# Variations in HIV risk by young women's age and partner agedisparity in rural South Africa (HPTN 068) 

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#### Abstract

Background—Nearly all population-level research showing positive associations between agedisparate partnerships and HIV acquisition among adolescent girls and young women (AGYW) has classified age disparity as $\geq 5$ or $\geq 10$ years. We describe variations in one-year risk of HIV infection after exposure to sexual partner(s) of continuous age disparities.

Methods-Longitudinal data from the HPTN 068 randomized trial in South Africa was used to estimate one-year risk of HIV infection at various age pairings. The parametric g-formula was employed to estimate risk at up to five annual time points, stratified by maximum partner age difference, maximum partner age, and AGYW age.

Results-AGYW reported an older partner in $86 \%$ of 5,351 age pairings. The one-year risk of HIV infection rapidly increased with maximum partner age difference among girls ages 13 to 14 , from 0.01 with a same-age partner, to 0.21 with a partner ten years older, and 0.24 with a partner 15 years older. A gradual increase occurred among AGYW ages 15 to 16 , up to $0 \cdot 13$ with a partner


[^0]15 years older, and 0.09 among AGYW 17 to 18 with partners 8 to 11 years older. Risk of HIV infection among AGYW ages 19 to 21 remained relatively constant across maximum partner age differences.

Conclusion-Age differences between AGYW and their sexual partners have a greater effect on HIV risk infection in younger compared to older AGYW. Considering both the age of an AGYW and her sexual partners provides granular insight into identifying key groups for HIV transmission prevention efforts.

## Keywords

adolescent girls and young women; South Africa; HIV; age-disparity

## INTRODUCTION

High HIV prevalence remains a serious problem among young women in South Africa. Population-based data from 2017 report a prevalence of $5.8 \%$ among female adolescents 15 to 19 years of age, increasingly rapidly to $15.6 \%$ among young women 20 to 24 years, and to $27.5 \%$ among those 25 to 29 years. ${ }^{1}$ Males have a much lower HIV prevalence than females within the same age group ( $4.7 \%, 4 \cdot 8 \%, 12 \cdot 4 \%$ respectively). ${ }^{1}$ Differences in HIV prevalence by gender are hypothesized to stem from adolescent girls and young women (AGYW) having sex with older men, connecting them to sexual networks with high HIV prevalence. ${ }^{2}$ High risk behaviors such as transactional sex and alcohol use are associated with age-disparate partnerships, ${ }^{3}$ and biological factors also play a role in increasing risk of HIV in women. ${ }^{4}$

Nationally representative data from South Africa in 2009, 2012, and 2017 consistently show that a third (34-36\%) of AGYW ages 15-19 or 16-24 years of age are at least five years younger than their sexual partners. ${ }^{2,5}$ Population-level research examining the association between age-disparate partnerships and HIV acquisition has produced mixed results. Among South African women, cross-sectional studies identified increased odds of HIV with a partner greater than five years older, ${ }^{6,7}$ while some prospective studies found no such association among partnerships with age differences greater than five or ten years at enrollment. ${ }^{8,9}$ Assessment of partner age rather than age difference has demonstrated associations between risk of HIV acquisition among women and male partners ages 25 to 34. ${ }^{10}$ Phylogenetic linkage and HIV prevalence results support the hypothesis that the main source of HIV transmission to AGYW ages 15 to 25 comes from older men ages 25 to 40 years. ${ }^{11}$

Research on age-disparate partnerships has traditionally classified age-disparity as a binary variable, usually categorized as an age difference of at least five or ten years between a participant and her sexual partner(s). ${ }^{7-9,12}$ Few studies have measured age-disparity using flexible models ${ }^{13,14}$ and research classifying age-disparity as a continuous variable has assumed a constant change in the effect estimate for every year of partner age difference. ${ }^{7,8}$ Yet other cut points to classify age-disparity may be more appropriate, as increasing or decreasing periods of risk exist within age-disparity categories of $<5$ years or $\geq 5$ years. ${ }^{13}$ The extent of age-disparity can also vary depending on AGYW age, with older AGYW
tending to have smaller age differences with their sexual partners as compared to younger AGYW. ${ }^{14}$

