Using dengue epidemics and local weather in Bali, Indonesia to predict imported dengue in Australia

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Abstract

Background: Although the association between dengue in Bali, Indonesia, and imported dengue in Australia has been widely asserted, no study has quantified this association so far.

Methods: Monthly data on dengue and climatic factors over the past decade for Bali and Jakarta as well as monthly data on imported dengue in Australia underwent a three-stage analysis. Stage I: a quasi-Poisson regression with distributed lag non-linear model was used to assess the associations of climatic factors with dengue in Bali. Stage II: a generalized additive model was used to quantify the association of dengue in Bali with imported dengue in Australia with and without including the number of travelers in log scale as an offset. Stage III: the associations of mean temperature and rainfall (two climatic factors identified in stage I) in Bali with imported dengue in Australia were examined using stage I approach.

Results: The number of dengue cases in Bali increased with increasing mean temperature, and, up to a certain level, it also increased with increasing rainfall but dropped off for high levels of rainfall. Above a monthly incidence of 1.05 cases per 100,000, dengue in Bali was almost linearly associated with imported dengue in Australia at a lag of one month. Mean temperature (relative risk (RR) per 0.5 °C increase: 2.95, 95% confidence interval (CI): 1.87, 4.66) and rainfall (RR per 7.5 mm increase: 3.42, 95% CI: 1.07, 10.92) in Bali were significantly associated with imported dengue in Australia at a lag of four months.

Conclusions: This study suggests that climatic factors (i.e., mean temperature and rainfall) known to be conducive of dengue transmission in Bali can provide an early warning with 4-month lead time for Australia in order to mitigate future outbreaks of local dengue in Australia.

This study also provides a template and framework for future surveillance of travel-related infectious diseases globally.

Keywords: Australia; Bali; dengue; early warning

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1. Introduction

Dengue is the most common and geographically fastest-spreading mosquito borne disease in the world, and is now present in more than 126 countries (Furuya-Kanamori et al. 2016). It has been estimated that there are 390 million dengue infections per year globally and 96 million of them manifest apparently (Bhatt et al. 2013). A large proportion of global dengue burden is borne by people living in Southeast Asia and Western Pacific region (WHO Western Pacific Region 2014). In Australia, local dengue transmission is restricted to northern Queensland and is seeded by importations, and dengue infections in other Australian states and territories are imported cases (Huang et al. 2016).

Indonesia, a dengue endemic country, has been considered as an important hub for dengue transmission in Asia Pacific region (Vainio et al. 2010; Yuan and Nishiura 2018). Indonesia is the most frequent international travel destination of Australians (Australian Bureau of Statistics 2018), and prior studies have suggested that a large proportion of Australian dengue cases acquired in Indonesia are from the island of Bali (Masyeni et al. 2018), the most famous tourist spot destination in Indonesia (Knope et al. 2013). Further, a considerable number of residents in Western Australia work in Bali, with these "fly-in-fly-out" workers traveling between Bali and Perth frequently due to cheap four-hour flights (Butt 2017). In Western Australia, during 2010 and 2011, more than 80% of dengue cases acquired in Indonesia were acquired in Bali (Knope et al. 2013). Although the relationship between dengue in Bali and imported dengue in Australia has been widely asserted (Asma et al. 2019; Ernst et al. 2015), no study has yet quantified this relationship, and the risk posed to Australia by local factors affecting endemicity in Bali remains unclear.

Climatic factors, including temperature, rainfall, relative humidity and wind speed, affect the occurrence of dengue cases through their impacts on the replication rate and transmission of dengue virus, mosquito ecology and human behaviors (Morin et al. 2013). The effect of climatic factors on the dengue transmission is therefore usually delayed (i.e., lag effect), and the lag period ranges from a few weeks to a few months (Xiang et al. 2017; Xu et al. 2017). This lag period potentially enables prediction of dengue occurrence a few months in advance and provides the opportunity to take proactive measures in a timely manner (Lowe et al. 2018).

If dengue in Bali can predict imported dengue in Australia, and climatic factors in Bali can predict dengue in Bali, our hypothesis is that imported dengue in Australia can be predicted using Balinese climatic data. The present study attempted to test this hypothesis by achieving two research objectives: 1) to quantify the temporal relationship between dengue in Bali and imported dengue in Australia; and 2) to explore the associations of climatic factors in Bali and imported dengue in Australia. To test the uniqueness of Bali in the role of spreading dengue to Australia, we also used data from Jakarta (the capital city of Indonesia) and examined the relationship between dengue in Jakarta and imported dengue in Australia.

2. Materials and methods

2.1 Data collection

Figure S1 (supplementary material) shows the geographical locations of Bali, Jakarta and Australia. It also shows the locations of Bali districts. Monthly dengue data and yearly population data in Bali and its districts from January 2007 to December 2017 as well as in Jakarta from January 2001 to December 2017 were provided by the Ministry of Health, Indonesia. Dengue data in Karangasem (a Bali district) from August to December 2010 were missing, and dengue data in all Bali districts in December 2010 were missing except for Klungkung. Daily weather data, including mean temperature, maximum temperature, minimum temperature, relative humidity, rainfall, and wind speed, from January 2007 to December 2017 in Bali were obtained from Meteorological, Climatological and Geophysical Agency, Indonesia (http://dataonline.bmkg.go.id/home). Daily weather data were merged into monthly climate data by averaging daily values.

Monthly dengue data (including both local dengue and imported dengue) in Australia and its eight states and territories (Australian Capital Territory, New South Wales, Northern Territory, Queensland, South Australia, Tasmania, Victoria, and Western Australia) from January 2001 to May 2018 were obtained from the National Notifiable Diseases Surveillance System (http://www9.health.gov.au/cda/source/cda-index.cfm). Queensland has both local and imported dengue cases (Hu et al. 2012). Monthly local dengue data and imported dengue data in Queensland from January 2007 to December 2013 were provided by Queensland Health, and we used this data to examine the relationships of dengue in Bali with imported dengue and local dengue in Queensland. This study aimed to quantify the temporal relationship between dengue in Bali and imported dengue in Australia, and there is regular conflation between imported dengue and local dengue in Queensland resulting in misclassification (Huang et al. 2013; McKerr et al. 2015). Thus, results for Queensland are presented as supplementary material in this study. In this paper, the term “imported dengue in Australia” refers to “imported dengue in Australia excluding Queensland”, unless stated otherwise. Data on monthly number of Australian residents returning from Indonesia from January 2001 to May 2018 were obtained from the Australia Bureau of Statistics (Australian Bureau of Statistics 2018).

