



# *International Journal of Home Science*

ISSN: 2395-7476  
IJHS 2018; 4(1): 236-239  
© 2018 IJHS  
[www.homesciencejournal.com](http://www.homesciencejournal.com)  
Received: 12-11-2017  
Accepted: 17-12-2017

**Ms Shelly Garg**  
M.Sc. in Dietetics and Applied  
Nutrition Amity Medical School,  
Amity University, Haryana,  
India

## A systematic review on the prevalence and management of PCOS through dietary modifications

**Ms Shelly Garg**

### **Abstract**

The objective of this study is to find out the widespread prevalence of PCOS across the world along with its causes, people who all are affected and results of this disease. PCOS is most severe in Asian and American females; both are found to be the most affected ones followed by Caucasian ones, which are further followed by the African ones. So, it's necessary to know about the disease, its pathogenicity, symptoms and causes in females of different origin and what can be the preventive measures like dietary modifications and controlling other health conditions and other factors so as to avoid the disease or at least lowering the impact of the disease. Avoidance and early curing of the disease is the main motto of the research. Common symptoms of the disease include marked decrease in the female characters. Other symptoms like irregular or no menstruation, excess hairs on face, chest, stomach, thumbs, or toes, decrease in breast size, hair loss, acne, depression, weight gain, pelvic pain and infertility are also checked. Most commonly, it affects the females of reproductive age. This is one of the most widespread diseases across the world and if left untreated, may result in infertility and even uterine cancer and hence this study is done. This study focuses on the prevalence, management and dietary modifications of the disease.

**Keywords:** prevalence, dietary

### **Introduction**

At the age of puberty both, male and female bodies start producing sex hormones, which differentiate them from each other. Female body produces estrogen, progesterone, gonadotropin releasing hormone, follicle stimulating hormone, and luteinizing hormone.<sup>[1]</sup> Along with this a small amount of male hormones are also produced in females namely androgen.<sup>[2]</sup> When the levels of androgen increases to a greater extend in females it leads to PCOS or Polycystic ovary syndrome.<sup>[3][4]</sup> In PCOS, there is irregular or no menstrual periods, excess facial and body hairs, heavy periods, patches of thick, darker, velvety skin, difficulty in getting pregnant, acne and pelvic pain.<sup>[5]</sup> Obesity, obstructive sleep apnea, heart disease, type 2 diabetes, mood swings and endometrial cancer are among the associated conditions of PCOS.<sup>[6]</sup> PCOS is the most common endocrine disorder among the age group of 18 to 44 years.<sup>[7]</sup> PCOS is majorly divided into five broad categories: Insulin Resistant PCOS/ Type 1 PCOS (due to underlying insulin and leptin resistance the risk of developing diabetes is increased along with the increase in testosterone levels. symptoms include weight gain, ovulatory interruptions, acne, facial hair, hair loss.), Non-Insulin Resistant PCOS/ Type 2 PCOS (women meet the criteria for PCOS but are nonresistant to insulin.), Non-Traditional PCOS 1(in this ovulatory issues can be seen but with normal testosterone levels, insulin resistance is seen and hence obesity is also seen.), Non-Traditional PCOS 2 (in this normal ovulatory pattern is seen with increased levels of testosterone and mild insulin resistance is also observed.) and Idiopathic Hirsutism (in this normal ovulatory pattern is seen with increased levels of testosterone and no resistance to insulin is observed.)<sup>[8]</sup> Not everyone having ovarian cysts is suffering from PCOS nor everyone with PCOS has polycystic ovaries.<sup>[10]</sup> It is diagnosed by the detection of two of the following three conditions: no ovulation, high androgen levels, and ovarian cysts.<sup>[3][8]</sup> The cyst can be detected by pelvic ultrasound.<sup>[9]</sup>

### **Background**

Due to number of reasons, PCOS is prevalent in different parts of the world. A large number o

