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Neonatal jaundice in association with autism spectrum disorder and developmental disorder

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Abstract

Objective—To examine the association between neonatal jaundice and autism spectrum disorder (ASD) and non-ASD developmental disorder (DD).

Study design—We analyzed data from the Study to Explore Early Development, a US multisite, case-control study conducted from 2007 to 2011. Developmental assessment classified children aged 2–5 years into: ASD (n= 636), DD (n= 777), or controls (POP; n= 926). Neonatal jaundice (n= 1054) was identified from medical records and maternal interviews. We examined associations between neonatal jaundice and ASD and DD using regression models to obtain adjusted odds ratios (aOR).

Results—Our results showed interaction between gestational age and neonatal jaundice. Neonatal jaundice was associated with ASD at 35–37 weeks (aOR = 1.83, 95%CI 1.05, 3.19), but not ≥38 weeks gestation (aOR = 0.97, 95%CI 0.76, 1.24). Similar results were observed with DD.

Conclusions—Further exploration of timing and severity of neonatal jaundice and ASD/DD is warranted.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent impairment in social interaction and communication, and restrictive and repetitive

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Compliance with ethical standards

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patterns of behaviors, interests, or activities [1]. In 2012, the prevalence of ASD in the United States was estimated to be 1 in 68 children aged 8 years [2]. ASD is a heterogeneous disorder, and its etiology is suspected to involve both genetic and environmental factors [3, 4]. While environmental factors associated with ASD are not well understood, previous studies have implicated several exposures in the perinatal period [5–7].

Jaundice, a yellow discoloration of the skin and the sclera of the eyes, occurs in about half of newborn infants and most preterm infants (<37 weeks gestational age) usually as a result of increased serum levels of unconjugated bilirubin (unconjugated hyperbilirubinemia) from the breakdown of fetal hemoglobin after birth [8]. While jaundice typically resolves without treatment in the first week of life [9], bilirubin can cross the blood–brain barrier and at high concentrations may have toxic effects on the developing brain [10–12]. Unconjugated hyperbilirubinemia in the neonatal period has been associated with intellectual disability, cerebral palsy, and brain dysfunction in children [10, 13]. Further, clinical manifestations of bilirubin-induced neurologic dysfunction include several impairments in communication similar to ASD [14].

Some studies have reported an association between neonatal jaundice or hyperbilirubinemia and ASD, [8, 15–18] while others have reported no association [19, 20]. Inconsistent results may be partly due to methodological differences in data collection and classification of jaundice. Although jaundice occurs more frequently among infants born preterm [21] and the risk of ASD increases as gestational age decreases among preterm infants [22], previous studies have not assessed for interaction between jaundice and gestational age in association with ASD. To address limitations of previous studies, we analyzed data from the Study to Explore Early Development (SEED), a US multisite case-control study with extensive data from the perinatal period, to investigate the association between neonatal jaundice and ASD.

Methods

Study population

SEED is a multisite case-control study of children with ASD, children with developmental delays or disorders other than ASD (DD), and children sampled from the general population (POP) [23]. At the time of enrollment, children resided in one of six study catchment areas (California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania). The children were required to be 30 through 68 months of age at the time of in-person assessment and living with a knowledgeable caregiver who spoke English (or Spanish in California and Colorado) and who was at least 18 years of age and able to provide legal consent.

Compliance with ethical standards

Institutional review boards at each site approved study protocols and informed consent forms. Informed consent was obtained for each participant. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional review boards.

Data collection

Details on the SEED data collection protocol are provided elsewhere [22]. Briefly, SEED collected detailed data on maternal reproductive health and pregnancy outcomes through a telephone interview, abstraction of prenatal, neonatal, and pediatric medical records, and linkage with birth certificates. Data on child health outcomes as well as on their development and behaviors were obtained through telephone interviews and in-person child developmental assessment, as described below.

