Managing Non-Communicable Disease Risk Factors in Developing Countries: Tobacco Control, Cardiovascular Disease Risk Surveillance, and Diabetes Prevention

MANAGING NON-COMMUNICABLE DISEASE RISK FACTORS IN DEVELOPING COUNTRIES: TOBACCO CONTROL, CARDIOVASCULAR DISEASE RISK SURVEILLANCE, AND DIABETES PREVENTION

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ABSTRACT

Non-communicable diseases (cardiovascular diseases, cancers, chronic respiratory diseases, diabetes, and mental illnesses) and associated risk factors (unhealthy diets, physical inactivity, harmful use of alcohol, physical inactivity) are on the rise in developing countries, posing a threat to the health and financial systems of emerging economies.

In response, international organizations and Ministries of Health alike have started to tackle chronic diseases and associated risk factors with policies and treatment programs. Yet to this day, the body of evidence for best practices regarding the monitoring, prevention, and control of non-communicable diseases in low- and middle-income countries remains small.

This doctoral thesis adds to this body of evidence. The first paper of my thesis assesses the impact of a national tobacco control program in high schools in Chile. Specifically, it evaluates the effectiveness and makes several policy recommendations based on the findings. My second dissertation paper assesses the modifying effect of a change in anti-retroviral treatment among HIV-positive subjects in KwaZulu-Natal, South Africa on cardiovascular disease risk factors of high body mass index and high blood pressure. The third paper is based on

a randomized controlled trial assessing the effectiveness of a social-network-based diabetes and weight management program in Jordan.

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INTRODUCTION

Non-communicable diseases (cardiovascular diseases, cancers, chronic respiratory diseases (COPD), diabetes, and mental illnesses) and associated risk factors (unhealthy diets, tobacco use, harmful use of alcohol, physical inactivity) are on the rise in developing countries. Globally, Ischemic heart disease, stroke, and COPD are the three leading causes of mortality[1], and non-communicable diseases (NCDs) constitute close to 54% of the overall disease burden, as measured in disability adjusted life years (DALYs).[2] NCD risk factors of high blood pressure and tobacco smoking topped the global burden of disease charts in 2010, usurping childhood underweight as the number one contributor to global DALYs in 1990.[3] NCDs are also major drivers of costs to national healthcare systems. A recent report on the Global Economic Burden of NCDs in low and middle income countries estimated that under 'business as usual' conditions, cumulative losses from cancer, diabetes, cardiovascular diseases, and COPD will surpass US$47 trillion between 2011 and 2025.[4]

In light of the increasing disease and financial burden of NCDs in low and middle income countries, international organizations and Ministries of Health alike have started to tackle chronic diseases and associated risk factors with policies and treatment programs.[5] However, the body of evidence for best practices regarding the monitoring, prevention, and control of NCDs in LMICs is small. The following three areas are in particular need of further studies: 1) Monitoring and assessment of national policies directed at curbing NCDs, particularly those focused on tobacco control[6]; 2) Monitoring and management of chronic-infectious disease co-morbidities in LMICs - it remains unclear how NCD prevention and treatment efforts interact with the rise in

comorbidities, especially in settings with high prevalence of HIV and TB[7,8]; 3) Evidence on effective NCD risk factor prevention programs in emerging economies.[4]

My doctoral thesis adds to this body of evidence. The first paper of my thesis assesses the impact of a national tobacco control program in high schools in Chile. Specifically, it evaluates the effectiveness and makes several policy recommendations based on the findings. It was accepted for publication by the *Bulletin of the WHO*. My second dissertation paper assesses the modifying effect of a change in ART treatment among HIV-positive subjects in KwaZulu-Natal, South Africa on cardiovascular disease risk factors of body mass index (BMI) and high blood pressure (*Abstract published by Lancet Global Health*). The third paper is based on a randomized controlled trial assessing the effectiveness of a social-network-based diabetes and weight management program in Jordan (*Invited for submission by Annals of Internal Medicine*).

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PAPER #1: CAN BANS BREAK BAD HABITS? AN INTERRUPTED TIME SERIES ANALYSIS OF THE IMPACT OF THE HIGH SCHOOL SMOKING BAN ON TEENAGE SMOKING BEHAVIOR IN CHILE, 2000 – 2011

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ABSTRACT

Objective. In 2005, Chile passed an anti-smoking legislation that included a complete smoking ban in all high schools and a tobacco sales ban within 300 meters of all schools. This study evaluates the bans' impact on smoking behavior among high school students.

Methods. We conducted an interrupted time series analysis, using repeated cross-sectional data from Chile's School Population Survey SENDA-SPS (2000-2011) for high school students (ages 12-18) and a university-age control group (ages 19-24). Poisson regression models were used to assess trends in smoking behavior before and after the policy change. The two outcome measures

were self-reported past 30-day smoking prevalence (binary), and prevalence of frequent smoking (smoking 15 or more days per month, yes/no).

Findings. From 2005 to 2011, smoking prevalence declined among high-school students by 6.8% per year, which was 2.9% (95% CI: 0.18, 5.00, p=0.009) greater than the analogous decline among the university students. We estimated that after 5-6 years of enforcing the law, smoking prevalence among high school students was 13.7% lower than the level it would have been without the ban. The impact of the smoking ban was primarily driven by declines in smoking prevalence among students in grades 8 to10. The smoking ban had no significant impact on frequent smoking.

Conclusion. The 2005 school smoking ban was successful in reducing smoking prevalence among younger high school students in Chile, but future interventions targeting older individuals and more frequent smokers may be needed.

INTRODUCTION

The detrimental health effects of smoking and tobacco use are widely documented.[1-7] Every year, five million deaths occur globally due to first-hand smoking.[8] Eight out of ten smoking-related deaths occur in low- and middle-income countries.[8,9] Despite the strong evidence that links smoking to increased mortality and morbidity and the potential effectiveness of strictly enforced policies such as public smoking bans[10], subsidized cessation programs[11-13], tobacco warning labels[14-16], and tax increases[17-20], countries with emerging economies and thus increased disposable incomes often play legislative catch-up to counter increased smoking trends, and the impacts of these legislative changes differ based on context.

One country that has experienced consistent economic growth, but is still battling high smoking rates, is Chile. As of 2011, Chile remained the country with the highest smoking rates in Latin America[21,22] and with the second highest teenage smoking rate globally.[9] To counter these trends, on June 13th, 2005, Chile ratified the Framework Convention on Tobacco Control (FCTC).[23] This provided momentum for the new tobacco Law #20.105[24], which took effect on January 1st 2006.

The strongest provision in the law is the high school smoking ban: it was the only provision of Law #20.105 that was enforced with 100% reported compliance, and that targeted a specific population subgroup (high school students) (See Supplementary Appendix 1.2 & 1.3). These two factors allow for an impact evaluation of the law by comparing its impact on teenagers versus young adults. Indeed, preliminary evidence suggests that smoking rates in high school students have declined from 2005 - 2011, but that smoking in the general adult population did not decline

significantly.[22] To our knowledge, this trend, as well as the overall effectiveness of school smoking bans, have not yet been rigorously evaluated in the scientific literature.[25] Hence, the goal of this paper is to evaluate the ban's impact on smoking prevalence among high school students.

METHODS

Study Design

The analysis followed an interrupted time series (ITS) design with a comparison group, quantifying the impact of the school smoking ban by evaluating trends in smoking prevalence before and after the ban in the target population (high school students 12-18 years), in comparison to trends over the same periods in a group presumed unaffected by the ban. We used the general population aged 19-24 years as the comparison population, given that over 40% of the 19-24 year old population attended university or a post-secondary institution in 2008 in Chile26 (and hence were in a similar institutional environment), that most Chileans who smoke started smoking in their last years of high school or first year after high school, and that the smoking ban was implemented in schools, but not in universities or workplaces. Notably, the comparison population in 2000/01 to 2006/07 included the surveyed general population age 19 – 24 years; in 2008/09 it included all 20-24 year olds; in 2010/11 it included all 22 – 24 year olds. This was to ensure the control group did not include anyone subjected to the ban when still in high school.

Data

For the intervention population, we used data from School Population Survey (SENDA-SPS) – a biennial, and regionally representative survey on substance abuse and addictive behavior in the

Chilean school population, including the last grade of primary school (equivalent to 8th grade), and the high school population (equivalent of 9th – 12th grade). SENDA-SPS was conducted in the fall of every odd year, and data starting in 2001 were included in the analyses.[27]

For the comparison population, we used data from the General Population Survey (SENDA-GPS), conducted in even years, for 2000-2010.[27] (See Supplementary Appendix 1 for more details on data structure).

We combined SENDS-SAP and DENDA-GPS, resulting in a dataset containing three waves before the law (2000-01, 2002-03, 2004-05) and three waves after (2006-2007, 2008-09, 2010-11), including different individuals each time, with an average sample size of ~50,000 individuals per biennium in SENDA-SPS and ~ 2,300 individuals in SENDA-GPS per biennium (See Supplementary Appendix 1, Tables S1.3 – S1.5). The SENDA-SPS and SENDA-GPS datasets are publicly available.

Statistical analysis

Trends in smoking prevalence rates in the high school population before and after the policy change were compared to those in the comparison population. The main outcome measure was self-reported, past 30-day smoking prevalence (yes/no). As a secondary outcome, we created a 'frequent smoking' variable that was a binary indicator for smoking 15 or more days per month during the last month (yes/no).

In general, the estimation of prevalence rate ratios (rather than odds ratios) is of interest when common outcomes are involved.[28] Thus, we used the robust Poisson model to model the binary outcomes of past 30-day smoking and frequent smoking, which allowed for robust and direct estimation of prevalence ratios.[9,29-31] In the first stage, the robust Poisson models were run

separately for control and intervention groups due to different variances arising from different samples and sample frames. Robust standard errors were clustered at the municipality level. In the Poisson models, the primary independent variables were coefficients reflecting the annual rate of change in smoking prevalence during the post-intervention period, relative to the annual rate of change in the pre-intervention period. In multivariable regression, we controlled for age, sex, an interaction term for age and sex, school type, grade-level, region, and grade point average in the intervention group; and for age, sex, age*sex, socioeconomic status, method of survey administration, and region in the control group. Missingness in covariates was generally lower than 2% and the complete case method was chosen for the main analysis. The second stage was a two-sample t-test with unequal variances conducted on the estimated coefficient for post-intervention change in the intervention group compared to the coefficient in the control group. All analyses were performed using STATA 12.

We conducted numerous sensitivity analyses to evaluate the robustness of our base-case results on smoking prevalence. These included: (1) including all 19-24 year olds in the control population; (2) running analogous analyses using past 30-day marijuana use as the main outcome (to test for the specificity of the school smoking ban on smoking behavior versus addictive behavior in general); (3) including only those municipalities measured in every survey year; (4) excluding individuals with less than high school education in the control group; (5-6) including past month alcohol prevalence, religion, and paternal education as additional control variables; (7) adjusting for survey weights; (8) adjusting for complex survey design; (9) using SENDA-GPS 19-64 year olds as the control population; and (10) using the missing indicator method to account for missingness.[32] For investigating the impact of the law on smoking frequency, we

conducted the following two sensitivity analyses: (1) adjusting for complex survey design; and (2) stratifying the analysis by grade level in the intervention group.

RESULTS

Descriptive statistics for the intervention and control samples are presented in Table 1.1. Unadjusted for covariates, 30-day smoking prevalence among high school students was highest in 2001, with a prevalence of 41.9%, slightly declining to 40.1% in 2004-05. After the law, the smoking prevalence in this population declined to 25.7% in 2010-11. Smoking prevalence among the university aged comparison population was overall higher. By 2008-09, the prevalence was 50.0%, and dropped to 44.9% by 2010. Immediately after 2005, there was a slightly steeper decline in smoking prevalence among high school students than among the university age population.

Smoking frequency (days smoked during last 30 days) was overall higher in the university-aged population than in the high school population. In 2002-03, high school smokers smoked an average of 16.5 days per month, which declined to 15.0 days/month in 2006/07, further dropping to 13.0 days per month in 2010-11. Number of days smoked per month in the comparison group was relatively flat over the examined time period, with a peak level of 21.4 days during 2004-05, and a level of 19.9 days smoked in 2010-11. Of note, smoking prevalence and frequency among smokers increased with increasing school grade. Smoking frequency was also highest in 12^{th} graders versus 8^{th} graders, and average smoking frequency was highest in 2002-03 and lowest in 2010-11 in all groups and grades (Data shown in Supplementary Appendix 1, Tables S1.3 – S1.7).

Table 1.1: Descriptive Statistics of key variables. The control university aged population values in 2000/01 to 2006/07 include the surveyed general population age 19 – 24 years. The main control population values in 2008/09 refer to the 20-24 year olds; the control population in for the year 2010/11 was the 22 – 24 year old population in the general population survey

	HS population age 12-22						University Aged Population age 19-24*					
Year	**2000/01**	**2002/03**	**2004/05**	**2006/07**	**2008/09**	**2010/11**	**2000/01**	**2002/03**	**2004/05**	**2006/07**	**2008/09**	**2010/11**
n overall	*56,817*	*57,032*	*59,101*	*51,432*	*48,213*	*33,509*	*5,466*	*1,945*	*1,927*	*1,937*	*1,517*	*902*
Age (SD)	15.5 (1.5)	15.6 (1.5)	15.2 (1.5)	15.4 (1.5)	15.4 (1.5)	15.5 (1.5)	21.5 (1.7)	21.6 (1.7)	21.6 (1.7)	21.5 (1.7)	22.0 (1.43)	23.0 (0.80)
Sex (Male, perc)	49.2%	49.3%	49.1%	49.5%	49.1%	49.3%	47.6%	56.2%	54.2%	51.7%	46.9%	45.3%
Past 30-day smoking prev (perc)	41.9%	38.9%	40.1%	34.9%	33.0%	25.7%	55.1%	58.2%	57.3%	54.8%	50.7%	44.9%
n smokers	*23,822*	*22,194*	*23,678*	*17,541*	*15,499*	*8,596*	*3,016*	*1,133*	*1,104*	*1,061*	*769*	*405*
# days smoked among smokers / month	NA	16.5	14.1	15.0	14.5	13.0	NA	21.3	21.4	19.8	20.9	19.9
Heavy Smoking (perc)	NA	19.42%	16.37%	15.46%	14.37%	10.04%	NA	42.78%	41.98%	37.38%	34.81%	31.04%
Past 30d marijuana use	7.8%	7.0%	6.1%	8.3%	8.0%	9.7%	6.7%	6.9%	7.1%	7.2%	7.8%	6.2%

* The main control population values in 2008/09 refer to the 20-24 year olds; the control population in for the year 2010/11 was the 22 – 24 year old population in the general population survey. This is to ensure that post-ban, the control group does not include anyone who was subjected to the ban when still in high school.

Impact of law on smoking prevalence

Adjusting for covariates in the multivariable regression model, smoking prevalence increased among high school students over the period 2000-2005, at an estimated annual rate of 0.6 % per year (p=0.014); the annual rate of change in the university-age control group over this same period was not significantly different from zero. Post 2006, there was an annual decline in smoking among the high school group of 6.8 % per year, which represents a 7.4 % improvement in the rate of change in smoking compared to the pre-intervention trend in the high school population alone. This improvement in the smoking trend in the high school group after the ban was 2.9 % greater (95% CI: 0.18, 5.00, p=0.009) than the analogous difference in the university-age group. Accounting for the additional change in the intervention group compared to the control, we estimate that smoking prevalence among high school students in the year 2010 was 13.7% lower than it would have been without the ban (Table 1.2).

Table 1.2: Main results from the 2-stage marginal fixed effects Poisson model testing the impact of the 2005 law on smoking prevalence. The presented RRs represent the annual dose response decrease in smoking prevalence. The first stage model of the high school population was adjusted for age, sex, region, school-type, course, and sex*age. The first stage model of the university-aged population included age, sex, region, SES, survey method, and sex*age. (CI = Confidence Interval; RR = Relative Risk).

Stage 1a: High School Students	**RR of 1-year prevalence change (95% CI)**	**RR of 1-year Difference in Prevalence change**	**RR of Difference in post-policy prevalence change**
Pre-Policy Annual Prevalence Rate change	1.01 (1.00, 1.01) p=0.014	0.926 (0.917, 0.934) p<0.001	Policy Intervention 1-year effect: 0.971 (0.950, 0.992) p = 0.0085 Policy Intervention 5-year effect: 0.863 (0.774, 0.961) p = 0.0085
Post-Policy Annual Prevalence Rate change	0.932 (0.927, 0.937) p<0.001		
Stage 1b: University-age Control Group			
Pre-Policy Annual Prevalence Rate change	1.01 (0.999, 1.02)	0.953 (0.935, 0.973) p<0.001	
Post-Policy Annual Prevalence Rate change	1.02 p = 0.065 0.964 (0.953, 0.974) p < 0.001		

Since the descriptive analysis (Table S1.6, Supplementary Appendix 1) revealed a stark difference in smoking prevalence among different high school grades, a grade-based stratified analysis was performed to determine the grades in which the law had the greatest impact. The results of these analyses are shown in Table 1.3. The smoking ban had the greatest impact on those students who were lowest prevalence smokers: the smoking ban was most effective among 8^{th} graders (leading to a 7.2 % (95% CI: 10.1%, 4.3%, $p<0.0001$) annual improvement in smoking trend in the HS population versus the control population after the ban), and least effective among 11^{th} and 12^{th} graders, for which the smoking ban had no significant impact on smoking prevalence.

Table 1.3: Main results from the 2-stage marginal fixed effects Poisson model testing the impact of the 2005 law on smoking prevalence for each high school grade. The presented RRs represent the annual dose response decrease in smoking prevalence. The first stage model of the high school population was adjusted for age, sex, region, school-type, course, and sex*age. The first stage model of the university-aged population included age, sex, region, SES, survey method, and sex*age. (CI = Confidence Interval; RR = Relative Risk).

Population and Study Period	8th grade	9th grade	10th grade	11th grade	12th grade
	Stage 1a: HS Group (Targeted Intervention Population)				
Pre-Policy Annual Prevalence Rate change	1.02 (1.001, 1.03) p=0.037	1.01 (0.999, 1.02) p=0.075	1.01 (0.999, 1.02) p=0.081	0.998 (0.990, 1.01) p=0.641	0.995 (0.941, 1.00) p=0.263
Post-Policy Annual Prevalence Rate change	0.898 (0.886, 0.910) p <0.001	0.930 (0.923, 0.938) p<0.001	0.930 (0.923, 0.937) p<0.001	0.940 (0.934, 0.947) p<0.001	0.948 (0.941, 0.956) p<0.001
Difference in Prevalence change	0.885 (0.864, 0.906) p<0.001	0.922 (0.908, 0.937) p<0.001	0.923 (0.911, 0.936) p<0.001	0.942 (0.930, 0.955) p<0.001	0.953 (0.940, 0.967) p<0.001
	Stage 1b: University-aged Group (Comparison Population)				
Pre-Policy Annual Prevalence Rate change	1.01 (0.999, 1.022) p = 0.065				
Post-Policy Annual Prevalence Rate change	0.959 (0.926, 0.993) p=0.02				
Difference in Prevalence change	0.931 (0.927, 0.935) p<0.001				
	Stage 2: Two sample mean-comparison test				
Intervention Effect	0.928 (0.899, 0.957) p<0.0001	0.967 (0.943, 0.992) p=0.01	0.968 (0.945, 0.992) p=0.0089	0.988 (0.965, 1.01) p=0.3276	1.00 (0.975, 1.02) p=0.9797

Table 1.4: Results from the 2-stage marginal fixed effects Poisson model testing the impact of the 2005 law on heavy smoking. The presented RRs represent the annual dose response in smoking frequency. The first stage model of the high school population was adjusted for age, sex, region, school-type, course residual, and sex*age. The first stage model of the university-aged population included age, sex, region, SES residual, survey method, and an interaction between sex and age. (CI = Confidence Interval; RR = Relative Risk).

Stage 1a: High School Group	**RR of prevalence change (95% CI)**	**RR of Difference in Prevalence change**	**RR of Difference in post-policy prevalence change**
Pre-Policy Annual change in frequency	0.975 (0.959, 0.992) p=0.004	0.947 (0.926, 0.969) p<0.001	Policy Intervention effect: 0.986 (0.938, 1.036) p=0.580
Post-Policy Annual change in frequency	0.924 (0.916, 0.932) p<0.001		
Stage 1b: University-aged Group			
Pre-Policy Annual change in frequency	0.992 (0.959, 1.03) p=0.669	0.961 (0.919, 1.00) p=0.079	
Post-Policy Annual change in frequency	0.953 (0.938, 0.969 p<0.001		

Impact of Law on Frequent Smoking

Prior to the change in law, in years 2000-2005, prevalence of frequent smoking (defined as smoking at least 15 of the past 30 days) in the intervention group declined by 2.5% annually 2000-2005 (95% CI: -4.1%, -0.8%, p=0.004); frequent smoking prevalence in the comparison group showed no significant trend in this period. Post – 2005, the difference in the frequent smoking prevalence change between the intervention and comparison group was not significant (p=0.58).

