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Article type : Original Article

Hepatitis E virus infection in swine workers: A meta-analysis

Running title: Hepatitis E virus in swine workers

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Summary

Hepatitis E virus (HEV) infects both humans and animals. Swine has been confirmed to be the principal natural reservoir, which raises a concern that HEV infection would be substantially increasing among swine workers. The present study calculated the pooled prevalence of IgG antibodies against HEV among swine workers and the general population in previous cross-sectional studies. We conducted a meta-analysis comparing the prevalence of HEV infection between swine workers and the general population, including local residents, blood donors, and non-swine workers. Through searches in three databases (PubMed and OVID in English, and CNKI in Chinese) and after study selection, a total of 32 studies from 16 countries (from 1999 through 2018) were included in the meta-analysis. A random effects model was employed in the study; an I^2 statistic assessed heterogeneity and the Egger's test detected publication bias. The comparative prevalence of anti-HEV IgG was pooled from the studies. Compared to the general population, the prevalence ratio (PR) for swine workers was estimated to be 1.52 (95% CI 1.38-1.76) with the I^2 being 71%. No publication bias was detected (*P*=0.40). A subgroup analysis further indicated increased prevalence of anti-HEV IgG in the swine workers in Asia (PR=1.49, 95% CI: 1.35-1.64), in Europe (PR=1.93, 95% CI: 1.49-2.50), and in all five swine-related occupations, including swine farmers, butchers, meat processors, pork retailors and veterinarians (PR ranged between 1.19 and 1.75). In summary, swine workers have a relatively higher prevalence of past HEV infection, and this finding is true across swine-related occupations, which confirms zoonotic transmission between swine and swine workers.

Key word: Hepatitis E virus, HEV; swine worker; meta-analysis; zoonosis

Impacts

- Hepatitis E virus is a zoonotic virus that has been wide-spread in low-, middle-, and high-income countries. Swine has been confirmed to be the principal natural reservoir.
- The pooled prevalence of anti-HEV IgG has been estimated to be significantly higher in swine workers than in the general population, especially in Asia and Europe, regardless of socioeconomic circumstances of country.
- We demonstrate that the prevalence of anti-HEV IgG increased across five swine-related occupations, including swine farmers, butchers, meat processors, pork retailors, and veterinarians, suggesting substantial risk of cross-species transmission.

Introduction

Hepatitis E virus (HEV) is a single-strand positive RNA virus that causes hepatitis E. HEV genome consists of 7.2 kb, with 3 or 4 overlapping open reading frames (ORF)

(Mushahwar, 2008; Nair et al., 2016). So far, HEV has been classified into seven genotypes (Smith et al., 2014). Genotypes 1 and 2 infect only humans, whereas other genotypes infect diverse species including humans (genotype 3, 4, and 7), swine (genotype 3 and 4), wild boar (genotype 3-6), rabbits (genotype 3), deer (genotype 3), mongooses (genotype 3), yaks (genotype 4), and camels (genotype 7) (Nan & Zhang, 2016). Swine has been confirmed to be a principal reservoir based on evidence from both epidemiological observations and experimental studies. The prevalence of antibodies against HEV (anti-HEV) has been reported to range between 8% and 93% among swine across the world which is much higher than other animal reservoirs, with variation in different swine herds and countries (Salines, Andraud, & Rose, 2017). Additionally, a phylogenetic analysis has demonstrated that human and swine HEV strains isolated from the same regions share high sequence identities of up to 91.3-100%, suggesting a close phylogenetic relationship (Liu et al., 2012). Experimental cross-species transmission of HEV has also been confirmed across humans, non-human primates, and swine with genotype 3 and 4 (Doceul, Bagdassarian, Demange, & Pavio, 2016).

Swine workers, including swine farmers, butchers, meat processors, pork retailers, and veterinarians are routinely exposed to swine and are consequently at possible risk of HEV infection. It has been documented that the prevalence of anti-HEV IgG in swine workers ranged between 3.3% (swine farmers, Italy) and 75.9% (swine farmers, China), which is higher than that in the general population in the same regions (De Schryver et al., 2015). However, some studies have reported a similar prevalence of HEV between swine workers and the general population, such as in one study in Thailand (Hinjoy et al., 2013). Additionally, it remains unclear which occupation is more likely to be infected with HEV. A study of anti-HEV IgG prevalence in occupations including butcher, meat processor, swine farmer and veterinarian reported relatively higher anti-HEV IgG in butchers and meat processors, but differences were not significant(Yan et al., 2007).

