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676 *Medicinal Chemistry*, **2015**, *11*, 676-682

Gestational Influenza Increases the Risk of Psychosis in Adults

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Abstract: Psychotic disorders are complex and caused by interplay of genetic and environmental factors. Influenza is a common infectious disease in humans, and it has been suggested that maternal influenza is an estimated risk factor for psychotic disorders, especially for schizophrenia. In view of conflicting results of this association in literature, we performed the strict meta-analysis to examine whether maternal influenza is a risk factor for psychosis in the children. Four ecological studies and three birth cohort studies were included in our meta-analysis. It has been observed that the Risk Ratio (RR) of maternal influenza on psychosis is 1.062 (95% Confidence Interval (CI) = 1.004-1.123) for the analysis of ecological studies and the RR is 1.564(95%CI=1.051-2.324) for the analysis of birth cohort studies. Furthermore, a survey of pregnant women and fetus' health in Nanjing of China indicated that only 1.5% of women received the influenza vaccine before pregnancy, 0.4% received it during pregnancy, and 5.1% were willing to receive the influenza vaccine if necessary. These results showed that gestational influenza could increase mental disorders risks in adult offspring besides its established harms for gravidas. Results suggest it might be effective to increase attention to gravidas to protect them from influenza infection through encouragement of vaccinations.

Keywords: Meta-analysis, schizophrenia, influenza.

INTRODUCTION

Psychotic disorders are severe and complex mental or behavioral patterns causing distress or disability that they lead to enormous social and economic burden. Several mental disorders feature psychosis, like Affective Disorders, Bipolar Disorder and most notable Schizophrenia. Among the psychotic disorders, Schizophrenia (SCZ) features typical and severe psychosis, and this disorder affects around 1% of the population worldwide [1]. It is widely accepted that the etiology of schizophrenia is composed by an interaction of environmental and genetic factors [2]. The concordance rate for schizophrenia in monozygotic twins is approximately 50%, indicating that environmental factors have a significant role in susceptibility to this disorder [3]. Accordingly, in order to account for the unexplained heritability, many studies on environmental exposures in Schizophrenia have focused on prenatal infection. Some initial clues indicate that birth during the winter and spring periods are related to an increasing risk of the psychotic disorder [4]. This suggests that influenza varying by season may contribute to the relationship.

Influenza is a common infectious disease with main symptoms including fever, chills, runny nose, sore throat, headache, coughing, muscle pains, fatigue and discomfort [5]. Pregnant women and elderly people are particularly vulnerable to influenza. Influenza is caused by the influenza viruses, of which influenza A virus is a negative-strand RNA virus. Its membrane proteins are made up of three important components [5]: M2 proton channel [6], neuraminidase (NA), and hemagglutinin (HA) [7,8]. Stimulated by the successful determination of the high-resolution 3D structure, recent literatures conclude that any of the three components can be the target for drug design against influenza virus [6,9-11].

More and more evidences have indicated that statistical analyses by means of various approaches and tools can provide very useful informations in stimulating the development of finding novel drugs as well as effective therapeutic treatments. For example, by means of the proteome analysis tools [12-15], scientists can acquire very useful information for designing drugs against cancer [16] and other major diseases (see, *e.g.*, [17,18]). This kind of tools can also be used to identify the PTM (posttranslational modification) sites in

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1875-6638/15 $58.00+.00

proteins [19-26], and the information thus obtained is very useful for treating various PTM-related diseases [27]. The tools developed recently for genome analyses [28-30a,b,c,d] can be used to identifying DNA recombination spots [31,32], DNA methylation sites [33], nucleosome positioning [34,35], translation initiation sites [36], splicing sites [37], and promoters [38]; all these informations are very useful for treating various genetic or genomic diseases [39].

In the present study, we are to use a different kind of analysis technique, the so called "mata-analysis" approach [40,41], to examine whether maternal influenza is a risk factor for psychosis. The motivation for us to do so is that prenatal influenza is considered as an estimated risk factor for schizophrenia and other psychotic disorders [42,43]. However, research results are controversial. It was reported by several papers that there were some potential associations between gestational influenza and mental disorders among those who were in utero, but some subsequent studies failed to repeat these findings [44-46]. A meta-anlysis of psychosis and gestational influenza will address this issue.

