Risk of HIV infection among adolescent girls and young women in age-disparate relationships in sub-Saharan Africa

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Objective: To determine the association between age-disparate relationships and risk of HIV infection among adolescent girls and young women (AGYW) aged 15–24 years.

Design: Systematic review and meta-analysis of published studies until January 5, 2020 in sub Saharan Africa (SSA).

Methods: We searched several electronic databases, grey literature, and hand searched reference list of included studies to identify eligible studies for data abstraction. We assessed the quality of included studies using Newcastle–Ottawa Scale for nonran-domized studies. The DerSimonian–Laird random effects model was used to pool the overall results using risk ratios (RR), presented in a forest plot with 95% confidence interval (CI) and predictive interval. Heterogeneity was assessed with Cochrane's Q-test and quantified with I^2 values. Publication bias was checked with funnel plots and Egger's test.

Results: We included 24 studies with an overall sample size of 33 390. Data show that age-disparate relationships were significantly associated with unprotected sexual intercourse (pooled RR, 1.57; 95% CI, 1.34–1.83; 95% predictive interval, 1.22–2.02), and higher risk for HIV infection (pooled RR, 1.39; 95 CI, 1.21–1.60; 95% predictive interval, 0.80–2.42). Studies included in pooling risk of unprotected sexual intercourse were largely homogeneous (I^2-value= 0.0, $P = 0.79$) whereas those for HIV infection were heterogeneous (I^2- value = 89.0%, $P < 0.01$). We found no publication bias and no study influenced the meta-analytic results.

Conclusion: Age-disparate relationships among AGYW are associated with increased risk of unprotected sexual intercourse and HIV infection in SSA. HIV prevention interventions should target this sub-population.

Keywords: age-disparate relationship, HIV infection, sub-Saharan Africa, unprotected sex

Introduction

Global estimates of HIV incidence by UNAIDS show that in 2018, there were at least 300 000 new HIV infections among adolescent girls and young women (AGYW) [1]. Efforts to reduce this high incidence have yielded modest gains and will unlikely achieve the UNAIDS fast-track target of 100 000 new infections per year set for 2020 [2]. Over 80% of the adolescents living

with HIV are in sub-Saharan Africa (SSA) [3]. The risk of HIV infection among AGYW in SSA is disproportionately high compared with that of men in the same age bracket, at least two-fold higher, and the women acquire HIV 5−7 years earlier compared with the males [4,5].

The reasons for the disparity in HIV incidence have been extensively explained and include biological factors, such as an immature genitocervical mucosa among AGYW

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that is more susceptible to HIV infection [6]. AGYW also have a higher prevalence of bacterial and viral sexually transmitted infections, which may increase their overall risk for HIV infection [7], structural, social and biological factors. Socioeconomic and cultural factors, such as gender-based violence, early drop out of school and food insecurity, which are common among AGYW, have been identified as potential risk factors for HIV infection [8,9]. Perhaps, the most discussed risk factor and still inconclusive is the question of age-disparate relationships (ADR). The ADR are those in which the male partner is 5 years or older than the female partner. These relationships, often transactional, and is therefore at high risk for HIV [10], provide financial and social security for AGYW in vulnerable financial states.

Studies to examine the relationship between ADR and incidence of HIV among AGYW have shown mixed results with a tendency to differ by study design. Overall, cross-sectional studies have generally shown that ADR are associated with an increased risk for HIV infection [11−13].

At least three cohort studies have shown null association [14−16]; however, some cohort study designs have shown a positive association [17,18]. Although biologic evidence of higher risk of HIV transmission has been demonstrated in phylogenetic testing [18], there has been no study done to aggregate existing evidence and hence discussion remains as to whether the association is real.

Consistent use of condoms is well known to protect against HIV infection [19]. Studies to examine whether AGYW in ADR are less likely to use condoms have yielded inconsistent results as well. The use of condoms among AGYW is generally low [20,21] and may even be lower among those in ADR. Analysis to examine HIV incidence should include assessment of condom use. Therefore, the purpose of this study was to conduct a systematic review and meta-analysis to collate all existing evidence with a dual purpose: First, to determine whether AGYW in ADR are less likely to use condoms; and second, to determine whether risk for HIV acquisition is higher among AGYW in age-disparate relationships in SSA.

Methods

Study design and registration
We designed a systematic review and meta-analysis in accordance with the elements of the Preferred Reporting Items for Systematic Reviews and Meta-analysis [22] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) [23] guidelines. We registered this study in PROSPERO with the registration number CRD42019143151 [24].