Because there are conflicting findings of increased prevalence of HEV infection in swine workers relative to the general population, this study combined previous findings in a meta-analysis. This study calculated the prevalence of HEV infection in swine workers compared to the general population, and further determined possible regions and occupations associated with increased prevalence of HEV infection.

Materials and Methods

Data sources

Two international databases, PubMed and OVID, and one Chinese database, CNKI, were searched for studies focusing on HEV infection among swine workers from their inception to April 2017. The data were subsequently updated until April 2018 by using the same strategy. The search terms "Hepatitis E Virus" and "swine" were used as shown in Table 1. Two independent investigators conducted the search and then determined if a study was potentially related to our study objective according to its title and abstract. Studies that were considered acceptable by either investigator were added to NoteExpress version 3.2 (Aegean Technology Co. Ltd., Beijing, China) for further selection.

Study selection

The full text of the retrieved studies was reviewed for selection. The inclusion criteria were as follows: 1) the study was cross-sectional; 2) the study included both swine workers and the general population in the same region; and 3) anti-HEV IgG was examined and reported. The exclusion criteria were as follows: 1) the study was a conference article or abstract; 2) the study repeated findings from a previous study; or 3) the study was about wild boars. The two investigators independently carried out the selection. Conflicting decisions were addressed by negotiation or further judged by a third investigator.

Data extraction

The selected studies were read for data extraction. The data of interest included author, year of publication, sampling site, country or region of sampling, time of sampling, definition of occupation and general population, sample size of both swine workers and general population, number of HEV infections in both swine workers and the general population, and laboratory examination methods. These data were retrieved by one investigator and then confirmed by another investigator. For studies that only provided sample size and prevalence of HEV infection, we calculated the number of infections.

Statistical analysis

The meta-analysis was conducted with R software version 3.4 (R Development Core Team, Vienna, Austria) and the package meta version 4.8 (Guido Schwarzer, Baden-Württemberg, Germany). To pool the comparison of HEV infection in swine workers and the general population, the prevalence ratio (PR) was estimated across the included studies with a random effect. An I^2 statistic was calculated to assess heterogeneity across studies, with an I^2 greater than 50% considered to be high heterogeneity. The Egger's test was used to detect potential publication bias. Additionally, a subgroup analysis was conducted by stratifying by continent of study and occupation.

Results

Data retrieval and study selection

As shown in Fig.1, a total of 1987 studies were initially found in CNKI, PubMed and OVID, in which 234 studies were potentially related to our study objectives and had a full text retrieved. Subsequently, 204 studies were excluded with reasons listed in Fig.1, and two studies were added in an updated search, yielding 32 studies for the meta-analysis (Bouwknegt et al., 2008; Caruso et al., 2017; De Sabato et al., 2017; Drobeniuc et al., 2001; Engle, Yu, Emerson, Meng, & Purcell, 2002; Galiana, Fernandez-Barredo, Garcia, Gomez, & Perez-Gracia, 2008;Hinjoy et al., 2013; Hongwei, 2009;Jiang Xin, Zheng Renshu, & Shijuan, 2009; Kang et al., 2017; Krumbholz et al., 2014; Krumbholz et al., 2012; Lange et al., 2017; Lee et al., 2013;

Liang et al., 2014; Liu Xiaogui et al., 2007;Love, Bjornsdottir, Olafsson, & Bjornsson, 2018; Lu Yihan et al., 2006; Masia et al., 2009;Meng et al., 1999; Meng et al., 2002; Nong Chushi, Li Yanping, & Yi, 2007; Olsen, Axelsson-Olsson, Thelin, & Weiland, 2006; Silva et al., 2012; Traore et al., 2015; Utsumi et al., 2011; Vivek & Kang, 2011; Wu Hongzhao, Liao Ziping, Wang Pingping, Lou Yongjin, & Wenzhong, 2018; Wu Yong et al., 2016; Yan et al., 2007; Yu et al., 2009; Zheng et al., 2006). Of the included studies, 24 were published in English and 8 in Chinese. The year of publication ranged from 1999 to 2018, and the majority of studies were conducted in either Asia (n=17) and Europe (n=11). In the studies, the swine workers included swine farmers, butchers, meat processors, pork retailers and veterinarians, whereas the general population included local residents and blood donors. Characteristics of the included studies are shown in the Supplementary Table.