Sensitivity analyses

Detailed results from sensitivity analyses are presented in the Supplementary Appendix 1, and key findings summarized here. When examining the pre- and post-law prevalence changes in

marijuana use, past 30-day marijuana use after 2005 increased by 14% (95% CI: 11%, 18%; p<0.0001) annually in the high school population versus the control population.

Further sensitivity analyses including only those municipalities included in all years yielded identical effect size estimates as the main analysis (Table S1.8). When including only those with a high school diploma in the control population, the effect size for the smoking ban increased to 4.5 % (CI: 1.3, 7.5; p=0.0056). Adjusting for past-month alcohol prevalence, religion, and paternal education (in the high school population) led to an almost doubling in effect size estimate (to 4.8% (CI: 2.4, 6.4; p<0.0001)).

With regard to the sensitivity analyses for the impact of the law on frequent smoking, sampling-weight and complex survey adjusted models (results not shown) also revealed no significant difference in heavy smoking prevalence change before and after the law in control versus comparison groups. This result remained robust when stratifying by grade levels, also (Table S1.11).

DISCUSSION

Using repeated cross-sectional data for 319,798 Chileans observed between the years 2000 and 2011, employing a strong quasi-experimental design, we find that the change in trends for past-30-day smoking prevalence before and after the 2005 smoking ban was significantly greater in high school students than in the university-age control group. Smoking prevalence declined by an additional 2.9% annually among high school students after the implementation of the plan, compared to the post-intervention trend observed in the control group; this is a considerable

decline given that the teenage smoking rate in Chile remains the highest in Latin America and among the highest in the world.[1]

The average intervention effect was driven by the decline in smoking prevalence among younger high school students. In contrast, the smoking ban proved ineffective in lowering smoking prevalence among older high school students, as well as in lowering the prevalence of frequent smoking (i.e. 15 or more days per month). In combination, these results suggest that the smoking ban prevented smoking initiation and selectively targeted low frequency smokers. These findings are consistent with Becker and Murphy's theory[33] that those with least myopic preferences (non-smokers or less frequent smokers) are most positively impacted by anti-tobacco policies. The results have policy salience and practical implications, highlighting that 100% smoke free zones including tobacco sales restrictions can be highly effective in the Chilean context. Nonetheless, our findings that the law did not impact frequent smokers stress the need for better-targeted programs and policies. Examples of proven-effective programs that focus on high frequency smokers include smoking cessation counseling programs (in high schools) and free prescription nicotine patches[11]. Legislation featuring such programs has been proposed, but not yet passed or funded in Chile, in large parts due to lobbying efforts by the tobacco industry.

Several sensitivity analyses confirmed the robustness of our results: When including all 19-24 year olds in all years in the control population, we found that the effect size estimate was lower. This was expected, since the control population in 2008 and 2010 also included people previously exposed to the law. In contrast, when including only those with a high school diploma in the control population, the effect size increased. A possible explanation is that those with at

least a high school diploma continued (rather than altered) their smoking behavior between ages 19-24 years. The sensitivity analysis with marijuana use as the main outcome revealed that relative to the control population, marijuana use in high school students increased by 14% in the examined period after the law. This is further evidence that the decline in teenage smoking rates is directly attributable to the high school smoking ban. Our findings confirm the conclusions by Horner et al. that the difficulty of obtaining cigarettes was associated with lower smoking prevalence among Chilean teenagers.[34] Thus, recreational drug use might increase after the introduction of stricter tobacco laws, and needs to be monitored closely and pre-empted in similar settings.

In addition to the immediate effect, another important consideration is the law's long-term impact on the disease burden. There is emerging evidence that adolescence is a most critical window to form (or prevent the forming of) long-term addictive behaviors.[35-37] A recent survey on societal factors associated with smoking in Chilean teenagers concluded that increased difficulty in obtaining cigarettes was associated with less positive views about smoking in adolescents.[38] Grucza et al. concluded that while there might be long-term effects of youth access laws, these might be limited to women only.[39] Messer et al. showed that smoking cessation rates in the US population were highest in the age group <35 years, which the authors hypothesized to be closely related to changing norms about smoking in the workplace.[40] Thus, emerging evidence points towards the plausibility that adolescent smoking bans can have long-lasting impacts.

How large could the long-term disease impact of the Chilean high school smoking ban be? For example, a life table approach to assess long-term impact on morbidity has been used to show that in male age groups as young as 35-39 years of a 1960-1972 American cohort, the death rate in those who never smoked regularly was 1.34, versus 2.55 in those who smoked one or more packs of cigarettes per day.[41] At age 40-44, the death rates in male never-smokers were 1.93, versus 4.59 in heavy smokers. Overall death rates in females were lower in both smokers and nonsmokers, but still substantially higher in heavy smokers versus non-smokers. Assuming that the mortalities from a 1960-1972 American cohort apply to the current Chilean high school cohort, and that the prevalence impact persists over the next 15 -20 years, the Chilean high school smoking ban potentially could affect a >2 fold reduction in mortality in those prevented from smoking by the ban as early as 20 years from now. This would be considerable both based on a public health as well as an economic perspective: smoking-related diseases like lung cancer or COPD (Chronic Obstructive Pulmonary Disease) are extremely expensive to treat, so reductions in long-term morbidity would also likely imply considerable cost savings in the long run.[42-46] However, given the strong assumptions associated with the assessment of future mortality and morbidity decline due to the high school smoking ban, and the associated uncertainty about the permanency of the effect, both programs to ensure the permanency as well as data collection efforts to assess the long-term impact are needed.

Notwithstanding, this study, comprised of a nationally representative sample of over 300,000 adolescents and young adults from over 100 municipalities and over 4000 schools across all parts of Chile between 2000 and 2011, is a very comprehensive study of a country's national tobacco legislation to date. Its findings that high school smoking bans can significantly reduce teenage

smoking rates, but fail to address frequent smokers, are relevant policy lessons for both national and global health policy makers.

An important limitation of this study is that individuals were not randomly assigned to the intervention group (high-school students) and comparison group (university-age). However, we would like to emphasize that, except for the high school smoking ban, all provisions of the 2005 law uniformly affected Chile's general population (Supplementary Appendix 1, Section 2, Table S1.10). Thus, even if the law affected the comparison group, it would have been by a section of the law that also affected the high school population.

A further weakness might be found in the fact that the average age of smoking initiation was 13.2 years in Chile and that older individuals are less likely to start or quit smoking. Hence, university-age students—both smokers and non-smokers—may have a lower propensity to change their behavior in response to a similar ban. This could have led to an upward bias in the effect size estimates. However, in a sensitivity analysis using the general population aged 25-64 years as a control group, the effect sizes were not significantly higher than when using the university aged population as a comparison group.

Another limitation is that no longitudinal individual-level data exist to distinguish between three effects that may account for our results: 1) that the ban prevented people from starting smoking, 2) that the ban made less frequent (or less addicted) smokers to smoke less, and a more unexpected effect, 3) that the ban caused smokers to smoke more often. Only a survival analysis using individual-level panel data or an analysis of total cigarette consumption adjusting for the

days smoked per month among smokers before and after the ban would allow to disentangle these effects. Additional data on compliance with the smoking ban at Chilean high schools (akin to data provided by Goel et al.[47] in India) could have further strengthened our conclusions.

Future studies could explore equity concerns relating to the school smoking ban in Chile, as smoking prevalence is often highly correlated with socioeconomic status (SES).[48] Targeting light smokers largely means targeting high SES smokers who smoke less frequently (and are less addicted) than low SES smokers (results available from the authors). Since SES variables in both intervention and control group were highly collinear with neighborhood and were subjective based on the coding by interviewers, SES variables were omitted from the main analyses. Furthermore, a stratification based on SES would not have been meaningful due to the relative (as opposed to absolute) scale of the SES variables.

Another limitation was that there were no data on how well schools followed the ban, a potential effect modifier. However, interviews with key anti-tobacco advocates and Chilean policy makers did not any parallel programs that might have substantially biased the results.

CONCLUSION

This quasi-experimental analysis lends support that the 2005 school smoking ban (enforced since 2006) helped reduce the smoking prevalence among Chilean high school students, particularly among teenagers and light smokers. These results signal to policymakers and school administrators that school-smoking bans can be highly effective. Our results send an encouraging signal that Chile's 2013 anti-tobacco legislation, extending the ban to bars, restaurants, and

universities, may help in further curbing smoking rates in Chile. But also, both the 2005 and 2013 tobacco-legislation in Chile offered little help to those in need for (proven-effective) cessation counseling and cessation programs.[11,12,49] Hence, future policies would benefit from including accessible cessation programs, funds for smoke free enforcement in additional public spaces, and other provisions to help smokers quit. As a country with roughly seven million smokers out of a population of 16 million, Chile needs anti-tobacco policies that are more comprehensive than instituting public bans alone.

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Statement regarding Ethics Approval

The study was exempt of ethics approval as it only utilized secondary data from SENDA following conventional ethics guidelines and void of personal identifiers.

Transparency declaration

The lead author (ABF) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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SUPPLEMENTARY APPENDIX 1

CAN BANS BREAK BAD HABITS? AN INTERRUPTED TIME SERIES ANALYSIS OF THE IMPACT OF THE HIGH SCHOOL SMOKING BAN ON TEENAGE SMOKING BEHAVIOR IN CHILE, 2000 – 2011

Andrea B Feigl[1], Joshua A Salomon[1], Goodarz Danaei[1], Eric L Ding[2], Esteban Calvo[3]

S1.1 DATA AND SAMPLING PROCEDURES

Data source

For the intervention population, we used data from School Population Survey (SENDA-SPS) – a biennial, and regionally representative survey on substance abuse and addictive behavior in the Chilean school population, including the last grade of primary school (equivalent to 8th grade), and the high school population (equivalent of 9th – 12th grade). SENDA-SPS was conducted in the fall of every odd year, and data starting in 2001 were included in the analyses.[1] Sampling was based on a two-stage process: two classes were sampled from strata that were defined at the municipality, type of school (public, non-profit, and private), and grade (8th through 12th) level. From each class, 20 students were sampled at random. Since the data did not include explicit sampling unit and stratum variables, sampling units and strata were recreated (based on the survey methodology documents), and complex survey analysis was performed as a sensitivity analysis (See below detailed sections).

For the comparison population, we used data from the General Population Survey (SENDA-GPS). SENDA-GPS was conducted in even years, and we included data for 2000-2010.[1] The SENDA-SPS and SENDA-GPS datasets are publicly available.

SENDA-GPS employed a three-stage sampling design, first randomly sampling census blocks within municipalities. Within these identified sampling blocks, households were selected at random, with the number of households sampled proportional to the census block size. Household members were selected at random to participate in the study. While stratum and cluster unit information were not available (except for 2010), synthetic clusters were created by sorting on municipality, year and educational attainment and assigning 15 consecutive observations to the same cluster, following the approach described by Jolliffe.[2] The results taking into account complex survey design are presented as sensitivity analyses.

The resulting dataset contains three waves before the law (2000-01, 2002-03, 2004-05) and three waves after (2006-2007, 2008-09, 2010-11), including different individuals each time, with an average sample size of ~50,000 individuals per biennium in SENDA-SPS and ~ 2,300 individuals in SENDA-GPS per biennium. (See Tables S1.1 – S1.3).

Table S1.1: Number of data records in the SENDA-SPS dataset used for the high school population. The drop in the total school population between 2009 and 2011 is due to widespread student protests and an associated drop in school enrollment.

Year	12-22 year old HS population*	# Municipalities	Total Chilean school population in surveyed municipalities aged 12-22
2001	58,722	86	825,908
2003	58,489	86	975,364
2005	59,881	86	988,149
2007	52,145	91	968,996
2009	48,980	99	969,339
2011	33,509	104	863,886

*The majority of the HS population is 12-18 years old, only less than 0.2% of all HS students are between
19 and 22 years of age

Table S1.1: Number of data records in the SENDA-GPS dataset used for the university-aged population. The number of Chilean municipalities included in the sample and the total general Chilean population in surveyed municipalities aged 12-64 years are shown, also.

Year	12-64 year olds	19-24 year olds		# Municipalities	Total Chilean population in surveyed municipalities aged 12-64
2000	44,421	5,466		86	7,779,905
2002	16,476	1,945		87	8,392,058
2004	16,166	1,927		87	8,715,567
2006	17,192	1,937		91	8,876,262
2008	17,113	1,807	*20-24yrs: 1,517*	95	8,954,639
2010	16,000	1,807	*22-24yrs: 902*	108	9,738,623

Table S1.3: Smoking prevalence in surveyed high school grades between 2000/01 and 2010/11 in Chile.

SMOKING PREVALENCE IN…	2000/01	2002/03	2004/05	2006/07	2008/09	2010/11
8th grade	26.4%	24.2%	26.1%	20.7%	19.1%	13.3%
9th grade	38.1%	33.2%	38.3%	31.0%	30.0%	23.8%
10th grade	45.4%	42.0%	45.7%	38.0%	36.4%	28.7%
11th grade	51.1%	47.7%	49.3%	44.2%	40.6%	33.0%
12th grade	53.9%	51.3%	51.6%	45.6%	43.5%	36.1%

Data Structure

Chile is geographically divided into 15 regions and 346 municipalities. Both the school and general population survey are representative at the regional level, but sample only among those municipalities with n ≥ 30,000 inhabitants. Both surveys use multi-stage sampling procedures, which are described in the paragraphs below. The information on sampling procedures was obtained via email communication with data managers and from data manuals associated with the datasets. The Spanish text was translated into English, and EL Calvo verified the translation.

a) SENDA school population survey (SENDA-SPS)

SENDA-SPS employed a stratified, probabilistic two-stage sampling procedure.
The sample was stratified based on municipalities, types of high schools (public, voucher school, and private schools), and grade levels (grades 8 - 12).

Thus, the Stratum S_{klm} is specified at 1,2, …, k municipalities ($86 \leq k \leq 103$), at l=1,..,3 types of schools (public, non-profit, or private), and at m = 1, …, 5 grade levels (8^{th} through 12^{th} grade).

From each stratum, 2 classes were sampled. (At each school, students are put into classes of size n~=35) based on grade level. All classes were enumerated at the national level, and 2 classes per stratum were chosen, with a probability to be chosen proportional to the exact class size. During

the second stage, 20 students were chosen at random (and without replacement) from the 2 sampled classes per stratum.

Therefore, the PSU is 'classes'. However, even after contacting the data provider, the PSU could not be provided for data analysis. The stratum variable was also not provided in the dataset, nor was specific information on non-response rates.

Further, while there are survey weights that provide the inverse of the probability of the selected individuals to have been chosen at the national level, how these weights were obtained was not described in the survey handbook. Therefore, we only used weights in the sensitivity analysis.

Missing an explicit PSU variable, stratum variable, and specific information on individual probability weights, the sampling strategy was taken into account as best as possible in the model by applying the following procedures:

-Cluster-robust standard errors. The robust variance estimate is also known as the Huber/White/sandwich estimate of variance.[3] In this specific case, we used a model-agnostic robust variance since the model could not be specified to include the psu, stratum, and information on the weight variable, the latter of which would have helped in determining the more specific variance type.

-The cluster variable was *comuna* (municipality), as most between-cluster heterogeneity and within-cluster homogeneity was expected at the *comuna* level

-Grade level and type of school were included as covariates in each analysis

As a sensitivity analysis, however, a stratum variable was recreated by grouping all observations in the same municipality, at the same grade level, and in the same type (private, non-profit, public) school. After receiving information on the survey methodology from SENDA in Chile, we were also able to establish that the PSU variable coincided with the weight variable (though the exact calculations for the weight variable could not be verified). Based on this information, a complex survey analysis (for the first stage of the analysis model) was conducted, using the svyset command. Single unit standard errors were estimated based on the 'scaled' version, where the scaling factor is based on the mean of the variances from the strata with multiple sampling units for each stratum with one sampling unit.

b) SENDA general population survey (SENDA-GPS)

SENDA-GPS employed a stratified, probabilistic three stage sampling strategy:

1st stage: census block (*manzana*) sampling, with probability to be picked proportional to its population size. (PSU = *manzana*).

In order to optimize the selection of census blocks (in order to pick as many small as large census blocks in each municipality), the census block-sampling frame was divided into strata based on size (where size was a function of the number of houses per census block).

The probability for a census block to be sampled was defined as:

$$p_h(i) = \frac{n_h}{M_h M_{hi}}$$

where n_h corresponds to the number of selected census blocks in municipality h; M_h is the number of households in municipality h and M_{hi} is the number of households in census block i in municipality h.

2nd stage: sampling of viviendas (households) (SSU). Each household in the sampled census blocks has equal probability of being sampled. Sampling was done at random, without replacement.

3rd stage: individual selected (at random) per household (if between 12 and 65 years of age). The Kish sampling method was followed.

Unfortunately, the psu and ssu variables were only available for data starting in the year 2010. Therefore, to account for the sampling design as best as possible, by applying the following procedures in the main model:

-Cluster-robust standard errors were modeled. The cluster variable was *comuna* (municipality), as most between-cluster heterogeneity and within-cluster homogeneity was expected at the *comuna* level

While stratum and cluster unit information were not available (except for 2010), synthetic clusters were created as suggested by Jolliffe.[2] Since the average cluster number in 2010 was 15, synthetic clusters were recreated in the entire control population dataset (19- 65 years) by sorting municipality, year, and on educational attainment and then assigning 15 consecutive observations to the same cluster. Municipality units were treated as stratum variables. Single unit standard errors were estimated based on the 'scaled' version. The results of the analysis taking into account complex survey design are presented as sensitivity analyses.

MODEL SPECIFICATION

As specified in the manuscript, the goal of this analysis was to estimate the smoking prevalence rate ratios (rather than the odds ratios) in the intervention and the control group, to then estimate the effect of the high school smoking ban on annual percentage changes of smoking prevalence due to the law.

In general, the estimation of prevalence rates ratios (rather than odds ratios) is of interest when common outcomes are involved.[4] Smoking is one such common outcome of particular public (health) interest.

The outcome variables of interest, last-month smoking behavior and heavy smoking are coded as a binary (0,1) variable. Thus, several methods to model binomial health outcomes are available: the log-binomial model, the robust Poisson model, and direct estimation of prevalence ratios from odds ratios [4-6]. The latter method is only the preferred method in case of rare diseases. In fact, using logistic regression to estimate the adjusted PR in a study with a common binary

outcome, is not recommended.[7] Since Poisson models are least affected by model misspecification[4,8], the Poisson model was chosen to model smoking behavior in the Chilean high school and university-aged population.

As specified in the introduction and methods section of the paper, the main aim of this analysis was to estimate the impact of the high school smoking ban. Before-after ban smoking rates in the high school population were compared to before-after smoking behavior in the control university-aged population. Since data about the intervention and control population come from different surveys, a two-stage model to estimate the impact of the law was applied (see below & Figure S1.1).

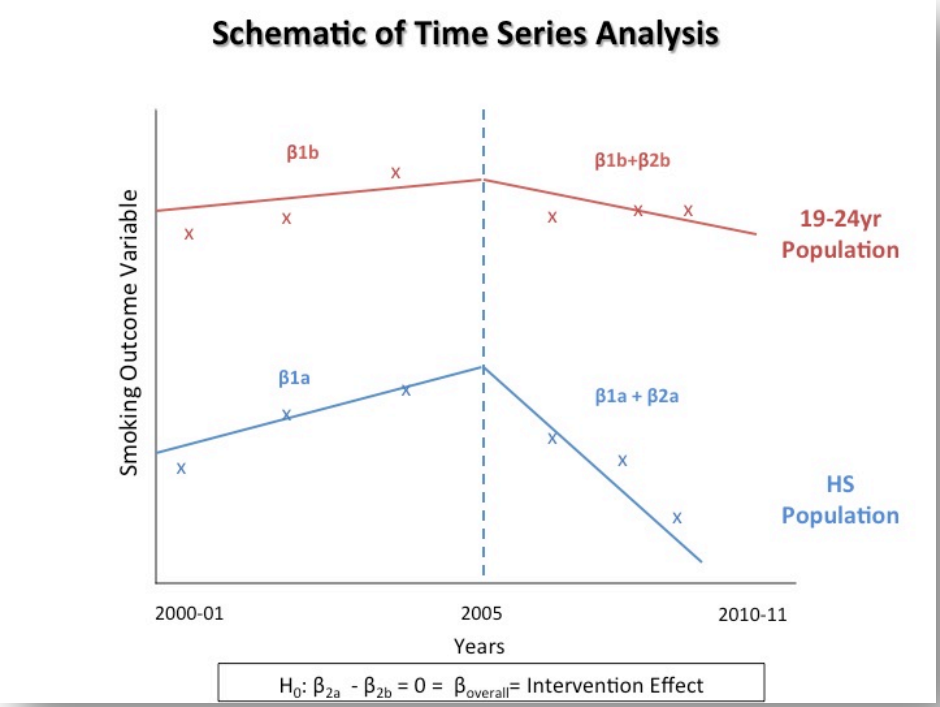

Figure S1.1: Schematic of Time Series Analysis with comparison group using non-linear spline modeling. The beta coefficients in the figure correspond to the coefficients in Equation 1. The hypotheses that were tested in the analyses are: H0: β2a = β2b; H02: β2a =0; H03: β2b =0. Because of the two-stage independent stratified analysis, H0 was tested via a two-sample t-test with unequal variances.