MATERIALS AND METHODS

Literature Search Strategy

The meta-analysis was conducted and reported in accordance with the PRISMA guidelines and the protocol was registered on the website of http://www.crd.york.ac.uk/prospero/ (registration number: CRD42014007165). Briefly, a search of the digital medical databases (PubMed, ISI Web of Science, EMBASE, and Chinese National Knowledge Infrastructure (CNKI)) published up to April. 30 2014, was performed, with the following keywords: "maternal infection", "gestational infection", "prenatal infection", "influenza", and "Schizophrenia" or "Bipolar Disorder" or "Affective Disorders" or "psychosis". Besides these, a search with Google Scholar was also conducted. Furthermore, reference lists of relevant articles were also reviewed for additional literatures.

Inclusion Criteria

We distinguished two types of studies. Those designated as type I included ecological studies in which an in-depth comparison was made between the risk of disorders among populations born in the 9 months after the pandemic (i.e., index period) and those born during corresponding periods in the previous or subsequent year (i.e., control periods). The studies of birth cohorts were designated type II, in which maternal influenza during pregnancy period is determined by medical records or serological testing.

In this meta-analysis, patients with mental disorders were diagnosed based on the International Classification of Diseases, 8th or 9th edition (ICD-9) or the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. For ecological studies (type I studies), although the mothers were not known to actually have influenza in the index period, their children were considered to be exposed at the infection rate of 50% [47]. Likewise, the infants born in the control periods were considered not to be exposed. Thus, infants born in the first month after the peak of influenza epidemic are viewed as being exposed to influenza, those born in the control periods are viewed as being non-exposed to influenza. In a strict way, the additional inclusion criteria for Type I are based on the following information provided: 1) the number of psychotic patients, 2) the number of live birth in corresponding period, 3) the statement of peak or last period of influenza epidemics. For those studies with overlapped population, only one study was included based on the above criteria.

The studies of birth cohorts revealed that infants of pregnant women with a record of influenza diagnosis results based on the medical records or serological tests, are viewed as being exposed to influenza with positive results and not being exposed to influenza with negative results. The inclusion criteria for Type II studies are based on the following information provided: 1) with the population number, 2) anti-influenza antibodies were measured or diagnoses of influenza during pregnancy were recorded.

Data Extraction

Data extraction was performed independently by two reviewers using a standardized protocol and reporting form [48]. The discrepancy between two reviewers was resolved by further discussion with the third party. Article titles, abstracts and references were initially screened to determine which studies were eligible for further evaluation based on the eligibility criteria. Then full-text was reviewed to complete the reporting form. The reporting form includes: 1) first author's name, 2) publication year, 3) type of mental disorder, 4) mental disorder diagnosis criteria, 5) country or region, 6) medical records of influenza, 7) the number of patients with mental disorders. For those without medical records of influenza, two additional items are required: 1) the peak time of influenza epidemic, 2) The index and control period, and 3) the number of live births. Table **1** provides an overview.

Survey

A survey of pregnant women and fetus' health was conducted in the obstetrical department from the four main hospitals in Nanjing, China from Jun. 1st to Jul. 31, 2013. The four hospitals are Nanjing maternal and child care service centre, Huashijiabao hospital for gynaecology and obstetrics, Military General Hospital, maternal and child care service centre of Jiangsu Province. Total, 493 questionnaires were retrieved for further statistical analysis.

Statistical Analysis

The strength of the associations between maternal influenza and risk of psychosis was measured by risk ratios (RRs) with corresponding 95 % confidence intervals (CIs). The pooled RRs were calculated for the psychotic exposed during pregnancy. As two models of meta-analysis for calculating the pooled RRs, the random-effects model and the fixed-effects model were conducted using the DerSimonian and Laird and Mantel–Haenszel methods [48], respectively. The between-study heterogeneity was assessed with Chi-square based Q-test (Cochran's Q statistic), and $P < 0.1$ was considered statistically significant. The I^2 was also calculated in order to quantifiably evaluate the proportion of the total

Table 1. Four ecological studies of psychosis risk for subjects in fetus.