Search strategy, screening of studies, and data extraction
Two reviewers (J.I. and D.S.) developed a sensitive and comprehensive search strategy using key concepts in the research question and Medical Subject Headings (MeSH). For certain key concepts, wildcards and truncations were formulated and the final search strategy was combined using Boolean operators namely 'AND', 'OR', and 'NOT'. An example of the search strategy that we used in PubMed is as follows:

['Adolescent girls' (All Fields) OR 'Young women' (All Fields) OR 'Adolescent girls and young women' (All Fields)] AND ['Age-disparate' (All Fields) OR 'Age discordance' (All Fields) OR 'Age disparate' (All Fields) OR 'age-discordant' (All Fields) OR 'age discordancy' (All Fields) OR 'age discordant' (All Fields) OR 'age-mixing' (All Fields) OR 'age mixing' (All Fields) OR 'sexual mixing' (All Fields) OR 'age differences' (All Fields)] AND ['HIV infection' (All Fields) OR 'Unprotected sex' (All Fields)]

Two reviewers (J.I. and D.S.) independently searched MEDLINE through PubMed, EMBASE, Web of Science, Google Scholar, and Google in an iterative process between 15 November 2019 and 5 January 2020. The reviewers also hand searched reference lists of selected articles to identify additional studies, which might have been missed by the search strategy. Further search included grey literature via LILACS, OpenGrey, dissertations/thesis, and reports. The overall results of this search strategy were presented in a PRISMA flow chart. All identified citations from each of the electronic databases were exported to *EndNote* and duplicated citations were excluded whereas the remaining ones were screened systematically for inclusion based on the titles and abstracts. We then retrieved and read the full texts of citations that met the eligibility criteria and abstracted the data.

J.I. and D.S. independently abstracted the following data items from studies that met the eligibility criteria using a validated data abstraction tool: first author's last name, year of publication, study design, sample size, study setting, country, outcome measures namely adjusted odds ratio (OR), adjusted risk ratio (RR), or adjusted hazard ratio. For studies that reported these effect measures in the opposite directionality of our study outcomes; namely as HIV-negative or protected sexual intercourse, we computed the reciprocal of the effect measure to synchronize the measures of effect. In studies where the associations between age-disparate relationships with unprotected sex and HIV infection were reported for varying strata namely by: partner age difference, such as 5−9 years or 10 years and beyond; and, differing age groups of AGYW, such as for 15−19 years and 20−24 years, data were abstracted and combined into one effect measure, provided there was no overlap. One publication by Evans *et al.* [25] in 2016 reported four independent effect measures for surveys

conducted in 2002, 2005, 2018, and 2012, and therefore each effect measure was reported separately. For studies where risk of HIV infection and sexual encounters were reported by timing of the relationship, the measure of effect for the most recent relationship was abstracted as the most representative effect measure. This approach ensured no single study contributed duplicated measures of effect.

Consensus in data abstraction and assessment of study quality

Disagreements in data abstraction were resolved by discussion with a third reviewer (F.B.). We computed and reported the degree of agreement in data abstraction using Kappa statistics. We employed the Newcastle–Ottawa Scale (NOS) to assess the risk of bias in the included studies as it has good inter-rater reliability and validity [26]. The NOS has three domains namely: selection domain assessed how exposed and unexposed groups in cohort studies, or cases and controls in case–control studies were selected; comparability domain assessed how the exposed and unexposed groups in cohort studies, or cases and controls in case–control studies were compared; and ascertainment domain assessed how outcomes in cohort studies, or exposures in case–control studies were measured. We rated the quality of individual studies as good when the total score was at least 7, fair when it was 2–6, and poor when it was 1 or less. Poor-quality studies were excluded from the meta-analysis.

Eligibility criteria

Studies were considered eligible for inclusion based on the population of interest, exposure, comparison, outcome, study design, study setting, and time period (PECOTS). Accordingly, we included studies where: type of participants involved were AGYW aged 15–24 years; exposure of interest: AGYW in age-disparate relationships — which was defined as being in a sexual relationship with an older partner with an age difference of 5 years or more; comparison group: AGYW who are not in ADR, which we defined as no age difference or age difference of less than 5 years; outcomes: primary outcome was HIV infection measured as testing positive for HIV based on standard national testing algorithm and the secondary outcome was unprotected sexual intercourse defined as sexual intercourse without the use of a condom in an age-disparate relationship, and time period: studies published until 5 January 2020; study designs: eligible studies included observational studies, such as cross-sectional, case–control, and cohort study designs or their hybrids; study settings: studies conducted within the SSA region. We excluded the following studies: studies with low-quality score on the quality assessment tool; non-English language studies; studies with inaccessible full texts; studies where the reporting of outcomes and definition of ADR were unclear; studies with incomplete data; studies where adjusted effect measure namely odds ratio (OR), risk ratio (RR), and hazard ratio for age-disparate relationship was not reported; studies conducted outside SSA; and studies where the AGYW in ADR was older than the male partner.

