

BMJ Open Association of *Chlamydia trachomatis* infection with cervical atypia in adolescent women with short-term or long-term use of oral contraceptives: a longitudinal study in HPV vaccinated women

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ABSTRACT

Objective We assessed the relationship between *Chlamydia trachomatis* infection, duration of oral contraceptive (OC) use and cervical atypia among young adult Finnish women.

Design A longitudinal study.

Setting and participants Women who were included in this study participated in a community-randomised trial on the effectiveness of human papillomavirus (HPV) vaccination and *C. trachomatis* screening at ages 18.5 and 22 years in Finland. They completed questionnaires on both visits about sexual behaviours. The cytology test results at age 18.5 and 22 years were also available for those women. The total number of participants in this study at 18.5 years of age were 11 701 and at 22 years of age were 6618.

Main outcome measure ORs with 95% CIs using univariable and multivariable logistic regression were used to assess the association between *C. trachomatis* infection, duration of OC and squamous intraepithelial lesions (SIL).

Results There were 940 cytological SIL cases at the first screening visit and 129 cytological SIL cases at the second screening visit. Among the 22 years old, more than fourfold adjusted risk of SIL was associated with *C. trachomatis* positivity. The HPV16/18, condom use, smoking and number of sexual partners adjusted joint effect of prolonged OC use and *C. trachomatis* was significantly increased (OR 4.7, 95% CI 1.7 to 12.8) in the 22-year-old women. This observed joint effect was 1.6 times higher than expected on a multiplicative scale. On additive scale, the observed relative excess risk from interaction was 1.8.

Conclusion The risk of SIL in HPV vaccinated women is significantly increased if they are *C. trachomatis* positive and have used OC for 5 or more years. The biological basis may be lack of condom facilitated protection against sexually transmitted diseases.

Trial registration number NCT00534638.

BACKGROUND

Chlamydia trachomatis infection is the most common sexually transmitted bacterial

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The longitudinal study design allows the prospective evaluation of oral contraceptive use.
- ⇒ The well-controlled sensitive testing of *Chlamydia trachomatis* by PCR.
- ⇒ The inadequate data on barrier methods of contraception might have confounded the results.

infection characterised by persistent inflammation of epithelial tissue and chronic, also neoplastic, disease sequelae.¹ *C. trachomatis* is especially common in sexually active young women with early age at first intercourse, multiple sex partners and use of non-barrier contraceptive methods.² Most notably, *C. trachomatis* infection is associated with the persistence of oncogenic human papillomavirus (HPV) infection.³ Like smoking, *C. trachomatis* infection is a cervical carcinogenesis cofactor possibly independent of HPV.^{4 5} On the other hand, concomitant infection with *C. trachomatis* and HPV types 18 or 45 is associated with synergistically increased risk of cervical intraepithelial neoplasia grade 3 (CIN 3), that is, high-grade squamous intraepithelial lesions (HSIL).⁶

The association between *C. trachomatis* infection and cervical neoplasia could be the result of confounding by overlapping HPV exposure and/or oral contraceptive (OC) use.^{7–10} While the role of *C. trachomatis* and HPV infections in cervical carcinogenesis has been documented,^{6–8} the interplay of *C. trachomatis* infection and duration of OC use has not been studied over time.

In this study, we have evaluated the risk of cytological SIL associated with the duration

of OC use among *C. trachomatis* positive and negative women. We have studied the joint effect of *C. trachomatis* infection and duration of OC use on the development of cytological SIL in a large community-randomised trial cohort followed-up for up to 10 years.¹¹

MATERIAL AND METHODS

Study conduct

The study material was obtained from the community-randomised trial on the effectiveness of gender-neutral or girls-only HPV vaccination strategies conducted in Finland.^{11 12} In 2007–2009, all 80 272 Finnish boys and girls (1992–1995 birth cohorts) resident in 33 Finnish communities were identified using Finnish Population Register in three study arms each with 11 communities. All the males and females received either Cervarix (HPV16/18) vaccine (90%) or Engerix (hepatitis B-virus, HBV) vaccine (10%) in arm A. All the females received either HPV vaccine (90%) or HBV vaccine (10%) and the males received HBV vaccine in arm B. In arm C all the males and females received the HBV vaccine. Virtually all 99.4% of the participants received all three vaccine doses at months 0, 1 and 6.¹³