Meta-analysis

By combining 32 studies with a random effect (Fig.2), the pooled prevalence of anti-HEV IgG was determined to be significantly higher in the swine workers (32.85%) than in the general population (21.70%), with a corresponding PR of 1.52 (95% CI: 1.38-1.76) (Table 2). However, the heterogeneity was high, as indicated by the I^2 being 71%. Publication bias was not indicated through the Egger's test (P=0.40).

The included studies that reported prevalence of anti-HEV IgG were conducted in different continents, including Asia (n=17), Europe (n=11), Africa (n=1), North America (n=2), and South America (n=1). According to a subgroup analysis stratified by continent (Fig.3; Table 2), the difference in the pooled prevalence of anti-HEV IgG between swine workers and the general population remained significant in Asia (PR=1.49, 95% CI: 1.35-1.64) and Europe (PR=1.93, 95% CI: 1.49-2.50), whereas it was not significant in North America (PR=0.97, 95% CI: 0.43-2.18). Because only one study was conducted in Africa and South America, estimates for these continents may be not generalizable. Additionally, heterogeneity was low (I^2=32%) in Europe, whereas it was high in other subgroups ($I^2 \geq 78\%$).

In our study, swine workers could be a part of any swine-related occupation. In the included studies, some contained more than one occupation. According to a subgroup analysis stratified by occupation (Fig.4; Table 2), the difference in the pooled prevalence of anti-HEV IgG between swine workers and the general population also remained significant. Compared to the general population, the PRs were higher for butchers (PR=1.75, 95% CI: 1.31-2.35), swine farmers (PR=1.51, 95% CI: 1.32-1.74), meat processors (PR=1.46, 95% CI: 1.13-1.89), veterinarians (PR=1.36, 95% CI: 1.15-1.61), and pork retailors (PR=1.19, 95% CI: 1.09-1.29). The heterogeneity was only low for swine veterinarians (I^2=14%) and pork retailers (I^2=0%), whereas it was high for all other occupations ($I^2 \geq 81\%$).

Discussion

Through a meta-analysis of previous studies, we determined that the PR of the pooled prevalence of anti-HEV IgG in swine workers compared to the general population was as high as 1.58, suggesting swine workers are more likely to be infected with HEV than the general population by 50%. It was confirmed that swine workers have substantially increased prevalence of HEV infection. As the majority of previous studies focusing on anti-HEV antibodies were cross-sectional, we included only cross-sectional studies to conduct the meta-analysis. So far, we are unware of any prospective study comparing seroconversion between the swine workers and the general population.

In fact, this heterogeneity is the reason that there is conflicting conclusions on the prevalence of HEV infection between diverse swine workers groups or between swine workers and the general population. A previous study even identified swine-related occupations as a protective factor (Engle et al., 2002). To overcome limitations and improve the efficiency of the meta-analysis, we further employed subgroup analyses. We determined that in Asia and Europe, and for specific occupations examined, swine workers had significantly higher pooled prevalence of anti-HEV IgG compared to the general population, suggesting an increased prevalence of HEV infection. For the subgroup analysis by continent, we concluded that there were relatively more Asian and European studies included in the meta-analysis, leading to a more stable estimate, whereas few studies were conducted in Africa, North America, or South America. Previous studies have revealed that HEV is very endemic in eastern and southeastern Asian countries. In China, HEV prevalence is increasing from a high starting point (Zhu, Liu, Fu, Zhang, & Mao, 2018). Simultaneously, HEV prevalence has become greater in European countries as confirmed hepatitis E cases have increased over 10 fold between 2005 and 2015 (Aspinall et al., 2017). Additionally, the gap in HEV infection between the swine workers and the general population did not vary between Asia and Europe. Traditionally, it is believed that there are different operational procedures in various regions, especially between industrialized countries (such as those in Europe) and resource-limited countries (such as those in Asia), which may result in a disparity in the prevalence of HEV infection through contact with swine. However, in our study, the included studies conducted in five Asian countries (China, Thailand, Japan, Indonesia, and India) and nine European countries (Germany, France, Italy, Norway, Finland, the Netherland, Sweden, Spain, and Moldova) did not differ. Thus, we have evidence that swine workers have substantially increased prevalence of HEV infection, regardless of the socioeconomic circumstances of their country.

