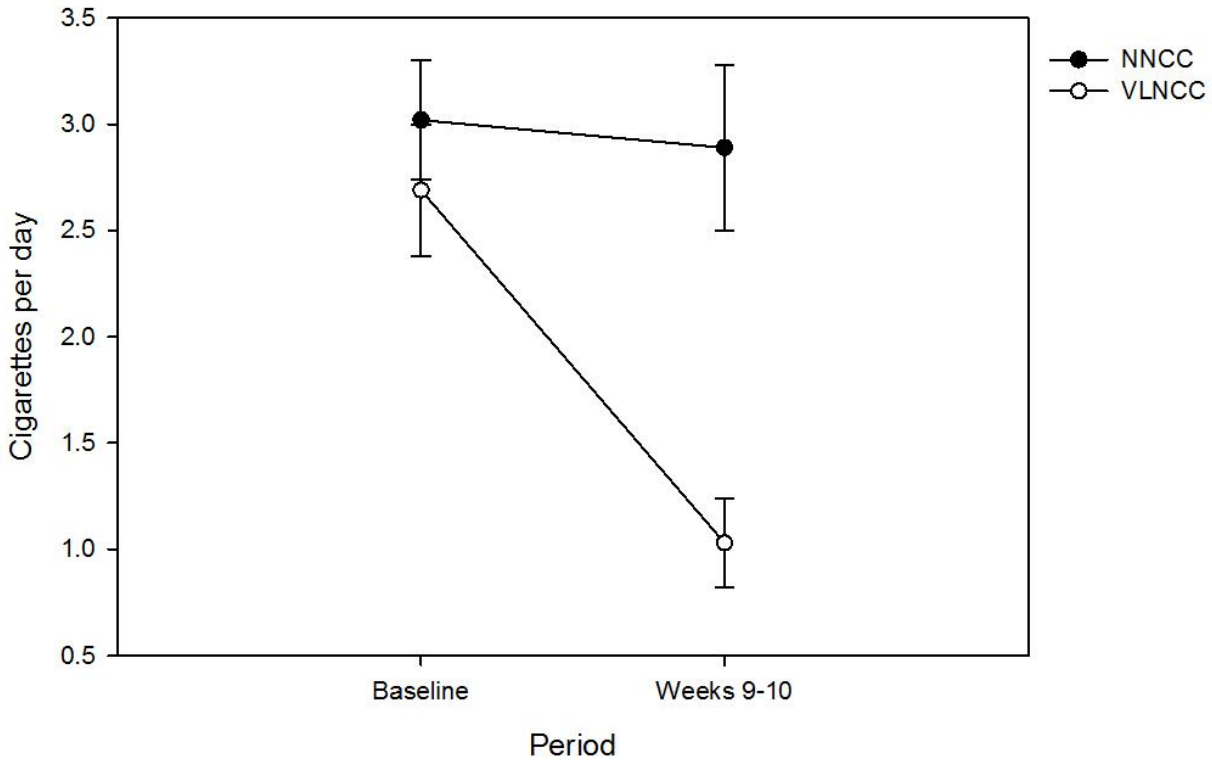
eFigure 14. Reported new use of e-cigarettes post-randomization, by treatment group and baseline smoking rate



CPD Cigarettes per day; NNCC normal-nicotine-content cigarettes; VLNCC very-low-nicotine-content cigarettes

Percentage of participants (± standard error) who reported using an e-cigarette at least once in the post-randomization period, among those who reported no use of e-cigarettes for at least 30 days preceding study enrollment and during the 2-week baseline period. Logistic regression indicated greater e-cigarette use in the VLNCC group vs NNCC, modified by a significant interaction with baseline CPD (log-likelihood test, P=.002), with baseline CPD dichotomized at the median of 2.3 CPD, indicating that this effect was primarily evident in the heavier smokers. Among the heavy (above-the-median) smokers, those in the VLNCC group had over 12 times higher odds than those in the NNCC group of newly reporting use of e-cigarettes post-randomization OR=12.22 [95% CI, 2.55 to 58.51]). In contrast, the relationship was much weaker, and non-significant, among the lighter (below-the-median) smokers (OR=1.89 [95% CI, 0.43 to 8.38]).

eFigure 15. Cigarette consumption at baseline vs end of study among subjects who did not increase their usage of other nicotine-containing products vs baseline



CPD Cigarettes per day; NNCC normal-nicotine-content cigarettes; VLNCC very-low-nicotine-content cigarettes

Cigarette consumption during the baseline and week 9-10 two-week time blocks by treatment group, excluding 1 subject who increased their use of other tobacco/nicotine products post-randomization by ≥1 unit/week. Observed data plotted (mean ± standard error). Analysis indicated that, while controlling for baseline CPD, the VLNCC group (n = 90) reduced their cigarette consumption significantly more than the NNCC group (n = 99) over the 10 week post-randomization period ($p < 0.001$). Mean decrease among VLNCC subjects (n = 90) was 1.65 CPD (95% CI, 0.93, 2.36) more than NNCC subjects.