Outcome assessment

We used the Social Communication Questionnaire (SCQ) [24] to screen all children for autism symptoms during the invitation phone call. Children who screened positive for possible ASD (SCQ score >11), had a previous ASD diagnosis, or were suspected to have ASD based on the study clinician's direct observation, were given a more extensive developmental assessment. The more extensive assessment included clinical observation of the child using the Autism Diagnostic Observation Schedule (ADOS) [25] and a structured interview administered to their caregivers, the Autism Diagnostic Interview-Revised (ADI-R) [26]. As these tools are considered the 'gold standard,' final ASD classification was based on the results from these two developmental assessments regardless of previous diagnoses [27].

Children suspected to have ASD but screened negative on the SCQ or did not meet ADOS and ADI-R criteria for ASD were classified as DD. Children with DD who had some ASD characteristics or did not complete the clinic visit to obtain a final ASD classification were excluded from this analysis. Children who screened negative on the SCQ and were sampled from birth records were classified as POP.

Study clinicians administered the Mullen Scales of Early Learning to all children to assess general development. The early learning composite standard score was used to identify children with ASD and intellectual disability (ID; score <70) or ASD without ID (score ≥70) [28]. The DD group consisted of children with a broad range of developmental disorders other than ASD, and was further restricted to exclude children with ASD characteristics [27]. More detail about the SEED outcome assessment is available elsewhere [23, 27].

Ascertainment of neonatal jaundice

Information on neonatal jaundice was obtained from the maternal interview, the neonatal medical record, and the first 28 days of pediatric medical records. The infant was classified as having neonatal jaundice if a diagnosis or treatment for jaundice was recorded in the medical record or through maternal interview. Treatment for neonatal jaundice included phototherapy (bili light or blanket) or, in severe cases, exchange transfusion. We classified neonatal jaundice as: (1) treated, if treatment for neonatal jaundice was reported in either the medical record or maternal interview, (2) definite, if a diagnosis of hyperbilirubinemia was available in the medical record, but treatment was not reported, (3) possible, if neonatal jaundice was reported only through maternal interview, or (4) no neonatal jaundice, if no report of jaundice or jaundice treatment was in the medical record or maternal interview.

Indicator variables were created for these mutually exclusive categories with a referent group of no neonatal jaundice.

Covariates

Covariates were derived from prenatal and neonatal medical records, birth certificates, and maternal interviews. We carefully considered infant race/ethnicity because differences in jaundice diagnosis can be affected by skin tone. Infant race/ethnicity was classified by combining maternal and paternal race as reported on the maternal interview, or from the birth certificate if missing from maternal interview. If both parents identified as Hispanic, the infant was classified as Hispanic, regardless of reported parental race. Among non-Hispanics, when parents were the same race, the infant was classified by the parent's race as White non-Hispanic (referent), Black non-Hispanic, or Other (primarily Asian, but those identifying as Pacific Islander or Native Hawaiian, or Native American, Alaskan Native, or American Indian). An infant was classified as Multiracial if the parents were of different races or ethnicities.

Gestational age was classified according to clinical practice guidelines from the American Academy of Pediatrics [29] for assessing neonatal jaundice: 35–37 completed weeks of gestation, or ≥38 completed weeks of gestation. Gestational age was also modeled as a continuous variable in some analyses.

Statistical analyses

We used multivariable logistic regression models to estimate odds ratios (OR) and 95% confidence intervals (CIs) for the association between neonatal jaundice and both ASD (vs. POP) and DD (vs. POP), adjusting for all confounders (aOR). We identified potential confounders through a thorough literature review and used a directed acyclic graph to determine a minimally sufficient set of confounders to obtain the least biased estimates of association [30]. Models included maternal age at conception (<20 years, 20–34 years (referent), ≥35 years), education at delivery (high school degree or less vs. some college or more), parity (nulliparous (referent), primiparous, multiparous), diabetes in pregnancy (yes vs. no), and infant sex (male vs. female), and race/ethnicity (White non-Hispanic (referent), Black non-Hispanic, Hispanic, Other, and Multiracial). A study site indicator was included for California, Colorado, Maryland, North Carolina, and Pennsylvania (referent: Georgia).