In 2010–2014, all the 1992–1995 born female residents in the trial communities were invited at the age of 18.5 years for a follow-up visit. They were offered cross-vaccination with either HPV16/18-vaccine or

HBV-vaccine, if they had not received them earlier in the trial. Cervical cytological sample taken by a study nurse and a self-collected cervico-vaginal sample for HPV and/or *C. trachomatis* testing were obtained.¹³ All the female participants during the follow-up agreed to participate in a *C. trachomatis* screening trial and filled in a questionnaire on demographics, life habits and sexual behaviour.¹³

Four years later (2014–2018) all the HPV16/18 vaccinated female participants were invited for the second follow-up visit at age 22 years. Again, cervical cytological sample and a self-collected cervico-vaginal sample for HPV and/or *C. trachomatis* testing were obtained, and the participants also filled in the questionnaires.¹³

In this study, we have four different types of datasets at both 18.5 years and 22 years of age: questionnaire dataset, *C. trachomatis* dataset, cytology dataset and HPV DNA dataset. All the four datasets were merged one-by-one at a time. All those which did not match/merge with any of the datasets were excluded from the study at the end (figure 1) of merging. The total number of study participants after merging all these datasets in this study at 18.5 years of age were 11 701 and at 22 years of age were 6618. The women were included if they merged with at least one or all the datasets. That is also the reason not all the merged women have complete data. However, during the analysis, complete case approach was applied and none of the missing values

