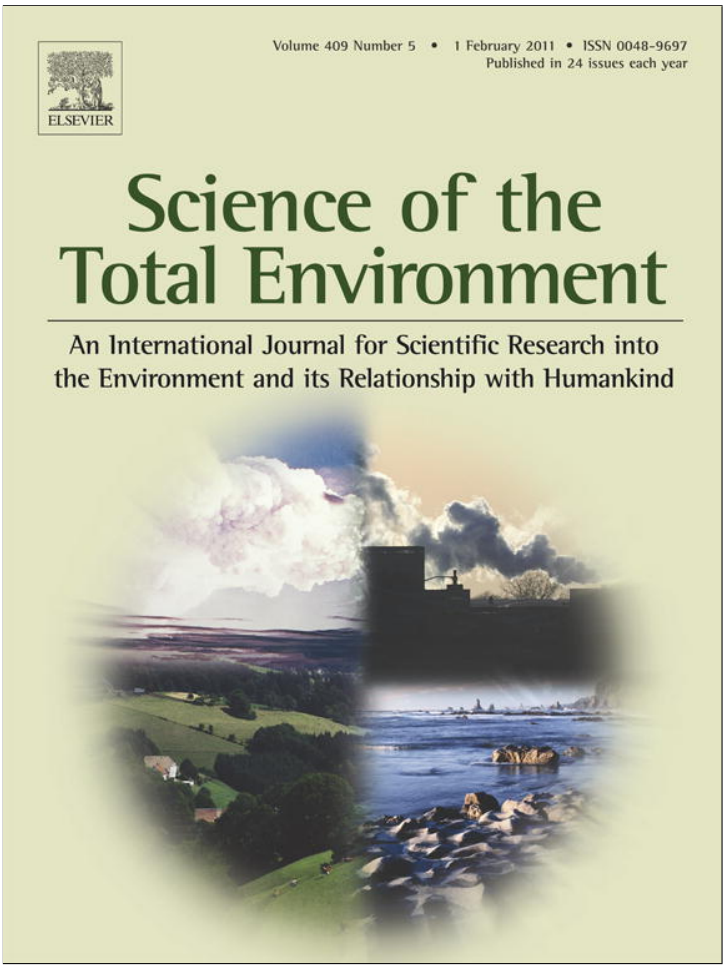

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# Health impacts associated with the implementation of a national petrol-lead phase-out program (PLPOP): Evidence from Taiwan between 1981 and 2007

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ABSTRACT

*Background and objective:* In 1981, a petrol-lead phase-out program (PLPOP) was launched in Taiwan for the abatement of environmental lead emissions. The present study was set out to examine whether the reduction of environmental lead emissions would result in the decrease in mortality rates of various diseases based on national data between 1981 and 2007.
*Method:* The national mortality data were obtained from the Office of Statistics of the Taiwan Department of Health (Taiwan DOH). Standardized mortality ratios (SMRs) were calculated based on 2000 WHO world standard population. Gasoline consumptions were obtained from the Bureau of Energy.
*Results:* The mean blood lead levels (BLLs) had decreased dramatically from approximately 20.14 μg/dl in the leaded petrol phase to 3 μg/dl or lower in the unleaded petrol phase. From 1981 to 2007, the mortality (per 100,000 people) was decreased from 146.2 to 43.8 for cerebrovascular disease, from 85.3 to 44.4 for heart disease, from 35.4 to 6.6 for hypertensive disease, from 21.3 to 17.3 for nephrosis, and from 810.2 to 491.6 for all causes. By taking the confounders (including economic growth rate, per capita income, tobacco consumption, and medical resources) into account, the decreases in SMRs for all causes, cerebrovascular disease, and nephrosis were found to be highly correlated with the decrease in petrol lead emissions ($p$-values = 0.001, <0.001, 0.020, respectively).
*Conclusion:* Our results clearly show that the implementation of the PLPOP was associated with a decline in mortality rates in several diseases that have been associated with lead exposure, even after adjustment for a number of relevant confounders.



