Regarding "Distorting influences", five studies were rated "adequate", adjusting for more than two potential confounders that are listed in Table 2. In four of the studies, age and gender were controlled for, by matching (Kronenberg et al., 2010) and statistical adjustment (Goenjian et al, 2009; Kilic et al., 2008; Kronenberg et al., 2010; McFarlane & Hooff, 2009). Two studies controlled for disaster-related loss (Goenjian et al., 2009; Jia et al., 2013), and two studies controlled for depression (Jia et al., 2013; Kilic et al., 2008) in their analyses phase. Pre- or post-disaster loss or trauma was treated in Jia et al. by restricting the enrollment, and in Kronenberg et al. by statistical adjustment. As for the method, three studies employed multivariate methods to control confounding. Two of them employed linear regression analyses: Jia and colleagues included depression, residence, gender, ethnicity, objective/subjective experience of the disaster, disaster-related loss, and perceived social support in their analysis, with the subject without any pre- or post-traumatic experience; also Kilic and colleagues included state/trait anxiety, anxiety sensitivity, gender, age, and depression, as explanatory variables to the PTSD scores. One study conducted multi-nominal logistic regression, including age, gender, recovery stressors related to the disaster, pre- or post-disaster significant loss or trauma, and current perceptions of life problems as explanatory variables to the recovery patterns (Kronenberg et al., 2010).

The Measurement and Prevalence of PTSD

The most commonly used outcome measure was the Child Post-Traumatic Stress Disorder Reaction Index or CPTSD-RI (Pynoos et al., 1987; Steinberg, Brymer, Decker, & Pynoos, 2004), which is a self-report questionnaire assessing the severity of PTSD symptoms and also probable PTSD prevalence using a cut-off score, and was employed in six studies (Agustini et al., 2011; Goenjian et al., 2005, 2009; Jia et al., 2013; Kilic et al., 2008; Najarian et al., 2011). Kronenberg et al. (2010) used the Hurricane Assessment and Referral Tool for Children and Adolescents developed by the National Child Traumatic Stress Network (2005), which is based on the CPTSD-RI and also includes a number of questions regarding depressive symptoms. McFarlane and Hooff (2009) employed the computerized version of the Composite International Diagnostic Interviews or CIDI (World Health Organization, 1997). Two other studies involved diagnostic interviews conducted by psychiatrists using the DSM-IV (Piyasil et al., 2011; Ulartinon et al., 2008).

The overall (probable) prevalence rates over three years post-disaster were available in six of the included studies. At three years after, the prevalence rates were 10.7% following Shichuan earthquake in 2008 (Jia et al., 2013) and 4.5% following South Asia tsunami in 2004 (Piyasil et al., 2011). At 4.5 to five years after the disaster, the rates were 22.4% and 2.7% following South Asia tsunami in 2004 (Agustini et al., 2011; Piyasil et al., 2011), and 18.5% following Bolu, Turkey earthquake in 1999 (Kilic et al., 2008). After 20 years, the rates were 15.2% following the Ash Wednesday fires in 1983 (McFarlane & Hooff, 2009) and 21.1% following Spitak earthquake in 1988 (Najarian et al., 2011).

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Three studies compared the subjects who experienced the disaster with the controls who did not experience the disaster in PTSD and related symptoms; of these, one compared these two groups in PTSD prevalence rates 20 years after the disastrous bushfire; McFarlane and Hooff (2009) found no significant difference in PTSD prevalence between the bushfire-exposed and non-exposed groups; however, bushfire-exposed participants who experienced other traumatic event showed a higher risk, with a rate 1.8 times as likely as the controls.

Changes Over Time in PTSD symptoms

Two studies examined change over time in the prevalence of PTSD. Piyasil and colleagues (2011) showed that the prevalence rate decreased over time: 57.3% (six weeks post-disaster), 46.1% (six months), 31.6% (one year), 7.6% (two years), 4.5% (three years), 3.9% (four years), and 2.7 % (five years); however, the statistical significance of the decrease was not tested. In Jia et al. (2013), the probable prevalence rate was 12.4% at 15 months and 10.7% at 36 months post-disaster, but the change was not significant. On the other hand, Goenjian et al. (2005) examined over time changes in the PTSD scores rather than the prevalence rate, and found a significant decrease from 1.5 to five years post-disaster.

Two studies examined post-disaster recovery. Ularntinon et al. (2008) followed 45 children diagnosed with PTSD a year after the disaster, and found that 11% of them still met the criteria for PTSD diagnosis at three years post-disaster, whereas 24% of them had a full recovery. Kronenberg et al. (2010) investigated the recovery patterns of post-traumatic symptoms including PTSD and depression from the second to the third post-disaster year, categorizing children into four different groups: (a) stress resistant; (b) normal response and recovery; (c) delayed breakdown; and (d) breakdown without recovery. The percentages of the children included in each of these groups were 45.2%, 27.1%, 4.7%, and 23.0%, respectively; the total percentage of children who scored above the cutoff was 50.1% and 27.7% at the second and third year post-disaster.

Influential Factors

1. Gender: Seven of the included studies investigated gender difference in PTSD symptoms. Of these, five studies found that females had higher scores than males on PTSD measures (Agustini et al., 2011; Goenjian et al., 2005, 2009; Jia, et al., 2013; Kronenberg et al., 2010). Piyasil et al. (2011) described that the PTSD prevalence at six weeks after the disaster for female to male was 1.7 : 1; however, the statistical siginificance of this difference was not tested. Additionally, Kronenberg and colleagues investigated gender influence on the recovery patterns from the second to the third year post-disaster, as well as on PTSD scores, with females being more likely to be classified in the "breakdown without recovery" compared to "stress resistant", although gender did not alter the relation between other variables and the recovery patterns in the moderation analysis. However, multiple linear regression analyses in Jia et al. (2013) and Kilic et al. (2008) revealed that gender did not contribute to the PTSD scores when entered with other variables at three and five years after the disaster, respectively, although girls showed signifiantly higher PTSD scores. One study found no significant gender

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difference in the recovery patterns among the clinical group with PTSD diagnosis from the first to the third post-disaster year (Ularntinon et al., 2008).