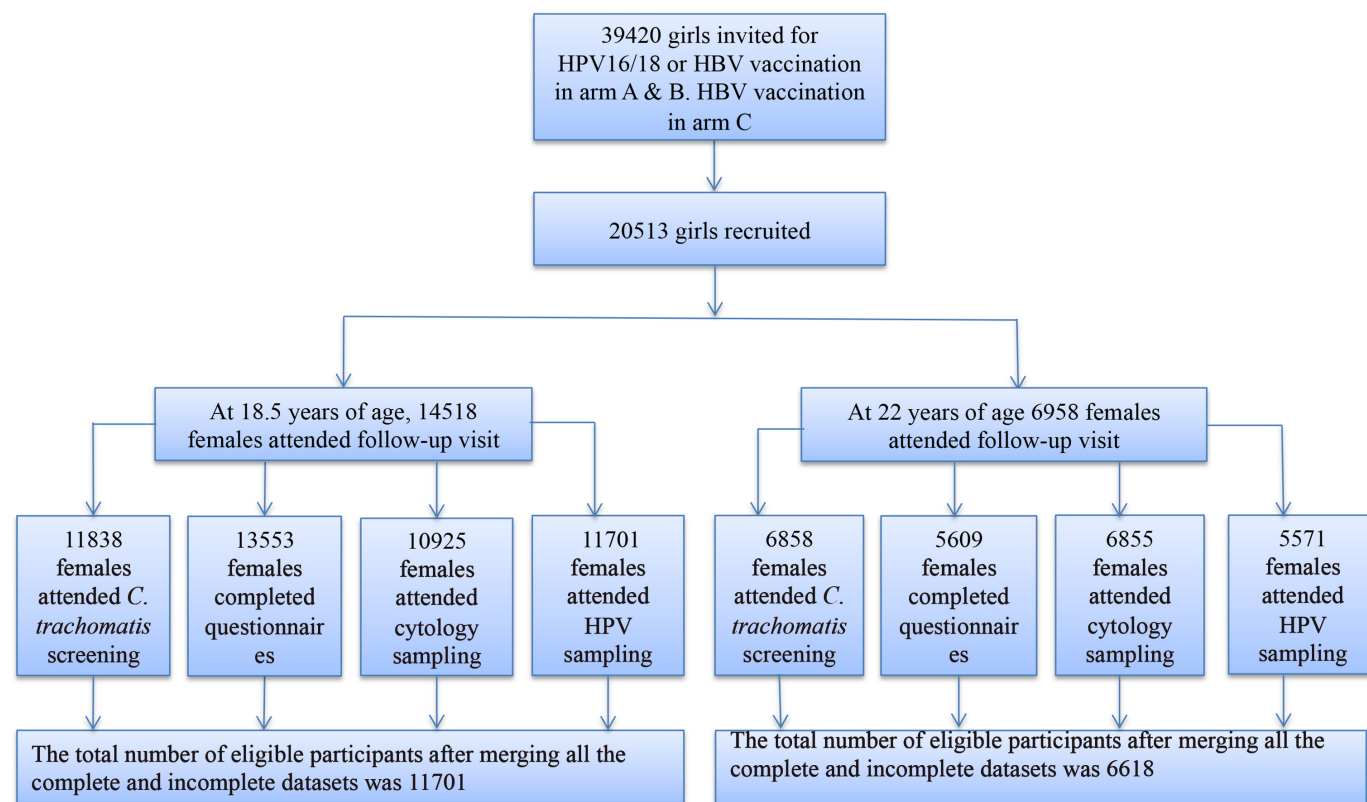


Figure 1 Flow diagram of female community randomised trial participants. 1852 participants at 18.5 years and 340 participants at 22 years of age were excluded from the study while merging the datasets as they did not merge with any of the other datasets. HBV, hepatitis B-virus; HPV, human papillomavirus.

were included neither in adjusted nor in unadjusted analyses.

Patient and public involvement

The study presents analysis of secondary data. There was no patient and public involvement.

Laboratory analysis

The self-collected cervical samples were analysed for the presence of HPV-DNA and further identification of the detected HPV types 6/11/16/18/31/33/35/39/45/51/52/56/58/59/66/68 by PCR (MGP primers) and matrix-assisted laser desorption time-of-flight (MALDI-TOF) mass spectrometry.¹⁴ The DNA sequence specific for the presence of *C. trachomatis* in the sample was detected by commercial PCR (Abbott-TM).

Statistical analyses

The main independent variables of the study were *C. trachomatis* status at ages 18.5 and 22 years, and duration of OC use (≤ 2 years and > 2 years at 18.5 years of age, ≤ 5 years and > 5 years at 22 years of age). Information about OC use was available from the questionnaires. Years since start of OC use was calculated using questionnaire information about years between start of OC use and sexual debut and information about age at sexual debut.¹⁵ The endpoint was cytological SIL divided into low-grade SIL and HSIL. The questionnaire dataset, *C. trachomatis* result dataset, HPV and cytology dataset were merged using personal ID.

ORs with 95% CI were calculated using logistic regression models to assess the risk of SIL associated with the *C. trachomatis* infection at age 18.5 and 22 years. In this study, we have interpreted OR as relative risk due to rare events. The risk estimates were adjusted to account for the potential confounding due to HPV DNA, condom use, number of sexual partners and smoking using multivariable logistic regression. Finally, the joint effect of duration of OC use and *C. trachomatis* was calculated and adjusted for potential confounders. In the main analysis, women with missing values on confounders were excluded from all regression models to ensure that the model included the same women (complete case analysis). As a sensitivity analysis, we repeated the crude analysis including women with missing values on confounders, to see whether this changed our estimates. All analyses were done by using Stata V.14.0 (Stata Corp: release 14).

RESULTS

At the first visit, the total number of cytological SIL cases was 940. The cytological results were missing for 781 participants out of 11 701 of the study participants (table 1). The number of cytological HSIL cases was 36 at 18.5 years of age. The baseline characteristics of 940 women with cytological SIL and 9980 women without cytological SIL were comparable. The age at first sexual intercourse, number of new sexual partners and OC use were

materially similar in the SIL cases and healthy controls at the first visit (table 1). There were no notable differences in HPV16/18 positivity. Also smoking and condom use were comparable at 18.5 years of age (table 1).

At the second visit, the total number of cytological SIL cases was 129 of 6618 (1.9%) of the study participants (table 1). The number of cytological HSIL cases was 27 at 22 years of age. At the second visit, while condom use did not differ between the 129 SIL cases and 6489 healthy controls, smoking and number of new sexual partners were somewhat higher in the SIL cases (table 1). There were double the SIL cases with three or more sexual partners compared with healthy controls. OC use was comparable between SIL cases and the healthy controls (table 1).