We tested the assumption of homogeneity of the association across strata of gestational age by including interaction terms for gestational age with neonatal jaundice in the model and evaluating significance at $\alpha < 0.05$. Furthermore, we also assessed whether there were any differences in the association between neonatal jaundice and ASD with and without ID to evaluate the potential for these phenotypes to be etiologically distinct. We evaluated this association across strata of gestational age and among subcategories of neonatal jaundice. Analyses were conducted using SAS statistical software, version 9.3 (SAS Institute Inc., Cary, NC).

Results

SEED recruited 3769 participants. For this study, we restricted analyses to the 2339 mother–child pairs born ≥35 weeks gestation who had data available on neonatal complications and had a final outcome classification of ASD, DD, or POP (Fig. 1). We excluded mother–child pairs enrolled in SEED due to missing data on neonatal jaundice (n= 502), were <35 weeks gestation (n= 222), or because they had a developmental disorder with some characteristics of ASD but insufficient to meet diagnostic criteria most likely due to an incomplete clinic visit (n= 706). Compared with the analytic sample, children in the excluded subset were more likely to be White, non-Hispanic and less likely to have a mother who attained a higher education. In our sample, 1054 infants (45.1%) had neonatal jaundice based on the maternal interview or medical records. Of these, we classified 42.9% with treated jaundice, 35.1% with definite jaundice, and 22.0% with possible jaundice (Fig. 1).

Our analysis was comprised of 636 children with ASD, 777 children with a non-ASD DD, and 926 POP children. Compared with POP, children with ASD and those with DD had a higher proportion of older and less educated mothers, multiple births, earlier gestational age, and males (Table 1). Children with neonatal jaundice (ASD, DD, and POP combined) had a higher proportion of older mothers, mothers with diabetes in pregnancy, and earlier gestational age, compared with those without jaundice.

The association between any neonatal jaundice and both ASD and DD varied across strata of gestational age, with significant p-values for the interaction term across any neonatal jaundice (ASD p= 0.031; DD p=≤ 0.001) and subgroups; thus all results are presented by strata of gestational age to improve model fit (Table 2). Neonatal jaundice was associated with higher odds of ASD and DD, but only among children born 35–37 weeks gestation (Table 2). For children born 35–37 weeks, the association was stronger with DD (aOR = 3.34 [95%CI 1.99, 5.61]) than with ASD (aOR =1.84 [95%CI 1.06, 3.20]). Jaundice was not associated with ASD or DD among those born ≥38 weeks gestation. In separate models we further adjusted for gestational age as a continuous measure to account for any possible residual confounding; while this subtly altered some estimates, it did not change our interpretation of results.

We evaluated three subcategories of neonatal jaundice and refined ASD subtypes (Table 2). Among those with treated jaundice, confidence intervals were above the null in the 35–37 weeks stratum for ASD (aOR = 2.33 [95%CI 1.19, 4.55]) and for DD (aOR = 4.27 [95%CI 2.30, 7.93]). Estimates were attenuated for definite and possible jaundice and both ASD and DD in the 35–37 weeks stratum. Jaundice was not associated with ASD or DD among infants born ≥38 weeks gestation in any subcategories. Associations were also present for both ASD with ID and ASD without ID in the 35–37 weeks stratum (Table 3). Effect estimates in this stratum were higher among those with treated jaundice compared with those with any neonatal jaundice, however, while the confidence intervals were above the null for treated jaundice and both ASD with ID (aOR = 2.29 [95%CI 1.01, 4.96]) and ASD without ID (aOR = 2.73 [95%CI 1.13, 6.60], the confidence intervals were also wider.

Discussion

Our results show an association between neonatal jaundice and both ASD and DD among infants born preterm. The association with both ASD and DD suggests jaundice may be associated with neurodevelopment generally, and not specifically related to ASD. Effect estimates were most precise for any neonatal jaundice as statistical power was limited in smaller subgroups. We observed no association between neonatal jaundice and either ASD or DD among infants born ≥38 weeks gestation.