Data analysis

We summarized and presented the characteristics of the included studies in an evidence table. We applied the DerSimonian–Laird random effects model to pool the association between age-disparate relationships with unprotected sex (analysis 1), and with HIV infection (analysis 2) using RRs. We presented the pooled effects in a forest plot with corresponding 95% confidence interval (CI) and prediction interval. Our analysis assumed that RR is the most appropriate measure of effect to approximate the odds ratios, prevalence risk ratios, and rate ratios reported in the included studies [27–29]. We examined the included studies for heterogeneity using Cochran's (Q) test and considered P less than 0.1 as indicative of statistically significant heterogeneity. We quantified heterogeneity with I^2-values and categorized it as follows: 0–25, 25–50, 50–75, and 75–100 to imply no, low, moderate, and high heterogeneity, respectively [29]. Except for no and low heterogeneity, we performed a sub-group analysis and random effects meta-regression analysis to investigate the sources of heterogeneity based on included study characteristics like study design, year of publication, country, and quality [30].

Assessment for publication bias

We assessed for publication bias with a funnel plot, regarding a symmetrical plot as suggestive of no evidence of publication bias and an asymmetrical one as otherwise [31,32]. To confirm funnel plot asymmetry, we performed Egger's test. We considered P less than 0.1 as confirmatory of significant publication bias [31]. To distinguish between publication bias and other causes of funnel plot asymmetry like genuine small study effect and differences in baseline characteristics between study participants [33], we performed contour-enhanced funnel plot to aid interpretation: when studies appeared missing in areas of low statistical significance ($P > 0.05$), we reported funnel plot asymmetry was likely caused by publication bias and when studies appeared missing in areas of high statistical significance ($P < 0.05$, $P < 0.01$, or $P < 0.001$), we reported publication bias was a less likely cause of funnel plot asymmetry [33]. For the former interpretation, a Duval and Tweedie nonparametric 'trim and fill' analysis was performed to estimate the number and outcome of missing studies [34].

Sensitivity analysis

We performed sensitivity analysis to establish the robustness of the study conclusions and the impact of methodological quality, sample size, and analytic approach on the overall meta-analytic result. The other reason was to determine the influence of a single study on the overall meta-analytic results and the extent to which the meta-analytic results and conclusions might be altered by changes in analytic approach [35]. To perform this analysis, we excluded one study at a time and then pooled the results. When the new pooled outcome was outside the 95% CI of the original pooled outcome, we concluded that the excluded study had significant influence and such studies were excluded

from the final meta-analysis. All analyses were performed in R version 3.5.2 [36].

Results

Selection of studies

We retrieved and screened 111 citations of which 19 were excluded as duplicates. The remaining 92 citations were assessed for eligibility based on titles and abstracts, and 37 were excluded as they had irrelevant titles and abstracts. The full texts of the remaining 55 citations were read thoroughly and 36 of them were excluded with reasons,

leaving 19 full text articles. From the reference lists of the included studies, four additional studies were identified to give a total of 23 studies [11−16,25,37−49] that were meta-analyzed as shown in Fig. 1.