## 1. Introduction

Lead has been added to petrol (gasoline) as an anti-knocking agent since the 1920s to improve fuel performance and reduce wear on vehicle engines. Leaded petrol has been reported to cause more lead exposure than any other source worldwide from that time (Landrigan, 2002). During 1970s, the health impacts associated with lead emissions from vehicles had become a widely concerned issue. Many studies have reported that environmental lead emissions had resulted in significant health effects to the central nervous system, haem-synthesis, reproductive system, and psychological and neurobehavioral functions (ATSDR – Agency for Toxic Substances and Disease Registry, 2007; Skerfving and Bergdahl, 2007; Bellinger, 2005; Fewtrell et al., 2004; Tong et al., 2000).

Recently, many large population-based studies have been conducted to explore the relationship between environmental lead emissions and various health outcomes. Here, it should be noted that BLLs have been considered representative to environmental lead exposures in these studies. Strong associations have been found between BLLs and increased risk of all causes, cancer, stroke and cardiovascular mortality. Even at BLLs between 5 and 9 μg/dl, a significant association with the disease risk can still be found (Lustberg and Silbergeld, 2002; Menke et al., 2006; Schober et al., 2006). However, it is well known that BLLs is an indirect estimate of the environmental lead exposure. Particularly, BLLs may vary overtime and thus may increase uncertainties in determining lead exposures in these studies. In addition, it is known that many other factors, such as the social economic factors and availability of medical resources, might also affect the incidence and survival rates of various diseases. Thus, it is expected that to effectively control the above

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mentioned confounders would be important for identifying the true effect of environmental lead exposure on the risk of various diseases.

In principle, the petrol lead emission is considered to be more representative to environmental lead exposure than BLLs. It has been observed that the lead content of various environmental components had been decreased after the replacement of leaded petrol worldwide (Bridbord and Hanson, 2009; Skerfving and Bergdahl, 2007; Landrigan, 2002; Stromberg et al., 1995). In Taiwan, environmental lead exposure had generally declined since the mid-1990s, largely because of the implementation of the petrol-lead phase-out program (PLPOP) in 1981 (Hwang et al., 2004). The PLPOP implemented in Taiwan, consists of four phases: (1) leaded petrol phase (before 1985, the petrol lead content were 0.72 and 0.34 g Pb/l), (2) low leaded petrol phase (1986–1992, the petrol lead content were between 0.20 and 0.12 g Pb/l), (3) transitional phase (1993–1999, the petrol lead content were between 0.08 and 0.026 g Pb/l), and (4) lead-free petrol phase (after 2000, the petrol lead content <0.013 g Pb/l). The above implement scenarios provided us with a unique opportunity to study the long-term effect of the reduction of the environmental lead exposure on the development of important diseases. Taiwan is an island country and hence is usually not affected by other lead contamination sources from neighbor countries. Taiwan also has a very complete the death registration system. In the event of a death in Taiwan, the decedent's family is required to obtain a death certificate from the hospital or local community clinic, which then must be submitted to the household registration office in order to cancel the decedent's household registration. The death certificate is required so that the decedent's body can be buried or cremated. Furthermore, the main cause of death must be recorded by physicians on all death certificates forwarded to the Taiwan DOH, and all certificates are reviewed and coded by trained medical registrars in the Taiwan DOH Office of Statistics.