Prior evidence from the HIV Prevention Trials Network (HPTN) 068 cohort in South Africa demonstrated a higher risk of HIV infection among AGYW with age-disparate partnerships $\geq 5$ years as compared to AGYW with no age-disparate partnerships, even after accounting for transactional or condomless sex. ${ }^{15}$ Building upon this research, the objective of the present analysis was to determine how the one-year risk of becoming newly infected with HIV changes after exposure to sexual partners of different ages, and how this risk is modified by AGYW age in the HPTN 068 cohort. To investigate the association between age pairings and HIV, we modeled risk of HIV by AGYW age, partner age difference, and partner age. Consideration of both AGYW age and partner age presents a multifaceted approach to identify key groups for HIV prevention efforts.

## METHODS

## Study design and population

The HPTN 068 study is a longitudinal phase III individually randomized controlled trial examining the effect of cash transfers, conditional on school attendance, on HIV acquisition among AGYW in South Africa. ${ }^{16,17}$ To be eligible, AGYW had to be between the ages of 13 to 20 years, enrolled in grades 8 to 11, not married or pregnant, and have a parent/guardian in the household. ${ }^{17}$ A total of 2,537 AGYW were enrolled from the health and sociodemographic surveillance system site of the MRC/Wits-Rural Public Health and Health Transitions Research Unit (Agincourt) in rural Bushbuckridge, Mpumalanga province, South Africa, in 2011 and 2012. HIV prevalence in this region was $5 \cdot 5 \%$ in girls ages 15 to 19 years, and $27.0 \%$ in young women ages 20 to 24 years around the time of study enrollment. ${ }^{18}$ Peak HIV prevalence in this population occurred in adults ages 35 to $39,45 \cdot 3 \%$ in men and $46 \cdot 1 \%$ in women. Our analysis includes AGYW who were HIV negative at enrollment and had at least one follow-up test. Given the 47 incident HIV infections among those who reported never having had sex, AGYW were included regardless of reported sexual history.

Participants were followed annually from enrollment until study completion in 2015 or until high school graduation, whichever came first. During study visits, participants completed an Audio Computer-Assisted Self-Interview (ACASI) and underwent HIV testing if they had tested negative at their previous visit. Some participants had an additional HIV test around the time of their expected high school graduation or at study completion to capture extra person time. Only HIV test information within six months of the previous visit was retained, and ACASI data carried forward from the previous interview. For all other visits, we carried forward missing covariate information from the last observation, except for sexual behavior information, as we did not expect answers to vary dramatically and missing data were minimal ( $<10 \%$ ). A post-intervention visit was also conducted one to two years after the end of the main trial.

IRB approval for this study was obtained from the University of North Carolina at Chapel Hill and the University of the Witwatersrand Human Research Ethics Committee.

## Exposure, outcome, and covariate assessment

Partner age difference was defined as the difference between a study participant's age and the age of up to three self-reported sexual partners at each study visit. The main exposure was classified as the maximum age differences of these partners; prior analyses conducted using both mean and maximum partner age differences showed similar results. ${ }^{15}$ Incident HIV infection was defined as a new diagnosis of HIV following study enrollment. HIV testing was performed using two HIV rapid tests with a confirmatory western blot. ${ }^{17}$

Fixed and time-varying covariates were selected using directed acyclic graph analysis and a review of the literature. ${ }^{15}$ We included time-varying self-report of any alcohol use, timevarying household socioeconomic status according to a principal components analysis of household assets measured in quartiles, time-varying multiple sexual partners, and timevarying AGYW age. We also adjusted for randomized cash transfer intervention assignment at baseline from the main HPTN 068 study, ${ }^{16,17}$ though this did not have an effect on incident HIV infection. ${ }^{15}$ Transactional sex and condomless sex were not included in the model as they are mediators on the pathway between partner age and HIV infection. To better guide our simulation, we also created a time-varying indicator for having had sex, assuming that AGYW who did not report any sexual partners did not have sex over the indicated time period. Other descriptive covariates included enrolled in school or completion of grade 12, double orphan, ever pregnant, age at first vaginal sex, number of sex partners in the last 12 months, children's depression inventory score $\geq 7$, and low sexual relationships power score (South African adaptation of the Sexual Relationship Power Scale; score in lower third of the distribution). ${ }^{19}$ All covariate information was taken from the visit prior to the study visit where a participant was tested for HIV, except for sexual partner age difference which refers to partners over the preceding one year.