Characteristics of included studies

The 23 studies were published between January 2002 and January 2020. Majority of the studies ($n = 16$) were from South Africa and had used cohort study designs ($n = 13$). The total sample size was 33 390 participants, with a range of 446 to 2826 participants for the individual studies. The characteristics of the included studies are as shown in Table 1.
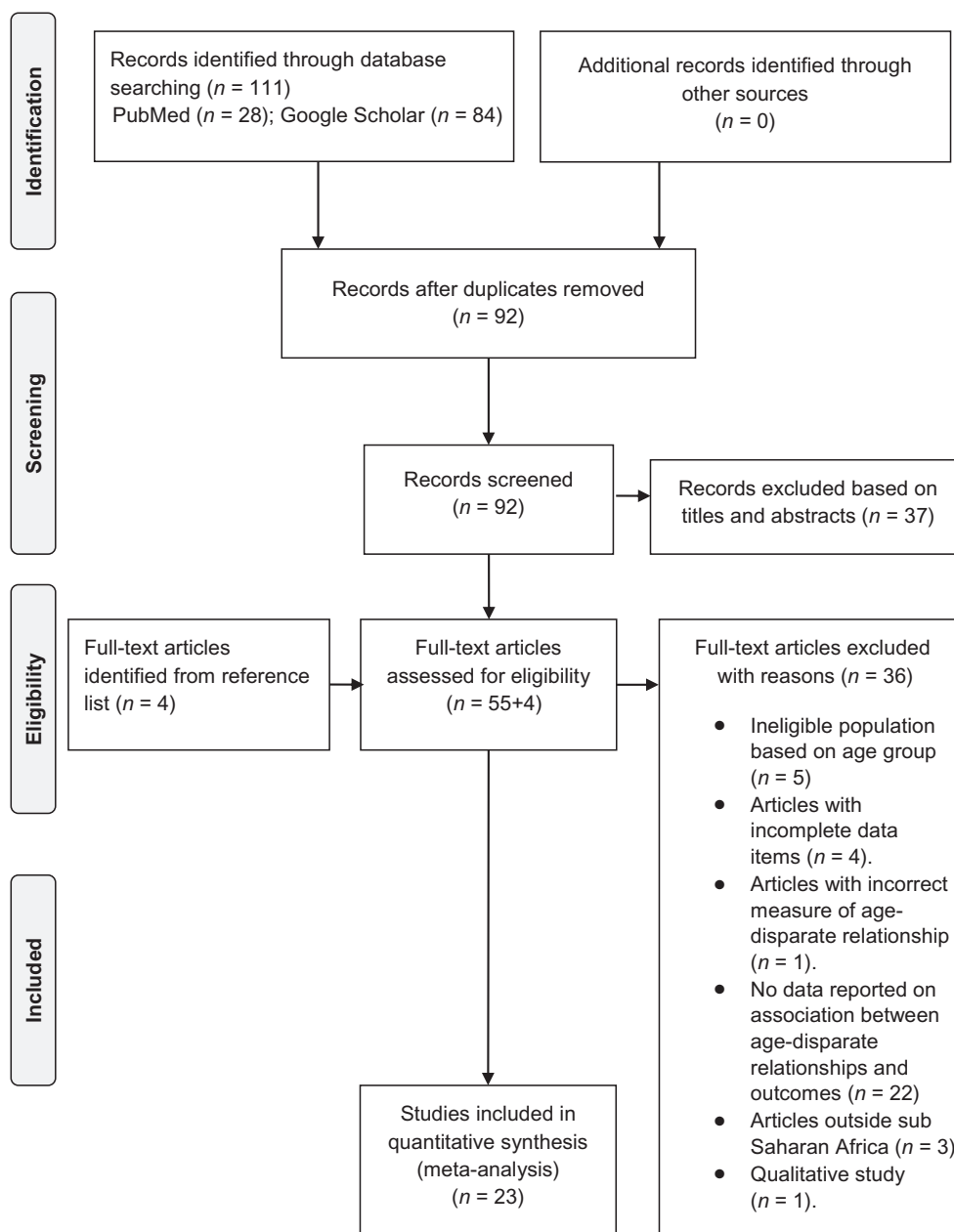

Identification

Records identified through database searching ($n = 111$)
PubMed ($n = 28$); Google Scholar ($n = 84$)

Additional records identified through other sources ($n = 0$)

Screening

Records after duplicates removed ($n = 92$)

Records screened ($n = 92$)

Records excluded based on titles and abstracts ($n = 37$)

Eligibility

Full-text articles identified from reference list ($n = 4$)

Full-text articles assessed for eligibility ($n = 55+4$)

Full-text articles excluded with reasons ($n = 36$)

- Ineligible population based on age group ($n = 5$)
- Articles with incomplete data items ($n = 4$).
- Articles with incorrect measure of age-disparate relationship ($n = 1$).
- No data reported on association between age-disparate relationships and outcomes ($n = 22$)
- Articles outside sub Saharan Africa ($n = 3$)
- Qualitative study ($n = 1$).

Included

Studies included in quantitative synthesis (meta-analysis) ($n = 23$)

Fig. 1. PRISMA flow chart showing the identification and selection of primary studies.

Table 1. Characteristics of all included studies.

