UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE: Seroquel Products Liability Litigation

MDL DOCKET NO. 1769

This document relates to:

Linda Guinn	6:07-cv-10291
Janice Burns	6:07-cv-15959
Richard Unger	6:07-cv-1581 2
Connie Curley	6:07-cv-15701
Linda Whittington	6:07-cv-10475
Eileen McAlexander	6:07-cv-10360
Sandra Carter	6:07-cv-13234
Clemmie Middleton	6:07-cv-10949
Hope Lorditch	6:07-cv-12657
David Haller	6:07-cv-15733
Charles Ray	6:07-cv-11102
William Sarmiento	6:07-cv-10425

DECLARATION OF DONNA K. ARNETT, PH.D., M.S.P.H.

My name is Donna K. Arnett. I am over twenty-one years of age, am of sound mind, have never been convicted of a felony, and am otherwise competent to make this Declaration. I have personal knowledge of all factual statements contained herein and all such factual statements are true and correct as outlined herein in this declaration-report.

A. Qualifications and Expertise

I am a cardiovascular epidemiologist with over twenty years of experience in the design, conduct, and analysis of epidemiologic studies. Since 1994, I have worked in leading academic research institutions for cardiovascular epidemiology and I have taught postgraduate (masters and doctoral levels) courses in theory, design, and analysis of epidemiologic studies.

I received a B.S.N. degree in 1981 in nursing (magna cum laude) and an M.S.P.H. degree in 1987 in epidemiology and biostatistics from the University of South Florida. In 1992, I received a Ph.D. in epidemiology from the University of North Carolina and was elected into Delta Omega, the honor society for public health. Prior to my graduate training, I worked as a critical care nurse for 5 years and was CCRN certified (i.e., critical care registered nurse) and as a research coordinator for pharmaceutical clinical trials at the University of South Florida for three years. My doctoral research was focused in the area of cardiovascular epidemiology. In 1992, I was awarded my first peer-reviewed

grant, a post-doctoral fellowship, and worked two years completing the fellowship at the University of North Carolina at Chapel Hill. From October, 1994 through August, 2004, I rose from a tenure-earning assistant professor to a full professor with tenure as well as holding an endowed chair in epidemiology at the University of Minnesota. During that time, I directed large, complex, multi-center epidemiologic studies funded from the National Institutes of Health, as well as a National Institute of Health T32 Training Grant and cardiovascular genetic epidemiology. At the time I left the University of Minnesota, I was ranked in the top 5% of all National Institute of Health researchers. Since 2004, I have served as chairman and a tenured professor of epidemiology at the University of Alabama at Birmingham, where I have maintained a strong research program. I currently am Principal Investigator for five National Institute of Health projects.

As further evidence of my qualifications and expertise in the field of epidemiology, I am an elected fellow of the American Epidemiologic Society, and serve as editor for the highest ranked journal in epidemiology, namely the *American Journal of Epidemiology*. In addition to serving on numerous research peer-review committees for multiple organizations, including but not limited to, the Veterans Affairs, the American Heart Association and the National Institutes of Health, I was named to the prestigious post of chair for the NIH Cardiovascular and Sleep Epidemiology study section for 2006-2008.

B. Responses to Particular Astra-Zeneca Statements

I have reviewed the brief of AstraZeneca that criticizes the veracity of the epidemiologic methodology employed as well as the timing and content of my opinions, and I herein offer a response to these criticisms.

1. AZ Counsel claim that I fail to extensively review the literature and use of flawed methodology

The AstraZeneca (AZ) Counsel state "Dr. Arnett... formed an opinion and submitted her report before she had time to extensively review all of the published literature", "spent at least three days reviewing literature after filing her report in an attempt to bolster her previously submitted litigation opinion", and "her methodology is scientifically flawed".

These assertions by AZ Counsel are incongruent with my expert report, testimony, and experience as an educator of epidemiologic methods and a researcher who employs sound epidemiological principles in her studies. As stated in my expert report[1] and my deposition,[2] my general causation opinions were formed mostly from the placebo-controlled randomized studies conducted as part of the New Drug Application (NDA) for Seroquel, submitted to the Food and Drug Administration in July, 1996. In fact, at least half of my Expert Report was devoted to data derived from the NDA. This approach is in congruence with sound epidemiologic methodology. As stated in my Expert Report:[3]

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[1] Expert Report, page 3
[2] Deposition, page 160, lines 1-4, page 255 line 9-14
[3] Expert Report, page 6

> "Randomized, double-masked, placebo-controlled clinical trials are the optimal design for testing a hypothesized association between an exposure (or treatment) and disease because such studies offer the best control for confounding (i.e., variables that are associated with the disease and associated with the exposure) and provide for the optimal test for temporality (i.e., exposure precedes disease). Placebo controlled studies are the gold standard for evaluating the risks and benefits of a new treatment."