## Statistical analysis

We used the parametric g-formula to simulate how one-year risk of HIV infection varies over AGYW age and partner age after removing the effect of confounding factors. The parametric $g$-formula has been described elsewhere, ${ }^{20,21}$ and additional information can be found in the Appendix (Technical Methods, Supplementary Digital Content). Briefly, we first modeled the conditional probabilities of time-varying maximum partner age difference, acquisition of HIV, and covariates, with flexible pooled regression models using the observed data. We next drew a large Monte Carlo sample of 950,000 AGYW drawn with replacement from the observed data, and retained each AGYW's baseline age and randomized cash transfer intervention assignment. We then used coefficients from the pooled regression models above to simulate time-varying confounders, maximum partner age difference, and HIV outcomes. Conditional probabilities were estimated at up to five time points, one for each annual study visit. Once a participant tested positive for HIV or turned 21 years of age, she was simulated as exiting the risk set.

We used logistic regression to obtain predicted probabilities of HIV by AGYW age, partner age difference, and partner age group in the simulated dataset. Bootstrapping provided 95\% confidence intervals. All analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary, NC) and R 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

A total of 2,362 AGYW were included in this analysis. Of these, the majority were enrolled between ages 13 to $16(1,748$ of 2,$362 ; 74 \cdot 0 \%)$ (Table 1 ). There was a low prevalence of any reported alcohol use ( 153 of 2,$351 ; 6 \cdot 5 \%$ ) and depression ( 415 of 2,$249 ; 18 \cdot 5 \%$ ). Low sexual relationship power scores ( 372 of $599 ; 62 \cdot 1 \%$ ) were observed across the entire cohort at baseline.

When accounting for all 10,148 baseline and follow-up study visits in our original data, the frequency of sexual activity risk behaviors ranged widely by age group; girls ages 13 to 14 reported unprotected sex acts in the previous three months at only 9 of $958(0.9 \%)$ study visits, as opposed to at 137 of the $554(24.7 \%)$ visits among AGYW ages 21 to 22 (Table 2). Girls ages 13 to 14 reported no sex partners in the previous year at the majority ( 886 of 955 ; $92.8 \%$ ) of study visits, in contrast to older AGYW ages 21 to 22 and 23 to 26 who indicated one or more sex partners at the majority of study visits (ages 21 to 22: 401 of 554, $72.4 \%$; ages 23 to 26: 62 of $87,71 \cdot 3 \%$ ). AGYW reported the age of their sexual partner(s) at over a third of all study visits $(3,767$ of 10,$148 ; 37 \cdot 1 \%)$. There were 193 seroconversions over the study period.

There were 5,351 total partner pairings in our original data, with each AGYW reporting up to three partners per study visit (Figure 1). The majority ( 5,$132 ; 95.9 \%$ ) of these partner-age pairings were reported at a visit where a participant tested HIV negative, and 219 ( $4 \cdot 1 \%$ ) at a visit where an incident HIV infection was recorded. The reported partner was older than the participant in 4,408 of $5,132(85 \cdot 9 \%)$ age pairings at a visit when the participant was HIV negative and 196 of 219 ( $89.5 \%$ ) age pairings at a visit where an incident HIV infection was reported. The median maximum partner age difference was 3 years (IQR: 1-4) at visits when no HIV infection occurred and 3 years (IQR: 2-6) when an incident HIV infection took place. Information on one-year risk of HIV among various age pairings can be found in the Appendix (Tables 1 and 2, Supplementary Digital Content).

In the observed data, the one-year risk of HIV infection increased as AGYW age increased, from 0.00 at ages 13 and 14 ( 0 of 265; 0 of 698), up to 0.09 at age 23 (7 of 75) (Figure 1, Supplementary Digital Content). The one-year risk of HIV infection among AGYW also independently increased as partner age increased, from 0.00 at maximum partner ages 15 and 16 ( 0 of 29,0 of 67 ), up to $0 \cdot 12$ at age 30 ( 3 of 26 ).