### **Correspondence**

**Ms Shelly Garg**  
M.Sc. in Dietetics and Applied  
Nutrition Amity Medical School,  
Amity University, Haryana,  
India

cases are being observed in India every year and an extensive study has been carried out to eliminate PCOS and its harmful effects. In different parts of India like Andhra Pradesh prevalence of PCOS among adolescents is 9.13%. [11] In Lucknow, U.P., India 3.7% females 18-25 years of age are found to have PCOS. [12] In a study conducted on 27,411 samples by Metropolis Healthcare Ltd. 17.6% (4,825) are found to have PCOS. The regional distribution of prevalence of PCOS is found to be 18.62% in North India, 25.88% in East India, 19.88% in West India, and 18% in South India. Thus, PCOS affects every fifth Indian female. [13] In the neighboring countries like Pakistan, around 21.9% females are infertile of the total population, among which 38.5% of the infertility is due to PCOS. [14] Another study conducted in The Aga Khan University Hospital, and Concept Fertility Centre, Karachi, Pakistan, from January 2003 till December 2004, a total of 508 were checked for the symptoms of PCOS. Among them 17.6% were found to have PCOS. [15] In Bangladesh, a study was conducted on 16700 infertile females among which 31.7% of the female population is suffering from PCOS. [16] Just like Pakistan and Bangladesh, Nepal's female population has been suffering from PCOS. About 5-10% of the total population of Nepal is suffering from PCOS. [17] The rate of female population having PCOS in Myanmar is 5%. [18] In China, 1,040 female who visited the Reproductive Medicine Center at Shandong Provincial Hospital Shandong University between January 2002 and December 2006 are found to be suffering from PCOS. [19] The rate of females suffering from PCOS is about 2% in South China. [20] The rate of prevalence of PCOS in Sri Lanka is found to be 6.3%. [21] The rate of prevalence of PCOS in Thailand is moderate, which is of 5%. [22] Individual studies were undertaken in Italy, Iran, and Japan and these studies have shown that the rate of PCOS is 4.3% in Italy, 14.6% in Iran and 26.2% in Japan. [38] The rate of PCOS has been found high among Indian women as compared to that of their Caucasian counterparts. [38] In the Asian subcontinent around 52% females are affected with PCOS. [23] From a study in South Europe, the rate of prevalence of PCOS is 9% in Greece while the rate of PCOS is found to be 6.5% in Spain. [24][25] While, in Europe as a whole the rate of prevalence is found to be as high as 20-22%. [26] Australians have a high rate of females suffering from PCOS which is of 11%. [27] Just like Australia, Africa has an alarming rate of female population affected with PCOS, which is about 10.48%. [28] Countries like UK have a moderate rate of 8% of the total population suffering from PCOS. [29] While in the USA the rate of PCOS is of 4% of the total female population. [30] In a research it was found that around 5 million women in US are suffering from PCOS. [32] Globally, the prevalence of PCOS changes with the change in the ethnic values of the person. Globally around 10% females are affected with PCOS. [31] Foremost reason of the widespread of PCOS is found to be imbalance in women's sex hormones namely estrogen and progesterone. [32] Other causes which play an important role in manifestation of PCOS are environmental conditions, natural selection of genes which directly affects the phenotype of the genes, [33] sociocultural difference, difference in eating habits and patterns. [34] Apart from these, the other reasons for the cause of PCOS are found to be excess of insulin (insulin is a hormone produced by the beta-cells of pancreas which helps in the glucose take up by the cells, when our body becomes resistant to insulin more amount of insulin is produced. this excess of insulin may lead to increased levels of androgen thus causing a problem in ovulation.), excess androgen (in

