

Ⅲ. 研究成果の刊行に関する一覧表

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書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
王子野麻代	新たな難病対策の概説	王子野麻代	日医総研ワーキングペーパーNo.344 新たな難病対策の概説第2版-平成27年7月 第二次指定難病の施行を受けた改訂-	日本医師会	日本	2015	68

雑誌

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Igarashi T et.al	A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment	Kidney International	87	225-232	2015
Igarashi T et.al	End-stage renal disease in Japanese children: a nationwide survey during 2006-2011	Clin Exp Nephrol	19	933-938	2015
Igarashi T et.al	Post-traumatic stress disorder in children following natural disasters: a systematic review of the long-term follow-up studies	Int J Child Youth Family Studies	6(1)	111-133	2015
Igarashi T et.al	Integrated genetic and epigenetic analysis defines novel molecular subgroups in rhabdomyosarcoma	Nature Communications	6	1-8	2015
Mizusawa H et.al	Clinical, biochemical and molecular investigation of adult-onset glutaric acidemia type II: Characteristics in comparison with pediatric cases	Brain & Development	38	293-301	2016
水澤英博、川田裕美	新しい難病制度を知る	内科	12	1248-1255	2015

Kanakura Y et.al	Two consecutive pregnancies in a patient with paroxysmal nocturnal haemoglobinuria treated with anticoagulant therapy at different doses	Blood Coagulation and Fibrinolysis	27(1)	109-112	2016
Kanakura Y et.al	Pregnancy outcomes of patients with paroxysmal nocturnal hemoglobinuria treated with eculizumab: a Japanese experience and updated review	Int J Hematology	DOI 10.1007/s12185-016-1946-x		2016(Published online)
Kanakura Y et.al	Efficacy and safety of rituximab in Japanese patients with relapsed chronic immune thrombocytopenia refractory to conventional therapy	Int J Hematology	102	654-661	2015
Kanakura Y et.al	Clinical significance of IPF% or RP% measurement in distinguishing primary immune thrombocytopenia from aplastic thrombocytopenic disorders	Int J Hematology	101	369-375	2015
西村純一、金倉讓	PNH患者におけるC5遺伝子多型	臨床血液	56	103-110	2015

IV. 研究成果の刊行物・別刷

End-stage renal disease in Japanese children: a nationwide survey during 2006–2011

Motoshi Hattori · Mayumi Sako · Tetsuji Kaneko · Akira Ashida · Akira Matsunaga · Tohru Igarashi · Noritomo Itami · Toshiyuki Ohta · Yoshimitsu Gotoh · Kenichi Satomura · Masataka Honda · Takashi Igarashi

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Abstract

Background End-stage renal disease (ESRD) in children is considered a rare, but serious condition. Epidemiological and demographic information on pediatric ESRD patients around the world is important to better understand this disease and to improve patient care. The Japanese Society for Pediatric Nephrology (JSPN) reported epidemiological and demographic data in 1998. Since then, however, there has been no nationwide survey on Japanese children with ESRD.

Methods The JSPN conducted a cross-sectional nationwide survey in 2012 to update information on the inci-

dence, primary renal disease, initial treatment modalities, and survival in pediatric Japanese patients with ESRD aged less than 20 years during the period 2006–2011.

Results The average incidence of ESRD was 4.0 per million age-related population. Congenital anomalies of the kidney and urinary tract were the most common cause of ESRD, present in 39.8 % of these patients. In addition, 12.2 % had focal segmental glomerulosclerosis and 5.9 % had glomerulonephritis. Initial treatment modalities in patients who commenced renal replacement therapy (RRT) consisted of peritoneal dialysis, hemodialysis, and preemptive transplantation (Tx) in 61.7, 16.0, and 22.3 %, respectively. The Japanese RRT mortality rate was 18.2 deaths per 1000 person-years of observation.

On behalf of the Japanese Society for Pediatric Nephrology.

M. Hattori (✉)

Department of Pediatric Nephrology, School of Medicine, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan
e-mail: hattori@kc.twmu.ac.jp

M. Sako

Division for Clinical Trials, Department of Development Strategy, Center for Social and Clinical Research, National Center for Child Health and Development, Tokyo, Japan

T. Kaneko

Division of Clinical Research Support Center, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan

A. Ashida

Department of Pediatrics, Osaka Medical College, Osaka, Japan

A. Matsunaga

Matsunaga Kids Clinic, Yamagata, Japan

T. Igarashi

Department of Pediatrics, Nippon Medical University, Tokyo, Japan

N. Itami

Kidney Center, Nikko Memorial Hospital, Hokkaido, Japan

T. Ohta

Department of Pediatric Nephrology, Hiroshima Prefectural Hospital, Hiroshima, Japan

Y. Gotoh

Department of Pediatrics, Nagoya Daini Red Cross Hospital, Aichi, Japan

K. Satomura

Department of Pediatric Nephrology and Metabolism, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan

M. Honda

Department of Nephrology, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan

T. Igarashi

National Center for Child Health and Development, Tokyo, Japan

Conclusion The incidence of ESRD is lower in Japanese children than in children of other high-income countries. Since 1998, notably, there has been a marked increase in pre-emptive Tx as an initial treatment modality for Japanese children with ESRD.

Keywords End-stage renal disease · Children · Epidemiology · Renal replacement therapy · Japan

Introduction

End-stage renal disease (ESRD) in children is considered a rare, but serious condition [1]. Information on the epidemiology, demographics, treatment modalities, and mortality of pediatric patients with ESRD are essential for a better understanding of this disease and for improving patient care [2]. This information is also useful for patients, their families, physicians, and other healthcare providers. The epidemiology and demographics of pediatric ESRD have been analyzed in the USA [3, 4], Europe [5–8], and Australia and New Zealand [9, 10]. However, limited information is available on pediatric ESRD patients in other areas of the world.

The Japanese Society for Pediatric Nephrology (JSPN) reported epidemiological and demographic data on Japanese children with ESRD in 1998 [11]. Since then, however, there has been no nationwide survey on Japanese children with ESRD. International comparisons of the epidemiological and demographic characteristics of pediatric ESRD patients may improve outcomes [12, 13]. Therefore, the JSPN ESRD Survey Committee, in collaboration with the Japanese Society for Dialysis Therapy (JSDT) and the Japanese Society for Clinical Renal Transplantation (JSCRT), conducted a nationwide survey of Japanese children with ESRD in 2012. This report describes the basic epidemiological and demographic characteristics of Japanese children aged less than 20 years with ESRD over the period 2006–2011.