In our simulated data, the age difference between an AGYW and her sexual partners appeared to have a more pronounced effect on risk of HIV in younger as compared to older AGYW, after controlling for multiple partners, alcohol use, and wealth. The one-year risk of HIV infection rapidly increased as age-disparity increased among girls ages 13 to 14 , from 0.01 with a partner of the same age, to 0.21 with a partner ten years older, and 0.24 with a partner 15 years older (Figure 2; Table 3, Supplementary Digital Content). More gradual increases were observed among AGYW ages 15 to 16 , with a 0.01 one-year risk of HIV infection with a partner of the same age, 0.11 with a partner ten years older, and 0.10 with a partner 15 years older. AGYW ages 17 to 18 had a one-year risk of HIV of 0.02 with a same-age partner, a maximum risk of 0.09 when with partners eight to 11 years older, and a
lower risk of 0.07 with a partner 15 years older. Partner age difference did not substantially change the risk of HIV in young women ages 19 to 21 ; estimates remained relatively constant from same-age partners at 0.05 , up to a maximum of 0.11 when paired with partners 7 to 9 years older, and fell to 0.02 when with a partner 15 years older.

After stratifying by maximum partner age difference in the simulated data, the one-year risk of HIV infection among AGYW ages 13 to 14 was lowest when paired with partners 0 to 4 years older $(0.02-0.03)$, and highest with partners 5 to 9 years older ( $0 \cdot 12-0 \cdot 13$ ) (Figure 3a). Among AGYW ages 15 to 18 , the one-year risk of HIV was lowest with younger partners ( $0.01-0.02$ ), and higest with partners $\geq 10$ years older ( $0 \cdot 08-0 \cdot 15$ ). Among AGYW ages 19 and 20, the one-year risk was lowest with partners 0 to 4 years older ( $0 \cdot 04-0 \cdot 06$ ), and highest with partners 5 to 9 years older ( $0 \cdot 08-0 \cdot 10$ ). Among AGYW age 21, the one-year risk was lowest with partners 0 to 4 years older ( $0 \cdot 08$ ), and highest with younger partners (0.13).

Crude partner age showed a large association with risk of HIV in girls ages 13 to 16 , ranging from 0.01 among 14 year olds paired with partners under 15 years of age, to 0.15 among 15 year olds paried with partners ages 25 to 29 (Figure 3b). Variation in risk decreased among AGYW ages 17 to 19 , with lowest risk estimates when paired with partners ages 15 to 19 (0.02-0.03), and highest risk when paired with partners ages 25 to 29 (0.09). Partner age and partner age difference both appeared to be less associated with risk of HIV among young women ages 20 to 21, ranging from a risk of $0.06-0.08$ with partners 20 to 24 years of age, to $0 \cdot 10-0 \cdot 11$ with partners 25 to 29 years.

## DISCUSSION

Results illustrate that the association between partner age disparity and one-year risk of HIV infection has a much more pronounced effect in younger than in older AGYW, after controlling for multiple partners, alcohol use, and wealth. In our study population, sexual partnerships with older men led to a dramatically higher risk of HIV acquisition among girls ages 13 to 14, a moderately higher risk of HIV acquisition in AGYW ages 15 to 16, and a marginally elevated risk of HIV among AGYW ages 17 to 18 . The one-year risk of HIV among AGYW ages 19 to 21 was high in partnerships with younger men and with moderately older men, but fell with significantly older partners. Focusing an analysis solely on partner age differences incorrectly assumes that the effects of age-disparity are constant across all AGYW ages.

Our results are somewhat consistent with prior research examining age pairings in KwaZuluNatal, South Africa, showing that reported partner age failed to demonstrate a linear relationship with HIV incidence. ${ }^{10}$ HIV incidence was highest among AGYW ages 15 to 24 who had older partners ages 30 to 34, followed by those with partners ages 25 to 29. In our cohort, the majority of high HIV risk estimates occurred between AGYW ages 15 to 18 with sexual partners ages 25 and older. Our results also align with research from Malawi, indicating that partner age did not demonstrate a linear relationship with HIV probability among women ages 18 to $49 .{ }^{13}$ A cross-sectional study in KwaZulu-Natal found that among AGYW younger than 25 years of age with HIV, $62 \%$ were phylogenetically linked with
partners ages 25 to 40 , a group in which HIV prevalence was over $40 \% .{ }^{11}$ Though
directionality was inferred from prevalence gradients and with no support from longitudinal data, it was hypothesized that HIV transmission could be galvanized by sexual partnerships in which older men concurrently partnered with older women ages 25 to 40 in whom HIV prevalence was nearly $60 \%$. The same transmission cycle could be occurring among the Agincourt rural study population. Interestingly, AGYW in our cohort ages 19 to 21 were at a higher risk of HIV when paired with younger partners ( $<0$ years age difference) than when paired with partners 0 to 4 years older, similar to findings among women ages 18 to 49 in Malawi. ${ }^{13}$