In the univariable analysis, the risk of cytological SIL associated with *C. trachomatis* was slightly, although non-significantly increased (OR 1.1) at 18.5 years of age (table 2). There was no further risk after adjusting for HPV16/18, condom use last year, smoking and number of sexual partners (table 2). At 22 years of age, the crude risk of SIL was highly significantly increased (OR 4.6, 95% CI 2.6 to 8.3) in *C. trachomatis* positive women compared with *C. trachomatis* negative women (table 2). In the multivariable analysis, the adjusted OR was still significantly high (OR 4.3, 95% CI 2.2 to 8.5) among the *C. trachomatis* positive women (table 2). When we repeated the crude regression analysis including women with missing values on confounders, the results were virtually unchanged.

Finally, the joint effect of *C. trachomatis* and duration of OC use was assessed. Among the 18.5 years old, the joint effect of *C. trachomatis* and duration of OC use on SIL was OR 0.9 (95% CI 0.4 to 1.7). The separate effects of *C. trachomatis* and duration of OC use were insignificant (table 3). The risk estimates were adjusted for HPV16/18, condom use last year, smoking and number of sexual partners. The missing values were not included in the analyses.

On the contrary, in the 22 years old, even after adjusting for the potential confounders (HPV16/18, condom use last year, smoking and number of sexual partners) the joint effect risk of cytological SIL was (OR 4.7, 95% CI 1.7 to 12.8) in *C. trachomatis* positive women who had used OC for 5 or more than 5 years compared with *C. trachomatis* negative and short-term OC users (table 4). The individual adjusted effects of *C. trachomatis* and duration of OC use on SIL were (OR 2.9, 95% CI 0.8 to 10.3) and (OR 1.0, 95% CI 0.5 to 1.9), respectively. Under a multiplicative model, the expected joint effect of *C. trachomatis* positivity and five or more than 5 years of OC use was (OR 2.9, 95% CI 0.6 to 14.0). The observed joint effect of 4.7 was 1.6 times higher than expected on a multiplicative scale. Under an additive scale, the relative excess risk from interaction was (OR 1.8, 95% CI -3.5 to 7.2). The missing values were not included in the analyses.

**Table 1** Cohort characteristics of study endpoints at 18.5 and at 22 years of age

Categories	At 18.5 years		At 22 years	
	SIL (N=940)	No SIL (N=9980)	SIL (N=129)	No SIL (N=6489)
Age at first sexual intercourse				
8–13 years	31 (3.3%)	316 (3.2%)	2 (1.5%)	162 (2.5%)
14–18 years	712 (75.7%)	7546 (75.6%)	85 (65.9%)	4392 (67.7%)
19–22 years	NA	NA	13 (10.1%)	697 (10.7%)
Missing	197 (21.0%)	2118 (21.2%)	29 (22.5%)	1238 (19.1%)
New sexual partners last year (n)				
2 or less	546 (58.0%)	6068 (60.8%)	61 (47.3%)	4209 (64.9%)
3 or more	197 (21.0%)	1793 (18.0%)	39 (30.2%)	1032 (15.9%)
Missing	197 (21.0%)	2119 (21.2%)	29 (22.5%)	1248 (19.2%)
Current smoking				
No	579 (61.6%)	5971 (59.8%)	49 (38.0%)	3273 (50.4%)
Yes	297 (31.6%)	3203 (32.1%)	38 (29.5%)	1518 (23.4%)
Missing	64 (6.8%)	806 (8.1%)	42 (32.5%)	1698 (26.2%)
OC-use				
No	152 (16.2%)	1645 (16.5%)	14 (10.8%)	573 (8.8%)
Yes	591 (62.8%)	6202 (62.1%)	85 (65.9%)	4648 (71.6%)
Missing	197 (21.0%)	2133 (21.4%)	30 (23.3%)	1268 (19.6%)
Condom use last year				
Not at all	182 (19.4%)	1978 (19.8%)	32 (24.8%)	1965 (30.3%)
Sometimes	207 (22.0%)	2216 (22.2%)	24 (18.6%)	1164 (17.9%)
In half of the intercourse	95 (10.1%)	985 (9.90%)	12 (9.3%)	603 (9.3%)
Almost always	135 (14.4%)	1160 (11.6%)	21 (16.3%)	669 (10.3%)
Always	111 (11.8%)	1433 (14.4%)	10 (7.7%)	776 (12.0%)
Missing	210 (22.3%)	2208 (22.1%)	30 (23.3%)	1312 (20.2%)
HPV16/18				
Negative	886 (94.3%)	9500 (95.2%)	106 (82.2%)	5307 (81.7%)
Positive	54 (5.70%)	480 (4.80%)	2 (1.5%)	49 (0.8%)
Missing*			21 (16.3%)	1133 (17.5%)