First Author (year)	Psychosis	Region or Country	Peak of Pandemic	Last of Pandemic	Index Period	Control Period
Izumoto (1999)	SCZ	Kochi, Japan	Three Peaks: Feb., Jun. and Nov. of 1957	Jan.-Feb., Jun.-Jul. & Nov.-Dec., 1957	Feb., 1957- Sep., 1958	Jan., 1955-Dec., 1956 and Jan., 1959-Dec., 1960.
Mcgrath (1994)	SCZ	Queensland, Australia	Aug., 1954 & Aug., 1957	Jul.2-Sept.1, 1957	Sept.1, 1954/1957-Aug.31, 1955/1958	Five years on either side of the epidemic year, except 1954, 1957 and 1959
Selten (2010)	MAD	Uusimaa County including Helsinki, Finland	n.a	Oct. 8, 1957- Nov. 14, 1957	Nov.15, 1957-Aug. 14, 1958	Nov.15, 1951-Aug. 14, 1956
Kimling (1994)	SCZ	Croatia	Mid-Oct., 1957	Mid-Sep., 1957-first week of Dec., 1957	Sept.1, 1957-Aug.31, 1958	Sept.1, 1955-Aug.31, 1957 & Sept.1, 1958-Aug. 31, 1960

SCZ: Schizophrenia; MAD: Major affective disorder; n.a: not available.

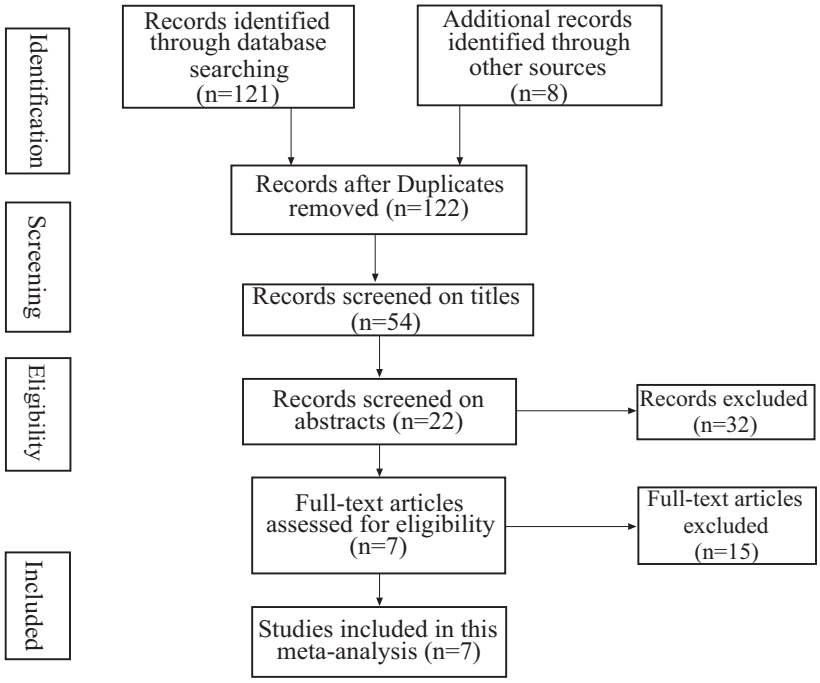


Fig. (1). Flow chart of the study selection process. Seven studies were included in the meta-analysis of whether maternal influenza was a risk factor for psychosis.