The most frequent causes of death in Taiwan have been malignant neoplasms, cerebrovascular disease, accidents and adverse effects, heart disease, diabetes mellitus, chronic liver disease and cirrhosis; nephritis, nephritic syndrome and nephrosis; bronchitis, emphysema and asthma; and hypertensive disease (Taiwan DOH – Department of Health, Taiwan, 2009). According to past studies, we selected lead-related chronic illnesses to observe, such as hypertensive disease, cerebrovascular disease, heart disease, nephritis, nephritic syndrome and nephrosis (ATSDR – Agency for Toxic Substances and Disease Registry, 2007; Bellinger, 2005; Fewtrell et al., 2004; Tong et al., 2000). In the present study, the national data between 1981 and 2007 were used to study the association between the reduction of environmental lead emissions and the decrease in the disease mortality rates. To adjust for possible confounding effects, both social economic and medical resources data were included in data analysis. The results obtained from the present study will be able to examine the health impact associated with the implement of the PLPOP in any given country.

## 2. Methods

### 2.1. Population in Taiwan

Taiwan, historically known as Formosa, is an island country located in East Asia with a total area of 35,980 km². The population of Taiwan was 23,063,027 (in June 2009) and the population density was 635 people per km² (the fifteenth most densely populated country in the world). According to the governmental statistics, 98% of population is made up of Han Chinese, while 2% are Taiwanese aborigines (Ministry of the Interior, Taiwan, 2009).

### 2.2. Data collection and mortality analysis

The national death records during the years from 1981 to 2007 were obtained from the Office of Statistics of the Taiwan DOH. By law, a death certificate must be registered within 1 month. All certificates are reviewed and coded by trained medical registrars in the Taiwan DOH Office of Statistics. The death record is defined according to the International Classification of Disease, Injury, and Causes of Death (9th revision) (ICD-9 code). Major causes of mortality were rearranged as malignant neoplasms (codes 140–208), cerebrovascular disease (codes 430–438), accidents and adverse effects (codes E800–E949), heart disease (codes 401–405, 410–414, 420–429), diabetes mellitus (code 250), chronic liver disease and cirrhosis (code 571), nephritis, nephritic syndrome and nephrosis (codes 580–589), bronchitis, emphysema and asthma (codes 490–493); and hypertensive disease (codes 401–405) (Taiwan DOH – Department of Health, Taiwan, 2009). According to past studies of lead-related illnesses, we selected mortality for all causes, hypertensive disease, cerebrovascular disease, heart disease, nephritis, nephritic syndrome and nephrosis for analysis (ATSDR – Agency for Toxic Substances and Disease Registry, 2007; Bellinger, 2005; Fewtrell et al., 2004; Tong et al., 2000). Direct standardization was applied to produce standardized mortality ratios (SMRs) for various diseases (per 100,000 people) by referencing to 2000 W.H.O. world standard population.

Information about the national economic index (economic growth rate %), per capita income ($), tobacco consumptions and medical resources were acquired from the Taiwan Directorate General of Budget, Accounting and Statistics. Motor gasoline consumption was obtained from Bureau of Energy, Ministry of Economic Affairs. The annual petrol lead emission (g Pb) was estimated by multiplying the annual motor gasoline consumption (L) to the annual petrol lead content (g Pb/L). The information on confounders was obtained for each year of the study period. However, the data on chronic beds per 100,000 population, health expenditure as of GDP (%), and tobacco consumption per capita aged 15 and over (pack) could be obtained before 1988.

### 2.3. Statistics

Multiple linear regression model was used to assess the association between petrol lead emissions and SMRs after controlling for the following factors, including the economic growth rate, per capita income, population served per physician, chronic beds per 100,000 people, total health expenditure (% of GDP), and tobacco consumption per capita (aged 15 and over). The statistical analyses were performed using SPSS for Windows (version 15.0). All statistical tests were two-sided with $p<0.05$ as the level of statistical significance.

## 3. Results

Twelve studies about BLLs of adult in Taiwan from 1983 to 2007 were included in Table 1 (Chang et al., 2006; Chiang and Chang, 1989; Chu et al., 1998; Ikeda et al., 1996; Liou et al., 1994; Liou et al., 1996a; Liou et al., 1996b; Soong et al., 1991; Wu et al., 2009; Yang et al., 2007). Recent studies have shown that the mean BLLs were substantially lower than those obtained from previous studies. Environmental lead exposures were found with a positive correlation on BLLs. The mean BLLs had been sharply decreased from approximately 20 μg/dl in the leaded petrol phase to 3.00 μg/dl or lower in the unleaded petrol phase (Table 2).