2. *Age*: Five studies investigated age-related differences. Four of them found no significant age diffrernce in PTSD symptoms. Further, Kilic et al. (2008) showed no age effect on PTSD symptoms in the linear regression analysis when entered with other variables at five years after the disaster. Conversely, Kronenberg et al. (2010) found that younger children (ages 9 to 11) scored higher than older children (ages 15 to 18) at both the second and third post-disaster years, and that the recovery patterns of older children were about four times more likely to be in the "stress resistant" group than the "breakdown without recovery" group when other factors were adjusted for; however, age did not alter the relation between other variables and the recovery patterns in the moderation analysis.

3. *Disaster experience and loss*: Goenjian and colleagues (2005) found that students who lived closest to the epicenter of the earthquake had higher PTSD symptoms at 1.5 years post-disaster, and their symptoms remained higher at five years post-disaster than students who lived a greater distance from the epicenter. Similarly, physical injury (Ularntinon et al., 2008), and both the objective and subjective experience of the disaster (Jia et al., 2013) were associated with PTSD symptoms at three years post-disaster. Regarding disaster-related loss, loss experience including family members, significant others, houses, and important belongings (Jia et al., 2013) and loss of parents (Agustini et al., 2011) were associated with PTSD at three and 4.5 years after the disaster, respectively. However, Goenjian et al. (2009) found no significant difference in PTSD symptoms at 6.5 years post-disaster between students who lost their parents and students without parental loss, although orphans had the highest depression scores followed by those who lost fathers, compared to those who lost mothers and those who did not have parental loss.

4. *Depression and anxiety*: Jia et al. (2013) found that PTSD symptoms were predicted by depression, together with objective and subjective experiences and disaster-related loss at three years post-disaster when entered with other variables into the regression analysis; however, Kilic et al. (2008) included anxiety factors into the linear regression analysis and found that PTSD symptoms were predicted by trait anxiety and anxiety sensitivity, but not by depression or state anxiety at five years post-disaster.

5. *Other traumatic experiences*: Ularntinon and colleagues (2008) showed that a history of previous trauma influenced the recovery of the children previously diagnosed with PTSD at three years post-disaster. McFarlane and Hooff (2009) found that there was a significant difference between bushfire-exposed adults and the controls in PTSD symptoms at 20 years post-disaster, only if the bushfire-exposed adults experienced additional trauma. Conversely, Kronenberg et al. (2010) found that previous loss or trauma, and post-disaster major loss or trauma did not affect the recovery patterns from the second to the third year post-disaster when other factors were adjusted for.

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6. Environmental factors: Kronenberg et al. (2010) found that family and school problems were associated with the recovery patterns from the second to the third year after the disaster, but that the current living conditions, family connectedness, or friend problems were not associated with them. The perceived support level was also found to be associated with PTSD symptoms at three and 4.5 years after the disaster (Jia et al., 2013; Agustini et al., 2011). However, the influence was no longer significant when entered into the regression analysis with other variables in the study of Jia et al; it decreased depression symptoms, rather than PTSD symptoms.

Discussion

This review exclusively looked at long-term follow-up studies of PTSD symptoms in children after natural disasters. The included studies followed children who experienced disaster for three to 20 years post-disaster. The results of the study selection in Phase 2 showed that the number of such studies has largely increased in the last 10 years. Of these studies, about 35% followed other types of disasters (e.g., war, terrorist attacks, ship sinking, accidents, etc.), indicating that natural disaster is the major focus of long-term PTSD research in children, as Furr et al. (2010) and Hoven et al. (2009) mentioned earlier. However, almost 80% of the natural disaster studies followed the subjects for less than three years after disasters. Although Hurricane Katrina in 2005 was the most studied event among the selected studies in Phase 2, only one of them was included in this review in Phase 3. In addition, all included studies were published between 2005 and 2013. The importance of the long-term follow-up study seems to have been recognized relatively recently in post-disaster research, and thus the research over time awaits further investigation.

The studies included in this review varied in the study design, sample size and age, assessment method and timing, magnitude of the disaster, etc. Considering this heterogeneity, we presented the results as a narrative synthesis of the individual findings from the original studies. The results of the quality assessment using SAQOR indicated that the included studies had mostly moderate to high quality; however two studies were rated "adequate" in only two categories. Thus, these findings need to be interpreted cautiously.

Long-term Course of PTSD and Recovery

As previous reviews have summarized (e.g., Furr et al., 2010; Vogel and Venberg, 1993; Wang et al., 2013), we have already learned that post-traumatic symptoms decrease substantially during the first year after the disaster; however, the course of PTSD after the first few years is not yet well known. The results reported by Piyasil et al. (2011) suggested that PTSD symptoms decrease largely during the first two years (from 57.3% to 7.6%), and there may not be a significant decrease after that up to five years post-disaster.

Although Piyasil and colleagues did not test the statistical significance of the decrease, this data delineated the course of PTSD symptoms. However, it should be noted that in their study, a school-based intervention was conducted in the targeted school, so

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there must have been some intervention effect on the prevalence rate. Although McFarlane and Hooff (2009) indicated that PTSD symptoms would be mostly remitted to the level of the non-exposed group by 20 years post-disaster, two studies that investigated change over time of between 15 months and five years showed inconsistent results: Goenjian et al. (2005) found a significant decrease in PTSD scores from 1.5 to five years post-disaster, whereas Jia et al. (2013) found no significant decrease in prevalence rate from 15 to 36 months post-disaster. The significance of the decrease of PTSD prevalence after the first post-disaster year may not be large enough to be captured in a short period.