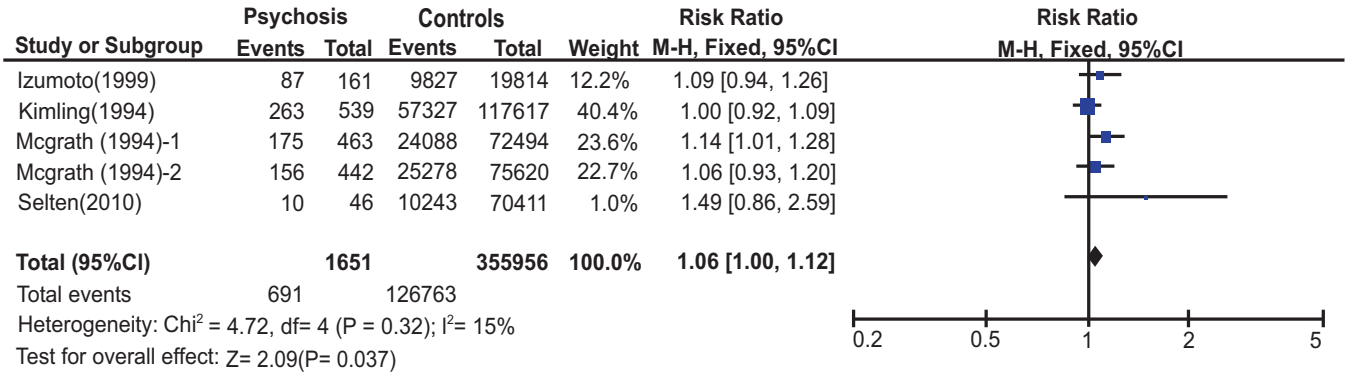
variation due to heterogeneity, and I^2>50 % was indicated as statistical significance. If the results of the heterogeneity test were $P > 0.1$, pooled RRs were evaluated according to the fixed effects model. Otherwise, the pooled RRs were calculated according to the random effects model. A sensitivity analysis was carried out in which one study at a time was removed and analysis was performed on the remainder to evaluate whether the results could be affected significantly by a single study. Publication bias was assessed through the Egger weighted regression method and Begg's test, and $P < 0.05$ was considered as statistically significant publication bias [49]. All statistical analyses were carried out using Review Manger 5.2 (The Nordic Cochrane Centre, Copenhagen, Denmark) and Stata version 11.2 (Stata Corporation, College Station, TX, USA).

RESULTS

Characteristics of the Included Studies

A total of four type I and three type II studies on the association between risk of psychosis and prenatal influenza infection were identified respectively after carefully and strictly screening based on full-text of the candidate articles (Fig. **1**) (Table **1**) [43,44,46,50-53]. One study only providing information on part of delivery term was excluded in this meta-analysis [45]. All the studies included information of studied region or country to prevent selection bias of psychotic patients and information on peak or last term of influenza epidemic enabling categorization of first month after the peak of pandemic as being exposed of influenza. In Izumoto *et al*'s study, there were three influenza epidemics in

A



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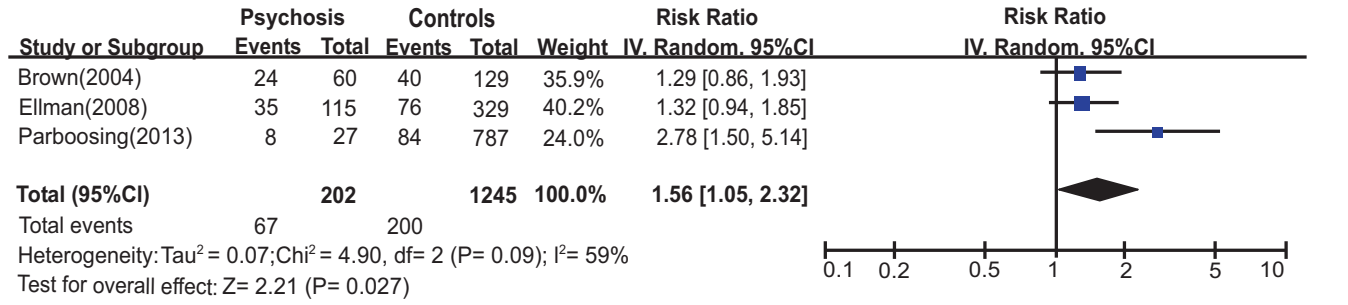

Fig. (2). Forest plots for meta-analyses of prenatal influenza infection and mental disorders in adolescence. A, Summary of RRs with 95% CIs for prenatal influenza infection from studies with ecological data; B, Summary of ORs with 95% CIs for prenatal influenza infection from studies with serologic data.

Kochi, Japan, the peaks of which were February, June and November of 1957 [50]. Thus, the gestational months for each wave of epidemics overlapped. The psychotic patients were calculated based on the non-overlapping gestational months of their mother. In McGrath *et al*'s study, there were also three influenza epidemics in Queensland, Australia, the two peaks of which were August of 1954 and 1957, the other peak was not clear [44]. Thus, the psychotic patients were calculated based on each qualified epidemics data.