abnormal conditions the ovaries produce high levels of androgen which leads to acne and excess hairs on body.), heredity or family history (a person with family history of PCOS has chances of having PCOS.), low grade inflammation (our body produce white blood cells as a defense mechanism to fight against infections. Extensive researches proved that females with low grade inflammation stimulate polycystic ovaries to produce androgens leading to PCOS.) [35], excessive release of LH (luteinizing hormone) by the anterior lobe of pituitary gland, [36] obesity (adipose tissue contains an enzyme, which converts androstenedione to estrone and testosterone to estradiol, namely aromatase. The excess of adipose tissue in obese women creates a condition where both androgens and estrogen are in excess which inturn leads to excessive hairs on the body and inhibition of follicle stimulating hormone by negative feedback of estrogen.). [36] Stress is also a major culprit for the occurrence of PCOS. [37] In countries like India, from a study undertaken in Lucknow, UP the major reason which lead to PCOS is the abdominal obesity. [12] From another study which took place in a residential college in Andhra Pradesh the main culprit of PCOS was found to be hyperandrogenism. [11] from another study which was conducted in Andhra Pradesh the reasons which lead to PCOS are found to be obesity, less or no physical activity, large hip to waist ratio, family history od diabetes mellitus (9%), hypertension (9%), hypothyroidism (9%), irregular dietary pattern, environmental factors, heredity which include early age of sexual maturation, family history of PCOS, premature fetal development, hyperinsulinemia, insulin resistance. PCOS has been observed more in the urban population as compared to that of rural population. A sudden weight gain has been observed in the PCOS females over a period of three months. [38] In countries like Pakistan, a study conducted in The Aga Khan University Hospital, and Concept Fertility Centre, Karachi, Pakistan, between the period of January 2003 to December 2004 and the major cause of PCOS was found to be hyperinsulinemia. [15] From another study conducted in the Aga Khan University, Karachi, Pakistan between the time period of 2 years which is from January 2005 to December 2006, the other leading causes of PCOS in Pakistan are found to be obesity, BMI greater than 30, increased waist to hip ratio, intrafamily marriages, insulin resistance, increased acanthosis nigrican (black or brown velvety patches on the skin) [39][40] Another study was conducted in the King Edward Medical University and associated Mayo Hospital, Lahore, Pakistan, from June 2009 to May 2010, the leading causes of PCOS there are found to be increased LH-FSH (luteinizing hormone and follicle stimulating hormone) ratio, increased levels of testosterone and androstenedione and prolactin. [41] Moving to Bangladesh, the leading causes of PCOS are found to be central obesity (81.4%), lipid abnormalities (dyslipidemia 45.7%), and glucose intolerance (47.1%), increased prolactin level (18.6%), increased thyroid function (11.4%), hypertension (24.3%), hirutism (88.6%), metabolic syndrome (15.3%). [42] In other countries like Nepal, the major reasons for the widespread of PCOS are insulin resistance, hyperinsulinemia, hyperandrogenism and anovulation. [17] Reasons like hyperinsulinemia, obesity, insulin resistance, heredity, hyperandrogenaemia, hypothyroidism, hyperlipidaemia, diabetes mellitus type 2 are most common in the region of Myanmar. [43][44] The causes of PCOS in China are found to be obesity, heredity, hormonal imbalance, insulin resistance. [45][46] Heredity and environmental factors are considered as the culprit behind the wide spreading of PCOS

in Sri Lanka.<sup>[47]</sup> In countries like Thailand, increased obesity, increased BMI, increased waist to hip ratio are the reasons behind the prevalence of PCOS.<sup>[48]</sup> In Asia, after a number of studies the major reasons behind the cause of PCOS are obesity, increased BMI, increased waist to hip ratio, environmental factors, and lesser sex hormone binding globulin, insulin resistance and heredity.<sup>[49]</sup> In European countries, insulin resistance, metabolic syndrome, hypertension, dyslipidemia, glucose intolerance and diabetes are the reasons behind PCOS.<sup>[50]</sup> Overweight and heredity are the causes of PCOS in Australia.<sup>[51]</sup> In South Africa, family history, environmental and genetic factors are the leading cause of PCOS. Apart from these, insulin resistance and hyperandrogenism are also the reasons behind the prevalence of PCOS in Africa.<sup>[52]</sup> In USA, obesity, environment, heredity, eating patterns, insulin resistance are the causes of PCOS.<sup>[49]</sup> Globally, it can be concluded that eating patterns, lack of physical activity, hyperlipidaemia, insulin resistance, obesity, family history and heredity are the major causes leading for the wide spread of PCOS across the globe.