Ethics approval was granted by University Human Research Ethics Committee of Queensland University of Technology prior to the data collection.

2.2 Data analysis

A three-stage analysis was conducted. In the first stage, there were two steps. Step I: we examined the relationship between each climatic factor and occurrence of dengue cases in Bali (i.e., one-climatic-factor model) and selected those climatic factors which were significantly associated with the occurrence of dengue cases. We found significant associations between each of mean temperature, maximum temperature, minimum temperature, relative humidity, and rainfall with the occurrence of dengue cases in Bali (Figure S2 (supplementary material)). Step II: using these significant climatic factors identified in step I, we built up models including two climatic factors. Because temperature indicators (i.e., mean temperature, maximum temperature, and minimum temperature) are highly correlated with each other and relative humidity and rainfall are also highly correlated with each other, we chose one variable from temperature indicators and one variable from relative humidity and rainfall to build up the models to avoid multicollinearity issues. By comparing the values of quasi-AIC (Akaike information criterion) of all models in step II (Gasparrini and Armstrong 2013), we found that the model with mean temperature and rainfall performed the best (Table S1 (supplementary material)). The optimal lags for mean temperature and rainfall in the model (i.e., three months) were selected based on the greatest values of pre-whitened cross correlation (Figures S3A and S3B (supplementary material)) (Chuang et al. 2017). For both two steps of the first stage, we used Poisson regression allowing for over-dispersion with distributed lag non-linear model (Gasparrini et al. 2010) as prior studies have reported non-linear climate-dengue associations (Lowe et al. 2018; Wu et al. 2018). We herewith use mean temperature as an example to elaborate the modeling details. A cross-basis defined by natural cubic spline with two degrees of freedom (*df*s) for the space of mean temperature was used. A maximum lag of three months was adopted in the analysis based on the findings of previous studies quantifying climate-dengue relationships (Lowe et al. 2018; Wu et al. 2018; Xiang et al. 2017) and model fit results. Month and year were included as dummy variables in the model to control for seasonality and long-term trend.

In the second stage, there were two steps. Step I: we assessed the correlation between dengue in Bali and imported dengue in Australia at different lags to ascertain whether there may be a quantitative association between dengue in Bali and imported dengue in Australia. Significant correlations between dengue in Bali and imported dengue in Australia at all lags were observed, with correlation coefficients at a lag of one month having the strongest correlation (Table S2 (supplementary material)). We've also calculated the pre-whitened cross correlation between dengue in Bali and imported dengue in Australia and found the correlation coefficient value was the greatest at a lag of one month (Figure S4 (supplementary material)). This finding echoes the result from Asma et al. whereby dengue cases in Australia were typically presented to emergency departments within 14 days of return from Bali (Asma et al. 2019). Step II: based on the findings of step I in the second stage analysis, we used a generalized additive model to quantify the relationship between dengue in Bali and dengue in Australia at a lag of one month. In this model, month and year were included as dummy variables to control for seasonality and long-term trend. The number of travelers in a log scale was included in the model as an offset. To make sure that a lag of one month was the optimal lag in the model, we compared the values of un-biased risk estimator (UBRE) of three models using three different lags (i.e., one month, two months, and three months), and found that the UBRE values of the three models were 5.4875 (one month), 6.1577 (two months), and 6.5031 (three months), respectively. The lowest value of UBRE was observed for the one-month-lag model, suggesting that the optimal lag was one month.

In the third stage, we used Poisson regression allowing for over-dispersion with a distributed lag non-linear model to assess the associations between mean temperature and rainfall in Bali with the occurrence of dengue cases in Australia. A lag of four months was used in the third stage analysis, and the choice of this lag period was based on the analyses results of the first and second stages. The logic behind this is: 1) Dengue in Bali drives the number of Australian imported dengue cases. 2) Number of dengue cases in Bali can be predicted by climatic factors in Bali several months in advance. 3) Therefore, import risk of dengue in Australia can be predicted by climatic factors in Bali several months in advance.

We replicated above mentioned second stage analysis in Jakarta to examine the relationship between dengue in Jakarta and imported dengue in Australia and test the specificity of the observed Bali association. All analyses in the present study were conducted in R statistical environment (version 3.4.4) with “dlnm” package used to fit the distributed lag non-linear model (Gasparini 2011) and “mgcv” package used to fit the generalized additive model.

3. Results

3.1 Monthly distributions of dengue cases in Australia, Bali and Jakarta

Figures S5A, S5B, and S5C (supplementary material) present the monthly distributions of imported dengue cases in Australia and dengue cases in Bali and Jakarta. The number of imported dengue cases in Australia increased after 2010. Dengue in Bali had a distinct seasonal pattern, with the biggest dengue outbreak occurring in 2016. The biggest dengue outbreak in Jakarta occurred in 2004.

3.2 Associations of climatic factors with dengue in Bali

Figure 1 shows the associations between mean temperature and rainfall with the occurrence of dengue cases in Bali, suggesting that the number of dengue cases increased with increased mean temperature. Number of dengue cases also increased with increasing rainfall, but only up to 16.2 mm beyond which cases started dropping off.

3.3 Association between dengue in Bali and dengue in Australia

Figure 2A illustrates a significant association between dengue in Bali and imported dengue in Australia at a lag of one month. At the Australian state level, dengue in Bali was also significantly associated with dengue in New South Wales, Northern Territory, Tasmania, Victoria, and Western Australia at a lag of one month. Most of the associations were practically linear. Figure S6 (supplementary material) shows that, from 2007 to 2013, there were significant relationships of dengue in Bali with imported dengue in Australia (including Queensland imported dengue) and local dengue in Queensland at a lag of one month.