No.	Author	Year	Country	Study design	Sample size	Quality score	Confounders adjusted in multivariate analysis
[37]	Beauclair *et al.*	2016	Malawi	Cross-sectional	1922	8	Age of participants and number of sexual partners.
[38]	Bezuidenhoudt *et al.*	2014	South Africa	Cross-sectional	2465	9	Employment status, area of residence, level of education, and sexual debut.
[25]	Evans *et al.*	2016	South Africa	Cohort	446	8	Age of respondent, race, marital status, locality, employment status, condom use at last sex, age of first sex, and multiple sexual partnerships.
[25]	Evans *et al.*	2016	South Africa	Cohort	994	8	Age of respondent, race, marital status, locality, employment status, condom use at last sex, age of first sex, and multiple sexual partnerships.
[25]	Evans *et al.*	2016	South Africa	Cohort	854	8	Age of respondent, race, marital status, locality, employment status, condom use at last sex, age of first sex, and multiple sexual partnerships.
[25]	Evans *et al.*	2016	South Africa	Cohort	1257	8	Age of respondent, race, marital status, locality, employment status, condom use at last sex, age of first sex, and multiple sexual partnerships.
[39]	George *et al.*	2018	South Africa	Cohort	1306	9	Women's age, education, household monthly income, being away for a period of greater than one consecutive month in the preceding year, HIV knowledge, self-reported HIV-positive status, perceived HIV status of sexual partner, partnership duration, and the nature of each relationship.
[12]	Gregson *et al.*	2002	Zimbabwe	Cross-sectional	715	8	Number of lifetime sexual partners, frequency of sexual intercourse, condom use, and cultural expectation that women should marry early.
[15]	Harling *et al.*	2014	South Africa	Cohort	2444	9	Age of respondent, highest educational attainment, household wealth quintile, current marital status, age at sexual debut, casual partnership, multiple sexual partners, and level of condom use.
[40]	Kelly *et al.*	2003	Uganda	Cohort	2250	9	Number of sexual partners in past 5 years, marital status, religion, and duration of relationships.
[41]	Low *et al.*	2019	Lesotho	Cross-sectional	2358	9	Age, residence, migration, education, food shortage, marital status, number of lifetime sexual partners, sexual activity before 15 years, ever having anal sex, ever sold sex, ever pregnant, HIV status of sexual partners in the past 12 months, and ever tested for HIV.
[42]	Mabaso *et al.*	2018	South Africa	Cross-sectional	565	8	Age, reported condom use at last sex, race, education, alcohol use, and number of sexual partners.
[14]	Mathur *et al.*	2015	Uganda	Cohort	2826	8	Age of partner, residence, proximity to partner residence, employment status of partner, duration before first sexual activity, partner use of alcohol before sex, sexual frequency with partner in the past year, frequency of condom use with partner in the past year, number of sexual partners had by the partner, knowledge of partner's HIV status, and partner HIV risk assessed.
[43]	Maughan-Brown *et al.*	2020	South Africa	Cohort	830	9	Participant age (years), educational level, area of residence, relationship duration, concurrent sexual partner at baseline, household income and alcohol use.
[11]	Maughan-Brown *et al.*	2018	South Africa	Cross-sectional	1072	8	Age of the woman, education, having always lived in the area, household asset index, and monthly household income, number of lifetime sexual partners, HIV-testing history, and number of useful sources of HIV information exposed to during the previous 12 months.
[44]	Maughan-Brown *et al.*	2016	South Africa	Cross-sectional	760	8	Age, education, employment status, household wealth, HIV testing history, HIV knowledge, partnership type, partnership length and knowledge of partner's HIV status, study design, and nonresponse.
[45]	Mwinnyaa *et al.*	2019	Uganda	Cohort	2319	9	Woman's age, education, number of sexual partners, location, alcohol before sex, and condom use.
[13]	Nguyen *et al.*	2019	South Africa	Cross-sectional	2140	9	Intervention arm, age, school enrolment, food insecurity, depression, relationship power, intimate partner violence, alcohol consumption, drug use, early sexual debut. number of sexual partners in the past 12 months, days since the last follow-up visit, and partner type.

Table 1 (*continued*)

No.	Author	Year	Country	Study design	Sample size	Quality score	Confounders adjusted in multivariate analysis
[46]	Pettifor *et al.*	2005	South Africa	Cross-sectional	647	8	Race, residence, partner age, educational level, sexual activity, Number of lifetime sexual partners (per additional partner), condom use with most recent partner, circumcision status, frequency of sexual intercourse in past month, unusual genital discharge in past 12 months, genital ulcers, and length of most recent sexual relationship.
[47]	Ritchwood *et al.*	2016	South Africa	Cross-sectional	657	8	Women's age, partnership status, partner's educational status, ongoing relationship, relationship duration, frequency of sexual intercourse, partner concurrent partnership, and transactional sex.
[16]	Schaefer *et al.*	2017	Zimbabwe	Cohort	2341	8	Age difference to partner, marital status, and survey rounds.
[49]	Street *et al.*	2015	South Africa	Cohort	596	9	Age and marital status.
[48]	Stoner *et al.*	2019	South Africa	Cohort	1626	9	Age at baseline, time-varying school enrolment or completion, time-varying alcohol use, and intervention assignment at baseline

Percentage agreement and quality of included studies

The percentage agreement between the two reviewers was 98.6%, which was good (Kappa statistics, 0.97; $P < 0.0001$). The quality of the 23 studies included in this meta-analysis was good, with 13 studies scoring 8, and 10 studies scored 9 on the NOS.

Meta-analysis

Association between age-disparate relationship and unprotected sexual intercourse (analysis 1)

This analysis included five studies [38,39,41,44,47] and the results are shown in Fig. 2. The analysis showed that age–disparate relationships were significantly associated

with increased risk of unprotected sexual intercourse among AGYW (pooled RR, 1.57; 95% CI, 1.34–1.83; 95% predictive interval, 1.22–2.02). The included studies were not heterogeneous (I^2 value $= 0$, $P = 0.89$), so we did not perform sub–group and meta–regression analyses, methods meant for exploring potential sources of heterogeneity. We did not test for publication bias with funnel plot and Egger's test as the number of studies meta-analyzed were less than 10 [50].