For the subgroup analysis by specific swine-related occupation, it was very interesting that all the subgroups gave positive findings in that the swine workers had significantly higher prevalence of anti-HEV IgG compared to the general population. These consistent findings demonstrate that swine workers have substantially increased prevalence of HEV infection, regardless of the specific occupation. Additionally, we found that the gap in HEV infection between the occupation group and the general population did not vary across occupations. Some swine workers such as butchers may be more directly exposed to swine blood and swine farmers may have more contact with swine feces, possibly indicating higher prevalence of HEV infection;

however, this meta-analysis showed that they had similar PR values compared with meat processors or veterinarians (and the latter is an occupation group who are trained to be careful in self-protection during the examination of animals). In one French study focusing on HEV infection in swine farmers, those who wore gloves had significantly lower prevalence of HEV infection, suggesting self-protection was crucial for the prevention of HEV infection (Chaussade et al., 2013). It is difficult to interpret our findings (the comparison of PR values and 95% CI) that, among all swine-related occupations, pork retailors had slightly lower prevalence of HEV infection and butchers had the highest prevalence. Pork retailors have only routine contact with pork; while butchers have more direct and frequent contact with animals that may carry HEV, and may even be more likely to consume uncooked or undercooked meat (Toyoda et al., 2008). However, the subgroups of meat processors and pork retailers were only examined in one study each, so the results might be not as stable as our estimates for other occupations.

Another way to protect individuals against hepatitis E infection and disease is through vaccination. A hepatitis E vaccine was licensed in China in 2012, and is currently the only hepatitis E vaccine available in any country (Wu, Chen, Lin, Hao, & Liang, 2016). Clinical trials in China have found the vaccine efficacious; at 4.5 years, the vaccine had an efficacy of 86.8% (95% CI: 71%-94%) (Zhang, Shih, & Xia, 2015). Nonetheless, in a position paper released in 2015, the World Health Organization did not issue a broad recommendation for routine vaccination, citing a lack of research outside of China and in certain populations ("Hepatitis E vaccine: WHO position paper, May 2015," 2015). Our analysis suggests that swine workers could be a targeted group for vaccination programs and for future research on the cost-effectiveness of hepatitis E vaccination. Our study examined seropositivity, and not clinical disease, as an outcome, but we can reasonably assume that risk of disease is also higher among swine workers than others in the general population.

In our study, a major limitation is the heterogeneity observed in the pooled prevalence of both anti-HEV IgG and in the subgroup analyses. This heterogeneity may be partly interpreted by different definitions of swine-related occupations and different operational procedures across regions. Another explanation is differing inclusion criteria for swine workers and the general population across studies. However, the consistency between the findings of original pooled analysis and the subgroup analyses could provide concrete evidence validating our hypothesis. It is also possible that other occupations (like hunters) could be a high risk group, but they were not explicitly considered in this study. Another limitation is that our finding was supported by only the pooled prevalence of anti-HEV IgG.

In summary, swine-related occupations including swine farmers, butchers, meat processors, pork retailors and veterinarians have substantially increased the prevalence of past HEV infection compared to non-swine-related population, suggesting swine workers are more likely to be infected with HEV. However, more evidence focusing on current HEV infection is warranted for further confirmation of zoonotic transmission among swine workers.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

This work was supported by the China National Natural Science Funds (grant number 81370081) and Shanghai Municipal Health and Family Planning Commission (grant number GWTD2015S05). Dr. Wagner received funding through a Fulbright Scholarship.