Fig. 1 shows the trends of SMRs for different diseases during 1981–2007. Mortality for cerebrovascular disease, heart disease, hypertensive disease, and nephrosis (per 100,000 people) declined from 146.2, 85.3, 35.4, and 21.3 in 1981 to 43.8, 44.4, 6.6 and, 17.3 in 2007, respectively. It also shows that the SMRs for all causes (per 100,000 people) decreased sharply from 810.2 in 1981 to 491.6 in 2007.

Table 3 presents results based on multiple linear regression models with standardized disease mortality rate as the dependent variable. Explanatory variables included in the model were petrol lead emissions, economic growth rate, per capita income, number of people served per physician, number of chronic beds per 100,000 people, total health

**Table 1**
Blood lead levels in Taiwan adult from 1983 to 2006.

| Reference studies | Collected date | Subject (*N*) | Area | Analytical techniques used | Reported BLLs |
|---|---|---|---|---|---|
| Chiang and Chang, 1989 | 1983 | 98 traffic policemen<br>118 control group | Kaohsiung city | GAAS | 24.43 ± 5.31 μg/dl (traffic policemen)<br>20.14 ± 5.07 μg/dl (control group) |
| Soong et al., 1991 | 1991 | Maternal and fetal cord blood ($n$ = 168) | Cities in Taiwan, (Kaohsiung, Taipei and Keelung) | GAAS | 6.48 μg/dl (maternal blood) |
| Chu et al., 1998 | 1993–01994 | 2803 subjects (1471 males and 1332 females) | Taiwan nationwide population survey | GAAS | 7.3 ± 5.2 μg/dl (males)<br>5.7 ± 3.9 μg/dl (females) |
| Liou et al., 1994 | 1993 | 2719 residents without occupational lead exposure | General population in Taiwan | GAAS | 8.29 ± 5.92 μg/dl<br>7.85 μg/dl (males) |
| Liou et al., 1996a,b | 1993–1994 | 5913 residents without occupational lead exposure | General population in Taiwan | GAAS | 8.28 ± 5.39 μg/dl |
| Liou et al., 1996a,b | 1993–1995 | 8828 residents without occupational lead exposure (4540 males; 4288 females) | General population in Taiwan | GAAS | 7.70 ± 5.23 μg/dl (all)<br>8.6 μg/dl (males)<br>6.7 μg/dl (females) |
| Ikeda et al., 1996 | 1994 | 52 adult non-smoking women | Tainan | GAAS | 4.45 μg/dl |
| Kuo et al., 2006 | 2000 | 1226 male & 1339 female (Aborigines 51.4% | Community-based survey in central Taiwan | GAAS | 5.60 μg/dL (male aborigines)<br>5.30 μg/dL (male non-aborigines)<br>5.40 μg/dL (female aborigines)<br>5.30 μg /dL (female non-aborigines) |
| Chang et al., 2006 | 2000–2001 | 64 infertile women & 29 their spouses<br>83 control women & 81 their spouses | Private infertility clinic in Kaohsiung City | GAAS | 3.55 ± 1.39 μg/dl (infertile women)<br>4.79 ± 1.50 μg/dl (spouses)<br>2.78 ± 2.05 μg/dl (fertile women)<br>3.23 ± 2.28 μg/dl (spouses) |
| Yang et al., 2007 | 2003 | 266 female nursing students | Kaohsiung country | GAAS | 2.64 ± 0.84 μg/dL (females) |
| Wu et al., 2009 | 2006 | 81 female general population | Central Taiwan | ICP-MS | 1.57 ± 1.01 μg/dl (female general population) |

expenditure (% of GDP), tobacco consumption per capita (aged 15 and over). The SMRs for all causes, cerebrovascular disease, and nephrosis significantly were shown to be highly correlated with the petrol lead emission ($p$-values were 0.001, <0.001, 0.020, respectively). Petrol lead emissions had a marginal effect on the SMRs of the hypertensive disease ($p$-value = 0.054).