Association between age-disparate relationships and HIV infection (analysis 2)

We considered 20 studies for this analysis and the results are shown in Fig. 3. The results showed that age–disparate
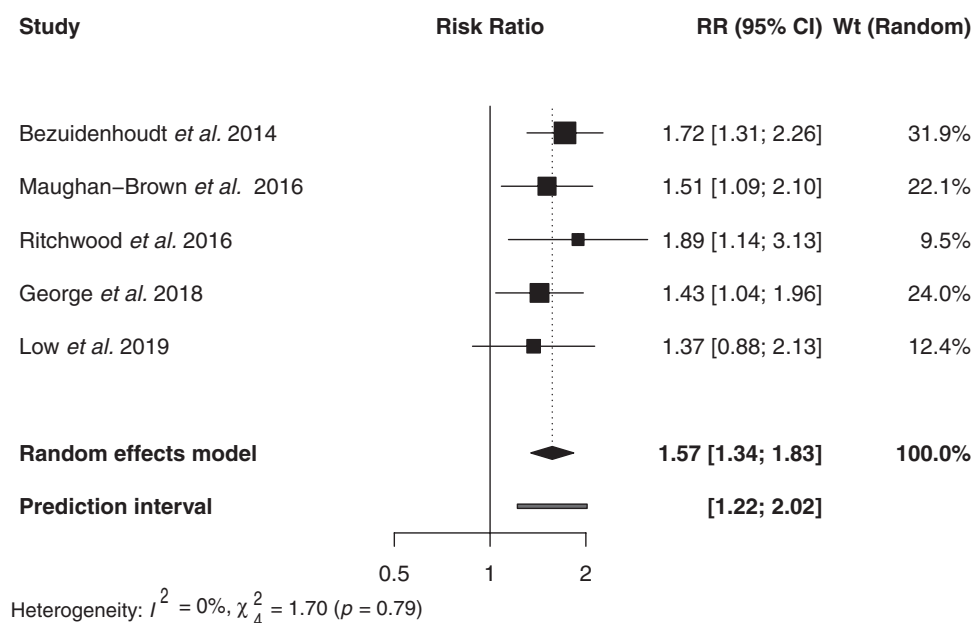

Fig. 2. Forest plot showing individual and pooled effect for the association between age-disparate relationships and unprotected sex among adolescent girls and young women in sub-Saharan Africa.

Study	Risk Ratio	RR (95% CI)	Wt(Random)
Gregson *et al.* 2002		1.04 [1.01; 1.07]	8.1%
Kelly *et al.* 2003		1.19 [1.03; 1.37]	7.5%
Pettifor *et al.* 2005		1.58 [1.48; 1.69]	8.0%
Harling *et al.* 2014		0.98 [0.81; 1.19]	7.0%
Bezuidenhoudt *et al.* 2014		2.06 [1.51; 2.81]	5.8%
Mathur *et al.* 2015		1.08 [0.65; 1.79]	4.0%
Street *et al.* 2015		0.99 [0.76; 1.29]	6.3%
Beauclair *et al.* 2016		1.33 [0.90; 1.96]	5.0%
Evans *et al.* 2016a		1.74 [0.81; 3.75]	2.4%
Evans *et al.* 2016b		2.11 [1.22; 3.65]	3.7%
Evans *et al.* 2016c		2.02 [1.24; 3.29]	4.1%
Evans *et al.* 2016d		1.53 [0.92; 2.54]	4.0%
Schaefer *et al.* 2017		1.30 [0.83; 2.04]	4.5%
Mabaso *et al.* 2018		1.26 [0.94; 1.68]	6.1%
Maughan Brown *et al.* 2018		1.56 [1.08; 2.26]	5.2%
Stoner *et al.* 2019		1.91 [1.33; 2.74]	5.3%
Mwinnyaa *et al.* 2019		1.83 [1.07; 3.12]	3.8%
Low *et al.* 2019		0.99 [0.57; 1.73]	3.6%
Nguyen *et al.* 2019		2.56 [1.23; 5.33]	2.6%
Maughan Brown *et al.* 2020		1.10 [0.55; 2.20]	2.7%
Random effects model		**1.39 [1.21; 1.60]**	**100.0%**
Prediction interval		[0.80; 2.42]	