2-stage model with time-dependent spline term for trend before/ after 2005

Stage 0: creation of time-period specific term

Stage 1: Separate robust Poisson regression models for each intervention and control group

Stage 2: Two-sample t-test of the β_2 coefficients of each model

Stage 1 Regression model:

$$Yij = \alpha + \beta_1 * timeperiod_{1i} + \beta_2 timeperiod_{2j} + \beta_{3\text{-}n}(covariates)_{ij} + \varepsilon_{ij}$$

•i… individuals; j… time; ε… standard errors clustered and the municipal level (HS) and regional level (Uni)

•2-stage model (separate models for 2 groups; model "a" for HS group, model "b" for Uni group)

•$H_0 1$: $\beta_{2a} = \beta_{2b}$ (two-sample t-test with unequal variances)

•$H_0 2$: $\beta_{2a} = 0$

•$H_0 3$: $\beta_{2b} = 0$

… where Y represents the binary smoking variable of interest, for individual i at time j. In the first stage, the models (model 'a' and model 'b') were run separately for each group, since the data from SENDA-SPS and SENDA-GPS had different weight variables and adjustment factors to ensure the representativeness of the results. The second stage of the model was a two-sample mean comparison test with unequal variances. The hypotheses that were tested in the analyses were: H_{01}: $\beta_{2a} = \beta_{2b}$; H_{02}: $\beta_{2a} = 0$; H_{03}: $\beta_{2b} = 0$. H_{01} was tested via a two-sample t-test with unequal variances, and H_{02} and H_{03} were tested via the significance test of the coefficient in each model.

Table S1.4: Values for time period variable in first stage Poisson regression

	2000/01	2002/03	2004/05	2006/07	2008/09	2010/11
timeperiod$_1$	1	3	5	7	9	11
timeperiod$_2$	0	0	0	2	4	6

Table S1.5: Covariates and specification of first stage of regression analysis

	High School Population	University-Aged Population
Covariates	Age, sex, age*sex, school grade, region, school type	Age, sex, age*sex, region, SES
Specification	Robust standard errors clustered at the district level	Robust standard errors clustered at the district level

Detailed Results - Sensitivity Analyses

As described in the methods section, several sensitivity analyses were carried out for both outcome variables (smoking prevalence and heavy smoking). The results of the sensitivity analysis are presented in the appendix tables.

(1) Including all 19-24 year olds in the control population (the base-case analysis excluded those from the control who would have been exposed to the intervention while in high school), we found that the effect size estimate of the impact of the law on curbing smoking prevalence in high school students was lower and no longer significant (RR 95% CI: 0.96, 1.00; p=0.0987). (2) When examining the pre- and post-law prevalence changes of marijuana use (a popular recreational drug in Chile: in 2010-11, 9.72% of HS students, and 6.03% of the control population responded that they used marijuana in the past month), past 30-day marijuana use after 2005 increased by 14% (95% CI: 11%, 18%; p<0.0001) annually in the HS population versus the control population. (3) Further sensitivity analyses including only those municipalities included in all years yielded identical effect size estimates as the main analysis (Table S1.6). (4) When including only those with a high school diploma in the control population, the effect size increased to a -4.5% (CI: -1.3%, 7.5%; p=0.0056) annual prevalence decline in the intervention versus the control population. (5-6) Adjusting for past month alcohol prevalence, religion, and

paternal education (in the HS population) led to a slight increase in the effect size estimate (showing a 4.8% annual post-law relative prevalence decline). (7-8) The sensitivity analyses using the survey weights or the re-created stratum and PSU variables in addition to the weights showed an annual decline of 3.8% of post-law smoking prevalence in the HS versus the control population. However, since the stratum and PSU variables were not explicitly included in the dataset (but rather, recreated based on the survey methods document), these analyses served as sensitivity analyses only (Table S1.7). Nevertheless, the effect size estimates in the main and the weighted analysis were close (showing a 2.9% vs 3.8% annual smoking prevalence decrease). Specification tests to assess model fit of two non-nested models require the same weights to be used in both models[9], hence no applicable specification test to contrast the goodness of fit of the main versus the survey-weighted model was available. (10) In another sensitivity analysis, using the missing indicator method, results remained unaltered with respect to effect sizes and standard error size compared to the main model. Lastly, the 2005 ban had the greatest impact in schools in high SES *municipalities* in the Greater Metropolitan Region of Santiago (results not shown).

With regard to the sensitivity analyses for the impact of the law on heavy smoking, sampling-weight and complex survey adjusted models (results not shown) also revealed no significant difference in heavy smoking prevalence change before and after the law in control versus comparison groups. This result remained robust when stratifying by grade levels, also (Table S1.9).

Table S1.6: Sensitivity analyses testing the impact of the 2005 law on smoking prevalence. The presented RRs represent the annual dose response decrease in smoking prevalence. The first stage model of the high school population was adjusted for age, sex, region, school-type, course, and sex*age. The first stage model of the university-aged population included age, sex, region, SES, survey method, and sex*age. (CI = Confidence Interval; RR = Relative Risk).

Population and Study Period	(1) Controls include 19-24 yr olds in 2008-2011	(2) Marijuana Prevalence as main outcome	(3) Only municipalities measured in every survey year	(4) Only those with at least HS diploma in the control population
Stage 1a: HS Group (Targeted Intervention Population)				
Pre-Policy Annual Prevalence Rate change	1.01 (1.00, 1.01) p=0.014	0.985 (0.970, 1.001) p=0.065	1.01 (1.00, 1.01) p=0.025	1.01 (1.00, 1.01) p=0.014
Post-Policy Annual Prevalence Rate change	0.932 (0.927, 0.937) p<0.001	1.06 (1.05, 1.07) p<0.001	0.931 (0.926, 0.936) p<0.001	0.932 (0.927, 0.937) p<0.001
Difference in Prevalence change	0.926 (0.917, 0.934) p<0.001	1.08 (1.05, 1.10) p<0.001	0.925 (0.927, 0.934) p<0.001	0.926 (0.917, 0.934) p<0.001
Stage 1b: University-aged Group (Comparison Population)				
Pre-Policy Annual Prevalence Rate change	1.01 (1.00, 1.02) p=0.019	1.04 (0.986, 1.09) p=0.167	1.01 (0.998, 1.02) p=0.112	1.00 (0.988, 1.02) p=0.666
Post-Policy Annual Prevalence Rate change	0.956 (0.946, 0.966) p<0.001	1.00 (0.965, 1.05) p = 0.850	0.962 (0.951, 0.973) p<0.001	0.973 (0.954, 0.992) p=0.005
Difference in Prevalence change	0.943 (0.924, 0.962) p <0.001	0.970 (0.899, 1.05) p=0.437	0.953 (0.932, 0.974) p<0.001	0.969 (0.940, 1.00) p=0.666
Stage 2: Two sample mean-comparison test				
Intervention Effect	**0.982 (0.960, 1.00) p=0.0987**	**1.14 (1.11, 1.18) p<0.0001**	**0.971 (0.948, 0.995) p=0.0176**	**0.955 (0.925, 0.987) p=0.0056**

Table S1.7: Sensitivity analyses testing the impact of the 2005 law on smoking prevalence. The presented RRs represent the annual dose response decrease in smoking prevalence. The first stage model of the high school population was adjusted for age, sex, region, school-type, course, and sex*age. The first stage model of the university-aged population included age, sex, region, SES, survey method, and sex*age and age. (CI = Confidence Interval; RR = Relative Risk).

Population and Study Period	(5) Additional covariates: Past month alcohol prevalence, religion	(6) Additional covariates: Past month alcohol prevalence, religion, paternal education	(7) Main results with sample weights
	Stage 1a ***HS Group (Targeted Intervention Population)***		
Pre-Policy Annual Prevalence Rate change	1.01 (1.00, 1.01) p=0.037	1.00 (0.999, 1.01) p=0.111	1.01 (1.00, 1.01) p=0.001
Post-Policy Annual Prevalence Rate change	0.932 (0.927, 0.937) p<0.001	0.934 (0.929, 0.939) p<0.001	0.931 (0.926, 0.937) p<0.001
Difference in Prevalence change	0.927 (0.918, 0.936) p<0.001	0.930 (0.922, 0.939) p<0.001	0.923 (0.914, 0.932) p<0.001
	Stage 1b ***University-aged Group (Comparison Population)***		
Pre-Policy Annual Prevalence Rate change	1.00 (0.993, 1.01) p=0.570	1.00 (0.993, 1.01) p=0.570	1.01 (0.987, 1.03) p=0.541
Post-Policy Annual Prevalence Rate change	0.977 (0.966, 0.987) p<0.001	0.977 (0.966, 0.987) p<0.001	0.965 (0.946, 0.984) p=0.001
Difference in Prevalence change	0.974 (0.955, 0.992) p=0.005	0.974 (0.955, 0.992) p=0.005	0.960 (0.924, 0.996) p=0.029
	Stage 2: Two sample mean-comparison test		
Intervention Effect	**0.952 (0.932, 0.973) p<0.0001**	**0.956 (0.936, 0.976) p<0.0001**	**0.962 (0.926, 0.999) p=0.049**

Table S1.8: Sensitivity analysis (8) of impact of smoking law on high school smoking rates using complex survey design. For stage 1 of the analysis in the intervention group, survey strata were recreated grouping municipality, type of school, and grade level. Primary survey units (PSUs) were recreated based on the survey weight variable, and standard errors in strata with only one PSU were scaled based on the average of variances from the strata with multiple sampling units. For stage 1 for the control group, since stratum and PSU variables were missing, clustering was induced using the Joliffe approach, and each municipality was treated as a separate stratum. Again, standard errors in strata with only one PSU were scaled based on the average of variances from the strata with multiple sampling units.

Stage 1a: High School Group	PR of prevalence change (95% CI)	RR of Difference in Prevalence change	RR of Difference in post-policy prevalence change
Pre-Policy Annual Prevalence Rate change	1.01 (1.01, 1.01) p < 0.001	0.923 (0.916, 0.930) p<0.001	
Post-Policy Annual Prevalence Rate change	0.931 (0.927, 0.935) p<0.001		
Stage 1b: University-aged Group			0.962 (0.928, 0.997) p=0.0340
Pre-Policy Annual Prevalence Rate change	1.01 (0.989, 1.02) p=0.489	0.959 (0.926, 0.993) p=0.02	
Post-Policy Annual Prevalence Rate change	0.931 (0.927, 0.935) p<0.001		

Table S1.9: Results from the 2-stage marginal fixed effects Poisson model testing the impact of the 2005 law on heavy smoking for each high school grade. RRs represent the annual dose response in smoking frequency. The first stage model of the high school population was adjusted for age, sex, region, school-type, course, and sex*age. The first stage model of the university-aged population included age, sex, region, SES, survey method, and sex*age. (CI = Confidence Interval; RR = Relative Risk).

	8th grade	9th grade	10th grade	11th grade	12th grade
	Stage 1a: HS Group (Targeted Intervention Population)				
Pre-Policy Annual change in frequency	0.939 (0.889, 0.990) p=0.020	1.01 (0.977, 1.043) p=0.591	0.976 (0.946, 1.01) p=0.122	0.969 (0.940, 0.998) p=0.036	0.952 (0.927, 0.978) p<0.001
Post-Policy Annual change in frequency	0.918 (0.893, 0.943) p<0.001	0.927 (0.914, 0.940) p<0.001	0.916 (0.904, 0.929) p<0.001	0.922 (0.911, 0.935) p<0.001	0.929 (0.926, 0.943) p<0.001
Difference in change in frequency	0.978 (0.912, 1.05) p=0.534	0.919 (0.883, 0.956) p<0.001	0.939 (0.903, 0.977) p=0.002	0.952 (0.918, 0.988) p=0.01	0.975 (0.940, 1.01) p=0.190
	Stage 1b: University-aged Group (Comparison Population)				
Pre-Policy Annual change in frequency	0.992 (0.959, 1.03) p=0.669				
Post-Policy Annual change in frequency	0.953 (0.938, 0.969 p<0.001				
Difference in change in frequency	0.986 (0.938, 1.036) p=0.580				
	Stage 2: Two sample mean-comparison test				
Intervention Effect	**1.02 (0.937, 1.06) p=0.675**	**0.957 (0.901, 1.02) p=0.1447**	**0.978 (0.921, 1.04) p=0.458**	**0.991 (0.935, 1.05) p=0.7672**	**1.02 (0.959, 1.08) p=0.5995**

Additional comments on limitations

An important limitation of this study is that individuals were not randomly assigned to the intervention group (high-school students) and comparison group (university-age). However, we would like to emphasize that, except for the high school smoking ban, all provisions of the 2005 law uniformly affected Chile's general population (Supplementary Appendix 1, Section 2, Table S1.10). Thus, even if the law affected the comparison group, it would have been by a section of the law that also affected the high school population. Therefore, our analysis addresses the differential impact of the law on high school smoking frequency as attributable to the smoking ban specifically and differentially targeting the Chilean high school population.

S1.2 CHILE'S EDUCATIONAL SYSTEM

The educational system in Chile involves both public and private (for profit and not-for-profit) schools, and is divided into the following categories: 1) Preschool (*educación parvularia*), which compares to kindergarten and is attended by children under six years of age, 2) Primary/ Elementary school (*educación básica*) (for pupils age six to 14), and 3) Secondary/High school (*educación media*), which consists of four grades and offers students a choice of two types of diplomas (the general science-liberal arts diploma, or the vocational-technical diploma (which combines the general studies program with preparation for a trade). Public schools are completely free to attend. Instead of attending public schools, students can choose to attend private schools, and the government will pay the attendance fees at these schools via a voucher: however, the government matches the exact same amount as it would cost to attend public

schools. The majority of private for-profit schools match the attendance costs of public schools. A small minority of elite schools (enrolling roughly 7% of the Chilean school population) has an attendance cost of about five times the value of the vouchers and in addition, have extremely stringent enrollment criteria. Since 2003, a constitutional reform mandated school attendance for twelve years, but at the same time, also guaranteed that education (in public schools) would be free. While school enrollment between the ages of 6 and 14 is close to 100%, this number drops off among older students; for example, only just over 70 percent of 17-year olds attend school in Chile, despite the fact that since 2003, 12 years of schooling are mandatory.

S1.3 CHILE'S TOBACCO LAWS

In Chile, smoking is the 4th leading cause of mortality and morbidity with 1 out of 11 deaths attributed to smoking.[10] Lung cancer mortality is increasing, especially in women, with 6 out of the 10 leading causes of death for women attributed to smoking.[11] The associated effects of tobacco smoking contribute to substantial costs. A study by Martinez-Gutierrez and colleagues calculated tobacco-attributable yearly direct costs (in pesos) in two hospitals in Santiago, Chile.[12] These direct costs tap into outpatient care, emergency care, hospitalizations, and medicine and health supplies and were estimated at $80,432 for ischemic heart disease, $285,230 for chronic obstructive pulmonary disease (COPD), and $70,420 for lung cancer. In addition to the economic burden due to associated medical cost, smoking substantially contributes to disability days and years of potential life lost due to premature death.

Aware of the public health and economic concerns, the Chilean government's efforts in addressing tobacco policy have been modest. In 1995, almost half a century after the landmark

paper by Sir Richard Doll on the causal link between smoking and lung cancer[13], Law nº 19.419 was introduced with aims to zone smoking and non-smoking areas in restaurants, hotels, and other establishments[6]. However, its provisions were weak and faced strong opposition from the tobacco industry. After enactment of Law 19.419, the number of smokers in Chile continued to grow.

Ten years later, Chile ratified the FCTC on June 13th, 2005. The law went into effect on September 11th, 2005, and provided momentum for legislation that would modify Law 19.419. The new Law 20.105 took effect in 2006 with the following key provisions: (1) tobacco ads were to be confined to points of sale; (2) the legal smoking age was elevated to 18 years of age; (3) information on the health risks of smoking as well as an annual report on the composition of tobacco products were made available to the public; (4) smoke-free environments were to be established, and (5) there would be sanctions for non-compliance with the new regulations.

However, the 2006 law fell short of several FCTC recommendations. Most importantly, however, it only created 100% smoke free spaces in public schools, but failed to do so in restaurants, bars, and universities. Particularly, the major shortfalls of the law as it relates to the FCTC are as follows:

Article 6 (Price and Tax Measures to reduce the demand for tobacco): Neither the 2005 law nor the 2011/12 amendment included the enforcement of tobacco taxes which is shown to be one of the most effective strategies in decreasing smoking rates, particularly among the poor and young.

Article 8 (Protection from exposure to tobacco smoke): The current law only mandates partially smoke-free zones (in schools and in restaurants). Compliance is low, and fines are not imposed. The only 100% smoke-free zones in Chile are public schools.

Article 11 (Packaging and Labeling of Tobacco Products): The Chilean Ministry of Health has only run one national anti-smoking campaign, and there are no official educational and tobacco awareness campaigns in schools. In addition, anti-smoking labels on cigarette packs only focused on one adverse health consequence of smoking: impotence. Among the five most severe smoking-related health consequences, knowledge about impotence provides the least motivation for smoking cessation.[14-16] Also, this current campaign only targets men; in Chile, the highest smoking rates are found in women of childbearing age (43%; ENS 09/10), endangering both current and future generations with this risky behavior.

Table S1.10: The 1995 and 2005 Chilean Tobacco laws in comparison (Articles in Bold in 2005 constitute a change from the 1995 law; Articles highlighted in orange represent the components of the 2005 that were very weakly implemented).

Article	1995 Law	2005 Law
1°	Definition of activities related to tobacco control	Definition of activities related to tobacco control
2°	No advertising aimed at minors less than 18 years of age	**No advertising except at points of sale**
3°	Tobacco sales only allowed at ages 16 or above	**Tobacco sales only allowed at ages 18 or above**
4°	Awareness of health risks (no specific campaigns)	**Public Health Campaigns: public ads, campaigns, and health labels on cigarette packages**
5°	Tobacco education programs in colleges	Tobacco education programs in colleges
6°	Authority of Health services	**Information about cigarette composition on an annual basis, made available freely online**
7°	Prohibition of smoking in public places	**Tobacco free environments**
8°	Failure to comply with the tobacco law constitutes an offense	**Sanctions if failure to comply: much stricter and with higher fines**
9°	Local Police Enforcement of Sanctions	Local Police Enforcements of Tobacco Regulations
10°	Individual Responsibility	Individual Responsibility
11°	Public Health Services act as part of legal processes	Public Health Services act as part of legal processes
12°	Legal enforcement and enactment of the law provisions	Legal enforcement and enactment of the law provisions
13°		**Prevention of Smoking Risk Factors**

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PAPER #2: THE EFFECT OF HIV AND THE MODIFYING EFFECT OF ANTI-RETROVIRAL THERAPY (ART) ON BODY MASS INDEX (BMI) AND BLOOD PRESSURE LEVELS IN RURAL SOUTH AFRICA

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ABSTRACT

Background. High body mass and blood pressure are two of the leading risk factors contributing to the burden of disease in South Africa**.** Long-term effects of HIV and ART on adiposity and blood pressure are not well understood, and direct comparisons of risk factor trajectories in HIV^- versus HIV^+ populations are rare.

Methods. In 2003 and 2010, height, weight, and blood pressure were recorded in a study population (n=505) in KwaZulu-Natal, South Africa, a region with high HIV burden (30% adult

prevalence). We modeled change in BMI and blood pressure over time in HIV^- individuals (n=315), seroconverters (n=32), HIV^+ patients not on ART (HIV^+ART^-; n=52), HIV^+ patients on ART for 0–<2 years as of 2010 ($HIV^+ART^{0-<2\ yrs}$; n=18), patients on ART for 2–5 years (HIV^+ART^{2-5yrs}; n=44), and a subgroup with unknown HIV status (n=44). Longitudinal differences-in-differences in BMI and blood pressure were assessed for groups in comparison to the HIV^- population. Uniquely, our study included weight and BP measurements at least one year prior to ART among eventual ART users in the sample.