## 4. Discussion

In this study we have shown that the SMRs for all causes, cerebrovascular disease, and nephrosis became much lower since the PLPOP was implemented in Taiwan. We believe this is the first evidence ever being shown in the lead literature based on the long-term observation of petrol lead emissions and disease mortalities.

Mortality data have been widely used to generate epidemiologic hypotheses, despite their inherent limitations (Morgenstern, 1982). The completeness and accuracy of the death registration system should be evaluated before any conclusion based on the mortality analysis is made. Taiwan also has a very complete the death registration system. Each death needs to be examined by a physician, and all deaths are mandatory to be reported to local household registration offices. We wrote this requirement has remained consistent throughout our study periods. Therefore the observed trends noted in this study are not considered to be attributed to the changes of the recording practices.

**Table 2**
Petrol-lead phase-out program and blood lead levels in Taiwan.

| Phase | Implementation date | Petrol type (lead content) | Blood lead levels* | |
|---|---|---|---|---|
| Phase 1 | Before 1981 | Leaded petrol (0.72 g Pb/l) | | Chiang and Chang, 1989 |
| | 1982 | Leaded petrol (0.56 g Pb/l) | | |
| | 1983–1985 | Half-leaded petrol (0.34 g Pb/l) | 20.14 ± 5.07 μg/dl ($N$ = 118) | |
| Phase 2 | 1986 | Low-leaded petrol (0.20 g Pb/l) | | Soong et al., 1991 |
| | 1987 | Low-leaded petrol (0.15 g Pb/l) | | |
| | 1988–1992 | Low-leaded petrol (0.12 g Pb/l) | 6.48 μg/dl (♀; $N$ = 168) | |
| Phase 3 | 1993–1996 | Tiny-leaded petrol (0.08 g Pb/l) | 7.70 ± 5.23 μg/dl ($N$ = 8828)<br>8.6 μg/dl (♂; $n_1$ = 4540)<br>6.7 μg/dl (♀; $n_2$ = 4288) | Liou et al., 1998; Liou et al., 1996a, 1996b; Liou et al., 1994 |
| | 1997–1999 | Tiny-leaded petrol (0.026 g Pb/l) | | |
| Phase 4 | After 2000 | Ban of leaded petrol | 5.40 μg/dl ($N$ = 2565)<br>5.45 μg/dl (♂; $n_1$ = 1226)<br>5.35 μg/dl (♀; $n_2$ = 1339) | Kuo et al., 2006 |
| | | | 3.00 μg/dl ($N$ = 164)<br>3.23 ± 2.28 μg/dl (♂; $n_1$ = 81)<br>2.78 ± 2.05 μg/dl (♀; $n_2$ = 83) | Chang et al., 2006 |
| | | | 2.64 ± 0.84 μg/dl (♀; $N$ = 266) | Yang et al., 2007 |
| | | | 1.57 ± 1.01 μg/dl (♀; $N$ = 81) | Wu et al., 2009 |

* The BLLs of subject was selected from no occupational lead exposure population or control group in those studies.