0.2 0.5 1 2 5

Heterogeneity: $I^2 = 89\%$, $\tau^2 = 177.42$ ($p < 0.01$)
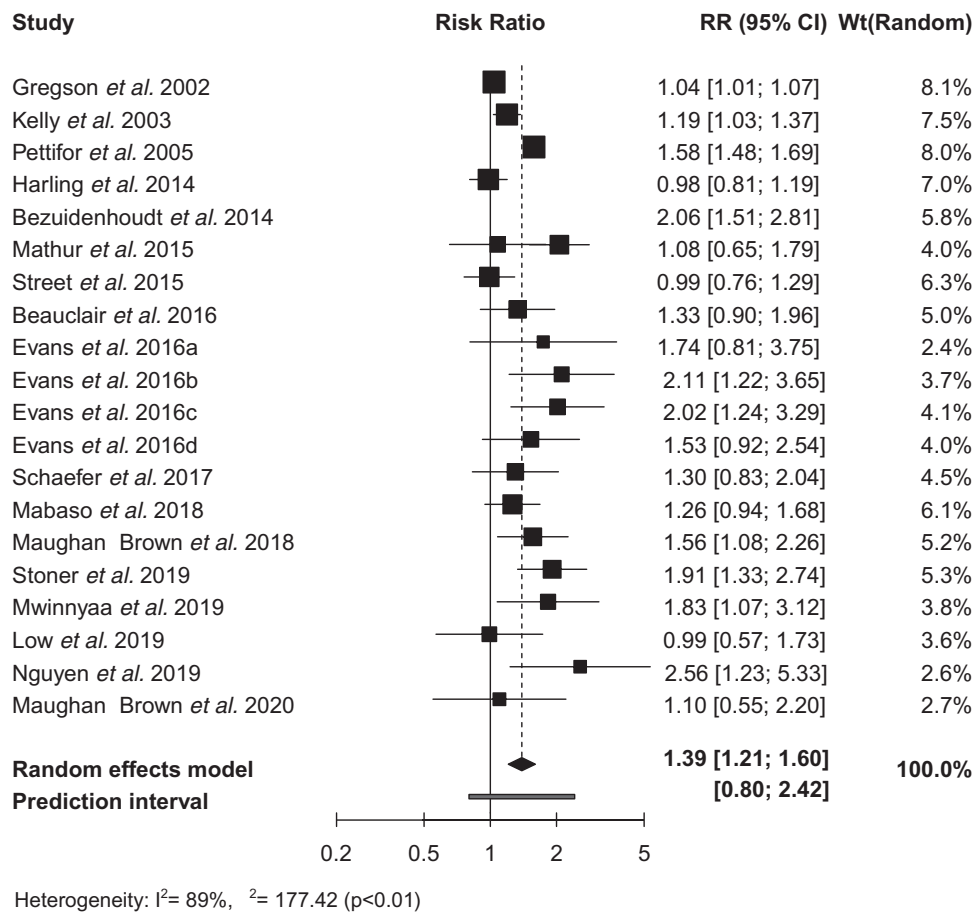
Fig. 3. Forest plot showing individual and pooled effect for the association between age-disparate relationships and risk of HIV infection among adolescent girls and young women in sub-Saharan Africa.

relationships were significantly associated with an increased risk of HIV infection among AGYW (pooled RR, 1.39; 95 CI, 1.21–1.60; 95% predictive interval, 0.80–2.42). We found statistically significant heterogeneity between the included studies (I^2-value = 89%, $P < 0.01$). We stratified the analysis by countries of origin into South Africa and the rest of SSA. Our data showed a pooled HIV infection risk of 1.50 (95% CI, 1.27–1.77; I^2-value = 72%, $P < 0.01$) in South Africa and 1.14 (95% CI, 1.02–1.28; I^2-value = 40%, $P = 0.13$ in the rest of SSA).

We explored the sources of heterogeneity in sub-group analysis. Here, we stratified by year of publication into three categories namely before 2015, between 2015 and 2016, and after 2016, and country of origin was categorized as South Africa versus the rest of Africa. The analysis showed that the country of origin of the study was the only source of heterogeneity as illustrated in Table 2.

Meta-regression analysis indicated a high risk of HIV infection among AGYW in South Africa compared with

Table 2. Sub-group analysis of the association between age-disparate relationship and HIV infection.

Characteristics	Level	Number of studies ($n = 20$)	Pooled RR (95% CI)	I^2 value	Q-test
Year of publication	≤2014	5	1.29 (1.01–1.65)	97.2	Statistics = 1.72, degree of freedom = 2, $P = 0.698$
	2015–2016	7	1.41 (1.10–1.80)	48.6	
	≥2017	8	1.47 (1.23–1.76)	21.8	
Country of origin	South Africa	13	1.50 (1.27–1.77)	71.9	Statistics = 7.13, degree of freedom = 1, $P = 0.008$
	Rest of Africa	7	1.14 (1.02–1.28)	39.7	
Study design	Cohort	12	1.34 (1.14–1.58)	95.3	Statistics = 0.20, degree of freedom = 1, $P = 0.658$
	Cross-sectional	8	1.43 (1.13–1.81)	56.6	
Quality of included scores	Score of 8	8	1.42 (1.16–1.74)	93.0	Statistics = 0.10, degree of freedom = 1, $P = 0.756$
	Score of 9	9	1.36 (1.10–1.68)	74.0	

CI, confidence interval.

the rest of Africa but this difference was not statistically significant (Beta coefficient, 0.22; 95% CI, −0.01 to 0.45, $P = 0.06$).