Regarding post-disaster recovery, Kronenberg et al. (2010) examined the recovery patterns proposed by Masten and Obradovic (2008) based on post-traumatic symptoms – including PTSD and depression – and reported that among the children who scored above the cutoff score on the screening at the second post-disaster year, 54% were considered to have recovered at the third year. These findings were similar to the result of Perkonigg et al. (2005) on youth PTSD, showing that about a half of the youth, previously diagnosed with PTSD, had recovered at 50 months after the disaster. Ularntinon et al. (2008) also found that about 25% of the children, who were diagnosed with PTSD at the first year after the disaster, had full recovery at the third year after the disaster, whereas 11% continued to have PTSD. Although the recovery rate would vary across studies due to the employed symptom measures, study time frame, study population, magnitude of the disaster, etc., these studies enable us to examine the course of PTSD in children, which is not captured by overall prevalence rates. Also, both risk and protective factors to the development of chronic PTSD could be examined. More studies that investigate recovery patterns or followed case samples would be needed in the future.

Risk Factors

Gender and disaster experience were the most studied influential factors on PTSD symptoms among the included studies. On the other hand, age effect was supported by only one study. These findings were consistent with the meta-analysis reported by Furr et al. (2010), which demonstrated that gender, but not age, was significantly associated with PTSD in youth. With regard to gender difference, although seven of the 10 included studies found that girls were more likely to have PTSD symptoms than boys, the linear regression analyses did not support the gender influence on PTSD symptoms (Jia et al., 2013; Kilic et al., 2008), indicating that the gender-related differences might be confounded or moderated by other variables. The gender difference in PTSD symptoms may due to the gender difference in depression, as it is known that girls report more depression symptoms than boys (see Hankin & Abramson, 2001; Jordan, 2013). It is necessary to determine whether gender has a significant influence on PTSD when other potentially influencing variables are accounted for. Furthermore, there might be a moderating effect of gender on the relation between some risk factors and PTSD symptoms; for example, lack of social support may impact girls more adversely than boys considering that women's coping style is more relational than men's (Jordan, 2013; Lazarus & Folkman, 1984).

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Regarding disaster experience, physical proximity and subjective experience were associated with PTSD symptoms, as has been suggested by Vogel and Venberg (1993) and Furr et al. (2010). However, the influence of parental loss on child PTSD was not clear: Two studies showed its influence on PTSD symptoms at three and 4.5 years after the disaster (Agustini et al., 2011; Jia et al., 2013), whereas Goenjian et al. (2009) demonstrated that parental loss was associated with depression, not with PTSD symptoms at 6.5 years after the disaster. Loss of parents may be a risk factor for developing PTSD after the disaster, but may not be a strong predictor for chronic PTSD. Children who lost their parents may continue to suffer from depression even after recovering from PTSD symptoms.

Depression is one of the most studied post-disaster symptoms except for PTSD (Hoven et al., 2009), and is known to often be comorbid with PTSD (45.9% in Eksi & Braun, 2009; 79% in Goenjian et al., 2001). As it has been suggested that depression symptoms predict subsequent PTSD symptoms (Roussos et al., 2005; Ying, Wu, & Lin, 2012; Zhang et al., 2012), so too Jia et al. (2013) found that PTSD symptoms were explained by depression. Considering that children with comorbid symptoms of PTSD and depression have poorer recovery (Lai, La Greca, Auslander, & Short, 2013), having depression symptoms seems to be a risk factor for prolonged PTSD in children. With regard to the risk factors for depression, Goenjian et al. (2009) showed that parental loss is associated with depression. On the other hand, Jia et al. (2013) demonstrated that depression was not predicted by disaster-related loss, but by perceived social support. Disaster-related loss may lead to impaired social support available to the child, which could increase the child's depression symptoms, but this relation was not yet known.

Anxiety is considered to be another influential factor: Asarnow et al. (1999), La Graca, Silverman, and Wasserstein (1998), and Weems et al. (2007) showed that pre-existing anxiety and trait anxiety significantly contributed to the subsequent development of PTSD in children, after controlling for the effects of other variables. Among the studies included in this review, Kilic and colleagues (2008) found that PTSD symptoms were explained by trait-anxiety and anxiety sensitivity, but not by depression and state-anxiety. Trait-anxiety and anxiety sensitivity are considered to be personal traits functioning as vulnerability factors, which precede post-traumatic symptoms, rather than symptoms following the disaster. As mentioned in Furr et al. (2010) and Hoven et al. (2009), pre-disaster assessment is rare in disaster research, since disaster research is usually initiated after the disaster occurrence. More studies are needed to understand these preceding and potentially predisposing factors to identify children at risk at an earlier stage.

Finally, the influence of being exposed to multiple traumas was not yet clear, with two studies showing a significant influence on chronic PTSD (McFarlane & Hooff, 2009; Ularntinon et al., 2008), which was consistent with the results of Pekonigg et al. (2005), while one study showed no significant influence (Kronenberg et al., 2010). All three studies employed different measures for assessing the experience of other traumas. There is a need to develop a more standardized measure to assess pre- and post-disaster traumatic experience.

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Limitations and Future Directions

Several limitations regarding study design were found. First, among the studies included in this review, none conducted a pre-disaster assessment. Although there are constraints, pre-disaster information would be beneficial for obtaining a better understanding of the risk factors for chronic PTSD, such as pre-existing anxiety. Second, a control/comparison group was included in only three studies, and none of them had longitudinal data for the comparison. There are many barriers to having comparable groups to in post-disaster research, as well as having representative samples in disaster research (Masten & Osofsky, 2010). However, it is ideal to include control groups in cohort studies as well so that the long-term impact of the disaster can be evaluated properly. Using some strategies to reduce confounding caused by sampling and selection flaws is also required. Third, some of the subjects in the included studies received psychological interventions after the disaster. Such information should be taken into account when evaluating the influence of the disaster on PTSD symptoms and the recovery from them. It is recommended to have both an intervention and a non-intervention group in the study, as with Goenjian and colleagues in their 2009 work, although we did not report that information in this review.

Regarding the risk of confounding, five of the included studies used one to two strategies recommended to avoid confounding by Lu (2009). Thus, some of the possible confounding was controlled in these studies. Such strategies, especially multivariate methods, enable us to have a better understanding of the mediation and moderation effects of the factors on the PTSD symptoms, as well as to avoid confounding. Gender influence was suggested to be more complicated than a simple risk factor in this review. Studies investigating dimensional factors, including pre-disaster trait (e.g., gender, trait anxiety), disaster experience (i.e., proximity, physical injury, threat to life, loss of important others), other post-traumatic symptoms (e.g., depression, anxiety), and current distress (e.g., social support, parental symptomatology, school stress, living conditions), using multivariate strategies would be beneficial and thus recommended in the future research.