Patients and methods

Data collection

The JSPN conducted a cross-sectional nationwide survey in 2012, in collaboration with the JSDT and the JSCRT.

ESRD patients were defined as those with irreversible kidney function disorders requiring renal replacement therapy (RRT) to sustain life. This survey evaluated Japanese patients aged less than 20 years who were newly diagnosed with ESRD between January 1, 2006, and December 31, 2011, and who were followed up until

December 31, 2011. Individual patient data included date of birth, gender, primary renal disease, date of starting RRT, treatment modality at the start of RRT, and important events such as death.

Questionnaires were collected in two steps. The first questionnaires, asking about patients newly diagnosed with ESRD, were sent to institutions at which members of the JSPN, JSDT, and JSCRT practiced, as well as to children's hospitals, and pediatric and nephrology departments of medical schools throughout Japan. The second questionnaires, which asked for data about individual patients, were sent to the institutions that reported having new pediatric ESRD patients.

This survey was in accordance with the ethical principles in the 1964 Declaration of Helsinki, and with the ethical guidelines for epidemiological studies issued by the Ministry of Health, Labour and Welfare, Japan. This survey was also approved by the central ethics board of Tokyo Women's Medical University (approval number; 2353) before study commencement.

Data analysis

The incidence of ESRD was defined as the number of new patients with ESRD per year, over the period 2006–2011, and was expressed as number per million age-related population (pmarp), with pmarp calculated using age-, sex-, and year-specific census data obtained from the Japanese data base [14].

Patient survival was analyzed by the Kaplan–Meier life table method. Mortality rates (deaths per 1000 person-years of observation) were also calculated. Data were analyzed using SAS system version 9 (SAS Institute, Cary, NC, USA).

Results

Patients with ESRD

The first questionnaires were sent to a total of 773 institutions, with 770 (99.6 %) responding; of these, 146 institutions had new pediatric ESRD patients during the period 2006–2011. The second questionnaires were therefore sent to these 146 institutions, with 136 (93.2 %) responding. These institutions reported a total of 540 new pediatric ESRD patients, including 322 male patients, 216 female patients and two patients not specified.

Incidence of ESRD

The per-year incidence of ESRD in the years 2006–2011 was 3.5, 3.9, 3.6, 4.7, 4.1, and 4.1 pmarp, respectively.

Table 1 Primary renal diseases of ESRD patients included in this survey

Renal diseases	Number of patients (%)					
	Male/female/unknown					
	0–4 years	5–9 years	10–14 years	15–19 years	0–19 years	
CAKUT	68 (43.0) 39/29/0	45 (45.0) 33/12/0	66 (40.2) 46/19/1	36 (30.5) 29/7/0	215 (39.8) 164/67/1	
Hereditary nephropathy	30 (19.0) 12/18/0	7 (7.0) 3/4/0	17 (10.4) 13/3/1	16 (13.6) 11/5/0	70 (12.9) 39/30/1	
FSGS	6 (3.8) 3/3/0	16 (16.0) 11/5/0	25 (15.2) 14/11/0	19 (16.1) 14/5/0	66 (12.2) 42/24/0	
Cystic kidney disease	17 (10.8) 6/11/0	10 (10.0) 5/5/0	19 (11.6) 8/11/0	6 (5.1) 2/4/0	52 (9.6) 21/31/0	
Hereditary nephropathy includes Alport's syndrome, congenital nephrotic syndrome, and other specified types.	Glomerulonephritis	0 (0) 0/0/0	6 (6.0) 1/5/0	10 (6.1) 6/4/0	16 (13.6) 2/4/0	32 (5.9) 19/13/0
Glomerulonephritis (GN) includes IgA nephropathy, membranoproliferative GN, membranous nephropathy, crescentic GN, and other types of GN. Cystic kidney disease includes polycystic kidney disease, nephronophthisis, and other specified types	HUS	4 (2.5) 1/3/0	1 (1.0) 0/1/0	2 (1.2) 1/1/0	2 (1.7) 0/2/0	9 (1.7) 2/7/0
CAKUT congenital anomalies of the kidney and urinary tract, FSGS focal segmental glomerulosclerosis, HUS hemolytic uremic syndrome	Ischemic renal failure	5 (3.2) 1/4/0	4 (4.0) 1/3/0	0 (0) 0/0/0	0 (0) 0/0/0	9 (1.7) 2/7/0
	Miscellaneous	20 (12.6) 11/9/0	7 (7.0) 6/1/0	12 (7.3) 6/6/0	8 (6.8) 4/4/0	47 (8.7) 27/20/0
	Unknown	0 (0) 0/0/0	4 (4.0) 2/2/0	6 (3.7) 3/3/0	8 (6.8) 5/3/0	18 (3.3) 10/8/0
	Missing	8 (5.1) 4/4/0	0 (0) 0/0/0	7 (4.3) 5/2/0	7 (5.8) 4/3/0	22 (4.2) 13/9/0
	Total	158 (100) 77/81/0	100 (100) 62/38/0	164 (100) 102/60/2	118 (100) 81/37/0	540 (100) 322/216/2

The average incidence of ESRD over the 6-year period was 4.0 pmarp.

Primary renal disease in patients with ESRD

Primary renal diseases, categorized according to the European Renal Association and European Dialysis and Transplantation Association (ERA-EDTA) codes [5], with a minor modification, in the 540 pediatric ESRD patients evaluated in this survey are shown in Table 1. The most frequent primary renal disease was congenital anomalies of the kidney and urinary tract (CAKUT), including hypoplasia/dysplasia ± reflux nephropathy and obstructive uropathy, present in 39.8 % of these patients, followed by hereditary nephropathy (12.9 %), focal segmental glomerulosclerosis (FSGS; 12.2 %) and cystic kidney disease (9.6 %). Glomerulonephritis was observed in 5.9 % of these patients. CAKUT were the main causes of ESRD across all age groups and were more common in males than in females. Hereditary nephropathies including congenital nephrotic syndrome and Alport's syndrome were common in the youngest ESRD group and the adolescent ESRD group. FSGS and glomerulonephritis were less common in children aged less than 5 years as causes of ESRD. Cystic kidney disease caused 5–11 % of ESRD across all age group.