Age-disparate partnerships in sub-Saharan Africa result from social and economic factors. In some cases, AGYW can be motivated by increased social status, and may view older men as a means to obtain financial support and economic stability, often resulting in less power to negotiate safe sex practices. ${ }^{4,22}$ Biological factors also play a role in increasing risk of HIV infection, including a greater mucosal surface area in women and vaginal practices or substances which disrupt the microbiome and epithelial tissue, facilitating HIV transmission. 4,23 Men may be motivated to partner with AGYW through the virgin-cure myth, "sexual rejuvenation" thought to be obtained through younger partners, and traditional gender roles. ${ }^{22}$ Further research is necessary to characterize the specific behaviors and motivations of older men who partner with AGYW in rural South Africa.

Globally, women also tend to partner with older men, ${ }^{24}$ and reducing the risks of agedisparate relationships is challenging. UNAIDS recommendations for AGYW ages 15 to 24 in high HIV incidence settings include incentives to keep girls in school and social and behavioral change activities to address sexual behavior, HIV risk perception, gender norms, power, and gender-based violence. ${ }^{25} \mathrm{PrEP}$ can be an effective intervention and integrated alongside reproductive health services. ${ }^{26}$ Previous research among the HPTN 068 cohort has shown that school attendance reduces HIV risk by preventing greater numbers of sexual partnerships and partnerships with older men. ${ }^{27,28}$ Programs like DREAMS and "She Conquers" support school attendance in South Africa, primarily targeting young women ages 15 to 24 for retention and tracing, and describing their male sexual partners for HIV intervention purposes. ${ }^{29,30}$ Specifically targeting men ages 15 to 34 years could further reduce infections, such as through HIV testing, linkage to care, and circumcision which has low uptake among male partners of young women in certain locales. ${ }^{31}$

A primarily limitation of this analysis is the potential misreporting of sexual behaviors; though HIV is not only transmitted sexually, there were 47 incident HIV infections detected in AGYW who stated they had never had sex. Other research in rural South Africa has identified underreporting of age-disparate partnerships among AGYW <25 years of age with a sensitivity of $74 \%$ and specificity of $90 \%$ for correctly reporting a partner $\geq 5$ years older. ${ }^{32}$ If comparable mis-reporting occurred in our study, we would underestimate the influence of age-disparate partnerships on HIV risk. Second, we found several unusually young and old partners reported, with age ranging from 11 to 82 years. Speculatively, these outliers could be the result of errors in data-entry or mis-reporting by AGYW who may not have known their partner's actual age. To diminish the influence of outliers, we limited the youngest sexual partners in our model to ten years of age and removed pairings with limited
observations from the figures to reduce the extent of model inference into areas where no original data exist. A third limitation is the potential for unmeasured confounding. We created flexible models, including interactions between known confounders and time, but residual confounding or model misspecification may exist. Finally, the study population was limited to a select group taking part in a randomized trial and who were enrolled in school at baseline; results may not be broadly generalizable to AGYW in rural South Africa. Nevertheless, methods can be translated to populations which would benefit from a more granular determination of age pairings most at risk for HIV transmission. Grouping our analysis by standard age-disparity definitions of $<5$ and $\geq 5$ years would have missed important variations in risk of HIV with older partners and the increased one-year risk of HIV among older AGYW with younger partners.