Age was not found to be an influential factor, with only one study showing a significant age effect on the PTSD symptoms (Kronenberg et al., 2010). The age range of the participants of the included studies was not small, especially the age at the time of the disaster (ages three to 16). Disaster experience may affect children's development differently depending on their developmental levels. Considering that younger children are more dependent on care from adults, loss of parents or impaired parental functioning associated with parents' symptomatology may influence younger children's recovery more adversely than that of older children. Additionally, Masten and Osofsky (2010) mentioned the possibility that psychological or physical adversity experienced become embedded in child development through a variety of pathways, from the effects of elevated cortisol on the developing brain to the effects of maternal deprivation on attachment, emotional security mastery, motivation, the development of self-regulation, and later relationships. Thus, not just an age difference among study participants, but also a difference in developmental stage needs be taken into account to examine its influence

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on PTSD symptoms and recovery. Also, an age-sensitive assessment method based on DSM-V (American Psychiatric Association, 2013), which separated PTSD in children younger than six years, await development.

Two of the included studies examined the post-disaster recovery patterns (Ularntinon et al., 2008; Kronenberg et al., 2010). However, the influential factors on the recovery patterns were not yet clear. Considering that there would be limited resources for psychological interventions in severely affected areas, and most of the children would show recovery over time, identifying children and adolescents at the highest risk for chronic PTSD would be particularly important. Several studies mentioned the importance of the ongoing life stress in the disaster research as well as the magnitude of the disaster (see Masten & Osofsky, 2010). Disaster magnitude and experience is known as a strong risk factor to the development of PTSD, whereas secondary stress associated with family loss, family symptomatology, peer support, et cetera may function as risk factors to the recovery from PTSD. Also, factors protective against the onset or later development of PTSD, and factors associated with resilient recovery from PTSD versus chronic forms of the disorder (Pynoos et al., 1999) may be different. More studies focusing on recovery would be needed in the future in order to reveal risk and protecting factors associated with chronic PTSD.

Conclusions

This article reported a systematic reiew of the long-term follow-up studies of PTSD symptoms in children and adolescents after natural disasters. The results of the database search demonstrated that the number of long-term follow-up studies has increased in the last 10 years. The synthesized results of the included studies indicated that PTSD symptoms decrease over time, especially during the first two years after the disaster, as mentioned in the previous reviews (Furr et al., 2010; Hoven et al., 2009; Vogel & Venberg, 1993); however, the long-term course is not yet clear. Among possible risk factors, gender, disaster experience, depression, trait-anxiety, experiencing multiple trauma, and parental loss were considered to be associated with PTSD; however, there is a possiblility that the gender effect on PTSD might be confounded by other factors, such as depression and anxiety. More detailed reseach, including assessments of, among others, children's pre-disaster traits, disaster experience, depression, current living distress, and social support, using multivariate analytical methods would be needed. Furthermore, studies that examine recovery would be beneficial in order to provide a better understanding of the factors associated with chronic PTSD, and thus await futher investigation.

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A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment

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In this multicenter, open-label, randomized controlled trial, we determined whether 2-month prednisolone therapy for steroid-sensitive nephrotic syndrome was inferior or not to 6-month therapy despite significantly less steroid exposure. The primary end point was time from start of initial treatment to start of frequently relapsing nephrotic syndrome. The pre-specified non-inferiority margin was a hazard ratio of 1.3 with one-sided significance of 5%. We randomly assigned 255 children with an initial episode of steroid-sensitive nephrotic syndrome to either 2 - or 6-month treatment of which 246 were eligible for final analysis. The total prednisolone exposure counted both initial and relapse prednisolone treatment administered over 24 months. Median follow-up in months was 36.7 in the 2-month and 38.2 in the 6-month treatment group. Time to frequent relaps was similar in both groups; however, the median was reached only in the 6-month group (799 days). The hazard ratio was 0.86 (90% confidence interval, 0.64–1.16) and met the non-inferior margin. Time to first relapse was also similar in both groups: median day 242 (2-month) and 243 (6-month). Frequency and severity of adverse events were similar in both groups. Most adverse events were transient and occurred during initial or relapse therapy. Thus, 2 months of initial prednisolone therapy for steroid-sensitive nephrotic syndrome, despite less prednisolone exposure, is not inferior to 6 months of initial therapy in terms of time to onset of frequently relapsing nephrotic syndrome.

Idiopathic nephrotic syndrome (NS) is a disorder affecting the kidneys that is mainly characterized by high excretion of protein in the urine. Pediatric idiopathic NS is understood to be the most common cause of primary glomerular diseases, and it frequently occurs in infants aged 2–6 years. Most patients are presumed to have minor glomerular abnormality. Cellular immunologic abnormalities are believed to contribute to the condition, although its pathology remains unknown. In Europe and the United States, two in 100,000 children will develop idiopathic NS in a single year.[1] An 8-week corticosteroid regimen is the standard initial treatment for children with idiopathic NS, as outlined by the International Study of Kidney Disease in Children (ISKDC).[2,3] Although corticosteroids induce the remission of proteinuria in more than 80% of children with idiopathic NS, ~60% undergo proteinuria relapse. Previous research has shown that a high number of children undergo frequent relapse, and corticosteroid toxicities occur after repeated therapy.[2,3] Although some controlled studies[4–7] and a meta-analysis[8] show that long-term corticosteroid treatment up to 7 months maximum leads to a longer sustained remission of NS than ISKDC-recommended administration, the optimum

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[10]See appendix.

dose and duration of initial therapy are still unknown. A Cochrane review concluded that a well-designed and adequately powered randomized controlled trial is required to establish the optimum dose and duration of treatment.[8] The purpose of this study is to investigate whether 2 months of initial prednisolone therapy (ISKDC regimen) is not inferior to 6 months of initial therapy with an increasing cumulative dose, and to compare adverse events between treatment regimens.