Type I and II Studies

The meta-analysis result with type I studies of psychosis and maternal infection during the influenza epidemic suggests that there was no significant heterogeneity between each study (P =0.32 and I^2=15%) and prenatal influenza exposure in whole pregnancy is significantly associated with an increased risk of mental disorders in adolescence including schizophrenia and major affective disorders [Risk Ratio (RR) = 1.062, 95% Confidence Interval (CI) = 1.004-1.123] (Fig. **2A**) using the fixed-effects model. And the analysis result with type II studies of psychosis and confirmed maternal infection indicates that the RR is 1.564, 95% CI=1.051-2.324 (Fig. **2B**) using the random-effect model since there was significant heterogeneity between each study (P =0.09 and I^2=59%). If the parboosing's study was excluded in the analysis [52], there was no significant heterogeneity (P =0.94 and I^2=0), and the RR of maternal infection on psychosis in adults that was not significantly affected was 1.313, 95% CI=1.014-1.693. Results suggest that prenatal influenza is associated to mental illness in offspring and therefore preventing prenatal influenza exposure may reduce the morbidity of mental illness in adulthood.

Publication Bias and Sensitivity Analysis

For type I studies, the funnel plot indicated that there was no significant publication bias (Fig. **3**). Furthermore, there was no indication of significant publication bias from both Egger's and Begg's tests in the overall meta-analysis (P = 0.124 and 0.327, respectively for type I studies; P = 0.221 and 0.117, for type II studies).

Moreover, a sensitivity analysis was performed by removing one study at a time to explore the source of heterogeneity of each study on the overall meta-analysis estimate. The analysis results suggested that for both type I and II studies, no individual study significantly affected the overall RRs, suggesting the results were statistically robust. See Supplementary Fig. **S1** in Supporting Information **S1**.

Survey of Pregnant Women's Vaccination Willingness

Our 2013 survey of 493 pregnant women in Nanjing displayed that only 1.5% of women received the influenza vaccine before pregnancy, 0.4% received it during pregnancy, and 5.1% were willing to receive the influenza vaccine if necessary.

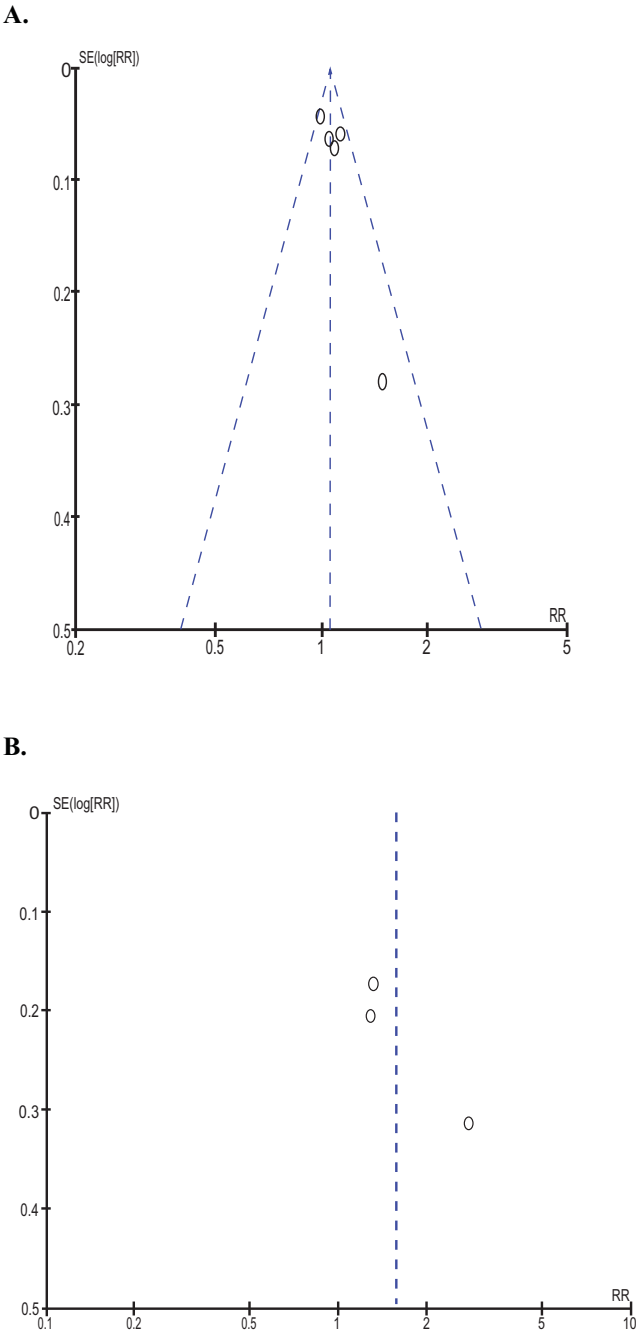

Fig. (3). Funnel plots for meta-analyses of prenatal influenza infection and mental disorders in adolescence. A, for type I studies; B, for type II studies.