The assertion that the experimental studies, such as the placebo-controlled randomized studies, are the most optimal design to test causal hypothesis is widely held among epidemiologists. Because of randomization of subjects and controlled administration of the agent under study, experiments are considered more useful than observational studies to demonstrate cause-effect relationships.[4] The U.S. Preventive Services Task Force[5] has established a ranking for the evidence about effectiveness of treatment, and has deemed evidence from the randomized controlled trial as the best level of evidence, Level 1. According to sound epidemiological principles, I relied most heavily on Level 1 evidence.

The publications from the earliest AZ clinical trials that I reviewed did not contain adequate information to evaluate the metabolic risks associated with Seroquel.[6] Therefore, I specifically requested the NDA files submitted by AZ with respect to the safety and so that I could fully evaluate the range of metabolic risk factors measured and the placebo-controlled clinical trials, and the impact of Seroquel on these risk factors. In fact, it was not until I evaluated the NDA that I discovered that a wide range of metabolic risk factor data, such as dyslipidemia and glucose were collected in the randomized controlled trials included in the NDA; these data were not readily available in the published literature. The aggregate of these Level 1 evidence data indicate a metabolic toxicity from Seroquel.

Following the review of the NDA, I also evaluated randomized controlled trial study summaries posted on the AZ website. These reports summarized in my expert report[7] demonstrated consistent weight gain findings in comparison to those reported in the NDA Integrated Safety Report. Given the consistent, clinically relevant (as defined by Astra Zeneca as a greater than 7% change in body weight in response to Seroquel treatment), I did not pursue lower levels of scientific evidence from observational epidemiologic studies with respect to weight or other metabolic toxicities, with the exception of type II diabetes. This approach is consistent with sound epidemiological principles.

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[4] Woodward, M. Epidemiology. Study Design and Data Analysis. 2nd Ed 2004. Chapman and Hall/CRC Texts in Statistical Science Series. 2004. Page 337)

[5] www.ahrq.gov/clinic/uspstmeth.htm

[6] Small JG et al, Quetiapine in Patients with Schizophrenia. Arch Gen Psych 1997;54:549-557 and Borison RL et al. ICI 204,636, An Atypical Antipsychotic: Efficacy and Safety in a Multicenter, Placebo-Controlled Trial in Patients with Schizophrenia. J Clin Psychopharmacol 1996; 16:158-169

[7] Expert Report, Page 8

2. AZ Counsel imply that I intentionally did not review the AZ Response to the FDA in June, 2008.

This document was not provided to me prior to my expert report and deposition. It was apparently provided to plaintiffs' counsel around Labor Day and was contained amidst a submission of apparently 15,000 pages and thus it was not promptly recognized as key information that needed to be promptly provided to me. Nonetheless, I have reviewed data regarding the characteristics of the participants that were included in the clinical trials provided in response to the FDA's request. Among the 6,870 adults taking Seroquel in the randomized placebo-controlled trials, 25% were exposed to the drug for 21 days or less, and some were exposed for only 1 day.[8] Most of the drop-outs occurred within the first two weeks of the study as evidenced in Table 16[9] where only 3,779 of the adult subjects in the placebo-controlled clinical trials had a weight measured. Despite the fact that there were so many drop-outs early in the follow-up for this combined analysis, there are statistically significant findings with respect to those who transition from normal to high glucose levels. I have calculated the relative risks and 95% confidence intervals for subjects in placebo controlled trials included in the AZ letter to the FDA. In Table 339, the relative risk of a glucose value $\geq$ 126 mg/dl among those with a glucose value < 100 mg/dl at baseline in Seroquel versus placebo users was 1.73, 95% CI 1.05 - 2.85, p=.03 and the results were stronger for the comparable calculation in the treatment naïve individuals (relative risk = 2.15, 95% CI 1.02 - 4.56, p=0.046, Table 450). Additionally, for Hba1C (Table 341) the relative risk was 1.50 (p=0.016), 95% CI 1.08-2.09, for a shift from a normal Hba1C (<6.1%) to elevated (≥6.1%). These data further support the diabetic potential of Seroquel treatment using the most robust of studies, the placebo-controlled clinical trial.