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Table 1. Search strategies and results

Database	Strategy	No. publications	Date of search	Date of updated search
PUBMED	(HEPATITIS E VIRUS[Title/Abstract]) AND (SWINE[Text Word] OR PIG[Text Word] OR PORCINE[Text Word] OR HOG[Text Word])	698	2017.4.8	2018.4.30

CNKI	(TI='戊型肝炎' OR TI='戊肝') AND (FT='猪')	528	2017.4.8	2018.4.30
OVID	hepatitis e virus.kw,ti,ab. and (swine or porcine or pig or hog).tw.	761	2017.4.10	2018.4.30

Table 2. Overall and subgroup analysis of anti-HEV IgG with random effects

Model	No. studies	PR	95% CI	I^2
Overall IgG	32	1.52	1.38-1.67	71%
Subgroup by continent				
Africa	1	1.59	1.25-2.03	Not applicable
Asia	17	1.49	1.35-1.64	74%
Europe	11	1.93	1.49-2.50	32%
North America	2	0.91	0.43-2.18	91%
South America	1	2.31	0.82-6.46	Not applicable
Subgroup by occupation				
Swine farmers	26	1.51	1.32-1.74	81%
Butchers	5	1.75	1.31-2.35	86%
Meat processors	1	1.46	1.13-1.89	Not applicable
Pork retailers	2	1.19	1.09-1.29	0%
Veterinarians	6	1.36	1.15-1.61	14%

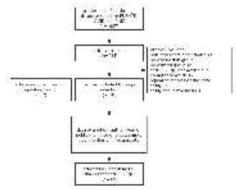
Figure Legends

Fig.1 Flow chart of the meta-analysis.

Fig.2 Overall analysis of anti-HEV IgG prevalence.

Fig.3 Subgroup analysis of anti-HEV IgG prevalence stratified by continent.

Fig.4 Subgroup analysis of anti-HEV IgG prevalence stratified by occupation.



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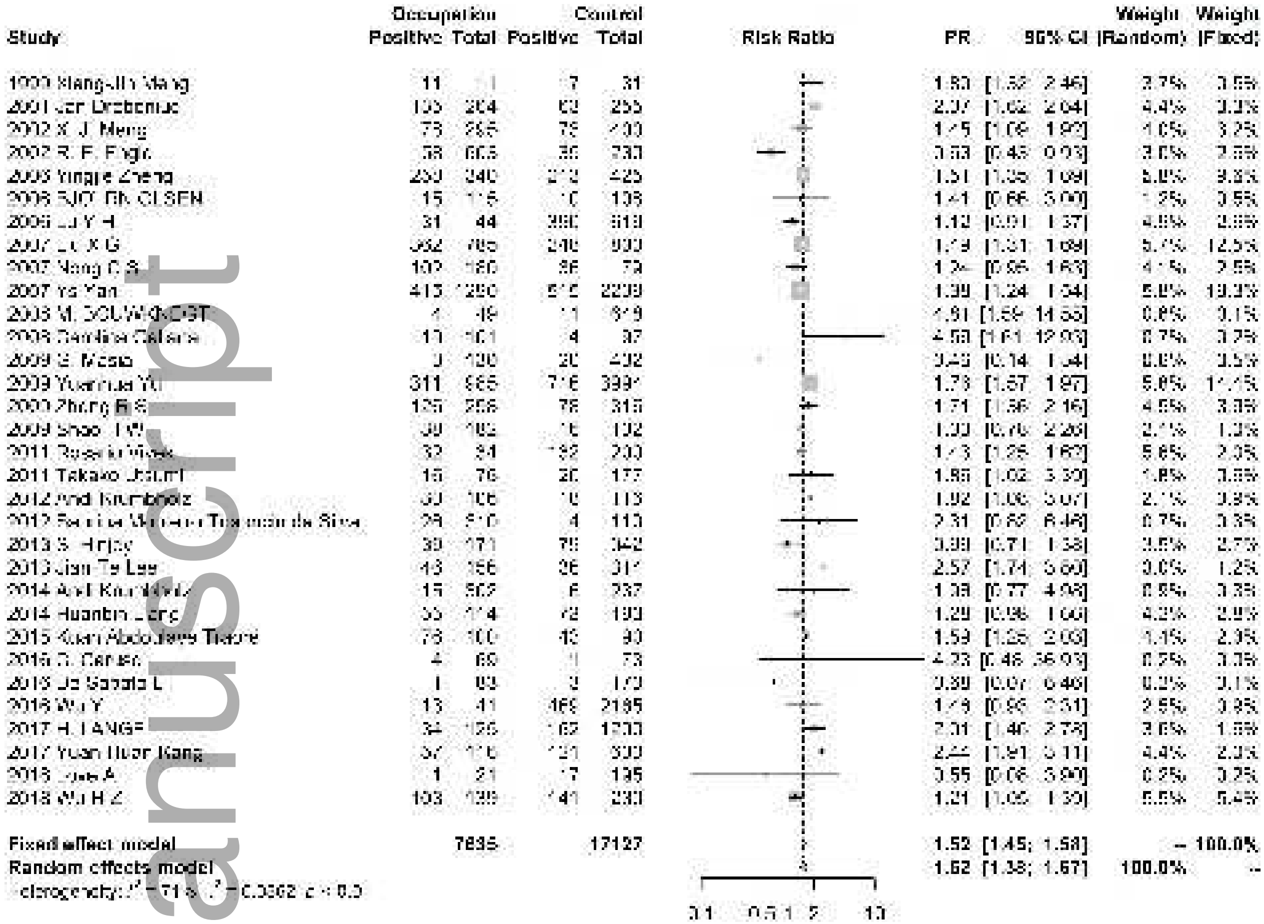