Dengue in Jakarta and imported dengue in Australia at a lag of one month is presented in Figure 2B, and demonstrates no clear association.

3.4 Association between Australian residents returning from Indonesia and dengue in Australia

Table S3 (supplementary material) shows the number of Australian residents returning from Indonesia and the number of imported dengue cases in Australia has the strongest correlation without a time lag and this was statistically significant (see Figure 3). Sensitivity analyses assessing the association of number of Australian residents returning from Indonesia with numbers of imported dengue cases in Australia at a lag of one month confirmed that the findings in Figure 3 were robust (Figure S7 (supplementary material)).

3.5 Association between dengue in Bali and dengue in Australia after including the number of Australian residents returning from Indonesia in log scale as an offset in the model

Figure 4 shows the association between dengue in Bali and imported dengue in Australia at a lag of one month after including the number of Australian residents returning from Indonesia in log scale as an offset in the model. Figure 5 disaggregates this to the Balinese districts level and indicates that dengue in all Bali districts (except for Bangli and Denpasar) was significantly associated with imported dengue in Australia. Table S4 (supplementary material) presents the thresholds of monthly dengue incidence in Bali and its districts beyond which imported dengue in Australia started to increase substantially, suggesting that when monthly dengue incidence in Bali was above 1.05 per 100,000, dengue in Australia started to increase. The thresholds in Bali districts including Badung, Klungkung, and Tabanan were stable.

3.6 Associations of climatic factors in Bali with dengue in Australia

Figure 6A and Figure 6B show the significant associations between mean temperature and rainfall in Bali with occurrence of imported dengue cases in Australia, with the most pronounced association found for the state of Victoria.

4. Discussion

Indonesia, in particular Bali, has been recognized as a primary source for dengue importations into Australia. Despite this, little has been done in terms of using case notification data from Indonesia to inform public health measures to mitigate dengue importation into Australia. In tweezing apart the associations between imported dengue, local Balinese endemicity and easily accessible climatic variables, this study identifies a statistically robust early warning signal for dengue imports into Australia with remarkably long lead-time. The mechanisms behind this lead-time may include a few weeks between suitable climate and increased mosquito activity and local dengue transmission in Bali, and the incubation time for infections in Australian travelers as well as time to diagnosis in Australia.

The life cycle of dengue viruses and the growth and survival of dengue mosquitos are inextricably linked to climate (Li et al. 2019; Morin et al. 2013; Naish et al. 2014). In this study, we observed that, in Bali, the number of dengue cases increased with the increase of mean temperature, which is partially consistent with prior findings in China (Wu et al. 2018), Singapore (Earnest et al. 2011), Sri Lanka (Goto et al. 2013), and Vietnam (Pham et al. 2011). The number of dengue cases generally started dropping when mean temperature reached a high level in prior studies but we did not observe this pattern in our study. We also found that the relationship between rainfall and the number of dengue cases was bell-shaped, which is in line with the findings in China (Yi et al. 2019) and the Philippines (Iguchi et al. 2018). Previous studies examining the associations of climatic factors with dengue in Indonesia found contrasting results in different regions. Tosepu et al. and Bangs et al. found that mean temperature was significantly associated with the occurrence of dengue cases in Sulawesi Province and Palembang (Indonesia), respectively (Bangs et al. 2006; Tosepu et al. 2018). However, Kesetyaningsih et al. reported that rainfall and relative humidity, rather than temperature, were associated with dengue in Yogyakarta, Indonesia (Kesetyaningsih et al. 2018). The reasons for the discrepancy in dominant climatic driver(s) of dengue across different regions still remain largely unclear (Morin et al. 2013). Moreover, the different analytical approaches used in these studies and our study might also result in the different findings as prior studies in Indonesia tended to assume a linear relationship between climatic factors and dengue. In recent years the biological mechanisms underlying the effects of temperature and rainfall on dengue have been increasingly explored. Specifically, increased temperature facilitates dengue virus replication within the vectors and shortens the extrinsic incubation period of dengue viruses (Morin et al. 2013). Temperature also affects the development and survival of dengue mosquitos (Morin et al. 2013). Adequate rainfall provides enough water for potential breeding sites of the principal vector mosquito *Aedes aegypti* (i.e, water containers), but very heavy rainfall may flush away larvae and pupae from containers which restricts the development of mosquitoes (Sarfraz et al. 2012). This may explain our finding that the number of dengue cases increased when rainfall increased but started dropping when rainfall exceeded 16.2 mm in Bali. The positive association between mean temperature and number of dengue cases is of additional concern as global surface temperature will continue to increase as climate change proceeds, and future temperature-related dengue burden in Bali might consequently change and necessitate changes in vector control (Ebi and Nealon 2016).

International travel related transmission of diseases has become a major global public health issue (Fang et al. 2018; Findlater and I 2018). There were more than 1.2 billion international tourists in 2016, and this figure is still growing (UNTWO 2017). Australia witnessed a substantial increase in the number of residents travelling internationally over the past decade, and the monthly number of Australian residents returning from Indonesia has increased substantially from an average of 28,100 in the first five months of 2008 to an average of 98,980 in the first five months of 2018 (Australian Bureau of Statistics 2018). International travel plays an important role in the dispersal of dengue across different countries (e.g., Europe) (Choe et al. 2017; Semenza et al. 2014; Tian et al. 2017). An appreciable proportion of returning Australian travelers hospitalized for dengue had unrecognized signs of severe disease (Tai et al. 2017). It has been reported that travelers with dengue infection returning from Bali (Indonesia) to Queensland (Australia) may present a risk of starting a local dengue outbreak (David et al. 2012). In this study, we observed that, from 2007 to 2013, there was a significant relationship between dengue in Bali and local dengue in Queensland at a lag of one month, and the magnitude of this relationship was much greater than that found between dengue in Bali and imported dengue in Australia (Figure S4 (supplementary material)). Identifying these relationships is of great importance when considered in the context of providing more solid evidence for the efficacy in ongoing and upscaling novel dengue vector control strategies employing *Wolbachia* (O'Neill 2018; O'Neill et al. 2018).