In our study, the magnitude of the association between jaundice and ASD or DD among preterm infants varied according to the jaundice definition. The treated and definite jaundice subcategories were most strongly associated with ASD or DD, while we observed weak or no associations with possible jaundice, which was defined by maternal report of jaundice only. The possible jaundice group may have higher potential for misclassification because the diagnosis was not confirmed in the medical record and the condition was presumably not severe enough to warrant treatment. In addition, data on the severity or length of hyperbilirubinemia were not available, and criteria for hyperbilirubinemia diagnosis in the medical record may have differed across the sample due to the introduction of new guidelines by the American Academy of Pediatrics in 2004 [29].

To our knowledge, our study is the first to account for interaction between gestational age and jaundice and to provide stratum-specific effect estimates by gestational age; prior studies restricted their analyses to term infants or adjusted for preterm birth as a confounder. The health of infants with jaundice, especially preterm infants with jaundice, can be more complex than for term infants with no signs of jaundice. There may be several unknown or unmeasured factors that commonly co-occur with jaundice in preterm infants that may contribute to brain development, which include other perinatal and neonatal complications and how such complications are treated or managed. However, our study did not have sufficient sample size to assess confounding or moderation by rare complications, for example infection. Thus, the potential for uncontrolled confounding needs further exploration.

We were also not able to assess if there was any participation bias in the study, as we could not determine the eligibility of all families we attempted to recruit because SEED could not obtain any data from targeted, but unreached or unrecruited, participants from multiple sources. One site had more data available to assess the generalizability of their sample. This assessment found response to be related to maternal age, education, and race/ ethnicity, but unrelated to available pregnancy and health variables. Accordingly, all analyses include adjustment for maternal age, maternal education, and infant race/ethnicity.

Our results were consistent with some previous studies [16, 17, 31, 32], but not with others [8, 19, 20, 33]. Inconsistencies between our results and prior studies may be due to differences in how ASD was ascertained or defined and adjustment of confounding. Most previous studies relied on ICD-9 codes or insurance databases that may reflect treatment codes that are not necessarily consistent with a final diagnosis [8, 16, 19, 32, 33]. Our analysis is unique in that information on neonatal jaundice was collected through medical

record and maternal report. SEED confirmed ASD through in-person evaluation, thus reducing the potential for outcome misclassification. Additional evaluation of children with DD also provides some insight that jaundice may be associated with development more generally rather than specifically associated with ASD.

Conclusion

We observed associations between neonatal jaundice and both ASD and DD among infants born 35–37 weeks gestation, but not among infants born ≥38 weeks gestation. These findings support results from some previous studies suggesting that preterm infants with jaundice may be at higher risk of adverse outcomes as compared with term infants. Our analysis did not have sufficient sample size to appropriately study bilirubin measurements or those born <35 weeks gestation, but plans to do so in future phases of the study. Future studies of neurodevelopment should explore the complexity of other neonatal conditions that accompany jaundice, and treatment profiles for jaundice, especially among preterm infants. In addition, monitoring children with jaundice or other early risk factors associated with ASD and developmental disabilities may lead to earlier diagnosis and treatment.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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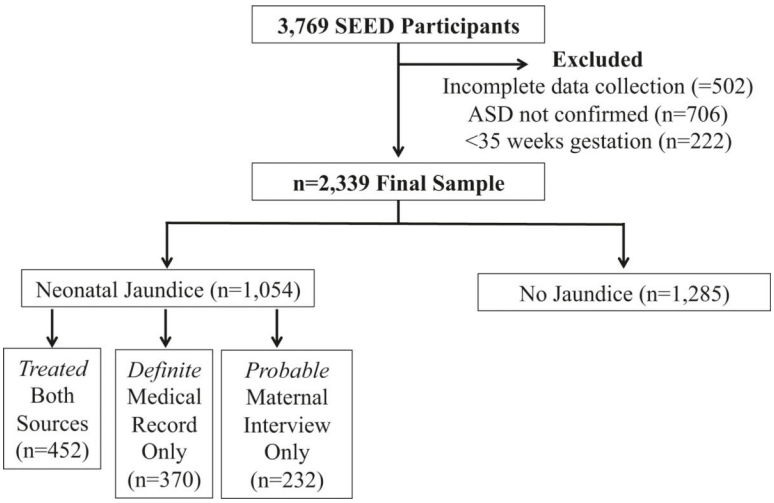

Fig. 1.