Findings. Between 2003 and 2010, BMI increased significantly in the HIV^- group, by 0.874 kg/m^2 (95% CI 0.339 to 1.41; p=0.001), to 30.4 kg/m^2. Relative to this change, BMI decreased by –5.21 kg/m^2 (95% CI –7.53 to –2.90; p=0.001) in the $HIV^+ART^{0-<2yrs}$ group, and by –1.35 kg/m^2 (95% CI -2.89, 0.189; p=0.086) in the HIV^+ART^{2-5yrs} group. Notably, the decrease in BMI was significantly greater in the $HIV^+ART^{0-<2yrs}$ versus the HIV^+ART^{2-5yrs} group (p=0.005). Overall, no major difference-in-differences in SBP were observed between 2003 and 2010, except for the HIV^+ART^- vs HIV^- group. Specifically, SBP dropped from 130.4 mmHg (95% CI 125.0 to 135.0) to 123.5 mmHg (95% CI 118.2 to 128.9) in the HIV^+ART^- group, resulting in a HIV^+ART^- vs HIV^- DID in SBP of –7.55 mmHg (95% CI –13.2 to –1.90; p=0.009).

Interpretation. Short-term ART (0–<2 years) was associated with a larger weight loss compared with no or long-term ART. Once on ART for two or more years, individuals 'caught up' on weight gain with the HIV^- reference population. Such a longitudinal finding of parallel trajectories of short-/long-term ART users and HIV^+ and HIV^- groups have, to our knowledge,

never been reported before. Our results showcase the importance of health system readiness to address the burgeoning double burden of disease in South Africa.

INTRODUCTION

South Africa, with a HIV prevalence of 25.2% among 25-49 year olds[1], is the country with the largest HIV^+ population in the world (6.4 million, out of a population of 52.3 million, in 2012[2,3]). In 2011, HIV/AIDS was the number one cause of years of life lost (YLL) in South Africa[4], and the 7th leading cause of death overall.[5] Extensive ART rollout has been underway since 2004, and even the poorest and hardest hit communities in rural KwaZulu-Natal (South-East South Africa) provided ART to over 31% of those in need in 2011.[6]

Whilst South Africa better controls the HIV-epidemic[7], the chronic disease burden is increasing.[8-13] In 2010, high body mass index (BMI) and blood pressure (BP) were the top two and three risk factors contributing to the burden of disease in South Africa.[4] Cerebrovascular diseases (CVDs), heart disease, and diabetes were the number three to five largest killers in 2011, respectively.[5]

Although CVD risk factors affect HIV-negative and HIV-positive populations alike[8,9], little is known about the modifying effect of ART on CVD risk factors, particularly in low-income settings. A recent meta-analysis of cardio-metabolic traits in HIV-positive and HIV-negative populations in Sub-Saharan Africa (SSA) concluded that HIV infection was associated with both lower systolic and diastolic blood pressure, but evidence on the effect of ART on blood pressure was largely lacking.[14] Our own literature revealed additional cross-sectional evidence that pre-ART weight was a predictor of onset of diabetes on ART[15], that ART was associated with non-HIV related, chronic morbidity[16], and that ART was associated with increased central fat (a cardio-metabolic disease marker) and reduced peripheral fat.[17] We were unable to identify longitudinal studies with a HIV^- control group and that spanned both long periods before and

after ART rollout. Nonetheless, such population-level evidence is of critical importance, as it is plausible that HIV and ART affect CVD risk factors via weight gain among individuals on ART, survival benefit of ART, chronic HIV-induced inflammation, and other ART side effects.

To address this research gap, our study assessed the effect of HIV and the modifying effect of ART on body mass and blood pressure in rural KwaZulu-Natal between 2003 and 2010, with the two following advantages over similar studies in this field: 1) we include a HIV^- group to account for the secular trend in risk factors, and 2) the first time point pre-dates ART rollout well over one year for all participants, serving as a unique baseline measure.

METHODS

Data source

Nested within a longitudinal, population-based HIV surveillance study, surveys on height, weight, and blood pressure were conducted both in 2003/04 and 2010 in rural umKhanyakude in KwaZulu-Natal, South Africa, where adult HIV prevalence was close to 30% in 2010.[6] The survey data from these two rounds are linked at the individual level. The 2003 survey antedated the large-scale rollout of ART , which started in August 2004 in this community. The 2010 survey took place against the background of widespread ART coverage of 24.7%.[6] The surveys are described in detail elsewhere.[8,9] Individuals were eligible for HIV testing and weight, height and blood pressure measurement if they were residents in the Africa Center's defined geographic surveillance area (DSA). In 2003/4, the eligible age range was 25-49 years for women, and 25-54 years for men; in 2010, the eligible age range for the HIV, BMI, and BP survey was >15 years of age.

Household membership was self-defined on the basis of links to other members.[18,19] HIV-infected participants on ART were all enrolled at 16 primary healthcare (PHC) clinics in the Hlabisa subdistrict of umKhanyakude. ART guidelines have indicated that treatment should be initiated at CD4 cell counts < 200 cells/μl between 2004 and 2010, the timeframe of this study.

Study population for weight and blood pressure measurements

In 2003, 2111 eligible individuals within the DSA completed weight, height, and blood pressure measurements as part of a WHO STEPS survey.[20] At the start of the second survey round in 2010, 306 of the original population had died, 11 persons had become very ill, and 335 had out-migrated. Of the remaining 1,459 participants, 582 refused all questions or did not fully complete the 2010 demographic survey; 283 did not consent to weight, height, and BP measurements in 2010, and 90 had faulty BMI or BP measurements. Thus, 505 individuals had survey, BMI, and BP measurements in 2003 and 2010 (Figure 2.1). These individuals constitute the main, complete case study population.

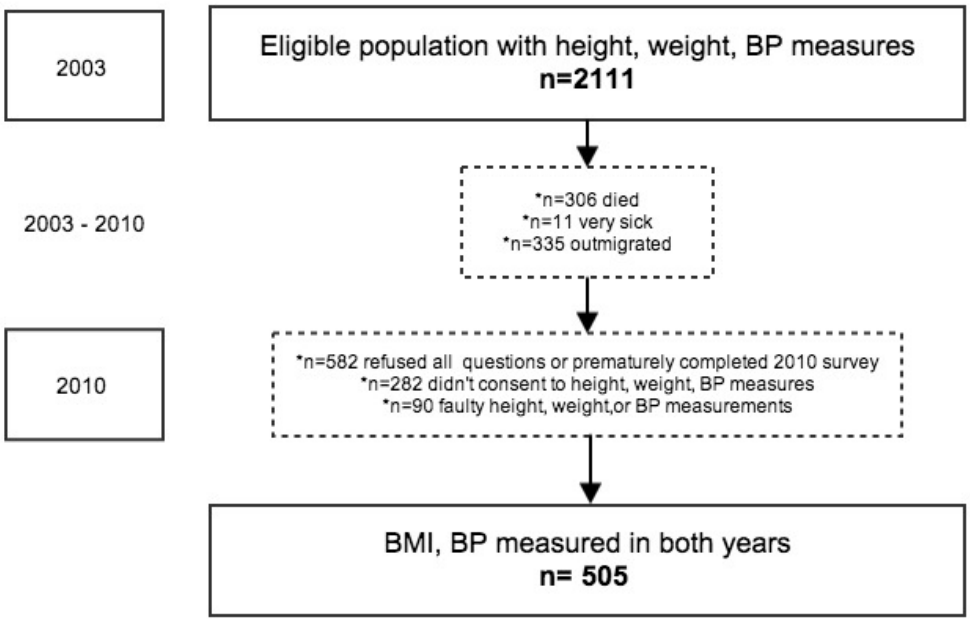

Figure 2.1: Study Population. 2111 individuals had both BMI and blood pressure measurements in 2003. This population was comprised of females 25-49yrs and males 25-54 yrs who lived in the ACDIS catchment area, were residents, were visited by a fieldworker, and completed the full demographic survey, in addition to the WHO STEPS survey which included BMI and BP measurements. 505 individuals had survey, BMI, and BP measurements both in 2003 and 2010. These individuals constitute the main, complete case study population. For the IPW sensitivity analyses, baseline information of all individuals except those who died and were very sick was used to calculate inverse probability weights.

Measurements

HIV status was assessed by enzyme-linked immunoabsorbent assay (ELISA) of EDTA anti-coagulated blood samples in the Africa Centre virology laboratory, using HIV-1/HIV-2 ELISA. Every first positive test was confirmed by a second test. None of the subjects included in the study had discordant HIV test results. Height, weight, and blood pressure were measured following the WHO STEPS protocol.[20] Blood pressure was taken three consecutive times, and the averages of the second and third measurements were used to estimate SBP and DBP. Underweight was defined as a BMI <18.5 kg/m^2, normal weight was 18.5 ≤ BMI <25, and overweight and obesity as a BMI 25 to <30, and ≥30, respectively. Stage 1 hypertension was defined as Systolic Blood Pressure (SBP) ≥140mmHg and (SBP) < 160 mmHg or Diastolic Blood Pressure (DBP) ≥ 90 mmHg, and stage 2 hypertension as SBP≥160mm Hg or DBP≥100 mmHg.

Statistical Analysis

The dependent variables for all models were BMI, SBP, and DBP. The exposures of interest were HIV status and (length of) ART use. We modeled change in BMI and blood pressure over time in HIV-negative individuals, seroconverters, HIV-positive patients not on ART (HIV^+ART), HIV-positive patients on ART for 0–<2 years ($HIV^+ART^{0–<2\ yrs}$), HIV on ART for 2–5 years ($HIV^+ART^{2–5\ yrs}$), and a subgroup with unknown HIV status. Difference-in-differences in body mass and blood pressure between 2003 and 2010 in all subgroups were assessed with reference to the HIV^- group. We adjusted our analyses for baseline levels of potential confounders, which were age (continuous), sex, and geographic sampling area.

We conducted an IPW (Inverse Probability Weighting) analysis to account changes in the distribution of population characteristics in the different comparison groups due to loss to follow

up between 2003 and 2010 (2111 versus 505 participants). Baseline information on all individuals except those who died and were very sick was used to compute stabilized inverse probability-of-censoring weights (IPCWs).[21] The IPCW method assigns a weight to each non-censored individuals and allows them to 'represent' those who have been lost to follow-up after adjusting for observed patient characteristics at baseline.[22-24] Censoring weights were estimated using age (continuous), sex, HIV (treatment) status, education, wealth quintile, geographic sampling area, and household assets.

We tested the robustness of the complete case analysis with several sensitivity analyses. First, we included information on those who died and fell ill to calculate the probability weights. For censoring weights, death and severe illness are often regarded as extreme events. Characteristics of individuals who die or are severely ill might therefore not be comparable to the characteristics of those who remain in the population. However, since the study population is a high HIV prevalence population, these conventional assumptions might not hold. Therefore, we conducted a sensitivity analysis that included baseline information on those who died and fell severely ill.[25,26]

To test for the sensitivity of our results to individuals with very high or very low weight, we excluded those with BMI≥50. As BMI might be an independent risk factor for high BP, we also adjusted for BMI at baseline (assuming no collider bias[27]). Further IPCWs included fewer covariates to calculate the probability weights: age, sex, general health, and the asset indicator at baseline. The results for the effects of HIV and ART on DBP over time are presented as sensitivity analyses, since SBP and DBP are generally highly correlated. All analyses were performed using STATA 13.

RESULTS

Baseline Characteristics

In 2003, the mean age of the complete case, main study population was 39.5 (SD: 7.2) years, and mean BMI was 29.0 kg/m^2 (SD: 7.2). 13.1 percent of respondents were in the highest asset index quintile, 23.6 percent had completed 2^{ary} or higher education, and 37.1 percent reported to be in very good or excellent health. Baseline SBP was 126.6 mmHg (SD: 20.2), and DBP was 80.6 mmHg (SD: 13.2) (Table 2.1).

We found several differences in the baseline characteristics between the '2003 only' and the 'complete case' population (Table 2.1). Most notably, the complete case population was older, heavier, had higher blood pressure, and had a higher percentage of females. The complete case population was also overall poorer and less educated, had lower self-reported health, and had a higher prevalence of HIV^- individuals (Table 2.1).

Table 2.3: Baseline characteristics. This table shows unadjusted sex, age, weight, height, BMI, SBP, DBP, HIV status, educational status, self-reported health status, and asset index characteristics of the following populations: The baseline cohort population (n=2111); the '2003 only' population (n=1289); the characteristics of those who died or fell very ill (n=317); and the complete case population (n=505). The '2003 only' population includes those who succesfully completed the 2003 survey, but outmigrated by 2010, prematurely completed the 2010 demographic survey, did not consent to biometric measurements in 2010, and had faulty biometric measurements in 2010. Note that those who died or fell very sick by 2010 were not included among the 2003 only population. The complete case population represents those with full measurements in both 2003 and 2010.

	Baseline Cohort (n = 2111)	2003 only, excluding dead & very sick (n=1289)	Died & Very Sick n=317	Complete Case population (n=505)
Years of age (SD)	**37.8 (7.3)**	**37.0 (7.1)**	**38.1 (7.7)**	**39.5 (7.2)**
HIV^-	39.0 (7.2)	38.5 (7.3)	42.1 (7.8)	40.8 (7.0)
HIV^+	36.0 (7.2)	35.7 (6.7)	36.6 (7.4)	38.0 (7.6)
$HIV^{unknown}$	36.5 (7.1)	36.2 (6.9)	37.8 (7.4)	38.0 (7.0)
Weight, kgs (SD)	**73.8 (18.9)**	**75.3 (19.3)**	**69.3 (18.7)**	**75.0 (18.8)**
HIV^-	74.8 (18.7)	75.3 (19.0)	71.0 (16.2)	75.9 (19.0)
HIV^+	69.0 (17.9)	70.8 (19.5)	66.9 (18.3)	69.4 (18.4)
$HIV^{unknown}$	75.6 (19.1)	77.0 (19.3)	71.3 (20.0)	76.1 (18.1)
BMI (SD)	**28.0 (7.4)**	**28.5 (7.5)**	**26.0 (7.4)**	**29.0 (7.2)**
HIV^-	28.4 (7.4)	28.5 (7.5)	26.5 (6.5)	29.4 (7.2)
HIV^+	26.3 (7.2)	27.0 (7.8)	25.6 (7.7)	27.1 (6.8)
$HIV^{unknown}$	28.6 (7.4)	29.1 (7.4)	26.3 (7.6)	29.4 (7.3)
SBP (SD)	**124.9 (19.0)**	**124.7 (18.0)**	**123.7 (22.1)**	**126.6 (20.2)**
HIV^-	126.9 (19.4)	126.3 (18.5)	131.9 (21.1)	127.8 (20.9)
HIV^+	122.4 (17.8)	122.6 (15.5)	119.9 (19.7)	126.2 (20.4)
$HIV^{unknown}$	124.1 (19.1)	124.1 (18.3)	124.1 (24.3)	125.9 (19.1)
DBP (SD)	**79.4 (12.5)**	**79.29 (12.0)**	**79.2 (13.7)**	**80.6 (13.2)**
HIV^-	79.7 (12.8)	79.0 (12.3)	82.4 (13.6)	81.0 (13.5)
HIV^+	78.6 (11.8)	79.1 (11.0)	77.6 (12.7)	79.4 (12.8)
$HIV^{unknown}$	79.4 (12.4)	79.5 (12.0)	79.6 (14.5)	80.5 (12.9)
Sex (female, %)	**68.7**	**66.1**	**57.1**	**81.8**
HIV^-	66.1	62.4	36.7	79.9
HIV^+	68.9	69.6	62.1	75.3
$HIV^{unknown}$	71.2	68.2	61.5	88.5
Asset Index (% in highest quintile)	**19.1**	**22.4**	**15.8**	**13.1**
HIV^-	16.5	18.4	18.3	15.2
HIV^+	14.5	18.5	12.9	15.4
$HIV^{unknown}$	24.4	27.8	18.0	23.6
Education (% 2^{ary} or higher)	**34.0**	**38.9**	**29.0**	**23.6**
HIV^-	28.2	32.8	20.0	20.5
HIV^+	31.3	35.2	30.0	24.7
$HIV^{unknown}$	41.3	46.3	32.5	28.2
Health (% Very good or excellent)	**37.1**	**39.7**	**31.9**	**34.3**
HIV^-	36.2	39.3	35.0	31.4
HIV^+	35.2	38.8	29.3	35.3
$HIV^{unknown}$	39.2	40.4	33.3	38.5
HIV status (%)				
HIV^-	40.3	40.7	18.9	52.3
HIV^+	20.9	17.2	44.2	16.8
$HIV^{unknown}$	38.8	42.2	36.9	30.9

Further examining the baseline differences between the HIV subgroups in the complete case population, we found that age differed significantly among the four HIV status groups, with the highest age in the HIV^- group (40.2 years, SD: 7.2) and the lowest age in the HIV^+ART^- group (37.3 years, SD: 7.1) (Table S2.1). BMI differed significantly among subgroups: it was highest in the $HIV^{unknown}$ group (30.1kg/m^2, SD 7.0), and lowest in the HIV^+ART^+ group (27.2, SD: 7.1). Among those on ART, the average time on ART was 2.5 years (SD: 1.4) between 2004 and 2010. 29% of ART users were on ART for 0-<2 years between 2004 and 2010. $CD4^+$ count (measured just prior to ART initiation) was 136.5 (SD: 78.7) for all subjects who initiated ART. Gender composition, SBP, and DBP at baseline did not differ significantly between HIV-status groups (Table S2.1). The minimum elapsed time between the first BMI and BP measurement and ART initiation was 1.2 years; the maximum time between these two measurements was 7.2 years (Figures S2.1-S2.3). The average time elapsed between the first BMI and BP measurement and ART initiation in the $HIV^+ART^{0-<2yrs}$ group was 6.0 years (SD: 0.6) years, and 3.5 years (SD: 1.0) years in the $HIV^+ART^{2-5\ yrs}$ group.

Effect of ART and HIV on change of BMI and Blood Pressure

Between 2003 and 2010, BMI increased significantly in the HIV^- group, by 0.874 kg/m^2 (95% CI 0.339 to 1.41; p=0.001), to 30.4 kg/m^2. BMI significantly decreased by -4.34 kg/m^2 (95% CI -6.58 to -2.10; p<0.001) in the $HIV^+ART^{0-<2yrs}$ population, to 25.9 kg/m^2 in 2010. All other groups experienced non-significant changes in BMI between 2003 and 2010 (Table 2a).

Relative to this change, BMI decreased by –5.21 kg/m^2 (95% CI –7.53 to –2.90; p=0.001) in the $HIV^+ART^{0-<2yrs}$ group, and by –1.35 kg/m^2 (95% CI -2.89, 0.189; p=0.086) in the HIV^+ART^{2-5yrs}

group. The relative changes in BMI between $HIV^{+}ART^{0-<2yrs}$ and $HIV^{+}ART^{2–5\ yrs}$ were significantly different from each other, as reflected in the global p-value for ART duration (p=0.005) (Table 2.2a). This attenuation of relative weight loss when individuals were on ART for two to five years, compared to 0 to <2 years, suggested a U-shaped association with long-term use of ART and BMI: Once on ART for two or more years, individuals 'caught up' on weight gain with the HIV^{-} reference population (See Figure S2.4 for plotted BMI and SBP trajectories in all subgroups).

The IPW sensitivity analysis showed qualitatively similar, quantitatively attenuated, results (Table 2.2b) compared to the complete case analysis. We confirmed an increase in BMI in the HIV^{-} group by 2010, but it was statistically non-significant according to the IPW model. BMI in the $HIV^{+}ART^{0–<2yrs}$ group dropped by –3.66 kg/m^2 (95% CI –6.32 to –0.984; p=0.007) compared to the HIV^{-} reference group. The relative drop in BMI of the $HIV^{+}ART^{2–5\ yrs}$ versus the HIV^{-} group was not statistically significant, paralleling the findings of the complete case analysis. The drop in BMI was significantly greater among $HIV^{+}ART^{0-<2yrs}$ versus $HIV^{+}ART^{2–5yrs}$ (p=0.032).

Further sensitivity analyses (Table S2.2) including the full baseline population to calculate probability weights confirmed the robustness of the complete case results (Table S2.2b). Excluding individuals with BMI > 50kg/m^2, the drop in BMI in the $HIV^{+}ART^{0–<2yrs}$ group was further attenuated (–2.43 kg/m^2 (95% CI –4.21 to –0.644; p=0.008)) (Table S22c). Notably, the change in BMI between 2003 and 2010 in the HIV^{-} group was slightly higher at 1.03 kg/m^2 (95% CI 0.614 to 1.45; p<0.001) compared to the analogous result of the complete case analysis. Overall, the findings of both sensitivity analyses were qualitatively in alignment with the results of the complete case analysis.