DISCUSSION

The current meta-analysis was aimed to examine whether maternal influenza was a risk factor for psychosis in the offspring. Since the researches included were well-designed retrospective studies for detecting the effect of maternal influenza infection, we did find an association of maternal influenza infection with psychosis in both ecological studies and birth cohort studies. Our findings are further supported by the observations in mice modeling studies. In mice, the offspring from mothers having received intranasal infusions of influenza virus during pregnancies also showed signs of diminished interaction with novel objects and reduced the "social" behavior [54]. Based on the cytokine imbalance model, the prenatal induction of proinflammatory cytokines caused by influenza viral pathogens may have an influence on the development of the fetal brain, thereby increasing the risk for psychosis [54].

In view of these, we suggest to increase attention to gravidas to protect them from influenza infection during influenza epidemic. However, in China, pregnant mothers tend to avoid vaccinations. For example, during the 2009 H1N1 epidemic, only about 28,000 pregnant women (~0.4% of all pregnant women) received the H1N1 influenza vaccine by February of 2010 in China, compared to 23.4% and 18.6% of all adults receiving the H1N1 influenza vaccine in whole 2009 and 2010, respectively in Beijing [55]. In 2010, a survey sample of 179 pregnant women in Changchun showed that only 10% of pregnant women were willing to receive the influenza vaccine [55]. Our 2013 survey of 493 pregnant women in Nanking displayed that only 1.5% of women received the influenza vaccine before pregnancy, 0.4% received it during pregnancy, and 5.1% were willing to receive the influenza vaccine if necessary. These statistical data have clearly indicated that Chinese gravidas have a low influenza vaccination rate, which may result from lasting influence of old policies of prohibiting gravidas to take influenza vaccinations and less education of new 2009 policy of permitting vaccination for Chinese pregnant women (http://www. chinacdc.cn).

There are some limitations about our meta-analysis, even though we have strict paper data extract criteria. One is using imprecise measures of exposure since influenza infection was not documented in individual pregnancies so that maternal influenza could not be assessed in individual mothers in type I studies. Hence, we initiated type II studies with birth cohort studies to evaluate whether pre-nantal influenza is a risk factor for psychosis. Another discussion point concerns the timing of gestation, which was based on the month of birth instead of 9-month deliveries. It should be noted that the proportion of premature births is expected to be relatively small and thus unlikely to explain the findings. The other is that the diagnoses in two studies recorded on psychiatric registries may have a poor validity, and thus obscure the findings. However, in an included study, reasonably good diagnostic validity is suggested by the fact that follow-up psychiatric examinations confirmed the hospital diagnoses of schizophrenia in 93% of a representative sample of the patients in Croatia's Psychiatric Case Register [46]. The similar percentage might happen in the other study, thus the issue seems to be less relevant.

In conclusion, our results showed that gestational influenza could increase mental disorders risk in adult offspring besides its established harms for gravidas. Further studies are required to identify whether specific types of influenza viruses have specific effects on the development of psychosis in the adult offspring.

CONFLICT OF INTEREST

The authors declare no financial or commercial conflict of interest.

ACKNOWLEDGEMENTS

The authors wish to thank the anonymous reviewers for their constructive comments, which are very helpful in strengthening the presentation of this study.

This work was supported by the 973 Program (2010CB529600, 2012CB910102), the Chinese National Science Foundation (No. 31101015, No.81421061) and the scientific research foundation for the returned overseas the Chinese Ministry of Education (No. 12Z102050009).

SUPPLEMENTARY MATERIAL

Supporting Information S1. Figure S1.

Supplementary material is available on the publishers Web site along with the published article.

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Received: January 21, 2015 Revised: April 21, 2015 Accepted: April 21, 2015