RESULTS

Patient population

The study was conducted from September 6, 2007 until February 8, 2013. Figure 1 shows the trial profile. We assessed 255 patients from 90 hospitals (61 general, 7 children's, and 22 university hospitals) for eligibility. We randomly assigned 128 patients to the 2-month prednisolone group and 127 patients to the 6-month prednisolone group. We excluded nine patients from the analysis: six did not receive trial medication because of either early relapse after remission during the initial 4-week prednisolone treatment, or withdrawn consent, and three were excluded owing to a lack of participant data. Thus, we analyzed data for 246 patients. Median follow-up was 36.7 months in the 2-month group (interquartile range 27.8–46.4 months) and 38.2 months in the 6-month group (interquartile range 28.6–48.5 months). There was no difference in characteristics between the two groups (Table 1).

Primary end point

The primary end point was defined as the duration from start of initial treatment to diagnosis of frequently relapsing nephrotic syndrome (FRNS), or 'time to FRNS'. By the end of the 24-month intervention period, we observed 54 events in the 2-month group (comprising 46 FRNS [definition 1, 28; definition 2, 18], and 8 requiring immunosuppressant administration) and 58 events in the 6-month group

(comprising 45 FRNS [definition 1, 23; definition 2, 22], and 13 requiring immunosuppressant administration). Twenty-one patients required immunosuppressants owing to steroid-dependent or steroid-resistant relapse. Times to FRNS were similar in both groups: however, the median duration of time to FRNS was reached only in the 6-month group (at 799 days). The hazard ratio (HR) was 0.86 (90% confidence interval (CI), 0.64–1.16; Figure 2), and noninferiority of the 2-month group was confirmed significantly, with an HR margin of 1.3 ($P = 0.01$). Post-hoc analyses showed that age groups did not affect the median duration of time to FRNS. The HRs (95% CI) were 0.92 (0.59–1.45), 0.86 (0.41–1.84), and 0.74 (0.31–1.77) for the age groups 1–5 years, 6–10 years, and 11–15 years, respectively.

Secondary end points

Times to first relapse were similar in both groups: the median was 242 days and 243 days in the 2-month and 6-month treatment groups, respectively (HR = 0.97; 95% CI, 0.72–1.31; $P = 0.86$; Figure 3). The number of relapses per person-year during the trial intervention period was 1.25 times in the 2-month group and 1.33 times in the 6-month group, and the ratio was 0.94 (95% CI, 0.71–1.22; $P = 0.65$, Table 2). The median cumulative dose of prednisolone during the 2-year trial period in the 2-month group was also significantly lower than in the 6-month group (4621.9 [interquartile range = 2191.3–7472.5] vs. 6484.8 [interquartile range = 3701.0–9577.9], $P < 0.001$).

Adverse events

Frequency and severity of adverse events were similar in both groups (Table 3). Most adverse events were transient and occurred during initial therapy or relapse therapy. In our study, steroid dependency did not greatly affect the occurrence of adverse events. Two patients in the 2-month group had severe adverse events requiring hospitalization. One patient discontinued because of acute kidney failure during
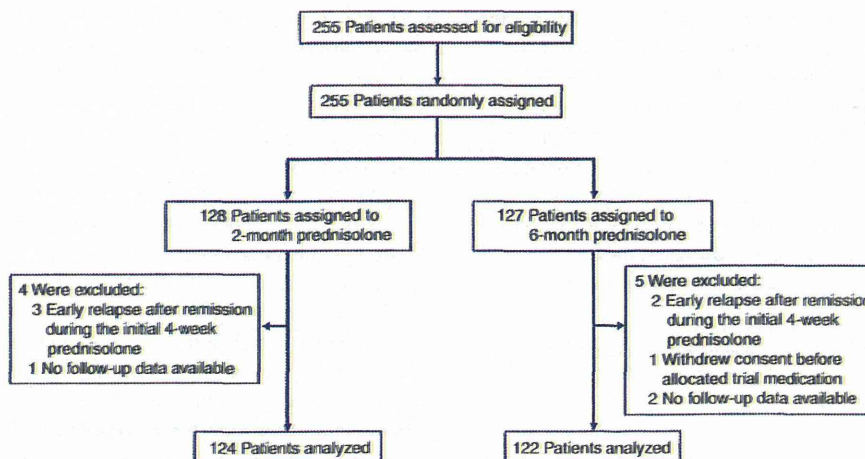

**Figure 1 | Trial profile.**

Table 1 | Baseline characteristics

	2-Month prednisolone (n = 124)	6-Month prednisolone (n = 122)	P-value
Male, n (%)	89 (71.8)	87 (71.3)	0.94
Age, mean (s.d.), years	6.7 (4.1)	6.3 (4.1)	0.42
Age group, years			
1–5, n (%)	67 (54.0)	66 (54.1)	0.99
6–10, n (%)	33 (26.6)	33 (27.1)	
11–15, n (%)	24 (19.4)	23 (18.9)	
Blood pressure, mean (s.d.), mm Hg			
Systolic	104.4 (10.7)	106.4 (12.0)	0.16
Diastolic	62.4 (10.0)	62.5 (11.3)	0.98
Serum albumin, mean (s.d.), g/l	1.4 (0.5)	1.4 (0.5)	0.90
Hospital, n (%)			
General	47 (65.3)	46 (64.8)	1.00
Children's	7 (9.7)	7 (9.9)	
University	18 (25.0)	18 (25.4)	
Quarterly distribution of disease onset, n (%)			
January–March	23 (18.7)	24 (19.7)	0.99
April–June	36 (29.3)	34 (27.9)	
July–September	30 (24.4)	31 (25.4)	
October–December	34 (27.6)	33 (27.0)	
Duration from the first episode to remission, mean (s.d.), days	9.7 (3.1)	10.0 (3.1)	0.45