Table 2.2ab: Effect of ART and HIV on longitudinal change of BMI. 2.2a: Population Average Model. BMI changed significantly between years 2003 and 2010 in the HIV-negative group and among ART users less than 2 years on ART**.** Data for people with unknown HIV status not shown. **2.2b: Population average model with IPW**. The results presented in this table are based on a population average linear regression model using IPW adjusting for missingness due to loss to follow up, migration, and non-consent (but not death and severe illness). The weights were based on age, sex, education, general health, and an asset index indicator. The model controlled for age, sex, HIV, and ART status.

2.2a: Population Average Model: Effect of ART and HIV on longitudinal change of BMI								
	BMI, 2003 (95% CI)	**BMI, 2010 (95% CI)**	**ΔBMI (03-10) (95%CI)**	**p-value for 1st diff**	**DID effect (95%CI)**	**p-value (DID)**	**Global p-value**	**ART duration p-value**
HIV^-	29.5 (28.7, 30.3)	30.4 (29.7, 31.1)	0.874 (0.339, 1.41)	0.001**	*(ref)*			
Seroconverters	28.6 (26.3, 30.9)	28.3 (26.0, 30.7)	-0.274 (-1.95, 1.41)	0.749	-1.15 (-0.252, 2.83)	0.202		
HIV^+ART^-	27.6 (25.8, 29.4)	27.4 (25.6, 29.2)	-0.196 (-1.51, 1.12)	0.771	-1.07 (-2.50, 0.361)	0.173	<0.001**	
$HIV^+ART^{0-<2\ yrs}$	30.2 (27.1, 33.3)	25.9 (22.8, 29.0)	-4.34 (-6.58, -2.10)	<0.001**	-5.21 (-7.53, -2.89)	<0.001**		0.005**
$HIV^+ART^{2-5\ yrs}$	26.5 (24.5, 28.5)	26.1 (24.0, 28.0)	-0.475 (-1.91, 0.957)	0.515	-1.35 (-2.89, 0.189)	0.086		
2.2b: Effect of ART and HIV on longitudinal change of BMI (adjusted for loss to follow up)								
HIV^-	29.8 (28.8, 30.9)	30.4 (29.4, 31.4)	0.554 (-.228, 1.34)	0.165	*(ref)*		0.0001**	
Seroconverters	29.0 (27.2, 30.7)	28.8 (27.1, 30.6)	-0.128 (-1.06, 0.806)	0.788	-0.682 (-1.90, 0.536)	0.273		
HIV^+ART^-	27.8 (26.3, 29.3)	27.4 (25.4, 29.4)	-0.404 (1.48, 0.675)	0.463	-0.958 (-2.29, 0.375)	0.159		
$HIV^+ART^{0-<2\ yrs}$	29.3 (26.0, 32.6)	26.2 (23.9, 28.5)	-3.11 (-5.66,-0.547)	0.017*	-3.66 (-6.32, -0.984)	0.007**		0.032*
$HIV^+ART^{2-5\ yrs}$	26.8 (24.8, 28.7)	26.7 (25.1, 28.4)	-0.012 (-1.20, 1.18)	0.984	-0.566 (-1.99, 0.860)	0.437		

Further, with wide-scale ART starting in 2004, those starting in 2004/05 might have been more urgently in need than those starting on ART in 2006 and beyond. Consequently, the modifying effect of ART on BMI and BP might have been different in the 'early starters'. We therefore conducted sensitivity analyses by excluding those on ART for four to five years (who initiated therapy between 2005 and 2007) for all models. None of the main results were changed with respect to the estimated effect size. However, the power was negatively impacted due to sample size reduction (results not shown).

Blood pressure change 2003 - 2010

Between 2003 and 2010, modeled SBP based on the complete case analysis dropped from 130.4 mmHg (95% CI 125.0 to 135.0) to 123.5 mmHg (95% CI 118.2 to 128.9) in the $HIV^{+}ART^{-}$ group ($p_{difference}$= 0.010). In the weighted analysis, the drop in SBP in the $HIV^{+}ART^{2–5yrs}$ group was also significant with a drop of –5.64mmHg (95% CI –11.2 to –0.07; p=0.047) (Table 2.3b). All other observed SBP changes between 2003 and 2010 were not statistically significant in both complete case and weighted analysis. The results for the modeled changes in SBP of the weighted analysis were qualitatively similar to that of the complete case analysis.

We further investigated SBP changes relative to the HIV^{-} comparison group. The relative change in SBP in the $HIV^{+}ART^{–}$ group was significant with –7.55 mm Hg (95% CI –13.2 to –1.90; p=0.009) (Table 2.3a). This relative decline was greater in the weighted analysis, where the difference in SBP change between the $HIV^{+}ART^{–}$ group and the control group was –9.09mm Hg (95% CI –14.6 to –3.61; p=0.001) (Table 2.3b). Overall, the relative change in SBP compared to

the HIV-negative reference group was not significantly different among all subgroups. The ART dose effect was also not statistically significant based on the complete case analysis.

Table 2.3ab: Effect of ART and HIV on longitudinal change of SBP. 2.3a: Population average model. SBP changed significantly between years 2003 and 2010 among ART users less than 2 years on ART. **2.3b:** Population average model with IPW. The results presented in this table are based on a population average linear regression model using IPW adjusting for missingness due to loss to follow up, migration, and non-consent (but not death and severe illness). The weights were based on age, sex, education, general health, and an asset index indicator. The model controlled for age, sex, HIV, and ART status.

2.3a: Effect of ART and HIV on longitudinal change of SBP								
	SBP 2003 (95% CI)	**SBP, 2010 (95% CI)**	**ΔSBP (03-10) (95%CI)**	**p-value for first diff**	**DID effect (95%CI)**	**p-value (DID)**	**Global p-value**	**ART duration p-value**
HIV^-	126.5 (124.3,128.3)	127.0 (124.8,129.1)	0.427 (-1.69, 2.54)	0.693	*(ref)*		0.070	
Seroconverters	123.6 (116.7,130.4)	129.1 (122.2,135.9)	5.5 (-1.17, 12.2)	0.106	5.01 (-1.94, 12.1)	0.156		
HIV^+ART^-	130.4 (125.0, 135.0)	123.5 (118.2, 128.9)	-6.86 (-12.1, -1.66)	0.010*	-7.55 (-13.2, -1.90)	0.009**		
$HIV^+ART^{0-<2\ yrs}$	118.9 (109.9, 127.9)	118.9 (109.9,127.9)	0.00 (-8.76, 8.76)	1.00	-0.36 (-9.44, 8.72)	0.938		0.853
$HIV^+ART^{2-5\ yrs}$	125.8 (120.0, 131.7)	124.8 (119.0, 130.7)	-0.977 (-6.64, 4.69)	0.735	-1.35 (-7.43, 4.73)	0.663		
2.3b: Effect of ART and HIV on longitudinal change of SBP (adjusted for loss to follow up)								
HIV^-	127.1 (124.8,129.4)	125.6 (123.4,127.7)	-1.53 (-3.88, 0.816)	0.201	*(ref)*		0.394	
Seroconverters	124.2 (118.9,129.5)	128.3 (123.3,133.2)	4.06 (-1.32, 9.44)	0.139	5.60 (-.275,11.5)	0.062		
HIV^+ART^-	132.0 (125.5,138.5)	121.4 (115.7,127.1)	-10.6 (-15.6, 5.66)	<0.001**	-9.09 (-14.6, -3.61)	0.001**		
$HIV^+ART^{0-<2\ yrs}$	118.0 (111.0,124.9)	116.3 (109.7,123.0)	-1.62 (-9.00, 5.75)	0.666	-.093 (-7.82, 7.64)	0.981		0.0016**
$HIV^+ART^{2-5\ yrs}$	128.2 (121.2,135.3)	122.6 (118.1,127.1)	-5.64 (-11.2, -0.070)	0.047*	-4.11 (-10.2, 1.93)	0.182		

The results of several sensitivity analyses of the effect of HIV status on blood pressure change are presented in Tables S2.3 – S2.7. Adjusting for BMI at baseline, the results of the change in SBP were qualitatively similar to the complete case results, and quantitatively fell between the results of the complete case and the weighted analysis (Table S2.3). Conducting a weighted analysis including information of those who died in the censoring weights, the drop in SBP in the $HIV^{+}ART^{2-5\ yrs}$ group was significant, similar to the results in the weighted analysis that excluded the information of the dead and very sick for weight estimation (Table S2.4b). The results of the sensitivity analysis that included fewer covariates were qualitatively similar to the results of the IPW analysis without the dead and very sick (Table S2.4c).

Overall, the effect of HIV status and ART on DBP differed from their observed effect on SBP: whereas there was a significant drop in SBP in the $HIV^{+}ART^{-}$ group, DBP significantly increased in the HIV^{-} and among seroconverters: both in the complete case and the IPW analysis (Table S25ab), DBP significantly increased by more than 4mm Hg in the HIV^{-} group ($p<0.001$) between 2003 and 2010. Seroconverters showed an increase in DBP of >7 mm Hg ($p=0.001$). None of the other observed DBP changes were statistically significant.

All DBP subgroup-specific relative changes compared to the HIV^{-} comparison group were non-significant based on the main model. When adjusting for BMI at baseline (Table S2.6), using IPWs that included information of the full baseline population, and using IPWs based on fewer predictors (Table S2.7ab), the results remained robust.

DISCUSSION

This study represents a population-based, longitudinal analysis of the modifying effect of HIV and ART on body mass and blood pressure. Our study includes a HIV^- reference group and spans periods before and after intensive ART rollout – two features thus far unique to chronic disease risk factor analyses in sub-Saharan (HIV) cohorts. Importantly, the HIV^- reference group allowed for an adjustment for the secular trend in BMI and BP. Further, the first BMI and BP measurement occurred well before wasting may have occurred in HIV^+ individuals[28,29], as the minimum difference between the first survey measurement and ART onset was well over a year (Figures S2.2-S2.3).

We present several novel findings. The $HIV^+ART^{0-<2yrs}$ group experienced a very significant decline in BMI compared to the HIV^- reference group. This relative decline was attenuated and no longer significant among those on ART between two and five years. Thus, our results suggest that ART allows individuals to recover toward a trend in weight gain experienced by the HIV^- population, without however surpassing their baseline weight.

This 'trend toward normal weight' has been postulated in previous studies.[30] It parallels the finding that large scale long-term ART can lead to a return to pre-HIV workforce productivity[31], but also allays concerns that ART might lead to net weight gain in the long-term. Nevertheless, the 'trend toward normal' in this study is a paradoxical benefit, as it represents a trend toward overweight and obesity. Food insecurity in rural KwaZulu-Natal remains a concern in the majority of the population, hence any programs to address the growing obesity rates will have to be sensitive to this underlying issue.

While the weight gain recovery on ART can be seen as a positive outcome – ART allows to a 'return to normal' - our results warrant careful reflection. Health care providers need to judiciously consider when and for how long to counteract harmful weight loss in the early stages of ART regimen, and when to advise to slow weight gain in order to lessen CVD risk and other overweight and obesity-related complications. Our data provide first evidence that after two years on ART, there is no longer a significant difference in weight trajectory compared to the reference population. Thus, nutrition and exercise interventions to curb weight gain might be sensible starting then.

As community health workers frequent HIV+ individuals, this offers an opportunity for greater sensitization of the HIV^+ population toward the risks of obesity and hypertension. If staff training and resources permitted, excessive weight gain and high blood pressure could be monitored and managed concurrent with HIV surveillance and ART therapy.

However, research on the effectiveness of infectious and chronic disease service integration is still ambivalent. It is not clear whether integration of infectious and chronic disease factor monitoring may weaken current HIV management efforts. In a systematic review on the impact of integrating primary healthcare services in LMICs at the point of delivery, Dudley & Garner examined the effect of integration on healthcare delivery, user views (satisfaction), and health status.[32] While adding services (i.e. diabetes screening being added to HIV treatment and care) improved the use of the added-on service, there was very little evidence that health status was improved by service integration. In some cases, integration also led to deteriorating service delivery.[32] Therefore, an important avenue of further study would be to assess the effectiveness

of chronic and infectious disease prevention efforts, and to arrive at best practice recommendations in emerging economies and low-income settings.

An additional recommendation emerging from our study was to also monitor waist circumference and the waist-to-hip-ratio (WTHR). There exists ample evidence that waist circumference and WTHR are much greater predictors of mortality and disease risk than BMI.[33-36] Several previous studies have shown that weight gain during ART therapy favors abdominal versus limb fat accumulation, thereby exposing someone on ART with the same BMI as a HIV-negative person to a higher CVD and mortality risk.[30] Women are particularly affected with visceral adipose tissue accumulation as an effect of ART. Therefore, despite the fact that the herein presented study did not allow for examination of the change of WTHR between 2003 and 2010 between the various HIV subgroups, it is highly likely that the 'return to normal' BMI in the long-term ART exposure group was characterized by an increase in VAT, and thereby, a relative increase in CVD risk compared to the HIV^- population.

For blood pressure changes, ART use (both short-term and long-term use) showed BP stabilization over seven years, similar to parallel HIV^- individuals in same cohort; in contrast, HIV^+ individuals with no ART use showed substantial drop in BP compared to ART users. Thus ART use yielded a positive blood pressure trajectory relative to HIV non-ART individuals. Notably, the HIV^+ART^- group had the highest average systolic blood pressure in 2003. This indicates a potentially unhealthier lifestyle in the HIV^+ART^- group compared to the HIV^- group. Further, compared to the HIV^- group, SBP in the HIV^+ART^- group showed a significant decline. We were unable to determine whether this overall drop in SBP from 130.4mmHg to 123.5 mmHg was due to HIV-related side effects or due to improved clinical care (a SBP >130mmHg

is considered elevated blood pressure, is associated with a higher risk of cardiomyopathies, and a higher risk of recurrent strokes[37]). Likely, the large drop in SBP in this population might be explained by additional blood pressure monitoring paralleling intensive health checks post HIV diagnosis. To test this hypothesis, detailed healthcare records, a larger sample size, and additional longitudinal data points would be necessary.

LIMITATIONS

There were several additional unknowns and potential time-variant confounders in our analysis, which we were unable to control for due to lack of data availability. The most important of these unmeasured potential confounders were detailed information on health status and the presence of other infections (particularly in HIV-positive patients), level of ART adherence, viral load information, drug resistance, and whether ART patients were on first or second line treatment regimen. Thus, our results are to be interpreted as population based associations, bearing in mind these potential confounders.

Furthermore, our study would have benefitted from more measurement points both between 2003 and 2010 and thereafter. This would allow to better evaluate the BMI trajectory differences in the various BMI subgroups and to draw stronger conclusions with regard to the 'back to normal weight' hypothesis. As only a subset of the demographically surveyed population in 2003 and 2010 were assessed for body mass and blood pressure, our study and results might lack wider external validity. In addition, our study experienced a large loss to follow up, which we addressed by conducting IPW sensitivity analyses. Our results were qualitatively robust to these analyses sensitivity analyses. Nevertheless, further research with planned, intensive follow up is

needed. This will help in planning to address to growing burden on non-communicable diseases in South Africa and surrounding nations.

CONCLUSION

Short-term ART (0–<2 years) was associated with a larger weight loss compared with no or long-term ART. Once on ART for two or more years, individuals 'caught up' on weight gain with the HIV^- reference population. Such a longitudinal finding of parallel trajectories of short-/long-term ART users and HIV^+ and HIV^- populations have, to our knowledge, never been reported before. Our results thus showcase the importance of health system readiness to address the burgeoning double burden of disease in Sub-Saharan Africa. As emerging economies face the double burden of non-communicable and infectious diseases, further research based on cohort studies with both HIV-positive and HIV-negative populations will be needed to shine light into the trends and treatment opportunities of chronic disease (risk factors) in these populations.

RESEARCH IN CONTEXT

We searched PubMed with the terms "HIV", "ART", "Africa", and ("Cardiovascular" or "BMI" or "Blood pressure" or "Weight" not "Pregnancy"), for articles published between Jan 1, 2000, and November 25, 2014. We restricted our search to articles available in English. We identified a comprehensive systematic review that included all articles identified through our original search up to January 1, 2012. We then restricted our search to articles published between Jan 1, 2012, and November 25, 2014. Among the 109 identified studies, 106 studies were excluded based on title, abstract, and data review.

The 2013 meta-analysis concluded that HIV infection was associated with both lower systolic and diastolic blood pressure, but evidence on the effect of ART on blood pressure was weak or non-existent.[14] Dillon et al emphasized the need for further research in this area to more reliably manage chronic disease risk in HIV-infected populations in SSA.

The additional three studies revealed during our review showed that pre-ART weight was a predictor of onset of diabetes on ART[15], that ART was associated with non-HIV related, chronic morbidity[16], and that ART was associated with increased central fat (a cardio-metabolic disease marker) and reduced peripheral fat.[17] We did not identify studies that were longitudinal studies including both a HIV^- control group and that spanned both periods before and after ART rollout.

INTERPRETATION

Based on our findings, short-term ART (0 to <2 years) is associated with a larger weight loss compared with no or long-term ART. This attenuation of relative weight loss when individuals were on ART for two to five years, compared to 0 to <2 years, suggests a U-shaped association with long-term use of ART and BMI: Once on ART for two or more years, individuals 'catch up' on weight gain with the HIV^- reference population. Our study revealed the need for additional evidence of the effect of HIV and ART on cardiovascular and chronic disease risk, particularly in high-prevalence, low-income populations. In addition, further evidence on optimal health systems solutions to address the double burden of chronic and infectious disease is needed.

AUTHORS' CONTRIBUTIONS

ABF conceived of the research question, designed the study, obtained and analyzed the data, and wrote the manuscript. TWB, JAS, GD, and DEB guided the data analysis, revised and reviewed the manuscript, and mentored the overall process. All authors have reviewed and approved of the final version of the manuscript. DP revised and reviewed the manuscript, and mentored the overall process.

Conflict of Interest Statement

The authors declare no conflict of interest

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Statement regarding Ethics Approval

The study was exempt of ethics approval as it only utilized secondary data from the DSA surveys following conventional ethics guidelines and void of personal identifiers.

Transparency declaration

The lead author (ABF) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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SUPPLEMENTARY APPENDIX 2

THE EFFECT OF HIV AND THE MODIFYING EFFECT OF ANTI-RETROVIRAL THERAPY (ART) ON BODY MASS INDEX (BMI) AND BLOOD PRESSURE LEVELS IN RURAL SOUTH AFRICA

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SUPPLEMENTAL TABLES

Table S2.1: Additional baseline characteristics of the complete case study population in 2003 (n=505), including p-values. This table shows the unadjusted sex, age, weight, height, BMI, SBP, DBP, and HIV status characteristics of the study population. Age, weight, and BMI differed significantly among the subgroups at baseline.

Characteristics mean (SD)	Overall sample population (n=505)	HIV^- (n=347)	HIV^+ART^- (n=52)	HIV^+ART^+ (n=62)	Refused Testing (n=44)	p-value
Sex (female, %)	81.78 %	81.27%	80.77%	77.42%	93.18%	0.23
Years of age (SD)	39.5 (7.2)	40.2 (7.2)	37.3 (7.1)	37.6 (7.8)	38.8 (5.5)	0.005**
Weight, kgs (SD)	74.9 (18.8)	76.1 (19.1)	69.1 (15.6)	71.2 (19.1)	77.44 (17.3)	0.024*
Height, cms (SD)	160.8 (7.3)	160.9 (7.3)	159.1 (9.1)	162.0 (6.9)	160.7 (5.9)	0.226
BMI (SD)	29.0 (7.2)	29.5 (7.4)	27.4 (6.0)	27.2 (7.1)	30.1 (7.0)	0.029*
Years on ART (SD)				2.5 (1.4)		
% on ART for 0-1.9 years				29.03%		
CD4+ count at ART initiation				136.5 (78.7)		
SBP, n=502, (SD)	126.7 (20.2)	127.1 (20.7)	129.3 (22.2)	122.3 (17.4)	125.6 (17.8)	0.270
DBP, n=502, (SD)	80.6 (13.2)	80.9 (13.5)	81.0 (14.0)	78.0 (10.7)	81.0 (12.5)	0.436

Table S2.2: Effect of ART and HIV on longitudinal change of BMI – robustness checks. S2.2a: The results presented in this table are based on a population average linear regression model using IPW adjusting for missingness due to loss to follow up, migration, and non-consent (but not death and severe illness). The weights were based on age, sex, education, general health, and an asset index indicator. The model controlled for age, sex, HIV, and ART status. S2.2b: Same as S2.2a, but weights included information at baseline of those who subsequently die or fell ill. S2.2c: The results presented in this table are based on a population average model (without IPW), but excluded all outliers with BMI<50kg/m^2 at baseline and follow-up.