3. AZ Counsel suggest that Study 125 did not cause a statistically significant change in glucose metabolism as measured by the oral glucose tolerance test and opine that I make no attempt to "explain away these results."

Study 125 was not a placebo-controlled randomized clinical trial, but rather, was an open-label study designed to contrast the effects of Seroquel on a glucose metabolism in comparison to two of their active comparators. Open-label studies fall into the Level II-1 evidence according to the U.S. Preventive Services Task Force[10], a level of evidence that falls below that of the double-blind randomized clinical trial, and one of the reasons I did not include it in my Expert Report. In addition to these limitations, as with other Seroquel randomized, controlled trials, there was a larger drop-out among Seroquel users, 59/168 compared to only 23/169 for olanzapine users and 40/173 for risperidone users, raising the possibility that people who had metabolic side effects could have dropped out more often among the Seroquel users. Nonetheless, even though the primary outcome measure (i.e., the change at 24 weeks of the "area under curve" in a 2 hour oral glucose tolerance test) was not significant, the secondary results indicate statistically significant increases in both mean fasting blood glucose (3.19 mg/dl) and HbA1c (0.122%), showing

[8] Table 2, page 43 and 44, AZ letter to FDA, 6/13/08
[9] AZ letter to FDA, 6/13/08, page 66
[10] See www.ahrq.gov/clinic/uspstmeth.htm

that Seroquel impacted regulation of glucose in a fasting state. Fasting C-peptide (a measure of endogenous insulin production and an indicator of insulin resistance) increased. Further, patients taking Seroquel experienced a mean weight gain of 3.65 kg (8 pounds) in 24 weeks. The observation of the increased insulin production could explain the lack of significance of the primary outcome for this study since it is possible that glucose could be cleared more quickly due to the higher level of insulin from Seroquel. In aggregate, these findings lend Level II-1 evidence in support of the effects of Seroquel on metabolic toxicities, including weight gain and insulin resistance.

4. AZ Counsel states "Dr. Arnett concedes that she is not an expert on the mechanism by which antipsychotics allegedly cause diabetes or weight gain."

This is a misrepresentation of both my Expert Report and my deposition testimony. Pages 3 and 4 of my expert report describe three different biological mechanisms that support the weight gain and diabetic consequences of Seroquel treatment. As stated in my deposition,[11] because of my work in pharmacogenetics I have to understand how drugs work in the body. Additionally,[12] I stated that I had evaluated the literature and had an understanding of how Seroquel worked specifically in relation to weight gain and diabetes.

5. AZ Counsel states "the weight gain mechanism is nothing but pure speculation" and Dr. Arnett indicates there is no correlation between Seroquel weight gain and diabetes.

The relation between weight and weight gain and diabetes is an established risk factor for diabetes. As stated in my Expert Report (page 4), weight gain is also associated with features of the multiple metabolic syndrome, and the metabolic syndrome is an important risk factor for diabetes incidence. Beyond weight gain, Seroquel causes metabolic derangements, such as increased waist size[13] and hypertriglyceridemia.[14] Data from the Atherosclerosis Risk in Communities Study, increasing the number of metabolic risk factors that make up the metabolic syndrome dramatically increases the risk for diabetes in the cohort.[15] Collectively these data point to the importance of Seroquel-induced weight gain and its impact on diabetes risk. Finally, with respect to the correlational analysis between Seroquel weight gain and diabetes I indicated in my deposition that Astra Zeneca has not evaluated the data in that way[16], and therefore, I cannot scientifically offer an opinion regarding that correlation.

6. AZ Counsel states "Dr. Arnett purports to give a dose response opinion, but it amounts to nothing more than a theory based on unsupported extrapolation from

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[11] Deposition, page 53, line 19-20
[12] Deposition, page 55, lines 2-4
[13] Meyer JM et al. Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: prospective data from phase 1. Schizophr Res. 2008;101(1-3):273-86
[14] Expert Report, Page 10
[15] Ballantyne CM et al. Metabolic syndrome risk for cardiovascular disease and diabetes in the ARIC study. *International Journal of Obesity* (2008) 32, S21–S24.
[16] Deposition, page 209, line 9-10

higher doses" and "Dr. Arnett does not even attempt to evaluate the existence of a dose threshold."