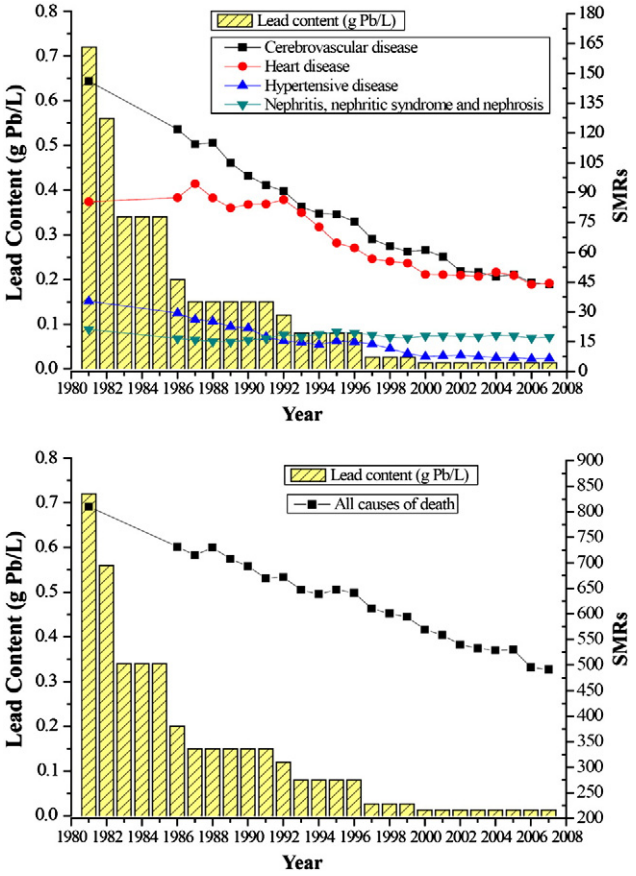


**Fig. 1.** The trends of SMRs for disease were shown in different petrol-lead phase-out phase. Based on 2000 W.H.O. world standard population were calculated.

**Table 3**
Multiple linear regression models for determinants associated with standardized mortality ratios (SMRs) for disease from 1981 to 2007.

| Variable | *B* | SE | *p*-value |
|---|---|---|---|
| Dependent variable: SMRs for all causes of death | $R^2$-adj = 0.967 | | |
| Petrol lead emissions (ton) | 0.131 | 0.025 | 0.001 |
| Economic growth rate (%) | 3.933 | 3.506 | 0.294 |
| Per capita income ($) | −0.012 | 0.006 | 0.088 |
| Population served per physician | −0.144 | 0.028 | 0.001 |
| Chronic beds per 100,000 population | 81.839 | 16.190 | 0.001 |
| Health expenditure as percentage of GDP (%) | −31.974 | 26.465 | 0.261 |
| Tobacco consumption per capita aged 15 and over (pack) | 0.076 | 0.040 | 0.092 |
| Dependent variable: SMRs for hypertensive disease | $R^2$-adj = 0.837 | | |
| Petrol lead emissions (ton) | 0.008 | 0.004 | 0.054 |
| Economic growth rate (%) | −0.022 | 0.529 | 0.967 |
| Per capita income ($) | <0.001 | 0.001 | 0.883 |
| Population served per physician | −0.005 | 0.004 | 0.248 |
| Chronic beds per 100,000 population | 3.770 | 2.441 | 0.161 |
| Health expenditure as percentage of GDP (%) | −3.779 | 3.991 | 0.371 |
| Tobacco consumption per capita aged 15 and over (pack) | <0.001 | 0.006 | 0.972 |
| Dependent variable: SMRs for cerebrovascular disease | $R^2$-adj = 0.991 | | |
| Petrol lead emissions (ton) | 0.027 | 0.004 | <0.001 |
| Economic growth rate (%) | −0.190 | 0.505 | 0.716 |
| Per capita income ($) | −0.001 | 0.001 | 0.228 |
| Population served per physician | −0.013 | 0.004 | 0.013 |
| Chronic beds per 100,000 population | 11.408 | 2.333 | 0.001 |
| Health expenditure as percentage of GDP (%) | −16.237 | 3.814 | 0.003 |
| Tobacco consumption per capita aged 15 and over (pack) | 0.009 | 0.006 | 0.142 |
| Dependent variable: SMRs for nephritis, nephritic syndrome and nephrosis | | | |
| $R^2$-adj = 0.375 | | | |
| Petrol lead emissions (ton) | 0.005 | 0.002 | 0.020 |
| Economic growth rate (%) | −0.226 | 0.247 | 0.386 |
| Per capita income ($) | <0.001 | <0.001 | 0.284 |
| Population served per physician | −0.003 | 0.002 | 0.202 |
| Chronic beds per 100,000 population | 1.854 | 1.140 | 0.142 |
| Health expenditure as percentage of GDP (%) | −0.757 | 1.863 | 0.695 |
| Tobacco consumption per capita aged 15 and over (pack) | −0.002 | 0.003 | 0.451 |