	S2.2a: IPW (without dead and very sick)		**S2.2b: IPW with all lost to follow-up**		**S2.2c: BMI < 50kg/m^2, general model**	
	ΔBMI (03-10) (95%CI)	**p-value**	**ΔBMI (03-10) (95%CI)**	**p-value**	**ΔBMI (03-10) (95%CI)**	**p-value**
HIV^-	0.554 (-0.228, 1.34)	0.165	0.747 (0.048, 1.45)	0.036*	1.03 (0.614, 1.45)	<0.001**
Seroconverters	-0.128 (-1.06, 0.806)	0.788	-0.047 (-0.956, 0.862)	0.920	-0.128 (-1.06, 0.806)	0.788
HIV^+ART^-	-0.404 (1.48, 0.675)	0.463	-0.294 (-1.45, 0.866)	0.619	-0.786 (-1.83, 0.254)	0.138
$HIV^+ART^{0–<2\ yrs}$	-3.11 (-5.66, -0.547)	0.017*	-3.99 (-7.82, -0.164)	0.041*	-2.43 (-4.21, -0.644)	0.008**
$HIV^+ART^{2–5\ yrs}$	-0.012 (-1.20, 1.18)	0.984	-0.270 (-1.10, 0.565)	0.527	-0.475 (-1.58, 0.633)	0.400

Table S2.3: Effect of ART and HIV on longitudinal change of SBP. SBP changed significantly between years 2003 and 2010 among ART users less than 2 years on ART. *Adjusted for BMI at baseline.*

Population average model – adjusted for BMI at baseline				
HIV Group	**SBP 2003 (95% CI)**	**SBP, 2010 (95% CI)**	**ΔSBP (03-10) (95%CI)**	**p-value for first difference est.**
HIV^-	126.6 (124.4,128.8)	126.9 (124.7,129.2)	0.368 (-1.75, 2.48)	0.734
Seroconverters	123.418 (116.6,130.2)	128.82 (122.1,135.5)	1.67 (-3.94, 7.28)	0.560
HIV^+ART^-	131.6 (126.4,136.8)	124.4 (119.2,129.62)	-7.23 (-12.4, 2.03)	0.006**
$HIV^+ART^{0–<2\ yrs}$	118.3 (109.8,126.9)	118.3 (109.8,126.9)	0.00 (-8.77, 8.77)	1.00
$HIV^+ART^{2–5\ yrs}$	127.226 (121.8, 132.6)	126.241 (120.9,131.6)	-0.984 (-6.64, 4.67)	0.733

Table S2.4: Effect of ART and HIV on longitudinal change of SBP – robustness checks. S2.4a: The results presented in this table are based on a population average linear regression model using IPW adjusting for missingness due to loss to follow up, migration, and non-consent (but not death and severe illness). The weights were based on age, sex, education, general health, and an asset index indicator. The model controlled for age, sex, HIV, and ART status. S2.4b: Same as S2.4a, but weights included information at baseline of those who subsequently die or fell ill. S2.4c: (population average model) with IPW (fewer covariates). The results presented in this table are based on a population average linear regression model using IPW adjusting for missingness due to loss to follow up, migration, and non-consent. The weights were based on age, sex, and education. The model controlled for age, sex, HIV, and ART status.

	S2.4a: IPW (without dead and very sick)		**S2.4b: IPW with all lost to follow-up**		**S2.4c: IPW without dead and very sick, fewer covariates**	
	ΔSBP (03-10) (95%CI)	**p-value**	**ΔSBP (03-10) (95%CI)**	**p-value**	**ΔSBP (03-10) (95%CI)**	**p-value**
HIV^-	-1.53 (-3.88, 0.816)	0.201	-1.72 (-4.10, 0.661)	0.157	-1.12 (-3.39, 1.14)	0.330
Seroconverters	4.06 (-1.32, 9.44)	0.139	4.13 (-1.22, 9.48)	0.130	4.04 (-0.938, 9.75)	0.106
HIV^+ART^-	-10.6 (-15.6, 5.66)	<0.001**	-11.4 (-16.5, -6.17)	<0.001**	-9.81 (-14.7, -4.90)	<0.001**
$HIV^+ART^{0–<2\ yrs}$	-1.62 (-9.00, 5.75)	0.666	-1.98 (-10.7, 6.79)	0.659	-.595 (-7.74, 6.55)	0.870
$HIV^+ART^{2–5\ yrs}$	-5.64 (-11.2, -0.070)	0.047*	-6.04 (-11.7, -0.387)	0.036*	-4.84 (-10.3, 0.628)	0.083

Table S2.5ab: Effect of ART and HIV on longitudinal change of DBP. S2.5a: Population average model. DBP changed significantly between years 2003 and 2010 among ART users less than 2 years on ART. S2.5b: Population average model with IPW. The results presented in this table are based on a population average linear regression model using IPW adjusting for missingness due to loss to follow up, migration, and non-consent (but not death and severe illness). The weights were based on age, sex, education, general health, and an asset index indicator. The model controlled for age, sex, HIV, and ART status.

S2.5a: Effect of ART and HIV on longitudinal change of DBP								
	DBP 2003 (95% CI)	**DBP, 2010 (95% CI)**	**ΔDBP (03-10) (95%CI)**	**p-value for first diff**	**DID effect (95%CI)**	**p-value (DID)**	**Global p-value**	**ART duration p-value**
HIV^-	80.6 (79.2, 82.0)	85.4 (84.0, 86.9)	4.85 (3.42, 6.28)	<0.001**	*(ref)*		0.735	
Seroconverters	78.9 (74.5, 83.4)	86.9 (82.5, 91.4)	8.00 (3.48, 12.5)	0.001**	3.15 (-1.59, 7.89)	0.192		
HIV^+ART^-	81.5 (78.0, 85.0)	84.7 (81.2, 88.2)	3.15 (-.374, 6.67)	0.080	-1.70 (-5.50, 2.10)	0.380		
$HIV^+ART^{0-<2\ yrs}$	77.0 (71.1, 82.8)	80.0 (74.2, 85.9)	3.06 (-2.87, 8.98)	0.312	-1.79 (-7.89, 4.30)	0.564		0.0683
$HIV^+ART^{2-5\ yrs}$	79.7 (76.0, 83.5)	79.7 (77.8, 85.4)	1.84 (-2.00, 5.67)	0.348	-3.01 (-7.11, 1.08)	0.149		
S2.5b: Effect of ART and HIV on longitudinal change of DBP (adjusted for loss to follow up)								
HIV^-	80.8 (79.2, 82.5)	85.0 (83.6, 86.4)	4.19 (2.57, 5.82)	<0.001**	*(ref)*		0.284	
Seroconverters	78.5 (74.6, 82. 3)	86.2 (81.7, 90.7)	7.76 (3.18, 12.3)	0.001**	3.56 (-1.29, 8.43)	0.150		
HIV^+ART^-	81.5 (76.6, 86.4)	83.9 (80.0, 87.8)	2.36 (-0.882, 5.61)	0.153	-1.83 (-5.46, 1.80)	0.324		
$HIV^+ART^{0-<2\ yrs}$	76.03 (71.0, 81.0)	78.8 (74.4, 83.3)	2.79 (-2.22, 7.80)	0.275	-1.40 (-6.67, 3.86)	0.602		0.0092**
$HIV^+ART^{2-5\ yrs}$	80.8 (77.2, 84.3)	80.1 (77.1, 83.0)	-0.691 (-4.62, 3.24)	0.730	-4.88 (-9.13, -0.631)	0.024*		

Table S2.6: Effect of ART and HIV on longitudinal change of DBP (population average model). SBP changed significantly between years 2003 and 2010 among ART users less than 2 years on ART. *Adjusted for BMI at baseline.*

Population average model – adjusted for BMI at baseline				
HIV Group	**DBP 2003 (95% CI)**	**DBP, 2010 (95% CI)**	**ΔDBP (03-10) (95%CI)**	**p-value for first difference est.**
HIV^-	80.6 (79.2, 82.0)	85.4 (84.0,86.8)	4.79 (3.36, 6.22)	<0.001**
Seroconverters	78.7 (74.4, 83.0)	86.6 (82.4, 90.8)	7.86 (3.35,12.4)	0.001**
HIV^+ART^-	82.5 (79.3, 85.7)	85.3 (82.1, 88.6)	2.85 (-.670, 6.36)	0.113
$HIV^+ART^{0–<2\ yrs}$	76.7 (71.4, 82.0)	79.8 (74.5, 85.1)	3.06 (-2.88, 8.99)	0.313
$HIV^+ART^{2–5\ yrs}$	80.8 (77.3, 84.3)	82.6 (79.2, 86.1)	1.82 (-2.00, 5.65)	0.350

Table S2.7: Effect of ART and HIV on longitudinal change of DBP – robustness checks. S2.7a: The results presented in this table are based on a population average linear regression model using IPW adjusting for missingness due to loss to follow up, migration, and non-consent (but not death and severe illness). The weights were based on age, sex, education, general health, and an asset index indicator. The model controlled for age, sex, HIV, and ART status. S2.7b: Same as S2.7a, but weights included information at baseline of those who subsequently die or fell ill. S2.7c: (population average model) with IPW (fewer covariates). The results presented in this table are based on a population average linear regression model using IPW adjusting for missingness due to loss to follow up, migration, and non-consent. The weights were based on age, sex, and education. The model controlled for age, sex, HIV, and ART status.

	S2.7a: IPW (without dead and very sick)		**S2.7b: IPW with all lost to follow-up**		**S2.7c: IPW without dead and very sick, fewer covariates**	
	ΔDBP (03-10) (95%CI)	**p-value**	**ΔDBP (03-10) (95%CI)**	**p-value**	**ΔDBP (03-10) (95%CI)**	**p-value**
HIV^-	4.19 (2.57, 5.82)	<0.001**	4.13 (2.51, 5.74)	<0.001**	4.57 (2.99, 6.16)	<0.001**
Seroconverters	7.76 (3.18,12.3)	0.001**	7.81 (3.04, 12.6)	0.001**	7.93 (3.76, 12.1)	<0.001**
HIV^+ART^-	2.36 (-0.882, 5.61)	0.153	2.01 (-1.40, 5.41)	0.248	2.05 (-1.41, 5.51)	0.245
$HIV^+ART^{0–<2}$ yrs	2.79 (-2.22, 7.80)	0.275	2.91 (-2.07, 7.89)	0.252	3.01 (-1.40, 7.42)	0.181
$HIV^+ART^{2–5}$ yrs	-.691 (-4.62, 3.24)	0.730	-.993 (-4.91, 2.92)	0.619	0.314 (-3.60, 4.23)	0.875

Table S2.8: Estimation and characteristics of the IPWs

	Estimated Inverse Probability Weights	
Weight Specification	**Mean (SD)**	**Min/ Max**
1. Probability of participation predicted based on geographic sampling block, HIV status (at baseline), age, sex, self reported health status (at baseline), highest education attained (at baseline), and asset index (at baseline); missing variables were coded via missing indicators; those lost to follow up due to death or severe illness were not included	0.999 (0.674)	0.357 / 5.92
2. Probability of participation predicted based on geographic sampling block, HIV status (at baseline), age, sex, self reported health status (at baseline); missing variables were coded via missing indicators; those lost to follow up due to death or severe illness were not included	1.01 (0.532)	0.364 / 3.85
As in 1., and those lost to follow up due to death or severe illness were included	1.01 (0.738)	0.314 / 7.29

SUPPLEMENTAL FIGURES

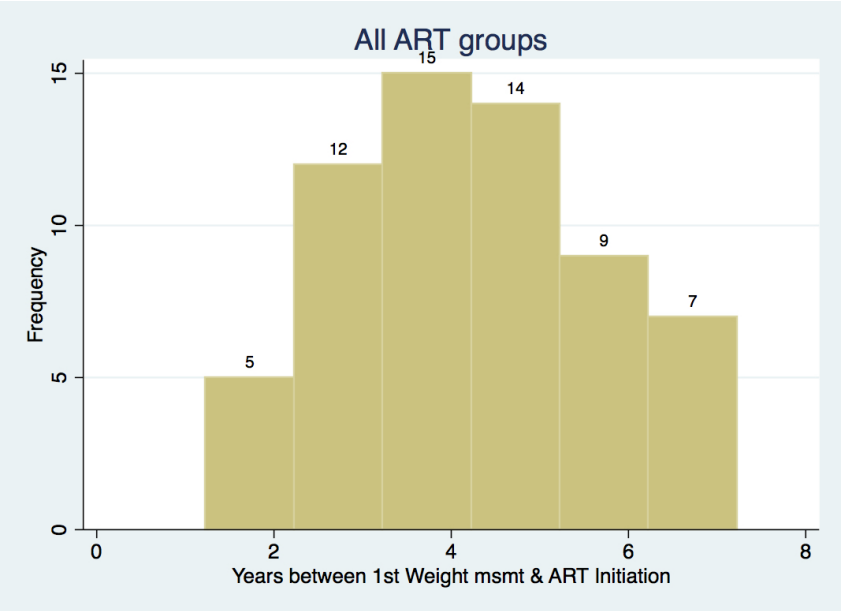

Figure S2.1: Years between first weight measurement and ART Initiation, All ART groups

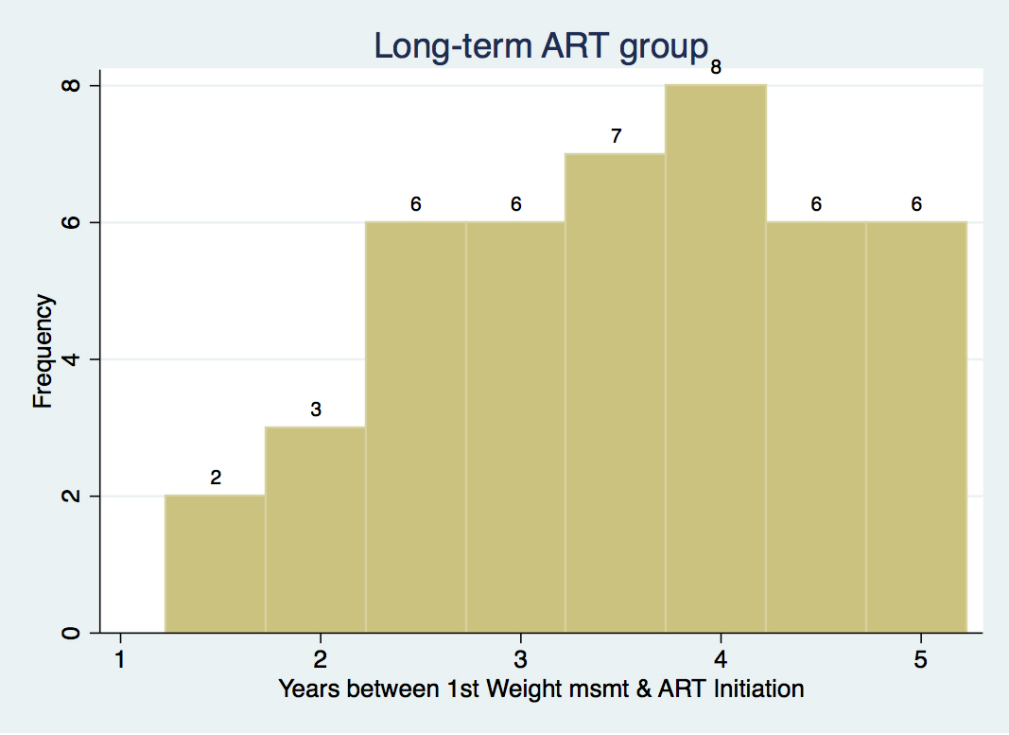

Figure S2.2: Years between first weight measurement and ART Initiation, long-term ART group

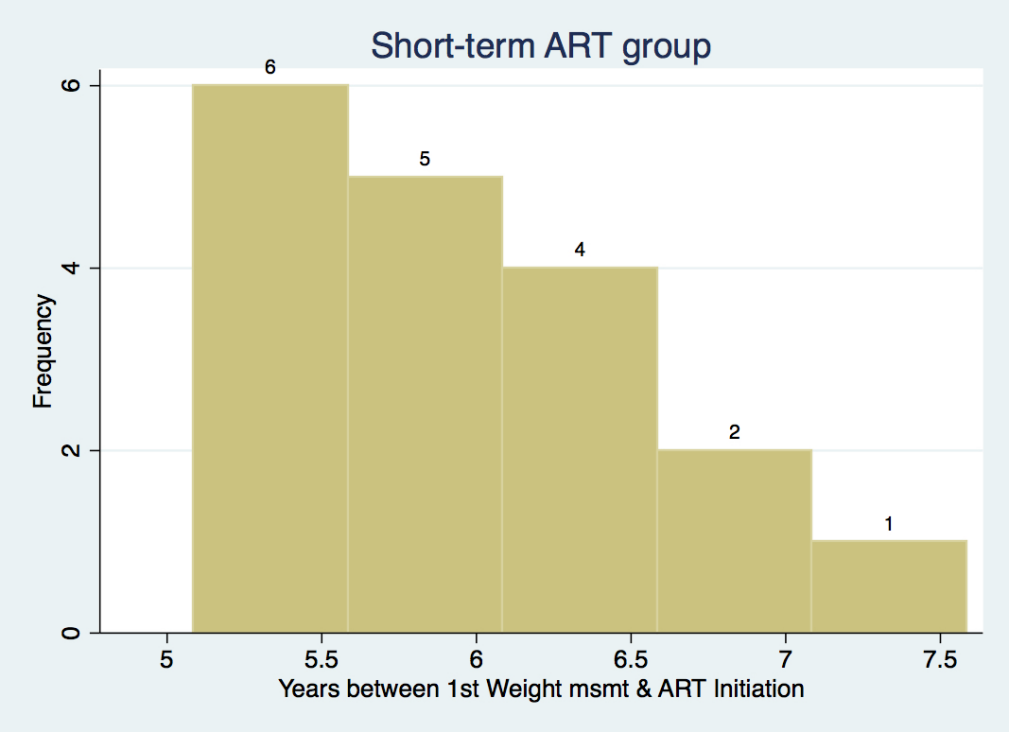

Figure S2.3: Years between first weight measurement and ART Initiation, short-term ART group

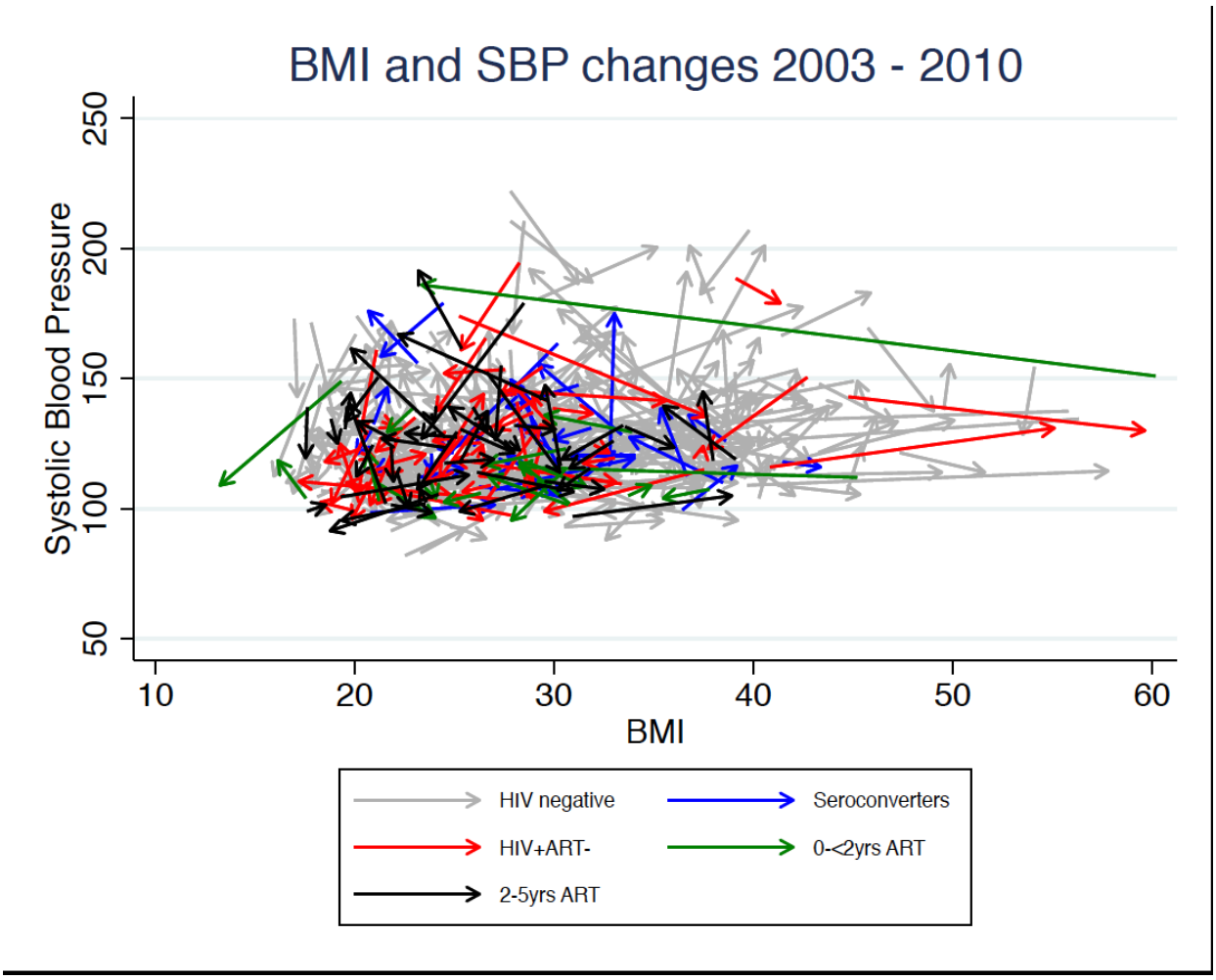

Figure S2.4: BMI and SBP Changes, 2003-2010

LITERATURE REVIEW

We searched PubMed with the terms "HIV", "ART", "Africa", and ("Cardiovascular" or "BMI" or "Blood pressure" or "Weight" not "Pregnancy"), for articles published between Jan 1, 2000, and November 25, 2014. We restricted our search to articles available in English. We identified a comprehensive systematic review that included all articles identified through our original search up to January 1, 2012. We then restricted our search to articles published between Jan 1, 2012, and November 25, 2014. Among the 109 identified studies, 106 studies were excluded based on title, abstract, and data review.