This is a misrepresentation of both my expert report and my deposition testimony. As just one example of several offered in my report, for study 13 alone, low dose Seroquel (75 or 150 mg) versus placebo was associated with a 3.54 greater relative risk of clinically significant weight gain and higher doses (300 or 600 mg) was associated with a 4.77 greater relative risk of weight gain.[17] Additionally, in my deposition[18] I stated the following:

> A. There's a dose response relationship with all of the metabolic parameters that are a part of the diabetic -- Type II diabetes. There's some indication from the observational studies that there is a dose response between diabetes incidence and dose of Seroquel.
> Q. Are you testifying to a reasonable degree of scientific certainty that there's a dose response relationship between Seroquel and diabetes?
> A. Yes.

7. AZ Counsel opines that I filed my reports in this case before my work was completed and I did not properly review or analyze the key clinical trial data, and that I rely instead on confounded observational epidemiology.

This is a ridiculously flawed interpretation of my expert report and a gross misrepresentation of the method by which my opinions in this case were generated. As stated previously under Section 1, my opinion relied heavily on Level 1 evidence, the double-blind, randomized clinical trials. In fact, rather than relying exclusively on observational epidemiology, I painstakingly went through the NDA provided to the Food and Drug Administration to comprehensively evaluate the metabolic impact of Seroquel since all data were not provided in the published literature. As a responsible scientist, I did this even though the data were provided by AZ in a format which did not include an index of the files included, making the task much more difficult than it needed to be. In light of the consistent and significant findings from the Level 1 evidence, I used the observational epidemiologic studies (Level II-B evidence) which support the findings from the randomized controlled clinical trials.

8. AZ Counsel asserts that I reached my conclusions before my review of the relevant scientific evidence, and that I simply "ran out of time."

The assertion that I "ran out of time" is patently absurd and was taken completely out of context from my deposition. In fact, it referred to the section where I described the methods used to evaluate the weight data from the AZ website. In fact, what I referred to in this section[19] was related to the findings regarding

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[17] Expert Report page 5
[18] Deposition, page 210-211, lines 16-25, and 1, respectively
[19] Deposition, page 177-178

weight. What I had observed in the randomized clinical trials from the AZ website is consistent with what I had found in the NDA, namely, that Seroquel was associated with significant increases in weight:

> Q. Your weight chart here, Table 1, you created this based on the clinical trial summaries, right, that were on the Web site?
> A. Yes.
> Q. Am I right that there were many more than just 11 clinical trial synopses on the AstraZeneca Web site?
> A. Yeah. I took them in sequential order from top to Number 11 until I ran out of time.

As indicated previously in Section 1, I principally relied on level 1 evidence from the randomized controlled studies, and supplemented that with evidence level IIb studies regarding Seroquel and diabetes. This does not in any way indicate that I formed my opinions before I completed review of the literature. In fact, it asserts that I used appropriate epidemiologic rigor into writing my opinions.

9. AZ Counsel expressed concern that I did not review the actual study reports.

Because of the method in which the data were provided to me through AZ it was nearly impossible to identify the individual clinical study reports. This is not a concern with respect to the formation of my opinions. The integrated safety report provided by Astra Zeneca to the Food and Drug Administration summarized all Phase I, II and III study safety measurements that were included in the New Drug Application. Therefore, unless Astra Zeneca withheld information from the clinical reports for this Integrated Safety Report, all safety information collected in phase I, II and II studies were reviewed and evaluated in the formation of my opinions.

10. AZ Counsel expressed concern that I did not review the Study 125, the AZ FDA 2008 letter (both discussed previously), and the additional results from the CATIE trial.

Issues related to Study 125, and the FDA 2008 letter, have been previously discussed, as has the important follow-up study from CATIE regarding the metabolic syndrome. I have reviewed the CATIE study publication, and formed my own opinions regarding its scientific merit[20] and its impact on metabolic risk.

11. AZ counsel asserts that statistical significance is the "accepted principle of epidemiology" and that "a non-statistically significant result lies at the heart of Dr. Arnett's opinion."

[20] Expert report, page 12

In my report, I presented numerous statistically significant findings with respect to weight gain, triglyceride increase, measures of insulin sensitivity, waist circumference, and thyroid abnormalities in relation to Seroquel treatment. Additionally, I presented epidemiologic studies that indicated Seroquel was associated with statistically significant increased risk of diabetes. Nonetheless, the assertion that statistical significance is an exclusive requisite for evaluation of causation is a frank misrepresentation of accepted epidemiologic methods. In the recent text, Modern Epidemiology, Third Edition, by Kenneth Rothman at al, page 159 states:[21]

> "Confidence limits and P value functions convey information about size and precision of the estimate simultaneously, keeping these two features of measurement in the foreground, the use of a single P value -- or worse dichotomization at the P value into significant or non-significant -- obscures these features so that the focus of measurement is lost. A study cannot be reassuring about the safety of an exposure or treatment if only a statistical test of the null hypothesis is reported. As we have seen, results that are not significant may be compatible with the substantial effects. Lack of significant alone provides no significance against such effects."