Abbreviation: s.d., standard deviation.
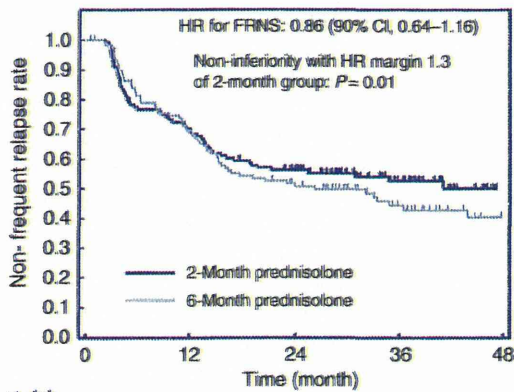
Figure 2 | Kaplan–Meier estimates of time to frequently relapsing nephrotic syndrome (FRNS). HR, hazard ratio.
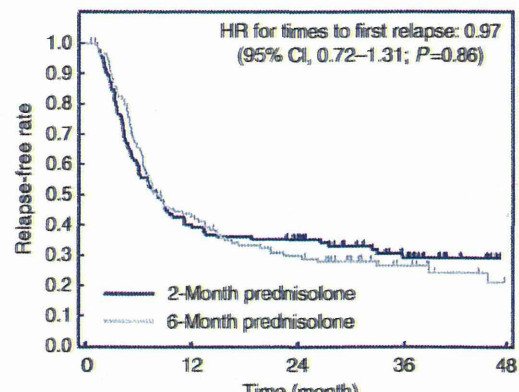
Figure 3 | Kaplan–Meier estimates of time to first relapse. HR, hazard ratio.

relapse (month 10) and recovered in 22 days. Another patient had pneumonia with influenza infection on the last date of the 2-month prednisolone treatment and recovered in 10 days. Height standard deviation scores show a significant decrease in growth at 2 months of follow-up compared with baseline ($P < 0.003$). In both groups, this was restored within 9 months after initial treatment commenced. Notably, one patient in the 6-month group was diagnosed with possible adrenal insufficiency owing to steroid withdrawal according to clinical symptoms (mild headache and mild nausea) when the patient switched to trial medication after the initial dose

of prednisolone. Symptoms disappeared on the same day of onset without further treatment.

DISCUSSION

Extension of initial steroid treatment for more than 3 months to decrease the risk of relapse in children with steroid-sensitive (SS) NS has been widely described in previous studies.[4–10] However, 80–90% of children diagnosed with SSNS who are given new corticosteroid treatments continue to relapse, and ~50% relapse frequently.[11] Therefore, initial approaches to SSNS therapy are likely to be substantially

Table 2 | Number of relapses

	Total number of relapses	Duration of observation (person-year)	The number of relapses (per person-year)	Ratio of the number of relapses (CI)	*P*-value
2-Month prednisolone	301	240.93	1.25	0.94	0.65
6-Month prednisolone	309	232.62	1.33	(0.71–1.22)	

Abbreviation: CI, confidence interval.

Table 3 | Adverse events during the 24-month trial intervention period[a]

Event	2-Month prednisolone *n* = 124	6-Month prednisolone *n* = 122	*P*-value
Hypertension[b]	15	9	0.24
Cushingoid appearance			
Cushing (moon face)[b]	54	61	0.46
Central obesity[b]	20	34	0.052
Striae	1	0	1.00
Adrenal insufficiency	0	1	1.00
Ophthalmological abnormalities			
Glaucoma[b]	19	13	0.31
Cataract	0	0	
Severe infections			
Pneumonia[c]	1	0	1.00
Peptic ulcer	1	0	1.00
Acute kidney failure[c]	1	0	1.00
Hyperglycemia	2	3	0.64
Increased laboratory data			
AST[b]	14	11	0.58
ALT[b]	26	16	0.14
Amylase	3	0	1.00

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase.
[a]Data are expressed as the number of events.
[b]Multiple reports were recorded for these adverse events.
[c]Severe adverse events requiring hospitalization.

different.[12] Our results demonstrate that extending initial steroid treatment, and even increasing the total dose of prednisolone (2240 vs. 3885 mg/m^2), does not improve clinical outcomes (time to FRNS, time to first relapse, the number of relapses, total prednisolone dose, and adverse events) for pediatric NS. Our results add to the Cochrane review by Hodgson *et al.*[8] by comparing treatment regimens of 2 vs. 6 months.

Our findings build on a 2013 study from the Netherlands. This well-designed, randomized, double-blind, placebo-controlled trial of children with NS clearly showed no improvement in clinical outcomes when the initial prednisolone treatment was extended from 3 to 6 months without an increasing cumulative dose.[13] However, despite the results of this trial, the most effective duration and dosage of prednisolone treatment for an initial episode of SSNS is still under debate.[14] Although our study has demonstrated that increasing the total dose in 2-month or 6-month regimens does not improve clinical outcomes, further investigation is still required to determine the most effective duration and dosage regimen for initial SSNS.

A key strength of our trial is its unique design. This is a multicenter, randomized, controlled trial for noninferiority that compares the efficacy of the 2-month ISKDC regimen with a 6-month, long-term prednisolone regimen. The most important clinical objective of initial treatment of SSNS is to prevent frequent relapses. Consequently, the primary end point was set to time to FRNS rather than initial relapses.

Our data from several analyses consistently support noninferiority of the ISKDC regimen. In the current trial, a HR threshold of 1.3 for noninferiority of the primary end point is slightly high given the feasible study size. However, the posterior probability that a HR would be smaller than 1.1 and 1.2 (HRs that are commonly used as an upper equivalence margin) was 91 and 97%, respectively.

In our trial, noninferiority was found in FRNS (primary end point) and first relapse (secondary end point) between the ISKDC and 6-month regimens. This means that many patients relapse even while taking tapering-dose prednisolone (Figure 3). Previous studies vary in their observation of (frequent) relapses from either the start or end of initial therapy.[8,13] However, if analyses are performed from the end of initial therapy, relapses during tapering-dose prednisolone cannot be counted, possibly resulting in an inadequate interpretation. Therefore, we selected observations primarily from the start of initial therapy. In our study design, steroid-dependent NS was predicted to occur more frequently because of its definition in the 6-month regimen. This is one reason why we selected FRNS as a primary end point, and not steroid-dependent NS. In fact, time to steroid-dependent NS was significantly higher in the ISKDC regimen group (data not shown).