### Conclusion

From the above review of literature, it has been found that PCOS is found globally irrespective of the area and climatic conditions. PCOS can be checked with the primary symptoms like marked decrease in the female characters. Other symptoms like irregular or no menstruation, excess hairs on face, chest, stomach, thumbs, or toes, decrease in breast size, hair loss, acne, depression, weight gain, pelvic pain and infertility. Obesity, insulin resistance, less or no physical activity, imbalanced diet, heredity, hyperlipidaemia, hypothyroidism and hyperinsulinemia are the culprits behind the wide spread prevalence of PCOS. The ill effects of the disease can be minimized by having proper medications and managing dietary intakes and patterns. PCOS is a life style disorder and medications like metformin is useful in infertility. Along with metformin, oral contraceptives help in improving acne and hirsutism. Loss of weight is also helpful in minimizing the effects of PCOS. Diet therapy along with exercise proves to be beneficial in PCOS. Following weight loss diets help in normalizing the female hormones and thus reducing the insulin resistance thus leading towards the cure of PCOS. A low carbohydrate diet is prescribed with moderate essential fatty acids and good amount of protein. A diet of 1200 to 1500 Kcal/day is prescribed depending upon the conditions. Complex carbohydrates are given and simple ones like juice, sugar, malt syrups are avoided. Processed foods like pasta, bread, sugary products, seed oils, Trans fats are also avoided. Protein rich foods like non-vegetarian products (beef, chicken, lamb, fish, salmon, eggs) are given. Fruits and vegetables like apple, orange, broccoli, spinach, pears, blueberries, strawberries, carrots, cauliflowers are given. Fat products like coconut oil, nuts, yogurt, cheese, butter, olive oil are also given. In case of hyperlipidaemia, oil and fat products are to be avoided and omega 3 and omega 6 and omega 9 fatty acids are to be taken. Vitamin D supplementation is done so as to increase fertility. The person need to restrict fried and oily food. All this is to be done along with physical activity of atleast half an hour or more per day as required. Concentrating of eating patterns and physical activity reduces the risk of PCOS.

### References:

1. <http://www.livestrong.com/article/127967-hormones-female-reproductive-system/> Retrieved. 2017.
2. <http://www.pathophys.org/sexhormones> Retrieved. 2017.
3. Polycystic Ovary Syndrome (PCOS): Condition Information. <http://www.nichd.nih.gov/>. Retrieved. 2013, 2015.
4. Polycystic ovary syndrome (PCOS) fact sheet. Womens Health. December 23, 2014. Retrieved, 2016.
5. What are the symptoms of PCOS? (05/23/2013). <http://www.nichd.nih.gov>. Retrieved, 2015.
6. Polycystic Ovary Syndrome (PCOS): Condition Information. <http://www.nichd.nih.gov/>. 2013. Retrieved 2015.
7. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med. 2010; 8(1):41. PMC 2909929 PMID 20591140. doi:10.1186/1741-7015-8-41.
8. <http://natural-fertility-info.com/types-of-pcos.html> Retrieved, 2017.
9. "How do health care providers diagnose PCOS? <http://www.nichd.nih.gov/>. 2013-05-23. Retrieved. 2015.
10. Marrinan, Greg. Lin, Eugene C, ed. "Imaging in Polycystic Ovary Disease. eMedicine. eMedicine. Retrieved, 2011.
11. Nidhi Choudhary, Venkatram Padmalatha, Raghuram Nagarathna, Amritanshu Ram. Prevalence of Polycystic Ovarian Syndrome in Indian Adolescents DOI: 10.1016/j.jpag.2011.03.002 Journal of Pediatric and Adolescent Gynecology. 2011; 24(4):223-227.
12. Harmandeep Gill, Pallavi Tiwari, Preeti Dabaghao. Prevalence of polycystic ovary syndrome in young women from North India: A Community-based study Indian J Endocrinol Metab. 2012; 16(Suppl 2):389-392. doi: 10.4103/2230-8210.104104 PMCID: PMC3603088
13. <http://www.indiatimes.com/health/healthyliving/1-in-5-women-affected-by-pcos-in-india-but-fret-not-we-have-the-solution-244753.html> Retrieved, 2017.
14. Arain F, Arif N, Halepota H. Frequency and outcome of treatment in polycystic ovaries related infertility Pak J Med Sci. 2015; 31(3):694-9. doi: 10.12669/pjms.313.8003.
15. Haq F, Aftab O, Rizvi J. Clinical, biochemical and ultrasonographic features of infertile women with polycystic ovarian syndrome J Coll Physicians Surg Pak. 2007; 17(2):76-80.
16. Fatima P, Ishrat S, Rahman D, Banu J, Deeba F, Begum N et al, Quality and quantity of infertility care in Bangladesh. Mymensingh Med J 2015; 24(1):70-3
17. Sangraula H, Paudel KR, Sharma M. Dec; Metformin and troglitazone in the treatment of female infertility associated with polycystic ovarian syndrome. JNMA J Nepal Med Assoc. 2009; 48(176):335-9.
18. <http://www.mims.com/myanmar/diagnoses/info/2223> Retrieved 2 September, 2017.
19. Shi Y, Guo M, Yan J, Sun W, Zhang X, Geng L. et al, Analysis of clinical characteristics in large-scale Chinese women with polycystic ovary syndrome. Neuro Endocrinol Lett. 2007; 28(6):807-10
20. Chen X, Yang D, Mo Y, Li L, Chen Y, Huang Y. Prevalence of polycystic ovary syndrome in unselected women from southern China. Eur. J Obstet. Gynecol. Reprod. Biol. 2008; 139(1):59-64
21. Kumarapeli V, Seneviratne Rde A, Wijeyaratne CN, Yapa RM, Dodampahala SH. A simple screening approach for assessing community prevalence and