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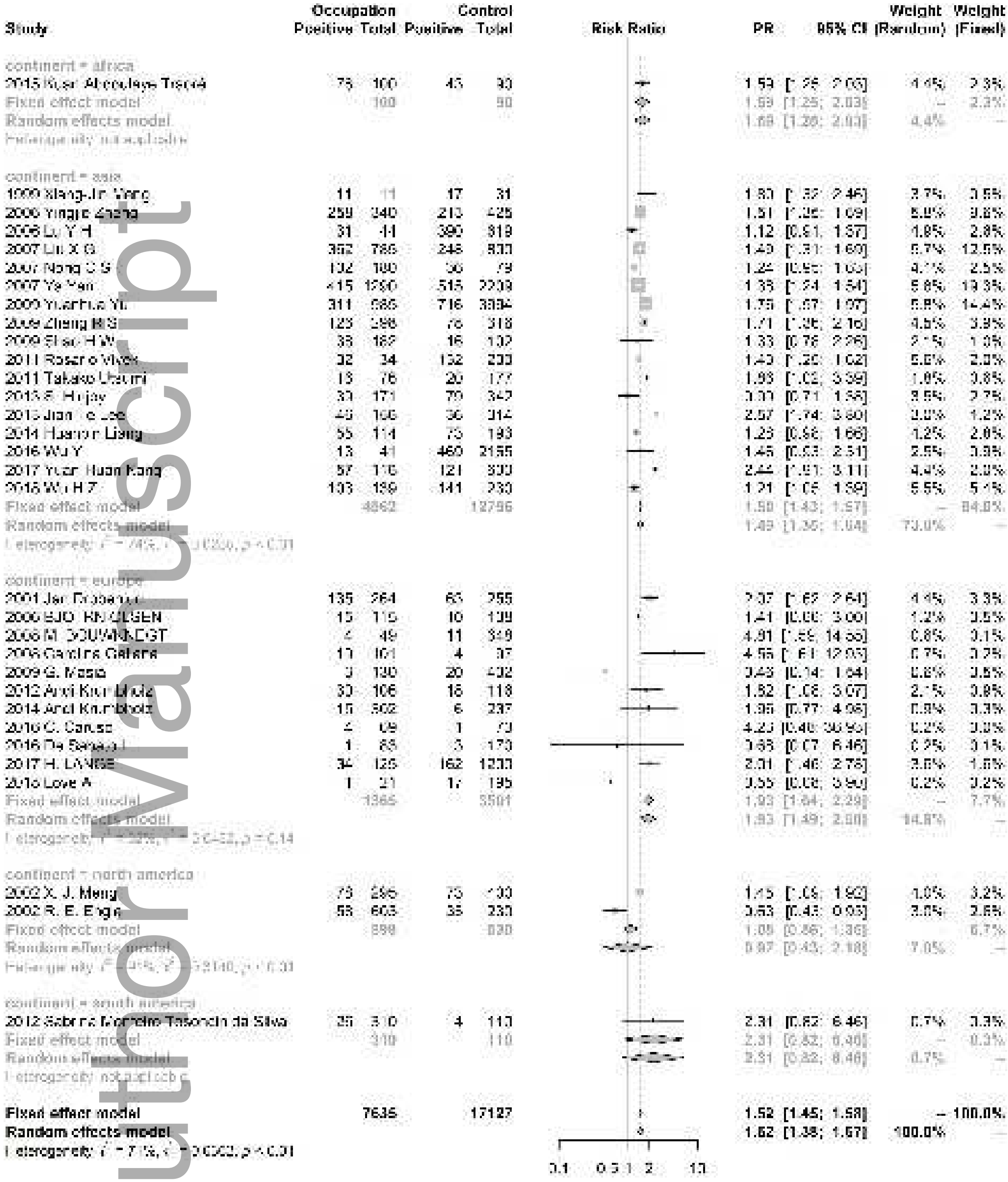