This study presents a unique accumulation of longitudinal sexual partnership data among a cohort of AGYW in rural South Africa. Our methodology allowed us to move beyond binary constraints to assess both AGYW age and partner age in one-year increments, while accounting for time-varying covariates. We showed that one-year risk of HIV infection in AGYW changes after exposure to partners of different ages, and that this relationship is modified by AGYW age. Future studies should model age-disparity flexibly, and stratify by AGYW age. Since our analysis observed AGYW annually and did not track sexual partners, we are unable to determine the transmitting partner and the risk of transmission per act, despite few reports of multiple partners ( 658 of 8,735 study visits; $7 \cdot 5 \%$ ). Future research should characterize older partners of AGYW in the target population. Defining both the level of risk and proportion of pairings that contribute to the most HIV infections are important steps in targeting interventions to slow the HIV transmission cycle in this high prevalence region.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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,' AGYW age = partner age

- no HIV infection
- incident HIV infection

Figure 1.
Scatterplot of reported age pairings ( $\mathrm{N}=5,351$ ) and associated incident HIV infections at all study visits. Each AGYW could report up to three sexual partners per study visit. Only 124 of the 193 total infections are shown; the remaining cases were missing data on partner age. The dashed line indicates points where AGYW age would equal partner age. Age is a discrete variable measured in years; a small amount of random variation is added to each pairing's location to reduce overplotting.


Figure 2.
AGYW risk of HIV in the next one-year (and 95\% confidence intervals) at various maximum partner age differences in the simulated dataset ( $\mathrm{N}=950,000$ ). Risk estimates are stratified by AGYW age group (years). Vertical dashed lines indicate maximum partner age differences of 0,5 , and 10 years. Bars indicate absolute risk of HIV in each AGYW age group, only among AGYW who were assigned partners in the simulation, regardless of partner age. Estimates from pairings in the 13 to 14 years stratum with a partner age difference less than 0 or greater than or equal to 10 years, and estimates from pairings in all strata with partner age differences above 12 years are extrapolated from sparse data in the observational cohort and should be interpreted with caution.


Figure 3.
AGYW risk of HIV in the next one-year (and 95\% confidence intervals) at various age pairings in the simulated dataset $(\mathrm{N}=950,000)$. Panel A: risk estimates are stratified by maximum partner age difference (years). Panel B: risk estimates are stratified by maximum partner age (years). Pairings between AGYW and partner age strata with fewer than five counts in the observed data are removed to avoid extrapolation from sparse data. Absolute risk was derived from the overall simulated cohort, regardless of if a sexual partner was reported or not.

|  | $\mathbf{N}(\%) /$ median (IQR) |
| :--- | :---: |
| Sample size | 2,362 |
| Age at baseline |  |
| 13 to 14 | $739(31 \cdot 3)$ |
| 15 to 16 | $1,009(42 \cdot 7)$ |
| 17 to 18 | $505(21 \cdot 4)$ |
| 19 to 21 | $109(4.6)$ |
| Household socioeconomic status |  |
| Low | $599(25 \cdot 4)$ | missing counts are displayed below.

Table 1. Participants were HIV-negative at enrollment and had at least one follow-up test. Percentages were calculated based on all available data for each variable,
Baseline characteristics of AGYW enrolled in HPTN 068 in Agincourt, South Africa from 2011 to 2012, and included in this analysis ( $\mathrm{N}=2,362$ ).

| Middle to Low | 627 (26.6) |
| :--- | :---: |
| Middle | $575(24 \cdot 4)$ |
| High | $557(23.6)$ |
| Cash transfer intervention arm | $1,215(51 \cdot 4)$ |


| Enrolled or completed school | 2,257 (95.6) |
| :--- | :--- |


| Double orphan | $102(4.4)$ |
| :--- | :--- |
| Ever pregnant | $192(8 \cdot 2)$ |
| Age at first vaginal sex | $16(15-16)$ |
| Any alcohol use | $153(6.5)$ |

Children's depression inventory score $\ggg \mid \quad 415$ (18.5)
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Missing values: socioeconomic status (4,0•2\%); orphan (27,1•1\%); pregnant (26,1•1\%); age first sex (1,772,75.0\%); alcohol (11,0.5\%); depression (113,4•8\%); low power (1,763,74•6\%)
one to two years after the end of the main trial and is included in the analysis.
Study visit characteristics of AGYW in Agincourt, South Africa from 2011 to 2017, stratified by age at study visit ( $\mathrm{N}=2,362$ ). Participants were followed annually from enrollment to study completion in 2014 or until high school graduation, whichever came first. A post-intervention visit was also conducted

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\text { AGYW Age } \\
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\end{array}
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