The first dengue case in Australia was reported in 1873 in Victoria (Medical Society of Victoria 1873), and local dengue cases were prevalent in Queensland, New South Wales, Northern Territory, and Western Australia until the 1940s (Mackenzie et al. 1996). Dengue reappeared in Queensland in 1981 and only Queensland has local dengue cases nowadays (Mackenzie et al. 1996). Nevertheless, existing literature reported that there is a potential of *Aedes aegypti* incursion into northern parts of Western Australia and Northern Territory as climate change continues (Russell et al. 2009). Another dengue vector mosquito, *Aedes albopictus*, may have been introduced into Australia due to illegal fishing activity originating from Indonesia (Beebe et al. 2013), implying that imported cases in Western Australia and Northern Territory may not just pose extra burden to local healthcare system, but also may present a risk of dengue endemic in these regions if climatic conditions are favorable for dengue mosquitos in the future. The quantitative associations of dengue in Bali with imported dengue in New South Wales, Northern Territory, Tasmania, Victoria, and Western Australia that we observed in this study suggest that routine surveys in Australian international airports including asking returned travelers about countries they visited and their clinical manifestations as well as follow-ups of travelers with warning signs of dengue (especially those who returned from Bali) can help identify dengue patients in a timely manner and alert public health communities to take measures accordingly. Intriguingly, we observed that the dengue incidence thresholds in Badung, Klungkung and Tabanan were stable (Table S4), and this may be due to the fact that most tourists visit places in these three districts because popular resorts, beaches, temples and natural parks are located in these districts (e.g., Uluwatu Beach, Kuta Beach, Nusa Dua, Tanah Lot, Bedugul, and Nusa Penida). Unexpectedly, we did not observe a significant relationship between dengue in Denpasar and imported dengue in Australia (Figure 5), although Denpasar is an important sightseeing destination for tourists.

This study quantified the relationship between dengue in Bali and dengue in Australia, and it provides novel insight to inform the development of dengue early warning systems in Australia. There are studies calling for actions to incorporate climate information into the development of dengue early warning systems (Lee et al. 2017; Morin et al. 2018), and there are studies elucidating the importance of using travel-related data in dengue early warning (Racloz et al. 2012). Our study suggested that the information on climatic conditions in and travelers returning from one city may be used as important early warning signals for another city/region. It also calls for future endeavors assessing how infectious disease outbreaks overseas affect infectious disease importation into Australia. However, several limitations of this current study should be acknowledged. First, because of data availability we used data on number of returning residents in the whole of Australia rather than the number in each state/territory, which may not be accurate as some states/territories may have relatively more or fewer travelers. Second, data on number of residents returning specifically from Bali were not available, and thus we could only use data on number of residents returning from the whole of Indonesia. Third, sensitivity of any associations detected using our methods is compromised by under-reporting which is characteristic of infections such as dengue that are highly asymptomatic or have non-specific symptoms. Finally, local dengue outbreaks in northern Queensland were triggered annually by the arrival of infected international travelers. In this study, we were only able to assess the relationships of dengue in Bali with imported dengue and local dengue in the whole of Queensland. Future research should try to improve the spatial resolution to allow for improved targeting of surveillance and control. In this study, we were only able to analyze the dengue data in Queensland from 2007 to 2013 due to data availability issue, and more up-to-date data on imported dengue and local dengue in Queensland will be collected in the future.

5. Conclusion

Dengue in Bali was quantitatively associated with imported dengue in Australia at a lag of one month. Incorporating information on dengue incidence in Bali one month ahead and information on mean temperature and rainfall in Bali four months ahead into the development of dengue early warning systems may assist the control of imported dengue and mitigate outbreaks of local dengue in Australia. Our findings suggest that Australia’s biosecurity program may need to look beyond its own borders and contribute to dengue control overseas. This study also provides a template and framework for future surveillance of travel-related infectious diseases globally.

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Figure 1. Associations of mean temperature and rainfall with the occurrence of dengue cases in Bali in the optimal model

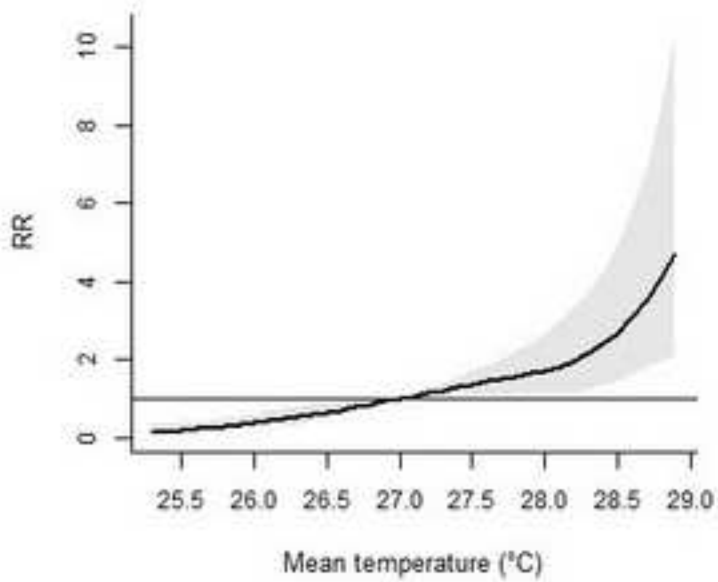

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Figure 2A. Relationship between dengue in Bali and imported dengue in Australia (excluding Queensland) at lag one month