Composition of final analytic sample from children born September 2003–August 2006 enrolled in SEED

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Table 1

Distribution of maternal and infant characteristics by outcome classification and jaundice type in children born ≥35 weeks gestation from September 2003–August 2006 enrolled in SEED (N = 2339)

Characteristics	Total population (*N* = 2339) *n* (%)	ASD (*n* = 636) *n* (%)	DD (*n* = 777) *n* (%)	POP (*n* = 926) *n* (%)	Jaundice diagnosis (*n* = 1054) *n* (%)
Maternal age at conception					
<20 years	136 (5.8)	36 (5.7)	50 (6.4)	50 (5.4)	48 (4.6)
20 to <35 years	1961 (83.8)	534 (83.9)	638 (82.1)	789 (85.2)	894 (84.8)
≥35 years	242 (10.4)	66 (10.4)	89 (11.5)	87 (9.4)	112 (10.6)
Maternal education					
High school degree or less	334 (14.3)	101 (15.9)	141 (18.2)	92 (9.9)	126 (12.0)
Any college	1394 (59.6)	397 (62.4)	441 (56.8)	556 (60.0)	666 (63.2)
Graduate school	609 (26.0)	137 (21.5)	195 (25.1)	277 (29.9)	262 (24.9)
Parity					
First birth	993 (42.5)	291 (45.8)	290 (37.3)	412 (44.5)	475 (45.1)
Second	850 (36.3)	219 (34.4)	293 (37.7)	338 (36.5)	359 (34.1)
Third or more	465 (19.9)	115 (18.1)	183 (23.6)	167 (18.0)	211 (20.0)
Plurality					
Singleton	2254 (96.4)	600 (94.3)	748 (96.3)	906 (97.8)	997 (94,6)
Multiple	85 (3.6)	36 (5.7)	29 (3.7)	20 (2.2)	57 (5.4)
Maternal diabetes					
Yes	215 (9.2)	57 (9.0)	85 (10.9)	73 (7.9)	112 (10.6)
Gestational age					
35–37 weeks gestation	410 (17.5)	119 (18.7)	173 (22.3)	118 (12.7)	262 (24.8)
≥38 weeks gestation	1929 (82.5)	517 (81.3)	604 (77.7)	808 (87.3)	792 (75.2)
Infant Race/Ethnicity					
White, non-Hispanic	1444 (61.7)	350 (55.0)	473 (60.9)	621 (67.1)	682 (64.7)
Black, non-Hispanic	348 (14.9)	118 (18.6)	118 (15.2)	112 (12.1)	116 (11.0)
Hispanic	176 (7.5)	50 (7.9)	72 (9.3)	54 (5.8)	70 (6.6)
Other	93 (4.0)	40 (6.3)	29 (3.7)	24 (2.6)	46 (4.4)
Multiracial	277 (11.9)	78 (12.3)	84 (10.8)	115 (12.4)	140 (13.3)
Child sex					

Characteristics	Total population (*N* = 2339) *n* (%)	ASD (*n* = 636) *n* (%)	DD (*n* = 777) *n* (%)	POP (*n* = 926) *n* (%)	Jaundice diagnosis (*n* = 1054) *n* (%)
Male	1526 (65.2)	522 (82.1)	507 (65.3)	497 (53.7)	692 (65.6)
Study site					
California	365 (15.6)	98 (15.4)	121 (15.6)	146 (15.8)	131 (12.4)
Colorado	459 (19.6)	132 (20.8)	140 (18.0)	187 (20.2)	238 (22.6)
Georgia	457 (19.5)	123 (19.3)	168 (21.6)	166 (17.9)	174 (16.5)
Maryland	336 (14.4)	103 (16.2)	101 (13.0)	132 (14.3)	165 (15.7)
North Carolina	405 (17.3)	88 (13.8)	148 (19.1)	169 (18.3)	219 (20.8)
Pennsylvania	317 (13.6)	92 (14.5)	99 (12.7)	126 (13.6)	127 (12.1)

ASD autism spectrum disorder, *DD* non-*ASD* developmental delays or disorders, *POP* population-based control group, *SEED* Study to Explore Early Development