No significant difference in adverse events was observed between the two regimens in our large-scale trial, which is a similar finding to previous small-scale trials.[4–7] Most adverse events were transient and occurred during initial or relapse therapy. However, because the ISKDC regimen is generally less likely to cause adverse events owing to the lower dosage and the shorter duration, its use can be recommended.

A limitation of our trial is the open-label design, which may have introduced preconception bias. However, as our trial design is a noninferiority trial with regular visits, and relapses are measured objectively, we cannot assume positive placebo effects. Therefore, the open-label design of this study may have limited impact on preconception bias. Moreover, the results of this trial may partially be due to the relatively high rate of relapse compared with other studies.[5] The high

rate of relapse may be owing to our definition of relapse (proteinuria 2+ or higher). It still remains unknown whether long prednisolone therapy consisting of a dose of 60 mg/m^2 per day for 6 weeks, followed by alternate-day doses of 40 mg/m^2 per 2 days for 6 weeks, is more effective against time to FRNS compared with the ISKDC regimen for treating idiopathic NS. In our study, only one patient withdrew consent. A low rate of consent withdrawal is common in Japan.[15,16] Cultural differences between countries may account for variations in rates of consent withdrawal.

In our study, steroid sensitivity was confirmed by day 21 in order to ensure time for eligibility screening. Generally, remission after 3 weeks is uncommon.[17] Therefore, as the effect of early confirmation of steroid sensitivity was slight, we decided to confirm steroid sensitivity by day 21.

We conducted a meta-analysis to address the differences between corticosteroid regimens in children with an initial episode of SSNS. We searched randomized controlled trials that compared durations of steroid therapy in children and reported the number of FRNS cases within 2 years (see the Supplementary Information online for a detailed search strategy). Meta-analysis of our study and five studies[6,13,18,19] showed a risk ratio (long vs short) of 0.99 (95% CI, 0.68–1.44, see Supplementary Figure 2A online), whereas meta-analysis of our study and the published studies only showed an risk ratio of 1.15 (95% CI: 0.95–1.40, Supplementary Figure 2B online). This result might indicate that long-term treatment is not superior but almost equivalent to ISKDC-standard therapy.

In conclusion, our study shows that extending initial prednisolone treatment from 2 to 6 months with an increasing dose does not improve clinical outcomes for pediatric NS. The original ISKDC regimen is not inferior to 6 months of initial therapy with an increasing cumulative dose. We assert that the ISKDC regimen is recommended as an initial treatment for pediatric idiopathic NS.

MATERIALS AND METHODS
Study design and patients
We conducted a multicenter, randomized, noninferiority, open-label trial at 90 hospitals in Japan and compared prednisolone treatment of 2 months (ISKDC regimen) with 6 months for children with a first episode of idiopathic NS. We diagnosed idiopathic NS and remission according to the ISKDC.[1] NS was defined as a urinary protein–creatinine ratio ⩾1.8 and albumin levels ⩽25 g/l in serum. Remission was defined as a negative dipstick analysis for 3 consecutive days. Patients aged 1–15 years with a first episode of idiopathic NS were eligible if they had remission within 3 weeks of prednisolone administration. Patients were ineligible if they had secondary NS, renal insufficiency defined as creatinine clearance of ⩽60 ml/min per 1.73 m^2, active infections, poorly controlled hypertension, severe liver dysfunction, pregnancy, or a history of immunosuppressant administration.

Before enrollment, patients' guardians provided written informed consent, and informed assent was obtained from older children. This study was approved by the institutional review boards of participating hospitals, complied with the Declaration of Helsinki

and the Declaration of Istanbul, and adhered to the International Conference on Harmonisation Guidelines on Good Clinical Practice.

Randomization
Patients were randomly assigned to either the 2-month or 6-month group in a 1:1 ratio at the Japan Clinical Research Support Unit. We applied a minimization method using a computer-generated sequence (SAS PROC PLAN) with age (1–10 years or 11–15 years), sex, and institution as adjustment (stratification) factors. Patients, patients' guardians, treating physicians, and individuals assessing outcomes and analyzing data were not blinded to the patients' treatment assignments. Apart from the trial statistician and the data-monitoring committee, all treating physicians and other investigators remained blinded to the trial results until follow-up was completed.

Procedures
The first patient was randomized in September 2007, and the last patient in January 2011. Follow-up started at diagnosis and was truncated when the last enrolled patients finished the 24-month intervention.

All patients diagnosed with a first episode of idiopathic NS started initial therapy of 60 mg/m^2 oral prednisolone in three divided doses (maximum of 80 mg/day) daily for 4 weeks. Patients underwent a screening examination and were registered after their eligibility, including remission, was verified. Participants switched to trial medication after initial doses of prednisolone were given (Figure 4). If participants relapsed after remission during the initial 4-week prednisolone treatment, they were excluded.