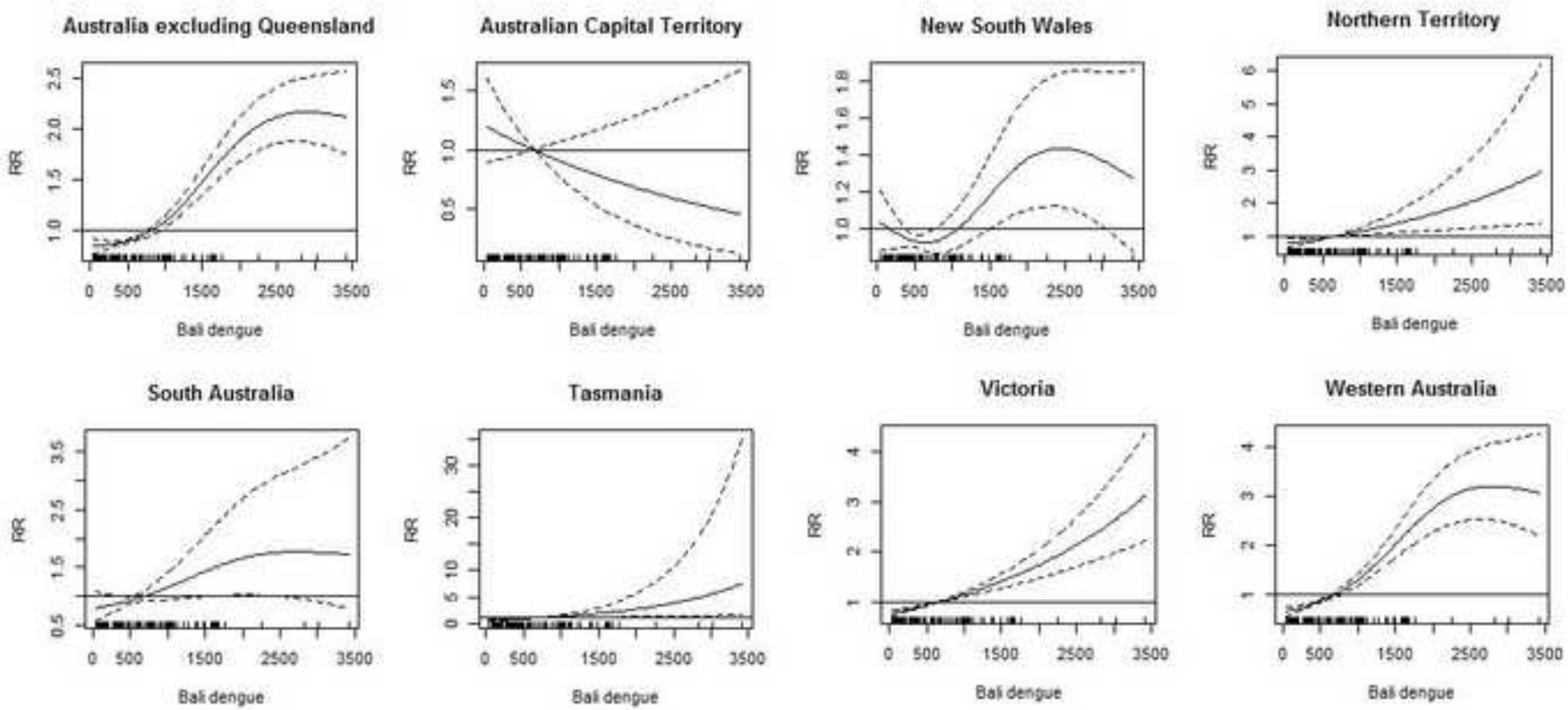

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Figure 2B. Relationship between dengue in Jakarta and imported dengue in Australia (excluding Queensland) at lag one month

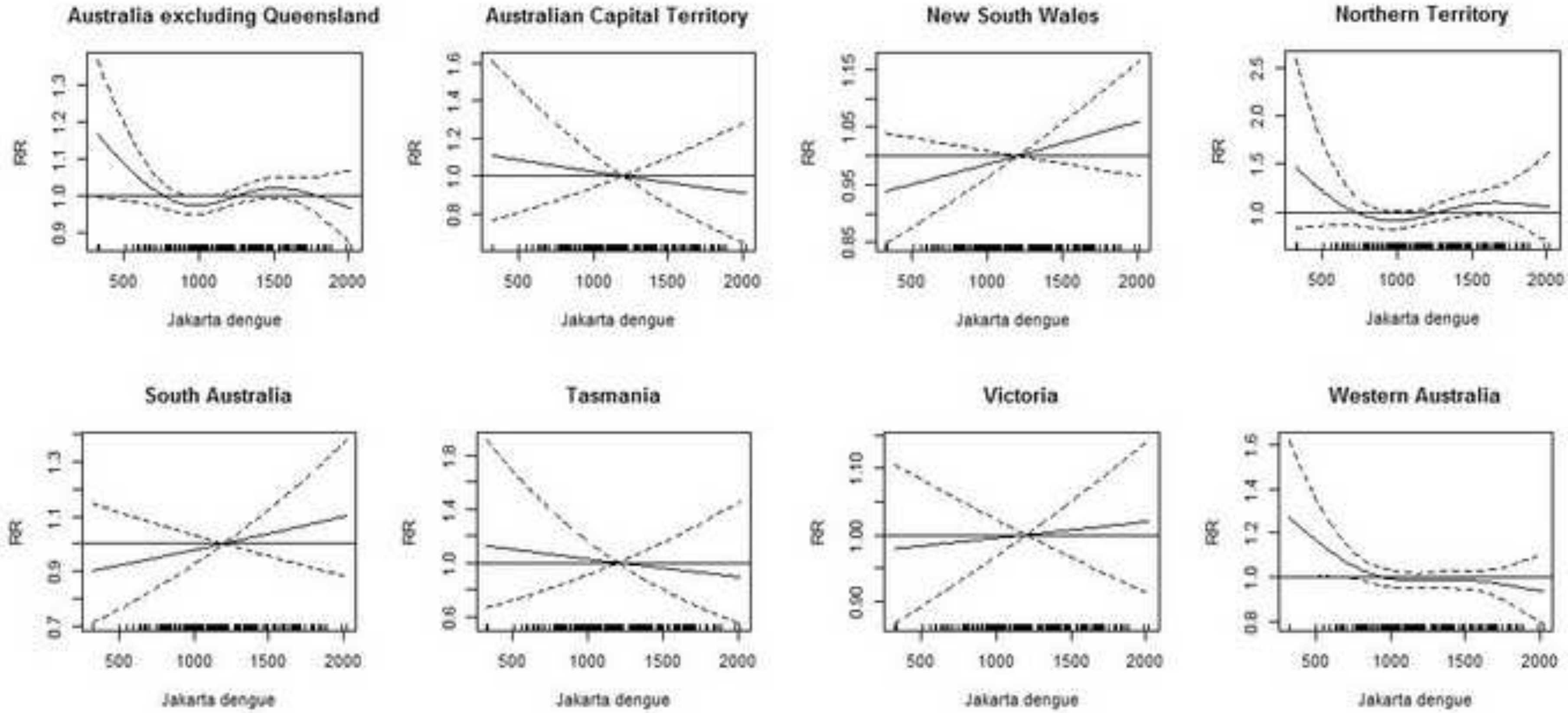

Figure 3. Relationship between number of Australians returning from Indonesia and imported dengue in Australia (excluding Queensland)