Initial treatment modalities of ESRD

Of the 540 patients newly diagnosed as having ESRD, six did not commence RRT because of their severe extra-renal comorbidities. In addition, RRT was not identified in four patients. Of the remaining 530 patients, 327 (61.7 %) were treated initially by peritoneal dialysis (PD), 85 (16.0 %) underwent hemodialysis, and 118 (22.3 %) underwent pre-emptive transplantation (Tx). The initial treatments by age group are shown in Fig. 1. Most children aged less than 5 years were treated initially by PD (89.0 %), with a small proportion undergoing pre-emptive Tx (2.6 %). In contrast, pre-emptive Tx was performed in 32.7, 29.2, and 30.2 % of children aged 5–9, 10–14, and 15–19 years, respectively. A comparison of initial treatment modalities in surveys of pediatric ESRD patients in 1998 [11] and 2006–2011 showed that the proportion of patients undergoing pre-emptive Tx markedly increased with time (Fig. 2).

Survival and cause of death

Survival analysis of the 530 patients who commenced RRT is shown in Fig. 3. The 1- and 5-year survival rates were 96.9 and 91.5 %, respectively. Patients were

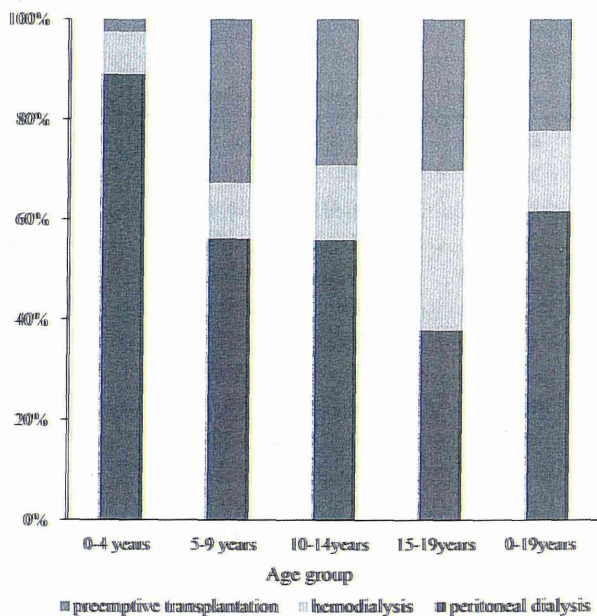


Fig. 1 Initial treatment modalities of end-stage renal disease by age group

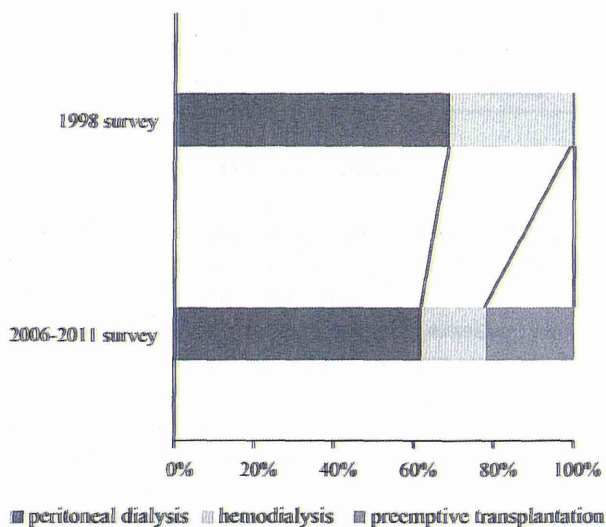


Fig. 2 Comparison of initial treatment modalities in Japanese patients with end-stage renal disease (ESRD) surveyed in 1998 [11] and in 2006–2011

followed up for a median 2.7 years (interquartile range 1.3–4.3 years). The mortality rate was 18.2 deaths per 1000 person-years of observation. During follow-up, 28 patients (5.4 %) died, all of whom were undergoing dialysis. Causes of death after the start of RRT, based on the United States Renal Data System [15] with a minor modification, are shown in Table 2. The main causes of death were infection ($n = 11$, 39.3 %) and cardiovascular causes ($n = 5$, 17.9 %).

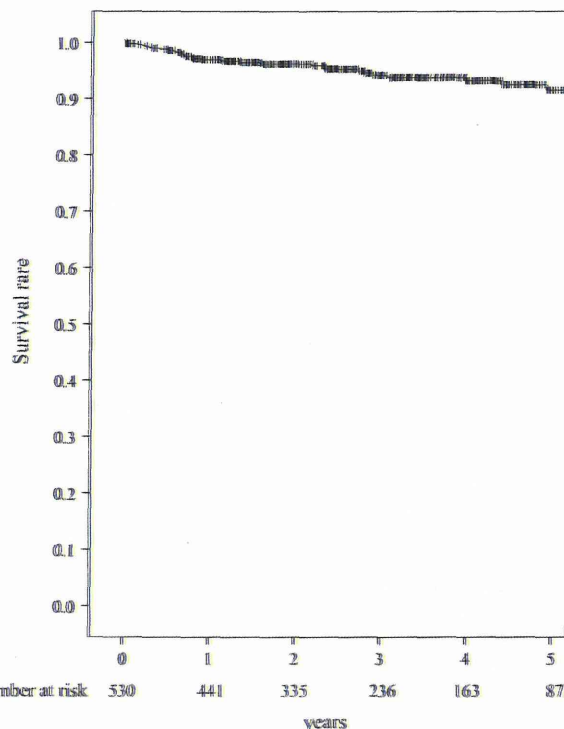


Fig. 3 Patient survival after the start of renal replacement therapy

Table 2 Causes of death after the start of renal replacement therapy

Renal diseases	Number of patients (%)
Infections	11 (39.3)
Cardiovascular	5 (17.9)
Cerebrovascular	0 (0)
Malignancy	0 (0)
Metabolic	0 (0)
Other	6 (21.4)
Unknown	4 (14.2)
Missing	2 (7.2)
Total	28 (100)

Discussion

The JSPN has updated the epidemiological and demographic information on the incidence, primary renal disease, initial treatment modalities, and survival in Japanese pediatric ESRD patients, aged less than 20 years, over the period 2006–2011. However, some important information, including the prevalence and probability of undergoing Tx, could not be updated in this survey.

There are marked variations in the incidence of pediatric ESRD across countries [13]. A previous survey by the JSPN, performed in 1998, reported that the incidence of ESRD in Japanese children aged less than 20 years was 4.0

pmarp [11], much lower than in other high-income countries, including 9.5 pmarp in 11 Western European countries and in Australia and 15.5 pmarp in the USA [13], despite Japan having one of the highest incidence rates of ESRD in adults [13, 16]. The current survey showed that the average incidence of ESRD in 2006–2011 was 4.0 pmarp, confirming the lower incidence of ESRD in Japanese children. Because the reasons for this lower incidence remain unclear [16], further research is needed to determine the specific factors responsible for the lower rate of ESRD in Japanese children.