Table 2

Stratum-specific estimates by gestational age for the association between neonatal jaundice and ASD or DD in SEED

	N			Unadjusted OR (95%CI)		Adjusted OR (95%CI)	
	ASD	**DD**	**POP**	**ASD vs. POP**	**DD vs. POP**	**ASD vs. POP**	**DD vs. POP**
No neonatal jaundice							
35–37 weeks gestation	47	43	58	Ref.	Ref.	Ref.	Ref.
≥38 weeks gestation	304	356	474	Ref.	Ref.	Ref.	Ref.
Any neonatal jaundice:							
35–37 weeks gestation	72	129	59	1.22 (0.94, 1.57)	1.71 (1.33, 2.19)	1.84 (1.06, 3.20)	3.34 (1.99, 5.61)
≥38 weeks gestation	213	248	331	1.00 (0.90, 1.12)	1.00 (0.90, 1.12)	0.97 (0.76, 1.24)	1.07 (0.85, 1.34)
Treated jaundice:							
35–37 weeks gestation	41	75	25	1.42 (1.04, 1.95)	2.01 (1.49, 2.72)	2.33 (1.19, 4.55)	4.27 (2.30, 7.93)
≥38 weeks gestation	84	108	119	1.05 (0.90, 1.23)	1.10 (0.95, 1.28)	0.98 (0.70, 1.39)	1.28 (0.94, 1.73)
Definite jaundice:							
35–37 weeks gestation	24	35	21	1.19 (0.84, 1.69)	1.50 (1.07, 2.10)	2.08 (0.97, 4.47)	2.86 (1.42, 5.73)
≥38 weeks gestation	66	90	134	0.88 (0.75, 1.04)	0.95 (0.82, 1.10)	0.81 (0.57, 1.15)	0.99 (0.73, 1.36)
Possible jaundice:							
35–37 weeks gestation	7	20	14	0.79 (0.48, 1.29)	1.39 (0.94, 2.06)	0.66 (0.23, 1.92)	2.27 (1.00, 5.17)
≥38 weeks gestation	63	50	78	1.13 (0.94, 1.35)	0.93 (0.77, 1.12)	1.19 (0.81, 1.76)	0.87 (0.59, 1.29)

Adjusted for maternal age, maternal education, maternal diabetes, parity, plurality, infant sex, infant race/ethnicity, and study site

Interaction term for gestational age and jaundice was significant at $\alpha < 0.20$ in all strata

ASD autism spectrum disorder, DD non-ASD developmental delays or disorders, POP population-based control group, SEED Study to Explore Early Development, OR odds ratio, CI confidence interval

Table 3

Stratum-specific estimates by gestational age for the association between neonatal jaundice and ASD with or without ID in SEED

	N			ASD with ID aOR (95% CI)	ASD without ID aOR (95% CI)
	ASD with ID	ASD without ID	POP		
No neonatal jaundice:					
35–37 weeks gestation	30	16	58	Ref.	Ref.
≥38 weeks gestation	189	112	474	Ref.	Ref.
Any neonatal jaundice:					
35–37 weeks gestation	45	26	59	1.97 (1.04, 3.72)	1.80 (0.84, 3.88)
≥38 weeks gestation :	130	79	331	0.98 (0.74, 1.32)	0.95 (0.67, 1.33)
Treated jaundice					
35–37 weeks gestation	23	17	25	2.29 (1.05, 4.96)	2.73 (1.13, 6.60)
≥38 weeks gestation	51	32	119	0.98 (0.66, 1.47)	1.08 (0.68, 1.73)

Adjusted for maternal age, maternal education, maternal diabetes, parity, plurality, infant sex, infant race/ethnicity, and study site

Interaction term for gestational age and jaundice was significant at $\alpha < 0.20$ in all strata

ASD autism spectrum disorder, *DD* non-ASD developmental delays or disorders, *POP* population-based control group, *ID* intellectual disability, *SEED* Study to Explore Early Development, *OR* odds ratio, *CI* confidence interval

Sample sizes were too small to observe associations among those with definite and possible jaundice

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