*Cytological results were missing for 781 of the HPV16/18 results among 18.5 years old.
HPV, human papillomavirus; OC, oral contraceptive; SIL, squamous intraepithelial lesions.

Table 2 Risk of cervical cytological squamous intraepithelial neoplasia by *C. trachomatis* at 18.5 and 22 years old

Category	N	SIL	OR (95% CI)	Adjusted SIL*
		n		OR (95% CI)
At 18.5 years				
<i>Chlamydia</i> seronegative women	10 512	901	1	1
<i>Chlamydia</i> seropositive women	408	39	1.1 (0.8 to 1.6)	1.0 (0.6 to 1.5)
At 22 years				
<i>Chlamydia</i> seronegative women	5352	86	1	1
<i>Chlamydia</i> seropositive women	198	14	4.6 (2.6 to 8.3)	4.3 (2.2 to 8.5)

N is the number of *C. trachomatis* in each age group. n is number of SIL cases.
*Adjusted for HPV16/18, condom use last year, smoking and number of sexual partners.
HPV, human papillomavirus; SIL, squamous intraepithelial lesions.

Table 3 Risk of cervical cytological squamous intraepithelial neoplasia (SIL) by joint effect of duration of oral contraceptive (OC) use and *C. trachomatis* positivity at 18.5 years

Risk factors	N	SIL		Adjusted SIL*	
		n	OR (95% CI)	OR (95% CI)	
CT#	Duration of OC use				
0	0	2746	233	1	1
0	1	3675	298	0.9 (0.8 to 1.1)	0.9 (0.7 to 1.1)
1	0	88	7	0.9 (0.4 to 1.9)	0.7 (0.3 to 1.7)
1	1	126	11	1.0 (0.5 to 1.8)	0.9 (0.4 to 1.7)

In duration (0=5 or less than 5 years/short-term OC use, 1= more than 5 years/long-term OC use).
 *Adjusted for HPV16/18, condom use last year, smoking and number of sexual partners.
 CT, *C. trachomatis* (0= CT negative, 1=CT positive); HPV, human papillomavirus.

DISCUSSION

This study shows that *C. trachomatis* positive HPV-vaccinated women have increased risk of cytological SIL. The adjusted risk of SIL associated with *C. trachomatis* positivity was significantly higher (4.3-fold) even after adjusting for the potential confounders among 22-year-old women. The observed joint effect of *C. trachomatis* positivity and long-term duration of OC use (more than 5 years) was higher than expected on both multiplicative and additive scale compared with *C. trachomatis* negative and short-term OC users (5 or less than 5 years) of OC use among 22-year-old women. The observed synergistic interaction was an unanticipated finding in this study.

In a number of other prospective studies, *C. trachomatis* has been proven to set the stage for cervical carcinogenesis leading to CIN3, possibly even independently of HPV.^{5–10} Our finding that *C. trachomatis* was associated with the increased risk of SIL in HPV-vaccinated women is in line with these studies since *Chlamydia* probably interacts also with non-vaccine HPV types. *C. trachomatis* is most common in adolescents and young adults of age 15–29,¹⁶ which is also the case in our study. The reason for increased susceptibility to sexually transmitted infections is because the young adults are more into casual sex and often do not use barrier methods of contraception.¹⁷ This was also the case in our study, where most of the

participants replied infrequent and less use of condom as well as having multiple sexual partners which predisposes to *Chlamydia* associated carcinogenesis.¹⁸