- phenotype of polycystic ovary syndrome in a semi-urban population in Sri Lanka. Am. J Epidemiol. 2008; 168(3): 321-328
22. Vutyavanich T, Khaniyao V, Wongtra-Ngan S, Sreshthaputra O, Sreshthaputra R, Piromlertamorn W. Clinical, endocrine and ultrasonographic features of polycystic ovary syndrome in Thai women. J Obstet. Gynaecol. Res. 2007; 33(5):677-680.
  23. Rodin DA, Bano G, Bland JM, Taylor K, Nussey SS. Polycystic ovaries and associated metabolic abnormalities in Indian subcontinent Asian women. Clin Endocrinol (Oxf). 1998; 49(1):91-9.
  24. Diamanti-Kandarakis E, Kouli CR, Bergiele AT *et al.* A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. J Clin. Endocrinol. Metab. 1999; 84(11):4006-4011.
  25. Asunción M, Calvo RM, San Millán JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin. Endocrinol. Metab. 2000; 85(7):2434-2438.
  26. Clayton RN, Hogkinson J, Worswick L, Rodin DA, Dyser S, Meade TW. How common are polycystic ovaries in normal women and what is their significance for the fertility of the population? Clinical Endocrinology. 1992; 37:127-34.
  27. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum. Reprod. 2010; 25(2):544-551.
  28. Saleh HA, Shawky Moiety FM. Aug; Polycystic ovarian syndrome and congenital uterine anomalies: the hidden common player. Arch Gynecol Obstet. 2014; 290(2):355-60. doi: 10.1007/s00404-014-3193-9. Epub 2014 Mar 11
  29. Michelmore KF, Balen AH, Dunger DB, Vessey MP. Polycystic ovaries and associated clinical and biochemical features in young women. Clin. Endocrinol. (Oxf.). 1999; 51(6):779-786.
  30. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. J Clin. Endocrinol. Metab. 1998; 83(9):3078-3082.
  31. Chandrika N, Wijeyaratne SA, Dilini Udayangani. Ethnic-specific Polycystic Ovary Syndrome Epidemiology, Significance and Implications. Adam H Balen Expert Rev Endocrinol Metab. 2013; 8(1):71-79.
  32. <http://www.healthline.com/health/polycystic-ovary-disease#overview1> Retrieved, 2017.
  33. Spielman RS, Bastone LA, Burdick JT, Morley M, Ewens WJ, Cheung VG. Common genetic variants account for differences in gene expression among ethnic groups. Nat. Genet. 2007; 39(2):226-231.
  34. González Burchard E, Borrell LN, Choudhry S. *et al.* Latino populations: a unique opportunity for the study of race, genetics, and social environment in epidemiological research. Am. J Public Health. 2005; 95(12):2161-2168.
  35. <http://www.mayoclinic.org/diseases-conditions/pcos/symptoms-causes/dxc-20342150> Retrieved. 2017.
  36. [https://en.wikipedia.org/wiki/Polycystic\\_ovary\\_syndrome#Cause](https://en.wikipedia.org/wiki/Polycystic_ovary_syndrome#Cause) Retrieved. 2017.
  37. Murri M, Luque-Ramírez M, Insenser M, Ojeda-Ojeda M, Escobar-Morreale HF. Circulating markers of oxidative stress and polycystic ovary syndrome (PCOS): a systematic review and meta-analysis". Hum. Reprod. Update. 2013; 19(3):268-88. PMID 23303572. doi:10.1093/humupd/dms059.