Causes of ESRD also vary across races and countries. FSGS is more common in blacks than in whites, genetic diseases are more prevalent in the Middle East than in Europe, and infection-related renal diseases are more frequent in less-developed countries [12, 13]. In the USA, Europe, and Australia and New Zealand, CAKUT are the main cause, accounting for around 40 % of pediatric ESRD patients [13]. The current Japanese survey showed that CAKUT were also the most common cause of renal disease, accounting for 39.8 % of all pediatric Japanese ESRD patients. In contrast, it has been indicated that the proportion of pediatric ESRD caused by glomerulonephritis, including FSGS, was higher in Japan than in Europe or the USA [12, 13]. The 1998 Japanese survey reported that the proportions of pediatric ESRD patients with FSGS and glomerulonephritis were 21.0 and 13.3 %, respectively [11], whereas the current survey showed that these proportions were much lower, 12.2 and 5.9 %, respectively. The Australia and New Zealand Dialysis and Transplant Registry also showed a decline over time in glomerulonephritis as a cause of ESRD [10]. Additional surveys are needed to confirm this trend in the etiology of ESRD in Japanese children.

The initiation of RRT is highly dependent upon the economy and availability of healthcare resources [12, 17]. In countries where RRT is readily available, the most favored renal replacement modality in children is Tx because dialysis is associated with cardiovascular damage, access complications, infection, retarded linear growth and cognitive development in children [12]. Pre-emptive Tx is an especially attractive option for children with ESRD because pre-emptive Tx potentially avoids exposure to negative outcomes associated with dialysis [18]. While the previous Japanese survey in 1998 reported that only one patient (0.9 %) underwent pre-emptive Tx [11], this survey notably found that 22.3 % of patients were initially treated by pre-emptive Tx. In the USA, Europe, and Australia and New Zealand, around 15–20 % of children newly diagnosed with ESRD undergo pre-emptive Tx [13]. Thus, the use of pre-emptive Tx as an initial treatment modality for Japanese children with ESRD is comparable to that of

USA, Europe, and Australia and New Zealand. The evolved immunosuppression protocols using calcineurin inhibitors, mycophenolate mofetil and basiliximab reduced acute rejection episodes and improved the patient and graft survival [19]. The improved treatment following Tx and the increased awareness of effectiveness of pre-emptive Tx seem to be responsible for the marked increase in pediatric pre-emptive Tx in Japan.

The 5-year survival rate of Japanese children with ESRD who received RRT was 91.5 %, which was similar to that reported from Europe (the 4-year survival rate was 92.9 % in European RRT children) [8]. The mortality rate of 18.2 deaths per 1000 person-years of observation was similar to that observed in the 1998 survey [11] and in pediatric ESRD patients in Australia and New Zealand [9]. The two main causes of death in Japanese ESRD patients receiving RRT were infections and cardiovascular disease, similar to findings in Western countries [12, 13]. Superior survival has been reported in patients with a functioning graft than in patients on dialysis, with the poorest survival rates observed in infants with ESRD [13]. Further studies are required to determine risk factors for mortality in Japanese pediatric ESRD patients.

Finally, epidemiological and demographic information on pediatric ESRD patients around the world is important to better understand this disease and to improve patient care. Because single country data may be underpowered to draw meaningful insights, international collaborations are required to improve the outcomes of children with ESRD [20, 21].

In conclusion, this survey of epidemiological and demographic information on Japanese children aged less than 20 years with ESRD over the period 2006–2011 confirmed that the incidence of ESRD is lower in Japan than in other high-income countries. Notably, there has been a marked increase in the use of pre-emptive Tx as the initial treatment modality for these patients.

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Conflict of interest The authors have declared that no conflict of interest exists.

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**POST-TRAUMATIC STRESS DISORDER IN CHILDREN
FOLLOWING NATURAL DISASTERS: A SYSTEMATIC REVIEW OF
THE LONG-TERM FOLLOW-UP STUDIES**

Akiko Terasaka, Yoshiyuki Tachibana, Makiko Okuyama, and Takashi Igarashi

Abstract: The objective of this article was to conduct a systematic review of long-term follow-up studies on Post-traumatic Stress Disorder (PTSD) symptoms in children and adolescents. The MEDLINE and PsycINFO databases were searched from 1980 through January 2014. Studies that examined PTSD symptoms in children for over three years after mass natural disasters were selected. Ten studies, including four cohort studies, four cross-sectional studies, one descriptive study, and one case-series study following disaster-exposed children, met all the selection criteria and thus were included in this review. The follow-up period ranged from three to 20 years after the disasters. Synthesized results regarding PTSD prevalence rate, changes over time, and influential factors on PTSD were summarized and discussed. The reviewed studies indicated that PTSD symptoms decrease rapidly during the first two years after a disaster; however, the long-term course is not yet clear. Several factors including gender and disaster experience appeared to be influential on PTSD symptoms; however, gender effect was possibly confounded by other factors. To examine moderating effects among those influential factors, as well as to avoid confounding, multivariate analytical methods would be beneficial and recommended in future research. Also, recovery patterns await further investigation for better understanding of the factors associated with chronic PTSD.

Keywords: natural disasters, PTSD, child, long-term, follow-up

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Akiko Terasaka (the corresponding author) is a post-doctoral fellow at the Division of Maternal-Child Psychiatry, Department of Psychosocial Medicine, National Medical Center for Children and Mothers, 2-10-1 Okura, Setagaya-ku, Tokyo, Japan, 157-8535.

E-mail: teakiko@gmail.com

Yoshiyuki Tachibana is Chief of the Division of Maternal-Child Psychiatry, Department of Psychosocial Medicine, National Medical Center for Children and Mothers, 2-10-1 Okura,

Setagaya-ku, Tokyo, Japan, 157-8535. E-mail: tachibana-y@ncchd.go.jp

Makiko Okuyama is the Department Head of Psychosocial Medicine, National Medical Center for Children and Mothers, 2-10-1 Okura, Setagaya-ku, Tokyo, Japan, 157-8535. E-mail:

okuyama-m@ncchd.go.jp

Takashi Igarashi is the President of the National Medical Center for Children and Mothers, 2-10-1 Okura, Setagaya-ku, Tokyo, Japan, 157-8535. E-mail: igarashi-t@ncchd.go.jp

According to *Annual Disaster Statistical Review 2012* (Guha-Sapir, Hoyois, & Below, 2013), 107,000 people were killed and 268 million were affected by natural disasters on annual average between 2002 and 2011. There are 25 natural disasters reported that produced more than 50,000 deaths between 1990 and 2011 in the EM-DAT database (www.emdat.be/database) (Lindell, 2013). Mass natural disaster can be especially traumatic to children. Many of the children who survived mass natural disasters, such as Southeast Asia Tsunami in 2004, Hurricane Katrina in 2005, and Great East Japan Earthquake and Tsunami in 2011, lost family members, friends, neighbors, houses and schools. Furthermore, disaster aftermath could usually last for months or even years. These negative impacts of disasters may create secondary stress and substantially interfere with the availability of support to the child from parents, family, school, and community (Pynoos, Steinberg, & Piacentini, 1999), thus disturbing children's recovery.