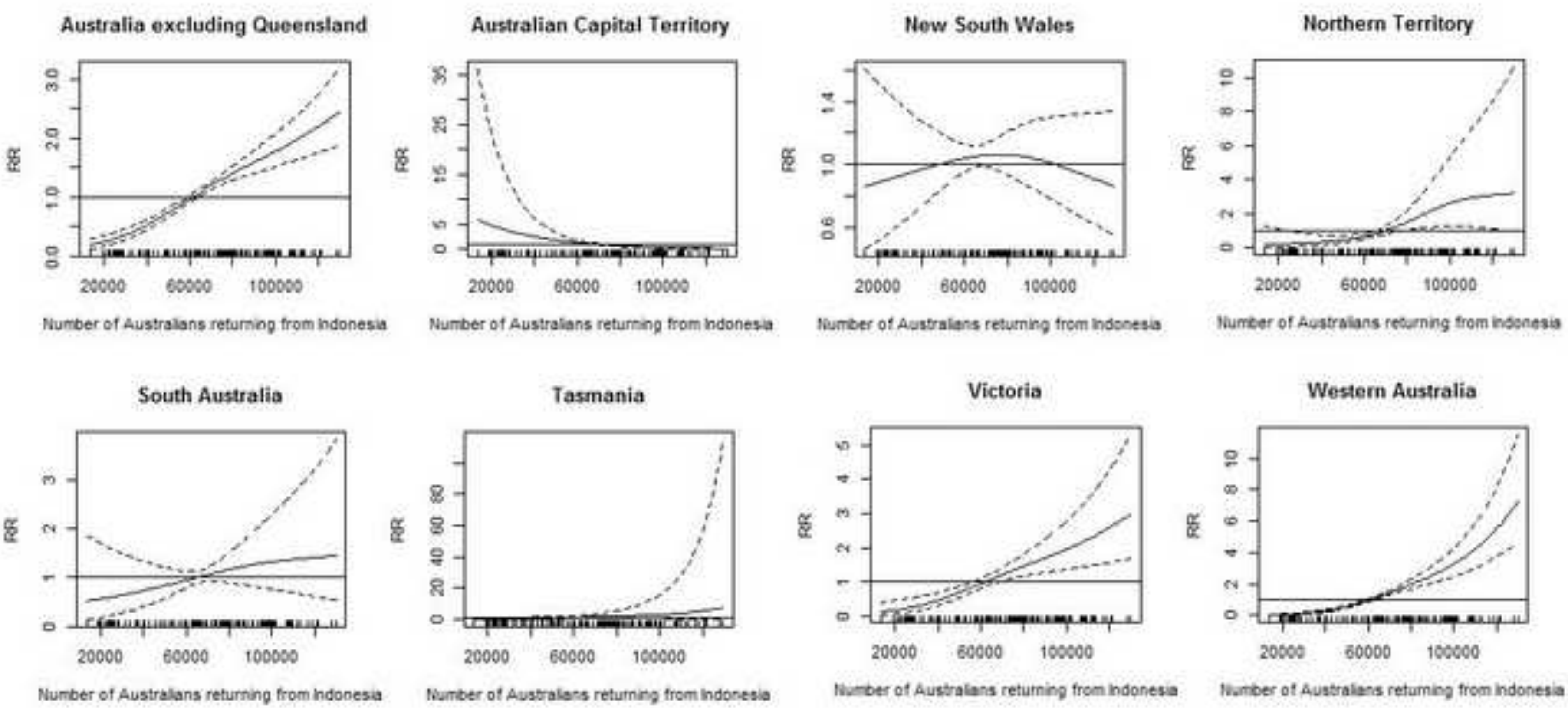

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Figure 4. Relationship between dengue in Bali and imported dengue in Australia (excluding Queensland) at lag one month after including the number of travelers in log scale as an offset in the model