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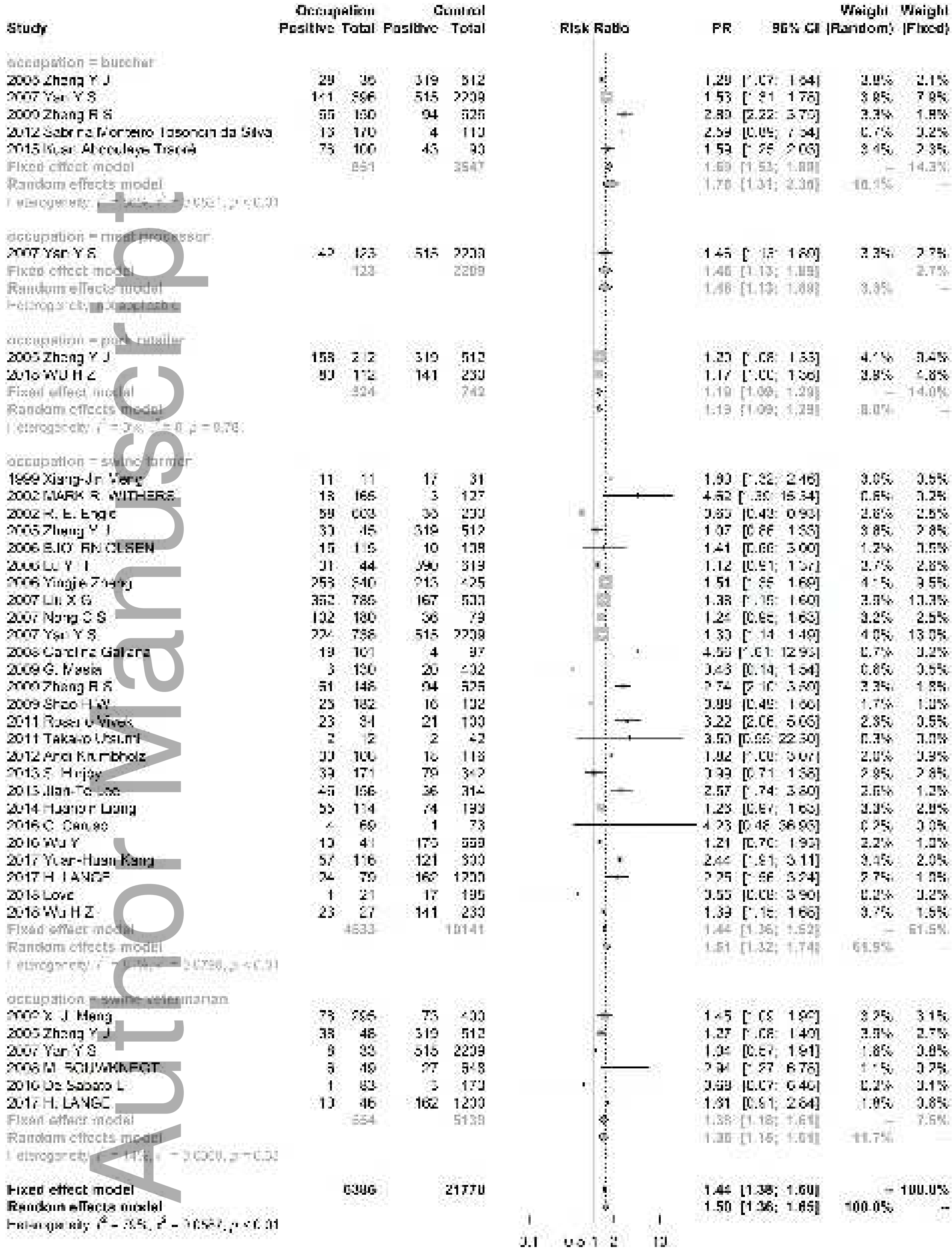

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