A set of psychological post-traumatic symptoms such as re-experiencing, avoidance, and hyperarousal, which last more than a month after the traumatic event, is known as Post-traumatic Stress Disorder (PTSD). PTSD has received a great deal of attention for the last several decades since the diagnosis was introduced in *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM-III) in 1980. Although the criteria for PTSD were originally developed based on the knowledge from adult samples, several age-related symptoms were added in the subsequent versions (DSM-III-R, DSM-IV, and DSM-V). There have been several comprehensive reviews of post-disaster research in children (e.g., Foy, Madvig, Pynoos, & Camilleri, 1996; Pfefferbaum, 1997; Vogel & Venberg, 1993). In recent years, Hoven, Duarte, Turner, and Mandell (2009) performed a systematic search, and reported 18 selected studies that included more than 100 participants, with first assessment of post-traumatic reactions conducted within a year after the disaster, and employed some type of randomization approach. Wang, Chan, and Ho (2013) identified 60 cross-sectional and 25 longitudinal/long-term follow-up studies of post-disaster research on child psychopathology including PTSD. Additionally, Furr, Corner, Edmunds, and Kendall (2010) conducted a systematic review and meta-analytic examination of 96 identified youth PTSD studies following natural and human-made disasters. These reviews indicated that children show symptoms most in the first year post-disaster, and the symptoms mostly decrease rapidly (Furr et al., 2010; Wang et al., 2013) by nine to 14 months post-disaster (Vogel & Venberg, 1993). However, the long-term course of PTSD is not yet well known since the majority of the identified studies were conducted during the first two years post-disaster. Although most of the children may recover shortly after, there seem to be several pathways of recovery, and PTSD symptoms persist longer for some of the children (Masten & Obradovic, 2008). Moreover, there are not enough longitudinal data that enable us to understand risk and protecting factors for chronic PTSD. As these authors suggested, there is a great need for long-term follow-up studies of PTSD in children and adolescents.

In this article, we focus on studies that investigated post-traumatic symptoms in children over a three-year period after they had experienced mass natural disasters so that we could learn more about the long-term course of PTSD in children and adolescents. We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement

(Moher, Liberati, Tetzlaff, & Altman, 2009), which consists of a 27-item checklist to help authors improve the reporting of systematic reviews and meta-analyses, in reporting this review.

Materials and Methods

Selection Criteria

Studies that (a) examined post-traumatic symptoms in children and adolescents after mass natural disasters, (b) followed the subjects for at least three years post-disaster, (c) assessed PTSD symptoms as outcomes, and (d) were peer-reviewed, were included in this review. Accordingly, studies reporting about the effects of other types of disasters (e.g., war, terrorist attacks, traffic accidents, industrial accidents, etc.), and studies that assessed only other psychiatric problems (e.g., depression, anxiety, serious emotional disturbance, etc.) were excluded from this review. Intervention studies were also excluded since they are beyond the scope of this review. The targeted population was children and adolescents who experienced mass natural disasters when they were under 18 years of age.

Data Sources and Searches

In order to identify potential studies for inclusion, we conducted an electronic database search on MEDLINE and PsycINFO for studies published from January 1980 through January 2014 using the following keywords: (post-traumatic OR posttraumatic stress disorder) AND (disaster OR disasters) AND (child OR children OR adolescent[s]) AND (long-term OR follow-up OR longitudinal). Only peer-reviewed articles were searched.

Study Selection and Data Extraction

After potential studies were identified by the database search (Phase 1), we reviewed all abstracts and titles (Phase 2). Studies that were written in a non-English language, that did not include original data or an assessment of child responses, and that were on irrelevant topics (e.g., the development of assessment tools, physical health related to disasters) were excluded. The full text of selected potential studies were further reviewed to determine their eligibility (Phase 3). Studies reporting other types of disasters, studies that followed the subjects for less than three years, studies that assessed only other psychiatric problems, and intervention studies were excluded in sequence. From the included studies, the study design, study time frame after the disaster, samples (sampling method, size, and age), PTSD measures, PTSD prevalence and classification were abstracted. For the age of the sample, since time frame varied across studies, we showed not only the age at the time of the study, but also the estimated age at the time of the disaster.

Quality Assessment

Observational studies are known to be vulnerable to some types of study bias, especially to selection bias and confounding compared to randomized controlled trials (Reeves, Deeks, Higgins, & Wells, 2008; Lu, 2009); thus including quality assessment is recommended when reporting systematic review by PRISMA. In this review, we used the checklist from SAQOR

(Systematic Appraisal of Quality in Observational Research), which was developed especially for observational studies (for details, see Ross et al., 2011), and also employed in the former review article (Wang et al., 2013), to rate the quality of the included studies. The SAQOR consists of six categories with two to five questions for each assessment category: Sample; Control/comparison group; Quality of exposure/outcome measurements; Follow-up; Distorting influences; and Reporting data.

Note that for cross-sectional studies, the “follow-up” category is excluded. and also for case-series studies, the “control/comparison group” category is excluded, due to the feature of the study designs. Each of the included studies was rated as “adequate” in all these categories when the study met the category’s requirements stated in SAQOR.

The category of “distorting influences” was developed to rate the risk of confounding (Ross et al., 2011). Confounding is defined as “a mixing of effects between the exposure of interest, the disease, and a third factor (i.e., the confounder) that is associated with the exposure that independently affects the risk of developing the disease” (Mann & Wood, 2012, p. 18). Several strategies are recommended to reduce confounding at three phases of study (Lu, 2009): At the design phase, (a) Restriction – inclusion to the study is restricted to a certain category of confounder (e.g., male); and (b) Matching of controls to cases to enhance equal representation of subjects with certain confounders among study group. At the analysis phase, (c) Stratification – the sample is divided into subgroups or strata on the basis of characteristics that are potentially confounding the analysis (e.g., age); and (d) Statistical adjustments for dissimilarities in characteristics between the study groups, including regression, propensity score, and instrumental variables.