The 2013 meta-analysis concluded that HIV infection was associated with both lower systolic and diastolic blood pressure, but evidence on the effect of ART on blood pressure was weak or non-existent.[1] Dillon et al emphasized the need for further research in this area to more reliably manage chronic disease risk in HIV-infected populations in SSA.

The additional three studies revealed during our review showed that pre-ART weight was a predictor of onset of diabetes on ART[2], that ART was associated with non-HIV related, chronic morbidity[3], and that ART was associated with increased central fat (a cardio-metabolic disease marker) and reduced peripheral fat.[4] We did not identify studies that were longitudinal studies including both a HIV^- control group and that spanned both periods before and after ART rollout.

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PAPER #3: MICROCLINIC SOCIAL NETWORK INTERVENTIONS FOR OBESITY AND DIABETES IN AMMAN, JORDAN: A 6-MONTH, 3-ARMED CLUSTER RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background In Jordan, close to 20% of adults are diabetic, and over 75% are overweight/obese. Diabetes (DM) preventive interventions are lacking and costly.

Objective To address this health burden, we evaluated the effect of leveraging current social networks of friends and family using the Microclinic Social Network (MSN) program via a multi-center, 28 week, 3-arm, cluster-randomized clinical trial in Jordan.

Design, Setting, and Participants Participants were diabetic or pre-diabetic, or had >=1 risk factor and family history of DM. Between 2011 and 2013, 920 participants were enrolled at four

centers and randomized at the group level to either (A) enhanced MSN program with interactive sessions; (B) basic MSN diabetes health education; or (C) standard monitoring and care.

Main Outcome and Measures Primary outcomes were cross-arm difference-in-differences (DID) in weight, BMI, and HbA_{1c} at 14 weeks, 28 weeks, and 12 month follow-up. DID in waist circumference, blood pressure, and fasting plasma glucose were also collected. Inverse probability weighting was used to address missingness.

Results Participants were 66% women, with mean (SD) age 55.1 years (10.2) and mean BMI=33.6 (3.2). After 14 weeks, the DID in weight change of Arm A (n=545) vs control (n=188) was -0.6 kg (95%CI: -1.1 to -0.1), and -0.2kg (-0.5 to 0.01) in Arm B (n=187) versus control. At 28 weeks, the DID of weight change of Arm A vs C -1.2 kg (-1.7 to -0.5), while the DID of Arm B vs Arm C was not significant. Analyses correcting for dropouts yielded significant results for weight -0.9kg (-1.8 to -0.1) and HbA_{1c} -0.2% (-0.4 to -0.1) for A vs C at 28 weeks. At 12 months, DID in weight and HbA_{1c} were not different across groups. However, loss-to-follow-up was 50%, and thus the 12-month results to-date are inconclusive. Further follow-ups are planned at 16- and 30-months.

Conclusions Overall, the enhanced MSN intervention was effective in significantly reducing weight over a 28 week intervention period; HbA_{1c} results also suggested modest improvements. Further studies that leverage social networks are needed.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01596244

INTRODUCTION

Non-communicable diseases (NCDs) comprise an increasingly large percentage of the overall disease burden in the Middle East.[1,2] In Jordan, NCDs were responsible for more than 50% of all deaths in 2005, and this fraction has increased since then.[3] Ischemic heart disease, congenital anomalies, and stroke were estimated to be the top three reasons for premature death in Jordan in 2013, with diabetes ranking at number five.[4-6] High body-mass index (BMI), dietary risks, high fasting plasma glucose (FPG), high blood pressure (BP), smoking, and physical inactivity contributed over 45% of all disability-adjusted life years lost (DALYs) in Jordan in 2010.[7]

Despite the large disease and economic burden of chronic diseases[8], national strategies to address NCDs in Jordan specifically, and the Middle East overall, have been lacking.[1,9] Ajlouni et al showed that 54% of diabetics in Jordan received insufficient care, and that women are disproportionately affected by the obesity epidemic in Jordan.[3] Chronic disease risk factor self-management in Jordan remains poor, and wanes with increasing time post-diagnosis.[3,10,11] Therefore, cost-effective community prevention programs are necessary to change the tide of chronic disease risk factors.

To achieve reliable and sustained control of chronic disease risk factors, long-lasting, low-cost self-management strategies, such as social-network focused interventions, are needed. Previous studies have established a strong effect of social networks on propagating behavior change related to chronic disease risk factors.[12,13] However, these have been based on passive observational designs, which do not allow differentiation between social network modalities.[14]

Since 2005, Microclinic International (MCI) has pioneered the research and development of a novel social network 'microclinic' model to study if and how specifically social networks can be leveraged for diabetes and weight management.[15-17] After a successful Microclinic trial in Kentucky, demonstrating sustained weight loss and improvements in blood glucose and cholesterol past the nine months of the intervention, MCI was invited to conduct a similar study in Jordan, to assess the potential success and transferability of this program to a low-resource setting.

We thus conducted a randomized control study specifically designed to test the effectiveness of the 6-month Microclinic program in influencing lifestyle behavioral risk factors to improve diabetes management that effect weight and metabolic outcomes through social networks in Amman, Jordan. MCI conducted trial NCT01596244 in close collaboration with Queen Rania's Royal Health Awareness Society and the Jordanian Ministry of Health.

METHODS

Trial Design and Setting

The MCI trial was a multicenter, three-arm, cluster-randomized controlled trial that enrolled participants from four community health centers in Amman, Jordan. The study protocol was approved by institutional review boards in both the United States (*Western Institutional Review Board*) and locally (*The National Center for Diabetes, Endocrinology, and Genetics, Amman Jordan*). All participants provided written informed consent. The trial was rolled out in five waves (cycles) in four participating centers, with gaps of 15 -28 weeks between cycles. (See Appendix for detailed timeline).

Participants

Recruitment through the local Ministry of Health (MoH) care centers utilized a combination of community outreach campaigns and patient recruitment within community health care centers. Active recruitment of the five cohort waves occurred during October 2011 – May 2013. The first intervention cohort started in January 2012.

Community members were invited to a presentation at the local medical center to learn about the government-sponsored program. At this meeting, potential participants were encouraged to bring friends and family members who met program eligibility criteria. All those interested in the program were eligible to register as a 'microclinic cluster'. Before registering, any questions about the program were explained and participants signed a consent form to allow periodic data collection of behavioral and metabolic risk factors for program evaluation purposes. Men and women 18 years or older were eligible to participate in the study if they had been previously diagnosed with diabetes, were diagnosed with diabetes or pre-diabetes during recruitment, or were at risk of diabetes. Diabetes and pre-diabetes were confirmed by means of a fasting plasma glucose (FPG) test at recruitment, using criteria of 100-125 mg/dL for pre-diabetes, and 126 mg/dL or higher for diabetes. Risk of diabetes was defined as having a history of diabetes in close family AND being overweight/obese, or as having a family history of diabetes AND having either high BP or high serum cholesterol. Pregnant and/or severely ill participants were not eligible to participate in the study. All participants needed to be able to understand, read, and sign the written consent form.

Data Collection

Three types of data were collected as part of this randomized trial: clinical measures (height, weight, waist circumference, blood pressure, HbA_{1c}, and fasting blood glucose), survey data (including knowledge about diabetes and obesity, healthcare access, exercise and dietary habits, education status, etc); and social network information (measuring how study participants were related and interacted with others within their social cluster and between others in their classroom group). The clinical data was collected by trained nurses and trained personnel at the MoH community health centers. The survey and social network data were collected via paper-based surveys, and proctored by nurses and study coordinators. The timeline for the measurements throughout the six-month (28-week) intervention period and follow-up period are described in Table S3.1.

Study Procedures

Recruitment occurred in three phases. In phase 1, potential participants were encouraged to participate via posters in the five MOH clinics, via direct contact by study nurses/clinic staff based on medical record review, during patient clinic visits (nurses/ doctors discussed study with prospective participants), and by recruiting participants who had formerly participated in a prior longitudinal, non-randomized social network program.[17] Upon declaration of willingness to participate, nurses invited prospective participants to an upcoming recruitment event on a specific day and at one of the five study centers (phase 2). Participants were required to fast eight hours before their appointment time. During phase 3, the recruitment event, eligibility criteria were verified, fasting blood glucose was measured, and a short lecture was given that described the purpose of the program and the associated study. To fulfill the social network component of the study, participants were encouraged to bring family members and close friends who might

also be eligible. After registering with the nurses as a social cluster, with one primary member of each cluster was designated as a 'node'; the eligibility of all cluster members was verified. All eligible individuals were randomized in a cluster-based randomization procedure, where each node plus cluster was randomized to one of the three treatment arms. Randomization was stratified by study center (five total), and study waves (four total), resulting in a total of nine study cohorts.

Biometric and Laboratory Measures

Height was measured using a hospital & homecare scale with height meter; weight was measured using Health Scale SVR 160. Fasting Plasma glucose was measured via the finger prick method, using AccuCheck Performa. Digital readings on this device converted blood glucose concentrations to plasma glucose concentrations, conforming to international reporting standards. Omron and A&D blood pressure cuffs were used to measure blood pressure; both types measured SBP and DBP three consecutive times. HbA_{1c} levels were tested at the Jordanian MoH Lab Centers via High Performance Liquid Chromatography (HPLC).

Study Intervention

The intervention was delivered over a timeframe of six months (28 weeks), and involved 14 program sessions (Arm A and B), or 14 check-in appointments (Arm C). Both the detailed curriculum and the treatment schedule (including timeline for biometric, survey, and social network measurements) are shown in Appendix 1 (Table S3.1 and S7).

Arm A received a full social-network based intervention, where participants in each classroom were encouraged and tasked to work within their assigned microclinic (MC) groups. These MCs

consisted of groups of two to six participants from pre-existing social networks (friends, relatives, coworkers, neighbors, etc)—with shared access to diabetes education, technology (via glucose meters), and group support to promote weight and metabolic control through diet, exercise, medication adherence, and blood pressure management. MC members played a role in the collective effort to combat diabetes and solidifying self-management behavioral skills through peer monitoring and encouragement of lifestyle behaviors. The detailed curriculum is shown in Appendix A, and included cooking and physical activity lessons, encouragement to work with assigned social networks (Arm A), a field visit to the gym, and several other behavioral and lifestyle intervention lessons.

Intervention Arm B received an individually-focused educational intervention, with lessons on weight and metabolic control through diet, exercise, medication adherence, and blood pressure management, but without fostering and levering the social network component of the full MSN intervention. Control Arm C also attended the clinics at the same time intervals and frequency throughout the six-month study period; however, only measurements were taken, and no lessons were delivered to participants in this control arm. Additional follow-up visits were conducted 6-months after the last intervention, and continuing data collection planned for 10-months, 14-months, and 18-months post-intervention.

Outcome Assessment

Per study protocol, the primary outcome variables of this trial were 1) change in weight (i.e. BMI) from baseline to 3 and 6 months, 2) change in HbA_{1c} (glycated hemoglobin) levels from baseline to 3 and 6 months. The secondary outcome variables were a) change in blood pressure from baseline to 3- and 6-months, b) change in waist circumference from baseline to 3 and 6

months, and c) change in FPG from baseline to 3- and 6-months. All primary and secondary outcome data were collected at the additional follow-up 12-months post-baseline measurement.

Adverse Events and Safety monitoring

The MOH nurses conducted safety monitoring throughout the trial and referred participants to clinicians if deemed necessary and rescue therapy was required.

Masking

Laboratory analysis for HbA_{1c} was masked, as lab workers were not made aware which treatment group the samples came from. No masking took place for other measurements.

Statistical Analyses

We estimated the required sample size for Arm A vs C and B vs C (SD, 1%) assuming a 0.6% or greater reduction in HbA_{1c} in Arm A vs C and B vs C over a 6-month intervention period.[18,19] Using a 2-tailed, 2-sample t test and .05 type I error, a sample size of 234 participants per group was required to achieve 90% power. In order to increase power and factor in potential attrition, the intended sample size was set at 300 per arm. Due to recruitment procedure modifications, the sample sizes at baseline were n= 545, 187, and 188 in arms A, B, and C, respectively.

The trial data was structured as a longitudinal, multi-level, panel dataset. Individuals were nested within microclinic clusters, which in turn were structurally nested within classrooms, days, and cohorts (of different neighborhoods and temporal waves). In order to take account the multi-level data structure, we utilized multi-level, mixed effects models (random intercepts, random slopes). A particular advantage of multi-level models, which use partial pooling, is that they correct for

multiple testing, particularly when close biological correlation of outcome data is present.[20] Another advantage of multi-level models is that they additionally adjust for cluster randomization by allowing for within cluster-correlation. Conventional methods to adjust for cluster randomization, such as permutation tests or the Tukey-Kramer method, cannot commonly be combined with multi-level models, as the hierarchical structure accounts for within-cluster correlation.[21] Further, for correcting potential regression to the mean, the residual change method as used, following the steps outlined by Blomquist.[22,23]

Primary and secondary clinical outcomes were analyzed using the intention-to-treat principle, using the complete-case method. At each follow-up and measurement point, there was some missingness/loss to follow up (Table S3.3). As missingness might have been non-random and correlated with covariates and observed outcome, we applied inverse probability-of-censoring weights to remove selection bias.[24] Baseline covariates, time-varying updated information, and change in primary outcome measure (HbA_{1c} and weight change from baseline) up to the last measurement prior to the missingness/loss to follow up were used to compute stabilized inverse probability-of-censoring weights (IPCWs).[25] The IPCW method assigns a weight to each non-censored individuals and allows them to 'represent' those who have been lost to follow-up after adjusting for observed patient characteristics.[24,26,27] Different covariates were used to calculate the censoring weights for missed measurements at 3-, 6-, and 12-months post baseline. The covariates for the equation estimating the weights, as well as the summary statists of the stabilized censoring weights are shown in Table S3.5. As age differed slightly among subgroups at baseline, all analyses are adjusted for age to account for residual effects of the age on the studied outcomes. All statistical analyses were performed using STATA 13.1.

RESULTS

Participants at Baseline

During the first recruitment phase, 1032 volunteers were screened for eligibility. Of these, 79 did not provide consent, and 33 did not meet the inclusion criteria (5 were pregnant, and 28 were neither diabetic or pre-diabetic) (Figure 3.1). Thus, 920 eligible individuals, who had presented themselves within 778 pre-existing social nodes (mode =1, cluster size range: 1-4), were randomized to the three treatment arms, in which 468 nodes (n=545) were randomly assigned to Arm A; 153 nodes (n=187) were randomized to Arm B; 157 nodes (n=188) were assigned to Arm C. The group intervention meetings for Arm A were held on Mondays, Tuesdays, and Wednesdays. Those for Arm B were held on Thursdays and Fridays. Participants of Arm C were able to choose a preferred day of the week to participate in the measurements. As the intended cluster size for the social network intervention in treatment Arm A was n=2 to 6, participants who had been randomized as individuals were asked to form groups of at least size 2-3 with relatives or friends also in the same class. This resulted in the formation of a total of 218 microclinics (MCs) (n=545 individuals), with group sizes ranging from 2-5 participants per MC in Arm A. These MCs formed the basis of the social network focused curriculum in treatment Arm A. Of the 545 participants of Arm A, 403 completed the measurement at 6-months; 285 completed the follow-up measurement at 12-month post baseline. In Arm B, 140/187 completed the 6-month measurements, and 109/187 completed the 12-month measurement. Similarly, in Arm C, 122/188 completed the measurements at 6 months, and 109/188 were present at the 12-month follow-up (Table S3.1).

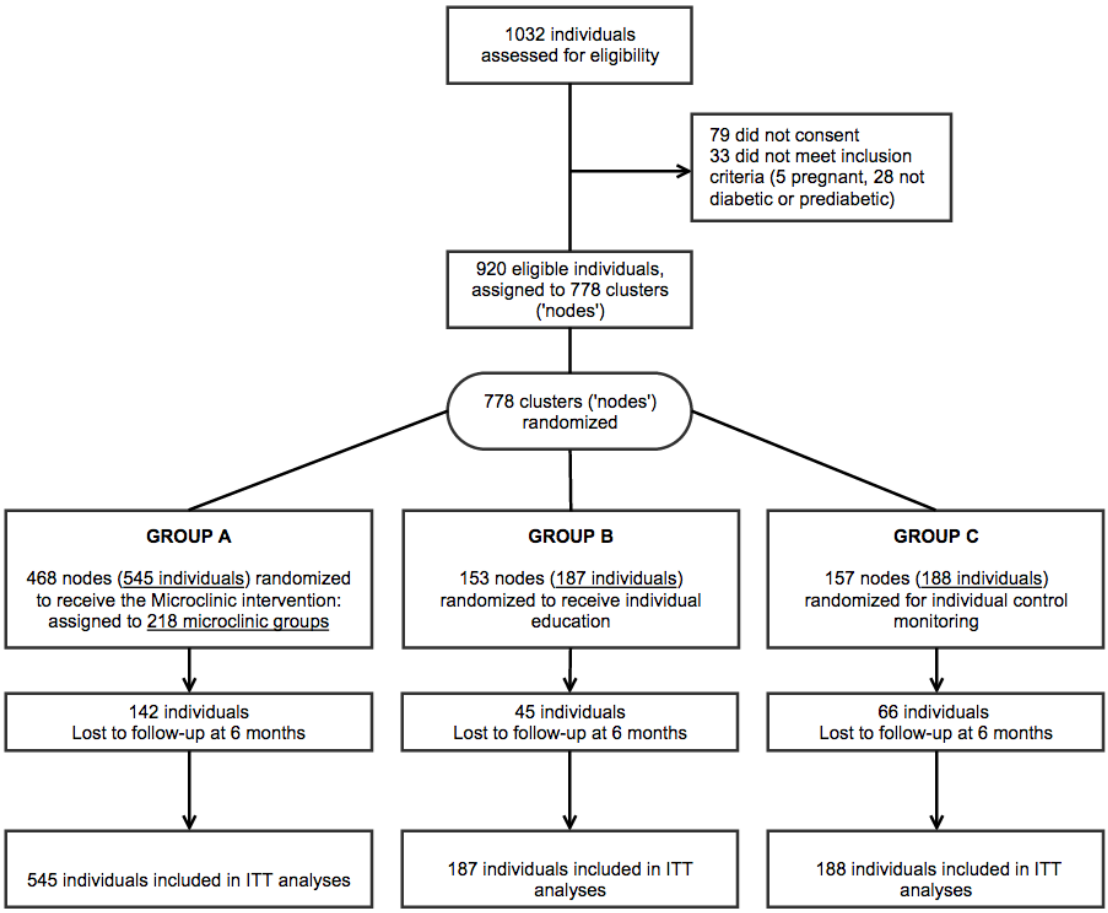

Figure 3.1: Study Flowchart, showing randomization and participation after 6-months

The baseline characteristics among the three treatment Arms were generally similar (Table 3.1), with minor exception of mean age in Arm A (mean = 54.1 years) vs Arm B (56.6 yrs) and Arm C (56.2 yrs). Overall, all study groups were comprised of >65% women, and >83% married participants. Prior diabetes education was extremely low (<3%), and mean BMI was > 33.4 kg/m^2 in all groups. Mean SBP was slightly lower in A (129.01mmHG) versus B and C (both > 131.7 mmHg). Mean FPG ranged from 142.78 mg/dL in Arm B to 148.07 mg/dL in Arm C. Following the CONSORT guidelines, we did not report on the p-values of the difference in baseline characteristics, based on the reasoning that any significant differences would have arisen through a random process.[28]

Table 3.1. Baseline Participant Characteristics, unadjusted

Characteristic	Microclinic Group A (n=545)	Individual Group B (n=187)	Control Group C (n=188)
Age, mean (SD), y	54.11 (10.8)	56.60 (8.81)	56.20 (9.46)
Women, No. (%)	66.42	67.38	65.96
Married, (%)	83.30	84.24	83.64
Prior Diabetes Education, (%)	2.85	1.81	1.81
Clinical Survey			
Anthropometrics, mean (SD)			
Weight, kg	85.96 (15.23)	84.87 (16.65)	86.12 (15.08)
Height, m	1.60 (.09)	1.59 (.09)	1.60 (.09)
BMI, kg/m^2	33.60 (6.36)	33.41 (6.39)	33.54 (5.31)
Waist, cm	104.98 (12.27)	105.85 (13.20)	105.83 (11.53)
Blood pressure, mean (SD), mm Hg			
Systolic	129.01 (23.51)	131.74 (22.74)	132.22 (21.67)
Diastolic	81.35 (12.92)	81.04 (12.80)	81.35 (11.27)
Diabetes Factors, mean (SD)			
HbA_{1c} (%) (SD)	6.89 (2.04)	6.92 (1.98)	6.90 (1.80)
Fasting plasma glucose, mean (SD), mg/dL	147.75 (63.88)	142.78 (60.34)	148.07 (57.96)

Primary Outcomes

Overall, weight and BMI difference-in-differences estimates for Arm A versus control were statistically significant at 3-months and 6-months of the intervention. At 3-months, the DID of weight change in Arm A vs C was -0.574 kg (95% CI: -1.09 to -0.086; p=0.019), reflecting a slower weight gain in Arm A vs C; meanwhile, weight change in Arm B versus C was not significantly different at 3 months (p=0.198). At 6-months, the DID of weight change of Arm A versus C was -1.22 kg (95% CI: -1.68 to -0.478; p<0.001); in contrast, the change in weight in Arm B was not significantly different than in C (DID: -0.384 kg (p=0.294)). Similar to weight change, BMI the DID estimator was greatest for the Arm A vs C comparison at the 6-month point, with a DID of -0.447 kg/m^2 (95%CI: -0.675 to -0.218; p<0.001). None of the DID estimates for BMI of Arms B vs C were significant. The net overall multi-arm test of A-B-C weight divergence over 6 month period was highly significant (p=0.0039).