  38. Swetha Balaji, Chioma Amadi, Satish Prasad, Jyoti Bala Kasav, Vandana Upadhyay, Awnish K. Singh *et al.* Urban Rural Comparisons of Polycystic Ovary Syndrome Burden among Adolescent Girls in a Hospital Setting in Indian BioMed Research International. 158951, 2015, 10.
  39. Haq, Rizvi J, Infertility and polycystic ovarian syndrome: a study of association between body mass index and intrafamily marriages. Gynecol Obstet Invest. 2008; 65(4):269-74.
  40. Tabassum R, Imtiaz F, Sharafat S, Shukar-Ud-Din S, Nusrat U. Prevalence and clinical profile of insulin resistance in young women of poly cystic ovary syndrome: A study from Pakistan. Pak J Med Sci. 2013; 29(2):593-6.
  41. Akram M, Roohi N. Endocrine correlates of polycystic ovary syndrome in Pakistani women. J Coll Physicians Surg Pak. 2015; 25(1):22-6. doi: 01.2015/JCPSP.2226
  42. Islam S, Pathan F, Ahmed T. Clinical and Biochemical Characteristics of Polycystic Ovarian Syndrome among Women in Bangladesh. Mymensingh Med J 2015; 24(2):310-8.
  43. [http://www.hopkinsmedicine.org/healthlibrary/conditions/endocrinology/polycystic\\_ovary\\_syndrome\\_pcos\\_85,P0\\_8334](http://www.hopkinsmedicine.org/healthlibrary/conditions/endocrinology/polycystic_ovary_syndrome_pcos_85,P0_8334) Retrieved, 2017.
  44. <http://www.mims.com/myanmar/diagnoses/info/2223> Retrieved, 2017.
  45. <http://vitalitymagazine.com/article/traditional-chinese-medicine-for-polycystic-ovarian-syndrome-pcos> Retrieved, 2017.
  46. Li R, Zhang Q, Yang D, Li S, Lu S, Wu X. Prevalence of polycystic ovary syndrome in women in China: a large community-based study. Hum Reprod. 2013; 28(9):2562-9. doi: 10.1093/humrep/det262
  47. [http://www.sundaytimes.lk/111016/MediScene/mediscene\\_5.html](http://www.sundaytimes.lk/111016/MediScene/mediscene_5.html) Retrieved, 2017.
  48. Techatraisak K, Wongmeerit K, Dangrat C, Wongwananuruk T, Indhavivadhana S. Measures of body adiposity and visceral adiposity index as predictors of metabolic syndrome among Thai women with PCOS. Gynecol Endocrinol. 2016; 32(4):276-80. doi: 10.3109/09513590.2015.1112785.
  49. Chandrika N, Wijeyaratne SA, Dilini Udayangani, Adam H Balen. Ethnic-specific Polycystic Ovary Syndrome Epidemiology, Significance and Implications Expert Rev Endocrinol Metab. 2013; 8(1):71-79.
  50. Susan M, Sirmans Kristen A Pate. Epidemiology, diagnosis, and management of polycystic ovary syndrome Clin Epidemiol. 6: 1-13 doi: 10.2147 PMCID: PMC3872139. 2014.
  51. <https://www.diabetesaustralia.com.au/news/11296?type=articles> Retrieved, 2017.
  52. Erin K. Barthelmess, Rajesh K Naz. Polycystic ovary syndrome: current status and future perspective Front Biosci (Elite Ed). 6: 104-119. PMCID: PMC4341818 NIHMSID: NIHMS663134. 2014.