In the literature of child PTSD, there is no confounder commonly recognized so far, although several factors such as children’s gender, age, and proximity to the disaster are considered to be affecting PTSD symptoms. Thus, we did not set “primary key confounders” in the quality assessment of this review, which is originally suggested by SAQOR. Studies that counted for at least two potential confounders, including age, gender, disaster experience, depression, etc., using strategies such as those listed above were rated “adequate”.

Results

Search Results

The search process is summarized in Figure 1. The database search identified 232 potentially relevant studies (Phase 1), 114 of which were selected for further screening after excluding irrelevant studies based on our screening the titles and abstracts (Phase 2). The numbers of papers published per year are presented in Figure 2, in order to allow readers to grasp the trend in post-disaster follow-up studies in children and adolescents. The earliest work selected in Phase 2 was published in 1987, following the Ash Wednesday fires in Australia in 1983 (McFarlane, 1987). The highest number of selected papers was published in 2009, representing 13.2% ($n = 15$) of the total 114 studies, followed by 2008 and 2011 ($n = 13$, 11.4%). Twenty-eight studies followed earthquakes (24.6%), 26 followed hurricanes (22.8%), and 10 followed two tsunamis (8.8%). The most studied event was Hurricane Katrina in 2005 ($n = 14$,

12.3%), followed by the South Asia tsunami in 2004 ($n = 9$, 7.9%), the World Trade Center attack ($n = 8$, 7.0%) in 2001, and the Jupiter shipping disaster in 1988 ($n = 7$, 6.1%).

In Phase 3, 104 of the 114 previously selected studies (88.6%) were excluded because they did not meet the selection criteria stated earlier; 39 studies followed other types of disasters (34.2%), 59 studies followed the subjects for less than three years (51.8%), two had non-PTSD symptoms as the outcome (1.8%), and four were intervention studies (3.5%). Finally, 10 of the 114 previously selected studies (8.8%) were included in this review as long-term follow-up studies of PTSD symptoms in children following natural disasters.

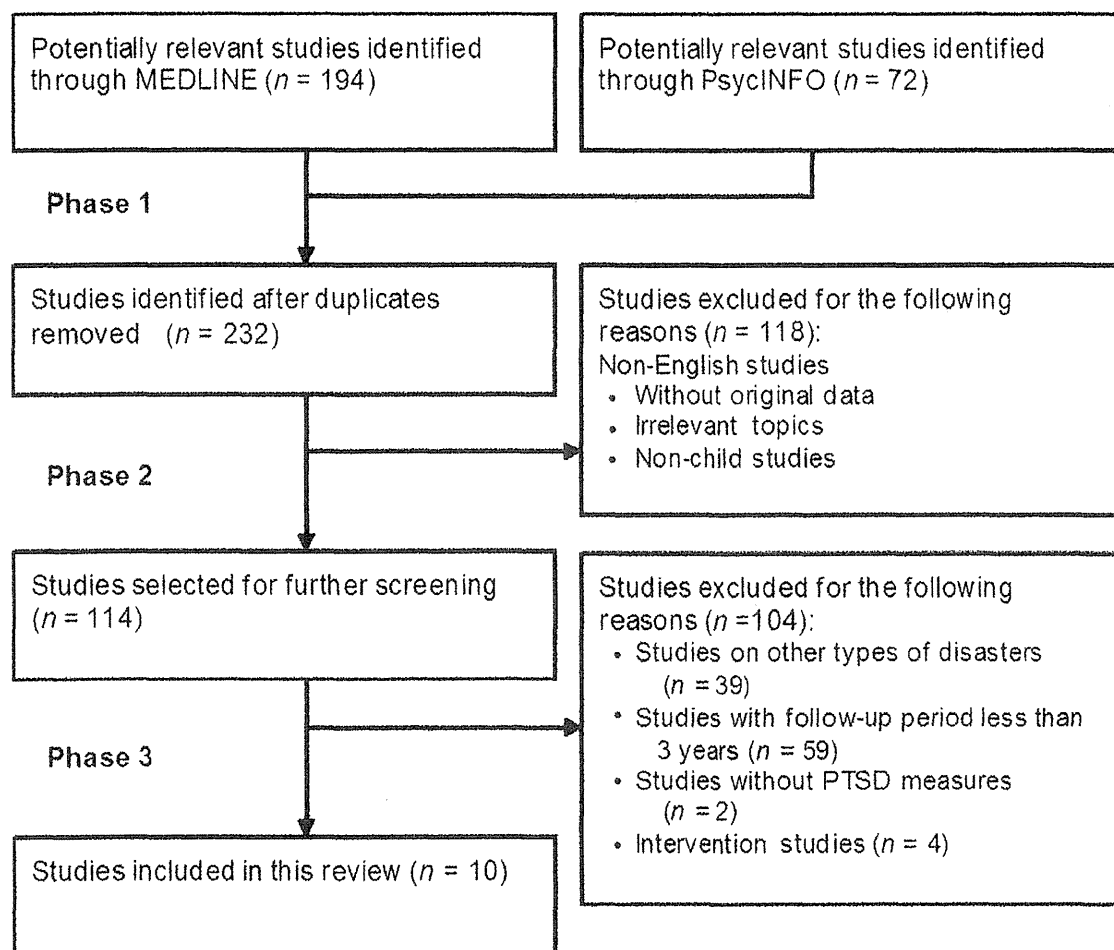


Figure 1. Flow diagram of the study selection

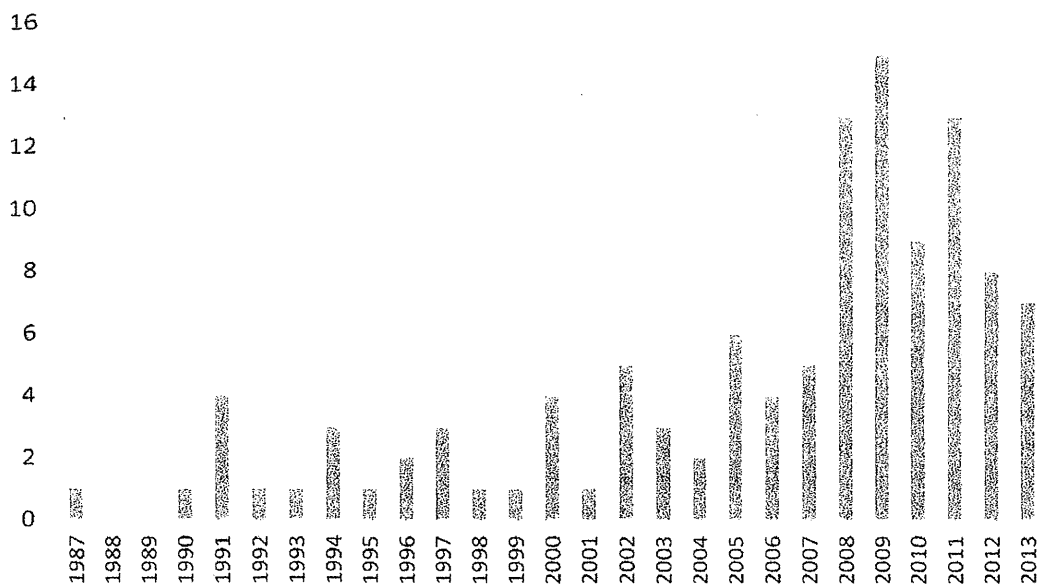


Figure 2. Number of the papers published on long-term follow-up studies of child PTSD