In our study, the mean age at first sexual intercourse was at 16 years of age. While OCs are one of the most common contraceptive methods among adolescents, they provide protection against unwanted pregnancies, but not against the sexually transmitted infections.¹⁶ There are several studies showing an increased risk of *C. trachomatis* infection associated with OC use.^{19–21} This is also in line with our findings. There is biological plausibility to assume synergistic interaction between OC use and cervical *C. trachomatis* infection. The long-term use of OC may increase the growth and persistence of *C. trachomatis* infection by altering the immune response especially among those, who do not use only barrier method of contraception.¹⁹ *C. trachomatis* infection also favours the persistence of all (both vaccine and non-vaccine) high-risk HPV types which facilitates progress of neoplastic lesions.¹⁸ Also, there are epidemiological studies which have found that the risk of cervical neoplasia/cancer increases with the increase in duration of OC use.^{22 23} Thus, both the *C. trachomatis* infection and long-term OC use are associated with the increased risk of cervical neoplasia, which is supported by our joint effect risk of long-term OC use and *C. trachomatis* infection.

Table 4 Risk of cervical cytological squamous intraepithelial neoplasia (SIL) by joint effect of duration of oral contraceptive (OC) use and *C. trachomatis* positivity at 22 years

Risk Factors	N	SIL		Adjusted SIL*	
		n	OR (95% CI)	OR (95% CI)	
CT#	Duration of OC use				
0	0	2293	30	1	1
0	1	1958	36	1.4 (0.9 to 2.3)	1.0 (0.5 to 1.9)
1	0	79	3	3.0 (0.9 to 9.9)	2.9 (0.8 to 10.3)
1	1	90	8	7.3 (3.3 to 16.6)	4.7 (1.7 to 12.8)

In duration (0=5 or less than 5 years/short-term OC use, 1= more than 5 years/long-term OC use).
 *Adjusted for HPV16/18, condom use last year, smoking and no. of sexual partners.
 CT, *C. trachomatis* (0= CT negative, 1=CT positive); HPV, human papillomavirus.



The main strength of our study is the large study population and longitudinal study design, which allowed the over time evaluation of OC use and timely measurement (and treatment) of the *C. trachomatis* infection. Another strength is the well-controlled and sensitive testing of *C. trachomatis* by PCR.

One limitation of our study is the number of cytological HSIL finding is small. Another limitation of our study is inadequate data on the use of barrier methods of contraception, which might have confounded the results. Yet another limitation of our study could be, that we have not considered the missing values in tables 2 and 3, which might bias the results. However, we checked including the missing values but the estimates did not differ much. Furthermore, we do not have information about the types of OC used. The risk might differ among the various types of OC depending on the hormonal composition.

In conclusion, we found increased risk of SIL associated with *C. trachomatis* positivity in HPV vaccinated population. Although based on small number of cases, the joint effect of *C. trachomatis* positivity and long-term use of OC on risk of SIL was higher than effects expected on the basis of additive or multiplicative interaction, which suggests synergism between the two variables. People who use OC as a means of contraception, may not use barrier methods of contraception and hence are prone to many sexually transmitted diseases. Thus, contraceptive and sexual health counselling should be enforced also among HPV vaccinated young women using oral/hormonal contraceptives. Additional studies are required to understand the biological basis of the interaction effect better.

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Contributors IA developed the research protocol, analysed the data, prepared the manuscript, revised and submitted the manuscript. TE contributed in data acquisition and data interpretation. KH and MH collected cervical cytological samples. PN made the cytological diagnoses and helped in the revision of the paper. TL commented on the draft of the paper and helped in the revision of the manuscript. DA commented on the draft of the paper. ML helped in data acquisition, contributed in the development of research plan, analysis plan, commented on the draft of the paper and the revision of the paper. ML is also an author acting as guarantor.

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Competing interests ML and DA have grants from Merck & Co Inc and GSK for HPV vaccination trials through their employers (Tampere University, ML; Family Federation Finland, DA).

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the ethical committees of the Pirkanmaa and Pohjois-Pohjanmaa hospital districts

(EUDRA-CT-2007-001731-55). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data available upon reasonable request, with appropriate ethics approval.

Addendum "Data availability statement " Data available upon reasonable request, with appropriate ethics approval. In Figure 1, all the red colored texts and numbers need to be changed into black. thank you.

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