Evidence has been given to show that the lead exposure is associated with the increased blood pressure, and ultimately circulatory disease. The increases in blood pressure, vascular reactivity and renal damage have been observed after ingestion of lead exposure in rodent models (ATSDR – Agency for Toxic Substances and Disease Registry, 2007; Chai and Webb, 1988; Victery, 1988). A recent systematic review has also provided sufficient evidence to infer a causal relationship of lead exposure with elevated blood pressure, and correspond with epidemiological causal criteria as consistency, temporality, strength of the association, biological gradient, and biologic plausibility and experimental data (Navas-Acien et al., 2007). Lead is also involved in the pathogenesis of atherosclerosis and hypertensive disease and may be related to cerebrovascular disease. Past study reported that long-term lead exposure as measured by body lead store might carry a potential risk of intracranial carotid atherosclerosis (Lee et al., 2009). BLLs were significantly associated with both myocardial infarction and stroke mortality, and the association was evident at levels ≧2 μg/dl (Menke et al., 2006). Hence, lead-induced hypertensive disease and may be hypertension associated mortality that it is possible.

Generally, the development of hypertension in subjects chronically exposed to high lead levels has been interpreted as a possible consequence of lead nephropathy. Ekong (2006) reviewed epidemiologic research in general, occupational, and patient populations to assess whether lead, at current exposure levels, still contributes to nephrotoxicity (Ekong et al., 2006). They reported that longitudinal data indicate that lead dose at baseline is associated with subsequent decline in renal function (Ekong et al., 2006; Kim et al., 1996). Adverse renal effects have been reported at mean BLLs < 5 μg/dl. Cumulative lead dose was also associated with worse renal function (Ekong et al., 2006). The general consistency of the results provides important evidence that lead-related nephrotoxicity remains a public health concern, particularly in susceptible populations (Ekong et al., 2006). We therefore believed that lead and nephropathy have highly association, even to cause the mortality for nephropathy.

Chronic lead exposure may contribute to arterial hypertension (Navas-Acien et al., 2007), cause impaired renal function (Ekong et al., 2006), and induce oxidative stress (Vaziri et al., 2001), inflammation and endothelial dysfunction of vessel wall (Vaziri et al., 2001) which eventually result in atherosclerosis. It is possible that reduction of environmental lead exposure might help preventing mortality for nephropathy and cerebrovascular disease.

Several strengths and limitations of this study should be considered. First, the major limitation of ecologic analysis for testing etiologic hypotheses is the “ecological fallacy”, results from making a causal inference about individual phenomena on the basis of observations of groups. However, ecologic studies can achieve certain objectives generally not met with nonecologic designs as combining existing data files on national populations, and generally less expensive and take less time than studies involving the individual as the unit of analysis. Second, the petrol lead emissions are not only representative to the environmental lead amounts, but also can reflect the actual changes in environmental lead exposure in Taiwan population.

The implementation of PLPOP in Taiwan provided us an opportunity to study the long-term effect associated with the reduction of environmental lead exposure on the development of important diseases. Our results show that a good plan for national control of petrol lead emission is

important to the improvement of the individual and national health quality.

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