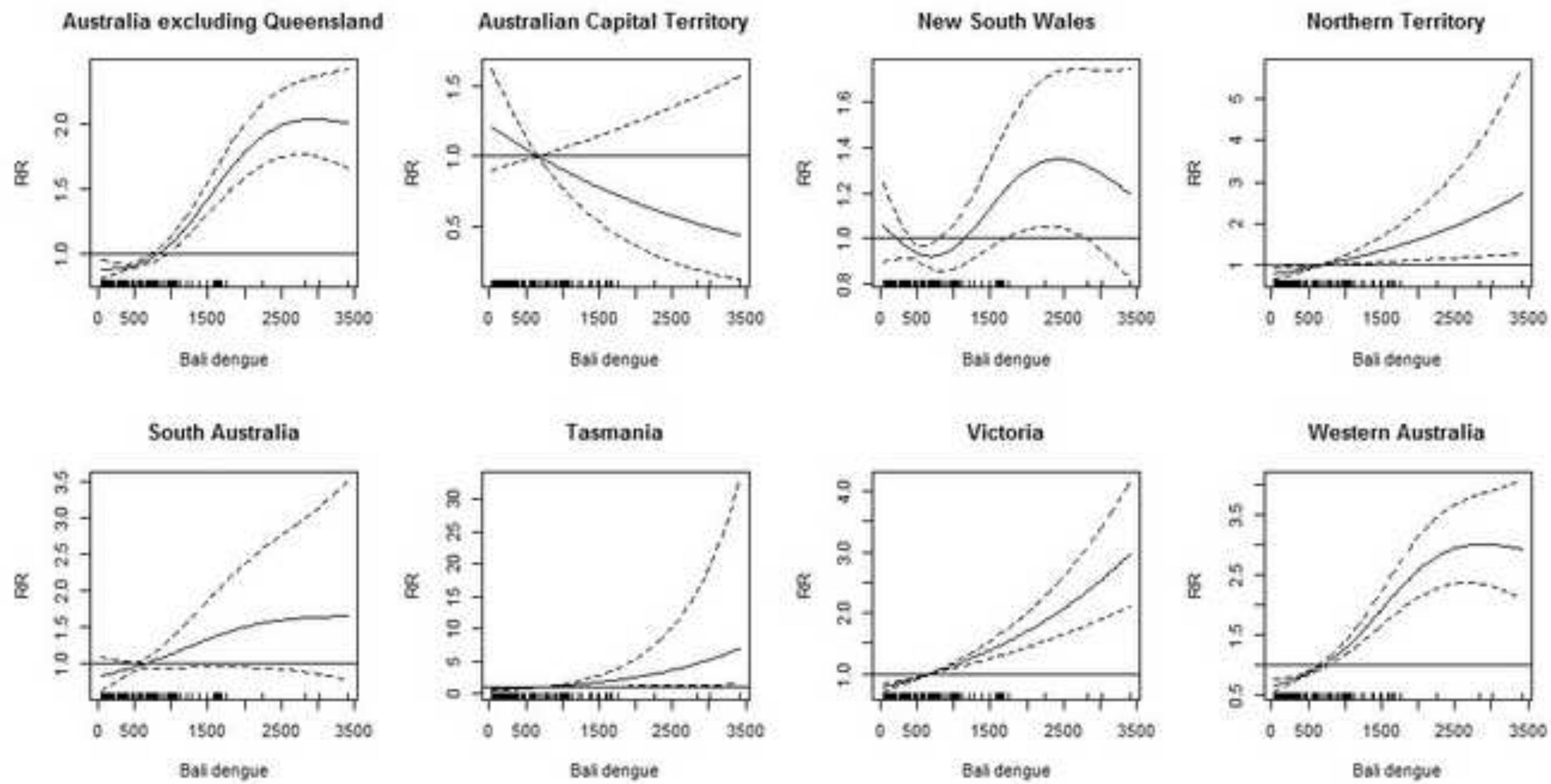

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Figure 5. Relationship between dengue in Bali districts and imported dengue in Australia (excluding Queensland) at lag one month after including the number of travelers in log scale as an offset in the model

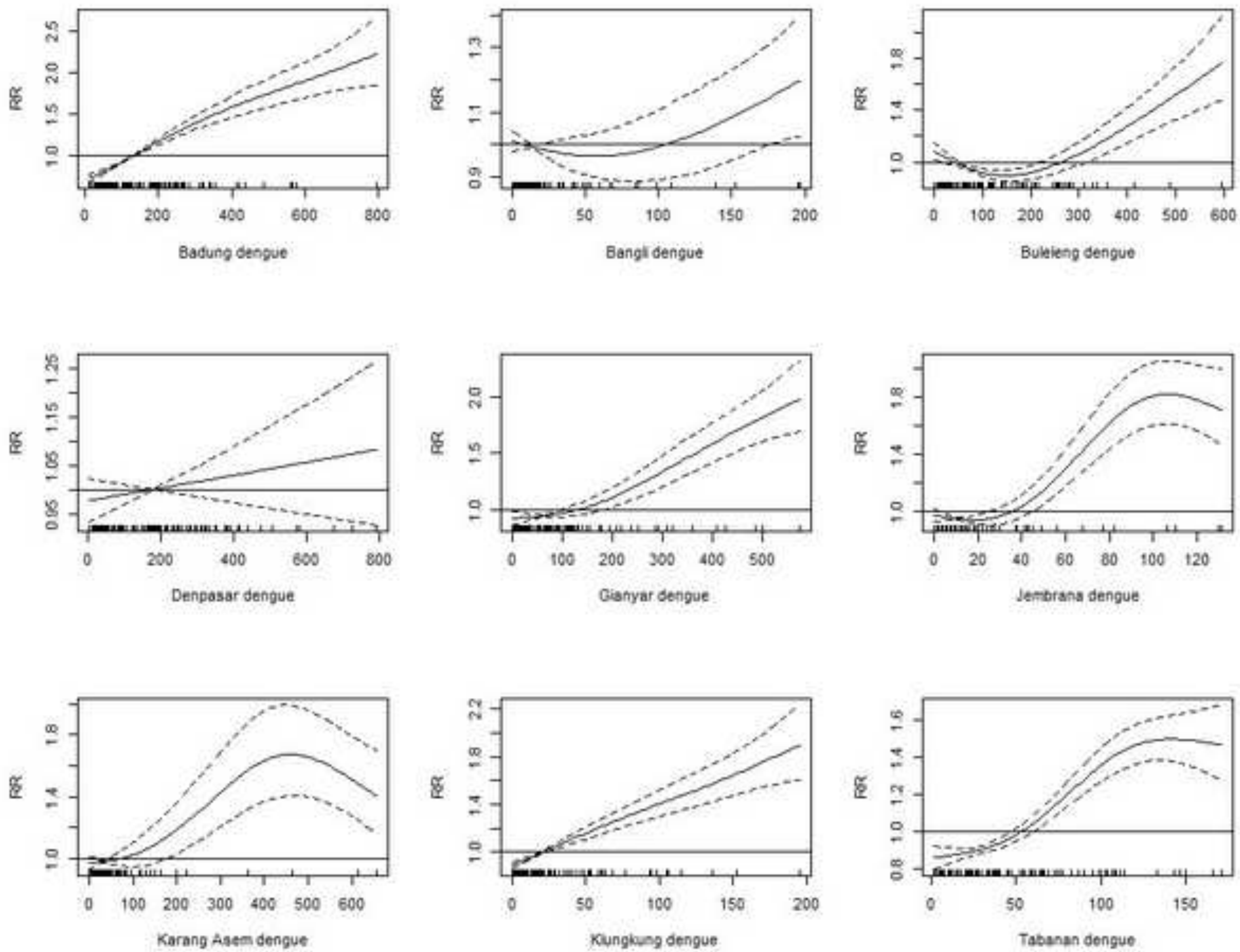

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Figure 6A. Relationship between mean temperature in Bali and imported dengue in Australia (excluding Queensland)