Trial medication consisted of initial treatment regimens and relapse treatment, and was completed within a total of 24 months in both groups (Figures 4 and 5). The duration of long-term prednisolone treatment was set to 6 months, which is consistent with recommendations from a non-Japanese randomized controlled trial.[8] The cumulative dose of initial treatment was 2240 mg/m^2 (2-month group) and 3885 mg/m^2 (6-month group). Participants
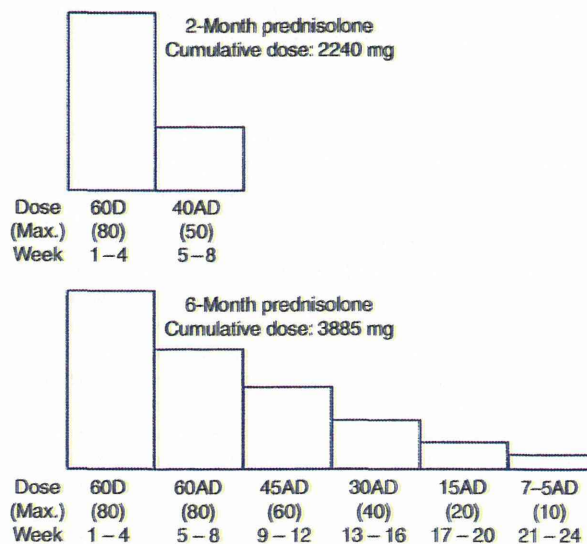
Figure 4 | Initial treatment regimens. Upper doses are in mg/m^2 per day. Maximum doses are in mg/day. D, daily; AD, alternate days.
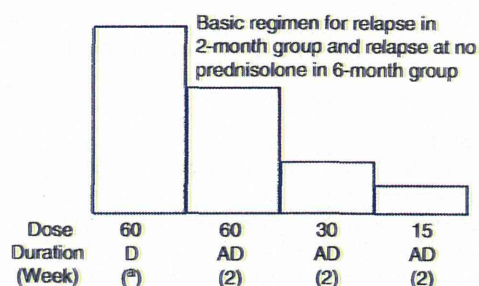
Figure 5 | Treatment regimens for relapse. [a]Until urinary protein is negative on 3 consecutive days using a urine dipstick test. Upper doses are in $mg/m^2/day$. A maximum dose of each is the same as initial treatments in Figure 4. AD, alternate days; D, daily.

who relapsed during the 24-month trial medication period received relapse treatment regimens (Figure 5). Relapse treatment was the same in both groups. However, relapse treatment given during the 6-month initial treatment was adjusted according to the initial treatment regimen in the 6-month group.

Participant characteristics (age, sex, physical characteristics, blood, and urine test results) were recorded at baseline. Clinical assessment and urine tests (urinalysis, qualitative and quantitative proteinuria, quantitative creatinine) were performed at 1, 2, 4, and 6 months after enrollment and every 3 months thereafter, and also on diagnosis of relapse. Blood analysis (complete blood cell count, blood chemistry) was performed at 1, 2, 6, and 12 months after enrollment, at the end of treatment, and at diagnosis of relapse only.

Adverse events were recorded throughout the trial period and assessed using Common Terminology Criteria for Adverse Events v3.0. Within 4 weeks of starting initial treatment, participants were screened for glaucoma by an ophthalmologist. Details about monitoring adverse events are described in the Supplementary Information online. Briefly, name of diagnosis, severity, seriousness, date of onset and disappearance, outcome, and assessment of causal relationship to the study drug were investigated at the start of study treatment and at 1, 2, 4, 6, 9, 12, 15, 18, 21, and 24 months after the start of study treatment (each within ± 2 weeks).

Outcomes

The primary end point was defined as the duration from start of initial treatment to diagnosis of FRNS, or 'time to FRNS'. Diagnosis of FRNS was based on the relapse dates according to the ISKDC. In our study, FRNS was defined as two relapses within 6 months of initial remission (definition 1), or four relapses within any 12-month period (definition 2), which included relapses during initial tapering treatment but excluded relapses with spontaneous remissions. Patients were observed for at least 2 years, on the basis of the Cochrane review, which states that the risk of relapse after 1–2 years was lower after long-term prednisolone treatment relative to the ISKDC regimen.[8] Relapse was defined as proteinuria 2 + or higher on dipstick analysis for 3 or more consecutive days or proteinuria 2 + or higher on dipstick analysis and serum albumin ⩽ 25 g/l. Immunosuppressant administration was prohibited in the protocol. However, if administration was undertaken for clinical necessity, e.g., steroid dependency, it was treated as an event in the primary analysis. Data for patients who did not experience these events were considered censored at the last examination. Important

secondary end points were time to first relapse, the number of relapses per person-year, total prednisolone dose, and adverse events.

Statistical analyses

The primary objective of this trial was to confirm noninferiority of initial therapy with 2-month treatment compared with 6-month treatment, with respect to time to FRNS. The noninferiority margin of HR for the 2-month to 6-month group was predefined to 1.3, and the significance level was set to 5% (one-sided). The former was determined based on surveys conducted among practicing pediatric nephrologists and other specialists before the protocol was developed.

On the basis of results from a previous study,[20] we assumed an event rate of 15 and 19% at 1 year in the 2- and 6-month groups, respectively. With a sample size of 125 patients in each treatment group, an HR test with a one-sided 5% significance level would have 70% power to confirm noninferiority. Accrual and follow-up times were specified to be 3 and 2 years, respectively.

As the previous study[20] was conducted more than 10 years earlier, it is possible that the current event rate of our study is lower than the previous study. We scheduled an interim analysis to take place just before the accrual completion date, which was performed in October 2010. A statistical test regarding the primary end point was not performed. The number of events observed matched that of the assumption, and the study plan was not changed.

Statistical analyses followed the protocol and the intention-to-treat principle. The Cox proportional hazard model was used to test noninferiority and estimate the HR with a 90% CI of the primary end point. The Kaplan–Meier method was used to summarize time to FRNS. These methods and the log-rank test were used to analyze time to first relapse. The number of relapses per person-year was calculated as the total number of relapses divided by the total observed person-years in each treatment group (Table 2). A permutation test was used to compare the number of relapses per person-year between groups. We compared the prednisolone total dose using the Wilcoxon test. The number of adverse events was compared using Poisson regression. For baseline characteristics, we compared distributions of continuous variables between groups using the t-test or Wilcoxon test, depending on the shape of the distribution. We analyzed categorical variables using the chi-squared test or Fisher's exact test. Posterior probability was calculated with the improper flat prior and the normal distribution to which log-HR was approximated. Except for noninferiority testing of the primary end point, we regarded a two-sided P-value < 0.05 to indicate statistical significance. We analyzed data using SAS software (version 9.3) and calculated the sample size using the SAS POWER procedure.

SUPPLEMENTARY MATERIAL
Figure S2. (A) Meta-analysis of studies comparing 2–3 months of prednisolone to 5–6 months of prednisolone for children with their first episode of nephrotic syndrome, with an outcome showing the number of children with frequent relapses after 1–2 years. (B) Sensitivity analysis excluding Sharma 2002 (unpublished conference proceeding) from Fig. A.
Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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APPENDIX
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