We found potential evidence of publication bias as some studies were not symmetrically distributed in the funnel plot. A contour-enhanced (confunnel) funnel plot superimposed on the funnel plot showed that small studies were not only in areas of nonstatistical significance but also in areas of statistical significance, suggesting asymmetry might have been caused by several factors, such as small study effect and differences in participant baseline charateristics but not solely by publication bias. Egger's linear regression test of funnel plot asymmetry showed that the slope of the graph significantly deviated from zero (t-test = 2.28, degree of freedom = 18, $P = 0.035$). This suggests that smaller studies gave different results relative to larger studies. Accordingly, we did not perform trim and fill analysis.

Sensitivity analysis
Our sensitivity analysis showed that all the new pooled RR were within the 95% CI of the original pooled RR. These results suggest that the pooled RRs for our outcomes (unprotected sexual intercourse and HIV infection) were robust with respect to the study design, analytic approach, and quality of included studies.

Discussion

Although various studies have shown contradicting results, our systematic review and meta-analysis shows age-disparate relationships are associated with unprotected sexual intercourse and HIV infection among AGYW in SSA. To the best of our knowledge, no other systematic review or meta-analysis has been conducted on this subject. The findings are consistent with several epidemiological studies from SSA. The plausible explanations for the high risk of HIV incidence are behavioral and biological. In age-disparate relationships, the older male partners are more likely to be HIV-infected, compared with the females and as our data show, also are more likely to have unprotected sex. In these partnerships, there is unequal power dynamics limiting the ability of the younger female partners to negotiate safer sex practices [51]. Second, there is inadequate comprehensive basic HIV knowledge and inaccurate information on sexual and reproductive health matters among adolescent girls in most countries in SSA [52,53], placing them at high risk for HIV acquisition. Third, there is a high drop-out rate for AGYW from school in SSA leading to limited access to education and early marriages increasing the risk for exposure to high risk ADR [54].

With respect to biological factors, immature cervix, large surface area offered by the female genital mucosa for HIV exposure time, susceptibility of vaginal or cervical lining to micro-abrasions and tears during sexual intercourse, high concentration of HIV in semen relative to vaginal fluids, increased duration of exposure to semen and expression of HIV co-receptors in cervical cells compared with cells in the foreskin, and high levels of activation of the immune cells in the female genital tract [55,56], all place AGYW at high risk of HIV infection.

The majority of studies in our meta-analysis were cohort studies. Our data show that eight cohort studies [14–17,25,40,43,49] showed a null association between ADR and HIV incidence. A recent publication [43] explains that this may be because of selection bias and that HIV incidence is more likely to occur early in the relationships. In our analysis, we were not able to distinguish between partnership duration for the cohort studies to tease out the recently formed from the longer duration partnerships.

Our findings have significant implications for public health programing and HIV prevention interventions for AGYW in SSA. The incidence of HIV among AGYW in SSA remains high and our data provide strong and compelling evidence that this population should continue to be the target for HIV prevention interventions. The AGYW in ADR are unlikely to negotiate barrier methods for safer sex. They should be a priority for preexposure prophylaxis (PrEP) programs. Experiences from pilot PrEP programs among AGYW in SSA show the program is feasible[57] and general interest in the program is very high [58]. These findings provide impetus to bring PrEP programs to scale, to enable curtailment of the high HIV incidence in this population. The PrEP programs should be implemented and integrated within ongoing efforts such as DREAMS [59], designed to eliminate structural drivers for HIV infection.

Study strengths and limitations
Our study has some important strengths. To the best of our knowledge, this is the first systematic review and meta-analysis to sum the association between age-disparate relationship with unprotected sexual intercourse and HIV infection among AGYW in SSA. Second, the sample size was large, and there was no publication bias detected.

Third, our methodology was robust and no study influenced the overall meta-analytic results, the review period was relatively long to generate sizeable evidence base, the search strategy was detailed and comprehensive, and included studies were of high quality. Despite these strengths, certain limitations should be considered. The included studies were from only five countries with a predominance of publications from South Africa, which could potentially limit the generalizability of the findings to SSA.

In conclusion, our study showed that AGYW in SSA in age-disparate relationship are at high risk for both unprotected sexual intercourse and HIV infection. AGYW should remain a focus for interventions to prevent HIV transmission. In addition to HIV prevention interventions, such as PrEP, HIV control programs should strengthen implementation of interventions that prevent initiation of age-disparate relationships and remove the associated structural barriers.

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Conflicts of interest

There are no conflicts of interest.

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