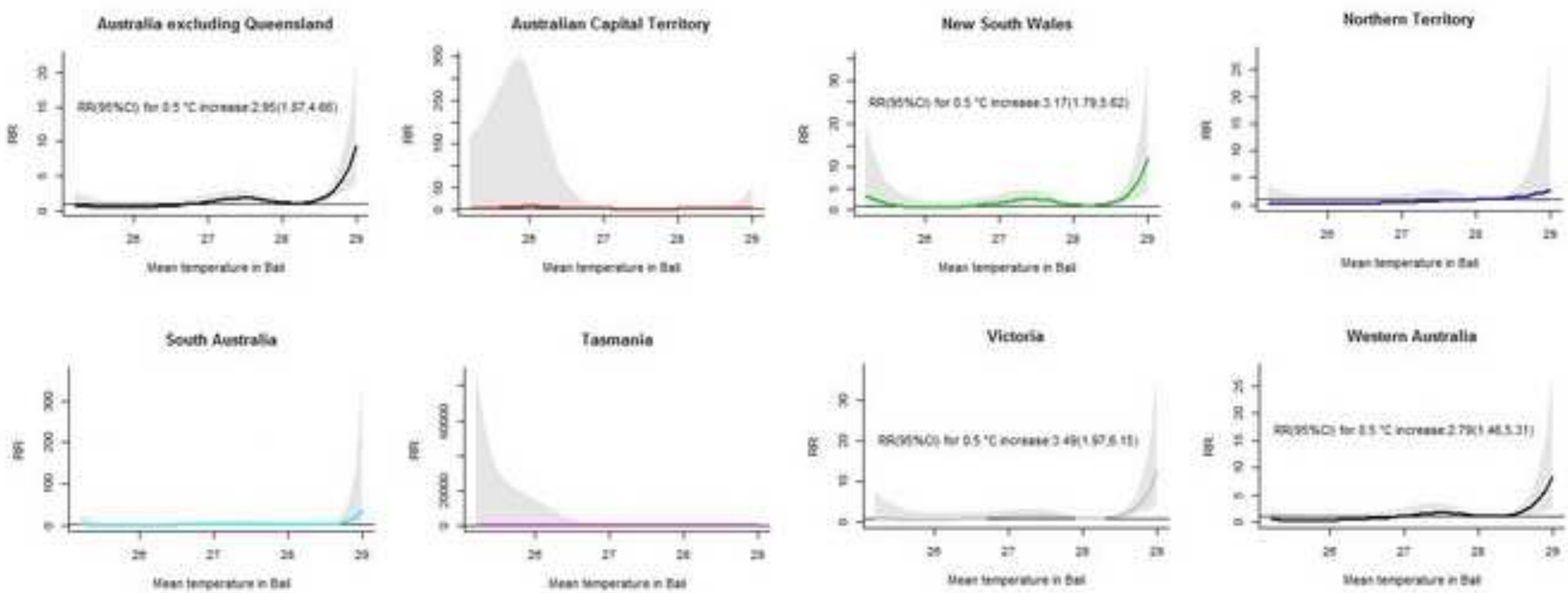

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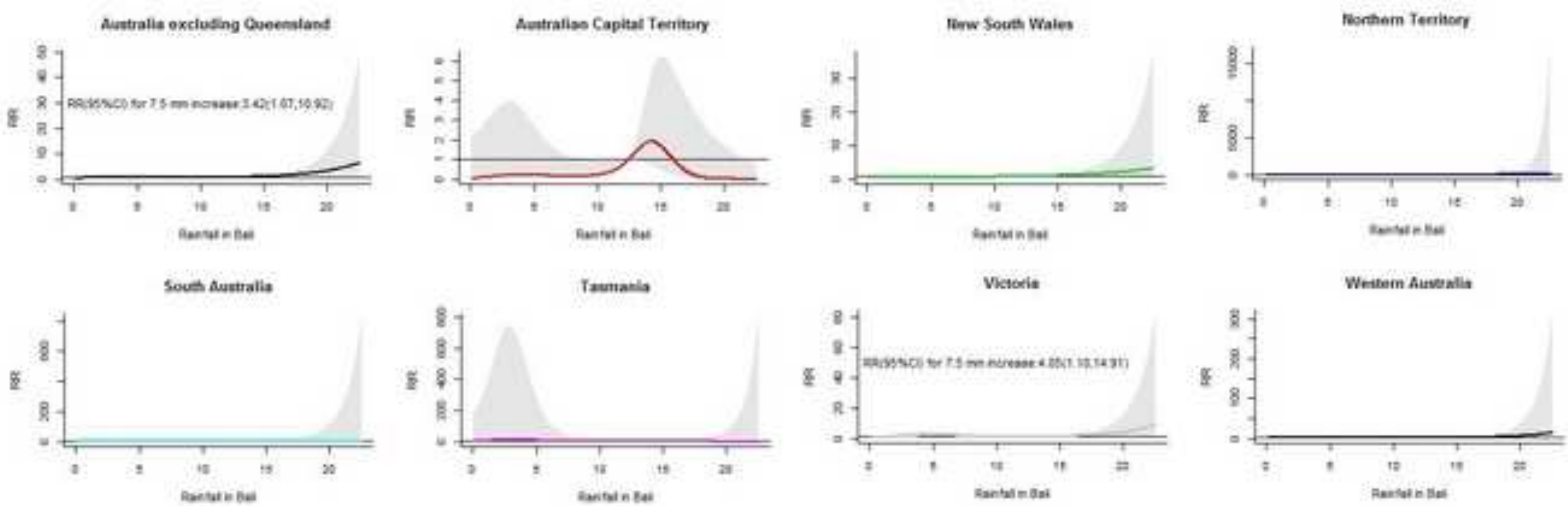
Figure 6B. Relationship between rainfall in Bali and imported dengue in Australia (excluding Queensland)



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