In CC- ITT analysis, HbA_{1c} DID estimates were not statistically significant in A vs C and B vs C at 3-months and at 6-months. The overall multi-arm A-B-C test for divergence of HbA_{1c} was non-significant (p=0.516).

Inverse Probability Censoring Weight Analysis for Loss to Follow Up

Since results based on a complete case ITT analysis are subject to selection bias from missingness, we also performed IPCW analyses to adjust for the loss to follow up for weight and HbA_{1c}.[29] Loss to follow-up appears to have been non-random, as reflected in differences in baseline measurements in Table S3.3: Those who missed the evaluation at 6-months or at 12-

months were more likely to be female, were slightly younger, were slightly heavier, and had a slightly higher waist circumference than the average participant at baseline.

Adjusting for missed examinations at 3-, 6-, and 12-months via IPW, the results for weight change in Arm A vs Arm C were similar to the results obtained via CC-ITT: the DID estimator for comparative weight change for Arm A vs C was statistically significant at 3-months (by -0.646 kg, p=0.001), and even greater at 6-months (-0.911 kg, p=0.034). Via IPW analysis, the net overall multi-arm test of A-B-C weight divergence at 6-months was again highly significant (p=0.0018).

When adjusting for loss to follow up via IPW, the change in HbA_{1c} for Arm A vs. C was significant, with a DID of -0.237% (95%CI: -0.403 to -0.070; p=0.005), while B vs. C was not statistically different. The overall multi-arm test for HbA_{1c} difference of A-B-C at 6 months was significant, p=0.020.

Note that the overall relative effect sizes based on the IPW analyses were very similar to the results from the complete case analysis (Table 3.2 and 3.3). An additional sensitivity analysis, using the baseline value carried forward method (Table S3.5), confirmed the findings from both the complete case and the IPW-adjusted analysis.

Table 3.2. Three-month, 6-month, and 12-month Change from baseline in Clinical outcomes by Treatment Arm. Per Protocol Analysis. Arm C reference group. Mixed effects, multilevel model. Model adjusted for age, sex, center, cohort, and cycle.

	Change from Baseline Difference-in-Difference Estimator, p-value, 95% CI					
	3 Months		**6 Months**		**12 Months**	
	Arm A	**Arm B**	**Arm A**	**Arm B**	**Arm A**	**Arm B**
Weight, kg	-0.574 p=0.019* (-1.09, -0.086)	-0.377 p=0.198 (-0.977, 0.242)	-1.22 p<0.001** (-1.68,-0.478)	-0.384 p=0.294 (-1.14,0.298)	-0.037 p=0.908 (-.669,0.59)	-0.274 p=0.481 (1.04,0.48)
BMI, kg/m^2	-0.279 p=0.009** (-.488,-0.07)	-0.239 p=0.057 (-0.485,0.007)	-0.447 p<0.001** (-.675,-.218)	-0.081 p= 0.563 (-.356,0.194)	-0.014 p=0.908 (-0.256,0.228)	-0.0859 p=0.564 (-0.377, 0.206)
Waist, cm	-0.714 p=0.268 (-1.978,0.56)	-1.31 p=0.088 (-2.82,0.194)	-0.856 p=0.175 (-2.09,0.380)	-0.762 p=0.315 (-2.25,0.725)	-1.17 p=0.078 (-2.48,0.132)	-1.70 p=0.035* (-3.28, -0.123)
SBP, mmHg	0.551 p=0.770 (-3.15, 4.25)	0.302 p=0.894 (-4.14, 4.75)	-2.02 p=0.296 (-5.82, 1.77)	-0.512 p=0.826 (-5.08, 4.06)	-1.61 p=0.432 (-5.63, 2.41)	-3.33 p=0.180 (-8.19,1.54)
HbA_{1c}	-0.091 p=0.458 (-0.334,0.150)	-0.093 p=0.528 (-0.38, 0.196)	-0.237 p=0.063 (-0.487,0.013)	-0.168 p=0.271 (-0.47, 0.131)	-0.145 p=0.291 (-0.415, 0.125)	-0.138 p=0.405 (-0.463, 0.187)
FPG	-2.03 p=0.684 (-11.8, 7.73)	0.823 p=0.889 (-10.8, 12.4)	1.49 p=0.770 (-8.54,11.5)	-1.25 p=0.837 (-13.2,10.7)	*NA*	*NA*

Table 3.3. Analysis account for missingness via Inverse Probability Weighting: 6-month, and 12-month Change from Baseline in Clinical outcomes by Treatment Arm. Arm C reference group. Mixed effects, multilevel model, addressing LTFU/missed examinations at each endpoint via stabilized Inverse Probability Censoring Weights. Model adjusted for age (cat), sex (age and sex interacted), center, cohort, and cycle.

	Change from Baseline Difference-in-Difference Estimator, p-value, 95% CI					
	3 Months		**6 Months**		**12 Months**	
	Arm A	**Arm B**	**Arm A**	**Arm B**	**Arm A**	**Arm B**
Weight, kg	-0.646 p=0.001** (-1.04,-0.253)	-0.447 p=0.185 (-1.11,0.214)	-0.911 p=0.034* (-1.75,-.069)	-0.220 p=0.757 (-1.62,1.17)	-0.138 p=0.801 (-1.21,0.935)	-0.329 p=0.625 (-1.65,0.991)
BMI, kg/m^2	-0.265 p=0.002** (-.435,-0.094)	-0.184 p=0.131 (-0.423, 0.055)	-0.393 p=0.005** (-.669,-.118)	-0.002 p=0.994 (-0.568, 0.564)	-0.008 p=0.958 (-0.303,.287)	-0.085 p=0.606 (-0.407,0.238)
Waist, cm	-0.559 p=0.373 (-1.78, 0.67)	-1.193 p=0.062 (-2.44, 0.059)	-0.433 p=0.730 (-2.90,2.03)	-0.440 p=0.710 (-2.76,1.88)	-1.09 p=0.168 (-2.64, 0.459)	-1.54 p=0.223 (-4.02,0.938)
SBP, mmHg	-1.43 p=0.416 (-4.87, 2.02)	-2.82 p=0.253 (-7.67,2.02)	-2.70 p=0.120 (-6.10,0.703)	-0.962 p= 0.764 (-7.24, 5.32)	-1.87 p=0.270 (-5.21,1.46)	-3.58 p=0.084 (-7.63, 0.47)
HbA_{1c}	-0.072 p=0.417 (-0.245,0.101)	-0.107 p=0.520 (-0.433,0.219)	-0.237 p=0.005** (-.403,-.070)	-0.206 p=0.318 (-0.609, 0.198)	-0.147 p=0.044* (-0.29,-0.004)	-0.130 p=0.494 (-0.502,0.242)
FPG	-2.36 p=0.645 (-12.4,7.69)	-0.807 p=0.891 (-12.3, 10.7)	2.18 p=0.744 (-10.9,15.3)	-1.85 p=0.817 (-17.6,13.9)	*NA*	*NA*

Post Intervention Follow-up: 12-months after Baseline

However, during additional 6 months follow-up after end of intervention, results were different: the DID in weight change in Arm A versus Arm C was no longer significant (12-month multi-arm A-B-C overall test p=0.882). None of the changes in weight in Arm B were significantly different from those in Arm C. Relative weight change never exceeded -0.4 kg in Arm B vs Arm C. These weight results were consistent based on CC-ITT, IPW, and BVCF analysis.

However, for HbA_{1c} results at 12-months post-baseline, IPW analysis found that HbA_{1c} change was maintained for A vs. C with a DID of -0.147% (95% CI: -0.29 to -0.004; p=0.044), while HbA_{1c} change was not maintained for B vs. C. The multi-arm A-B-C comparison of HbA_{1c} at 12 months was borderline significant at p=0.122.

Secondary Outcomes

The DID estimators for WC, FPG, and SBP failed to reach significance at 3-month, 6-month, and 12-month post baseline comparing the MC intervention to controls. These results remained robust to IPW (Table 3. 3) and BVCF specification. Qualitatively, we observed a relative decline in WC and SBP measures of A vs C, with the greatest magnitude in DID at 6-months of the intervention. No such trend was observed for FPG. The DID estimators for WC, FPG, and SBP at the reported evaluation points were not significantly different in B vs C, except for the 12-month follow up point for WC, were the relative decline was -1.70 cm (95% CI: -3.28 to -0.123; p=0.035). These findings were no longer significant based on the IPW sensitivity analysis.

DISCUSSION

Overall, the 6-month MSN intervention program was effective in preventing weight gain and in somewhat improving HbA_{1c} versus controls, while effects on secondary measures of WC, BP, and FPG were not supported. To our knowledge, the three-arm MSN trial represents the first multicenter randomized trial to test the effectiveness of leveraging social networks to improve obesity and diabetes in a developing country setting.

Social Networks for Preventive Interventions

Social network interactions may play a meaningful role in lifestyle modification for prevention and management of chronic diseases.[30-33] From smoking, to alcohol use, to weight gain, the emerging evidence indicates that social network mechanisms are a major driver of patterns of lifestyle and risk factors that contribute to obesity and metabolic risks[12,34,35], often to multiple degrees of social network separation. Thus, if behaviors may naturally aggregate and spread in social networks, then interventions that leverage social networks hold potential promise to induce and propagate positive health behaviors by harnessing the mechanisms of social support, social influence, and social contagion.[30,31,34,36,37]

While some lifestyle programs have involved simple social support and group-based interventions [38,39], few programs directly harness existing social networks to propagate and leverage an intervention.[12,31,34,35] Moreover, existing social network-based interventions are often limited in scope. For instance, the study by Vissenberg et al. recognizes the intrinsic importance of social networks in self-management programs to create sustainable health behavior change among enrolled participants. Furthermore, while there is growing literature that social network

mechanisms drive many lifestyle factors, much of this work has been based on passive observational designs.[12,34,35]

The *Microclinic Social Network Model*, developed by Microclinic International, is a novel health program designed to leverage social network effects to improve and socially propagate positive health behaviors for those with, or at risk for, chronic diseases.[40] More than merely providing social support, the Microclinic model catalyzes and leverages pre-existing clusters of friends and family to set healthy social norms, provide social engagement, and to create a network of resources with the goal of bringing about sustainable positive change.

Our study directly addresses the question of whether health programs can harness social networks and if these programs are of significant clinical value. Moreover, given the inability of past studies to differentiate sources of social aggregation, our longitudinal trial data helps clarify the role of causal induction.

In the light of this body of evidence, the overall results of this study reflect positively on the potential of leveraging social networks in propagating healthy lifestyles and in affecting large-scale, sustained, low-cost behavior change. This will be most critical in successfully managing chronic disease in emerging economies.

Considerations on intensity of intervention

While the primary outcomes in the A vs C comparison were statistically significant, the magnitude of the observed relative change in weight, BMI, and HbA_{1c} were smaller than expected based on evidence from similar social network trials, and weight loss and diabetes management trials, in general. Arguably, the detected intervention effect of a 0.237% relative

drop in HbA_{1c} in Arm A versus control did not reach clinical significance, which would be reflected in a drop of 0.6% or greater, based on other existing evidence.[18] However, the long-term effects of the intervention post 12- months are yet to be analyzed. For example, longitudinal studies and randomized controlled trials, with both 4-month and 10-month versions of the MSN demonstrated significant results at 16 and 24 months.[17] We thus recommend that intervention intensity be augmented if the MSN intervention was to be rolled out at the national level in Jordan, as currently planned. A modification of the MSN program is currently in the recruitment phase in a new trial in Qatar. Lessons learned from this trial should be applied in this new setting, as contextually and culturally appropriate. Of particular importance will be to adhere to suggested sample size recommendations to fully power this landmark intervention, as well as to strongly intensify the social network interventions (to match the intensity of the previous trial in Kentucky), as well as to add incentives to ensure greater participant retention.

Limitations

A limitation of the herein reported results, and the trial in general, were the missed measurements at 6-months as well as the 12-month post-baseline follow up, at 24% and 45%, respectively. Study nurses reported that the large dropout at 12-months was most likely due to a change in phone numbers in a large number of participants (most used prepaid cellphones and hence changed phone numbers periodically). Additionally, instability caused by geo-political developments created some recruitment challenges. Tracing participants via mail also proved difficult, as mailing addresses were only introduced mid-way through the study, and this information had hence not been systematically collected at baseline. We addressed this attrition issue by performing several sensitivity analyses, including IPW and the BVCF method. While

missingness might not have been random, our main results were insensitive to our robustness checks.

To reduce attrition at 16-month to 30-month follow up measurements of this trial, nurses were incentivized with prizes if they met the goal of 90% retention. For future trials, mid-point phone calls between the last treatment appointment and the first follow-up measurement appointment are recommended.

Another important limitation was the modification in recruitment protocols such that the n=300 participant requirement in both Arm B and Arm C were not met. This modification was a result of a petition of the nurses and on-site study personnel to provide some form of intervention to as many participants as possible, thereby shunting more people to be randomized to the full MSN Arm A program. This modification in participant size in Arm B and C reduced the power to detect significant intervention effects.

As briefly mentioned above, the intensity of the social network intervention, compared to the education only intervention, could have been stronger. The Jordanian MSN trial represented was modeled on a successful MSN trial held in Kentucky, US, over a 9 to 10-month period.[15,16] Due to staffing and resource constraints, the curriculum in Jordan was shortened and modified. This modification in program duration likely impacted the results, which were weaker with respect to clinical outcomes. Thus, an important lesson learned is that for social network effects to affect diabetes and obesity risk factors at clinically significant levels, high intervention intensity and duration to maintain network-related accountability post-treatment period are also of essence.

Notwithstanding the limitations and the lessons learned, the results of the MSN trial in Jordan buttress existing evidence that social networks can be leveraged to propagate healthy behavior,

and that social network interventions might prove essential to reduce the disease and economic burden of non-communicable diseases in low-resource settings. Future studies that apply the lessons learned from this trial as well as similar studies in the US are needed to optimize treatment intensity, treatment length, and explore factors that can ensure sustainability of the intervention past the intervention period.

CONCLUSION

Overall, the MSN intervention was effective in significantly improving weight and BMI over a 6-month intervention period; HbA_{1c} results were suggestive of an improvement. The MSN intervention did not significantly improve waist circumference, FPG, and BP over the 6-month period of the trial. Further studies that leverage social networks are needed.

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SUPPLEMENTARY APPENDIX 3

MICROCLINIC SOCIAL NETWORK INTERVENTIONS FOR OBESITY AND DIABETES IN AMMAN, JORDAN: A 6-MONTH, 3-ARMED CLUSTER RANDOMIZED CONTROLLED TRIAL

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SUPPLEMENTAL TABLES

Table S3.1: Timing of interventions and data collected at each intervention time. Abbreviations used: Wt (Weight); WC (Waist circumference); FBG (Fasting Blood Glucose); Ht (Height); BP (Blood Pressure: both SBP and DBP); SN (Social Network information);

Week	Session #	Data collected
1	1- baseline	Consent form, Wt, WC, FBG, HbA1c, Ht, BP, SN, Survey
2	2	FBG, Wt
3	3	FBG, Wt
4	4	Wt, WC, FBG, BP
6	5	Wt, FBG
8	6	Wt, WC, FBG, BP
10	7	Wt, FBG
12	8	Wt, WC, FBG, BP
14	9	Wt
16	10	Wt, WC, FBG, HbA1c, BP
19	11*	FBG, Wt
22	12	Wt, WC, FBG, BP
25	13	Wt
28	**14-final**	**Wt, WC, FBG, HbA1c, BP, SN, Survey**
53	12-month	Wt, WC, HbA1c, FBP, BP

Table S3.2: Completion rates at 6- and 12-months follow-up for weight

Variable: Weight	**Arm A**	**Arm B**	**Arm C**
Baseline	545	187	188
Completed month 6	403/ 545	140/ 187	122/ 188
Completed month 12	285/ 545	109/ 187	109/188

Table S3.3: Additional Baseline data for those who missed the examination ('ME') at 6- and 12-months

	ME 6mo	**ME 12mo**
Sex (%women)	70.87	71.43
Age (SD)	53.53 (10.8)	53.0 (11.6)
Weight	87.3 (17.7)	86.15 (17.2)
Height	159.7 (9.2)	159.8 (8.6)
BMI	34.3 (6.4)	33.9 (6.7)
Waist Circumference	106.9 (13.6)	103.8 (13.0)
HbA_{1c}	6.86 (1.96)	7.20 (2.2)
FPG	148.6 (62.3)	147.3 (65.2)

Table S3.4: Unadjusted weight (kgs) at baseline, 3 months intervention, 6-month intervention, and 12-month follow-up.

Overall weight (SD)	Arm A	Arm B	Arm C
Baseline	85.9 (15.1)	85.3 (16.0)	85.8 (15.0)
3 months	83.7 (15.0)	83.8 (15.1)	85.2 (15.4)
6 months	83.5 (15.0)	81.7 (15.3)	85.8 (14.9)
12 months	84.6 (14.4)	83.9 (15.6)	84.2 (14.6)

Table S3.5: Summary statistics for Inverse Probability Censoring Weights used to adjust for loss to follow up; standard errors clustered at cohort level

		3 mo		6 mo		12 mo	
	Predictors	Stabilized IPW (SD)	Min, Max	Stabilized IPW (SD)	Min, Max	Stabilized IPW (SD)	Min, Max
Stabilized IPW for weight, BMI variables	Sex and age (cat, interacted), cohort, day, center, treatment group, FPG at baseline, weight at baseline, weight change up to last visit before event, prior knowledge of diabetes type, highest education level achieved, smoking status, family encouraging of diabetes program, perception of need to change weight, self body image	1.03 (0.171)	.471, 2.60	1.03 (0.196)	0.491, 3.16	1.04, (0.225)	0.625, 2.55
Waist Ci, SBP, HBa1c, FPG	As for weight and BMI, including FPG at baseline, weight at baseline, waist, SBP, and HbA1c at baseline	1.03 (0.184)	.457, 2.62	1.03 (0.188)	0.530, 3.11	1.04, (0.215)	.563, 2.52

Table S3.6: Sensitivity analysis: BVCF; Variable: Weight

Weight Change from Baseline (BVCF)	**Arm A**	**Arm B**	**Arm C**
3 months	-0.592kg p=0.011*	-0.447kg p=0.117	(Reference)
6 months	-0.851kg p=0.003**	-0.291kg p=0.405	
12 months	-0.122kg p=0.728	-0.217kg p=0.604	
p for program*time interaction	**p<0.001**		