Overview of the Included Studies

The characteristics of the included studies are summarized in Table 1. All included studies were published between 2005 and 2013. Six events were studied in the 10 included studies: three earthquakes, one tsunami, one hurricane, and one wildfire. The earliest event was the Ash Wednesday fires in Australia in 1983 (McFarlane & Hooff, 2009), and the latest was Sichuan earthquake in China in 2008 (Jia et al., 2013). Three of the studies followed the Spitak earthquake in Armenia in 1988, and another three followed South Asia tsunami in 2004. The age of the participants ranged from eight to 19 years for child and adolescent samples, and 23 to 34 for adult samples who had experienced disasters in their childhood (McFarlane & Hooff, 2009; Najarian, Sunday, Labruna, & Barry, 2011). The estimated age of the participants at the time of the disasters ranged from three to 16 years old.

With respect to study design, four of the 10 studies were cohort studies (Goenjian, Walling, Steinberg, Karayan, & Pynoos, 2005; Jia et al., 2013; Kronenberg et al., 2010; Najarian, et al., 2011), another four were cross-sectional studies (Agustini, Asniar, & Matsuo, 2011; Goenjian et al., 2009; Kilic, Kilic, & Yilmaz, 2008; McFarlane & Hooff, 2009), one was a descriptive study (Piyasil et al., 2011), and the other study was based on a case-series design (Ularntinon et al., 2008). One of the cohort studies compared PTSD symptoms between the subjects who had and had not received group/individual psychotherapy (Goenjian et al., 2005). Since intervention studies were not the focus of this review, we did not include the information regarding treatment effect in the summary table, and included the results of non-treated subjects only. The length of the follow-up period ranged from three to 20 years after the disasters. Four

studies followed disaster-experienced children for three to four years after the disaster (Agustini et al., 2011; Jia et al., 2013; Kronenberg et al., 2010; Ularntinon et al., 2008), four studies followed them for between five and six-and-a-half years after (Goenjian et al., 2005, 2009; Kilic et al., 2008; Piyasil et al., 2011), and two followed them for more than 20 years after the disaster (McFarlane & Hooff, 2009; Najarian et al., 2011). None of the included studies conducted a pre-disaster assessment.

Two studies included subgroups of the subjects: Goenjian et al. (2005) included groups of children from three different cities located at increasing distances from the epicenter of the earthquake; Goenjian et al. (2009) included groups of children with different types of parental loss (loss of both parents, loss of father, and loss of mother). Four studies included control/comparison groups: Three studies had non-affected groups as controls (Kilic et al., 2008; McFarlane & Hooff, 2009; Najarian et al., 2011); however, two of them did not include PTSD assessment of the control group (Kilic et al., 2008; Najarian et al., 2011). One study had children who were exposed to the disaster but did not experience any parental loss as a comparison group to bereaved children who lost one or both of their parents (Goenjian et al., 2009).

Three of the studies stated that the subjects did not receive any psychological treatment following the disaster (Goenjian et al., 2005, 2009; Najarian et al., 2011). Two studies stated that some of the subjects received psychological intervention during the follow-up period (Jia et al., 2013; Kronenberg et al., 2010; Piyasil et al., 2011), and one study stated that school-wide intervention was conducted at the targeted schools (Ularntinon et al., 2008).

Risk of Bias

A summary of the quality assessment for six categories is presented in Table 2, together with a summary of the findings of each study. Four cohort studies were rated for all six categories: three studies were rated “adequate” in four (Goenjian et al., 2005; Jia et al., 2013; Kronenberg et al., 2010) and one study was “adequate” in three of the six categories (Najarian et al., 2011). Four cross-sectional studies were rated for five categories (the category of “Follow-up” was excluded): One was rated “adequate” in all five categories (Kilic et al., 2008); one was “adequate” in four (McFarlane & Hooff, 2009); one was “adequate” in three (Goenjian et al., 2009); and the remaining was “adequate” in two of the five categories (Agustini et al., 2011). One case-series study was rated for five categories (the category of “Control/comparison group” was excluded), being “adequate” in four of them (Ularntinon et al., 2008). One descriptive study was rated for all six categories, being “adequate” in two of the six categories (Piyasil et al., 2011).

Table 1. Summary of the included studies

Author (year)	Study design	Time After	Sample	Size	Age ¹		Control/ comparison group	PTSD ² Measure	PTSD prevalence and classification
					Study	Disaster			
2008 Sichuan earthquake, China (May 12, 2008)									
Jia et al. (2013)	Cohort	15mths 36mths	Random sample of students in the severely affected areas	430	8-16	7-15	-	CPTSD-RI	12.4% to 10.7%, from 15th to 36th month (probable PTSD) 4.2% to 4.7% (comorbid with depression)
2005 Hurricane Katrina, U.S. (August 29, 2005)									
Kronenberg et al. (2010)	Cohort	2yrs 3yrs	Students in 4-12th grades from the targeted community	387	9-18	7-16	-	NCTSN screener	23.0% (breakdown without recovery), 4.7% (delayed breakdown), 27.1% (normal response and recovery), 45.2% (stress resistant)
2004 Southeast Asia tsunami (December 26, 2004)									
Agustini et al. (2011)	Cross-sectional	4.5yrs	Students from 4 boarding schools in the same community	482	11-19	6-15	-	CPTSD-RI	22.4% (probable PTSD)
Piyasil et al. (2011)	Descriptive	0yrs, 6mths 1, 2, 3, 4, 5yrs	Students in 2 selected schools from the most affected area	1,625	9-14	8-14	-	Psychiatric interview	57.3%, 46.1%, 31.6%, 7.6%, 4.5%, 3.9%, and 2.7% from 0yrs to 5yrs after disaster, respectively.
Ulaminnon et al. (2008)	Case-series	1y 3yrs	Children diagnosed with PTSD at 1y post disaster	45	11.35	8.31	-	Psychiatric interview	11.1% (Chronic PTSD), 11.1% (Depressive Disorder), 11.1% (Anxiety Disorder), 46.7% (Partial remission), 24.4% (Full recovery)
1999 Bole earthquake, Turkey (November 12, 1999)									
Kilic et al. (2008)	Cross-sectional	5yrs	Children in the households randomly selected from the city center	81	8-15	3-10	Non-exposed (n = 67)	CPTSD-RI	18.5% (probable PTSD)
1989 Spitak earthquake, Armenia (December 7, 1988)									
Najafian et al. (2011)	Cohort	2yrs 20yrs	Adults who experienced the disaster, and were selected for the previous study at 2 years after the disaster	19	28-30	8-10	Non-exposed (n = 44)	CPTSD-RI DICA-R	21.1% (probable PTSD) at 20yrs post disaster
Goenjian et al. (2009)	Cross-sectional	6.5yrs	Students at a trade school for bereaved students	48	13.8	7.3	Exposed no-parental loss (n = 44)	CPTSD-RI	N/A
Goenjian et al. (2005)	Cohort	1.5yrs 5yrs	Students in the selected schools from 3 cities located at increasing distances from the epicenter	125	15-17	10-12	-	CPTSD-RI	N/A
1983 Ash Wednesday Fires, Australia (February 16, 1983)									
McFarlane & Hooff (2009)	Cross-sectional	20yrs	Adults who experienced the disaster, and were recruited as children 2y after the disaster	540	23-34	3-13	Non-exposed (n = 484)	CIDI PTSD	15.2% (past month PTSD) 35.7% (lifetime PTSD)

¹ The range of participants' ages at the time of the study and the disaster. Mean age was noted when the range was not available.

² CPTSD-RI = The Child Post-Traumatic Stress Disorder Reaction Index (Pynoos et al., 1987; Steinberg et al., 2004).

NCTSN screener = NCTSN Hurricane Assessment and Referral Tool for Children and Adolescents (NCTSN, 2005). CIDI = Composite International Diagnostic Interview (WHO, 1997).

Table 2. Quality assessment and major findings of the included studies

Author (year)	Study design	SAQOR ¹						Summary of the findings
		Sample	Control/comparison group	Exposure/outcome measurement	Follow-up	Distorting influences	Reporting of data	
2008 Sichuan earthquake, China Jia et al. (2013)	Cohort	+	-	+	+	+	-	Overall prevalence rates of PTSD and depression symptoms did not change significantly from 15 to 36 months post disaster. The linear regression model showed that depression, objective experiences, subjective experiences, and earthquake-related loss had influence on PTSD symptoms at 36 months after the disaster. Gender was not significant in the regression analysis, although females scored higher than males.
2005 Hurricane Katrina, U.S. Kronenberg et al. (2010)	Cohort	+	-	-	+	+	+	Not only did overall symptoms decrease from the 2nd to the 3rd post disaster year, but also 72.3% of the children were classified as 'stress resistant' or 'normal response and recovery'. However, 27.7% of the children were classified as 'breakdown without recovery' or 'delayed breakdown'. Younger age, female gender, consulting with a mental health professional, and addressing family and school problems were found to be the most associated with the recovery patterns. Pre- and post-disaster loss or trauma and current living conditions were not associated with the recovery patterns.
2004 Southeast Asian tsunami Agustini et al. (2011)	Cross-sectional	+	-	+	n/a	-	-	Gender (female), loss of parents, somatic response and support level were significantly associated with PTSD symptoms among the tsunami-affected adolescents at 4.5 years after the tsunami.
Piyasil et al. (2011)	Descriptive	+	-	-	+	-	-	The prevalence of PTSD was 57.3% after the disaster, and gradually decreased to 2.7% throughout the 5 year follow-up period. Female to male ratio of the students with PTSD was 1.7: 1.
Urantinn et al. (2008)	Case series	+	n/a	+	+	-	+	About 28% of the students, who were diagnosed with PTSD at 2 years post disaster, had full recovery at 3 years post disaster. The history of previous trauma and physical injury at the time of the disaster were associated with the outcome. Gender was not associated with the outcome. Previous work: Piyasil et al. (2007)
1999 Bole earthquake, Turkey Kilic et al. (2009)	Cross-sectional	+	+	+	n/a	+	+	No significant difference on anxiety and depression between the earthquake exposed group and the non-exposed group at 5 years post disaster. Trait anxiety and anxiety sensitivity contributed to the severity of PTSD reactions in the subject group, but not depression. Gender and age were not significant factors in regression analysis.
1988 Spitak earthquake, Armenia Najarian et al. (2011)	Cohort	-	+	+	+	-	-	Earthquake exposed group had higher scores on several symptoms than the non-exposed adults, and 4 out of 19 earthquake exposed adults scored probable PTSD at 20 years post disaster. 63% of the earthquake experienced adults had at least one clinical elevation in the symptom checklist 80R, whereas 84% of the control group had no clinical elevation. No correlation was found between Time1 and Time2 depression scores and number of the PTSD symptoms. Previous work: Najarian et al. (1996)
Goarjian et al. (2009)	Cross-sectional	+	+	+	n/a	-	-	No significant difference was found in PTSD symptom scores by the type of parental loss at 6.5 years post disaster. However, orphans had the highest depression scores, followed by those who lost fathers, those who lost mothers, and those who did not have parental loss.
Goarjian et al. (2005)	Cohort	+	+	-	+	+	-	Students from the city located the closest to the epicenter had higher PTSD reactions at 1.5 years after the disaster, and remained higher at 5 years after the disaster than the other 2 groups farther from the epicenter, although scores decreased over time significantly in all 3 groups. Meanwhile, depression scores did not decrease over time in all 3 groups; even a significant increase was found in the group second closest to the epicenter from 1.5 to 5 years after the disaster. Previous work: Goarjian et al. (1998)
1983 Ash Wednesday Fires, Australia McFarlane & Huff (2009)	Cross-sectional	+	+	-	n/a	+	+	Although 79% of the bushfire exposed group still reported some degree of distress in relation to the bushfires, there was no significant difference between bushfire group and the controls in the prevalence of PTSD resulting from the self-nominated worst lifetime event. In the bushfire exposed group, individuals who nominated the bushfire as their worst event had lower risk than individuals who nominated other traumatic events as their worst event. Previous work: McFarlane et al. (1987)

¹ '+' = adequate, '-' = inadequate