The authors further state that the confidence limits around a point estimate must be interpreted with respect to the point estimate, namely that points nearer to the center of the range are more compatible to the data of them than points farther away from the center. In this particular example from the deposition[22], this would mean that the true effect of Seroquel on diabetes would be nearer to the point estimate of 2.02 rather than from the extremes of the 95% confidence limits. This value is comparable to a range of point estimate derived from the observational epidemiologic studies (e.g., range of 1.15 – 3.02) reported in my expert report.[23]

12. AZ Counsel is concerned that I did not calculate post-hoc power calculations.

In light of the totality of statistically significant data discussed in my export report and deposition concerning the effects of Seroquel on diabetes risk, I did not find it necessary to calculate statistical power in the setting of the consistent and statistically significant findings previously cited. In my twenty years of work in epidemiology, and having served as Chair of the NIH Study Section on Cardiovascular and Sleep Epidemiology Study Section where I routinely evaluate statistical power, I assert that I have a solid understanding of the factors that contribute to statistical power. In the case of the specific calculation requested by AZ Counsel, the idea that the study was inadequately powered (i.e., the error or claiming the null hypothesis is true when indeed it is not) was due to the number

[21] Rothman, Greenland and Lash. Modern Epidemiology, Third Edition, Lippincott Williams and Wilkins 2008, pages 157-159.
[22] Deposition 286:15-287:2
[23] Expert Report, page 11.

of events required for adequate power. Therefore, I did not invest time in calculating the power as it was most assuredly low.

13. AZ Counsel accuses me of "cherry picking" the data.

As stated in my deposition, the method I used to derive the list of observational epidemiologic studies was a PubMed search for studies that contained the words "Seroquel" and "diabetes" in the title or abstract. All published cohort or case-control published manuscripts detected from this search, with the exception of one article from a low-impact journal, were included in my report.

I hold additional relevant opinions as set forth in my expert report in this matter, which is attached and incorporated by reference. Additional opinions were elaborated in my deposition. The documents I reference in this Declaration-Report are annexed as exhibits to the Declaration of Paul Pennock, Esq.

I declare under penalty of perjury that the foregoing is true and correct. Executed this 24th day of November 2008.

Donna K. Arnett

Donna K. Arnett, Ph.D., M.S.P.H.

Expert Report of Donna K. Arnett, Ph.D.

A. Brief Report of Professional Qualifications

I am an epidemiologist with more than 20 years of experience in the design and conduct of experimental and observational epidemiological studies, including clinical trials, family studies, cross-sectional surveys, cohort, and case-control studies. I am Professor and Chair of Epidemiology at the University of Alabama at Birmingham, Department of Epidemiology. I am a Fellow of the American Heart Association and the American College of Epidemiology, and an Elected Member of the American Epidemiology Society. I have served as an Associate Editor for the *American Journal of Epidemiology* since 1996 and as an Editor since 2004. I currently serve as a Guest Editor and as relief Guest Editor-in-Chief for *Circulation*. I am routinely asked to evaluate epidemiological research studies for publication in peer-reviewed journals, including the *New England Journal of Medicine* and the *Journal of the American Medical Association*. I have served on numerous National Institutes of Health (NIH) review panels for epidemiological research. For the past two years, I have served as Chair for the Cardiovascular and Sleep Epidemiology Study Section (CASE) for the National Institutes of Health.

My principle professional interests include cardiovascular and metabolic disease epidemiology, genetic epidemiology, and pharmacogenetics. I have published more than 225 peer-reviewed articles and more than 12 book chapters or invited review papers.

Since 1994, I have designed and taught graduate level courses in fundamental and advanced concepts of epidemiology, methodological and theoretical aspects of epidemiology, and grant writing. From 1998-2001, I served as Chair of the Epidemiology Master's Degree Program at the University of Minnesota and as Director for the National Heart, Lung, and Blood Institute funded Training Program in Cardiovascular Genetic Epidemiology. For the past 10 years, I have taught a two-week summer course in Epidemiology and Prevention to physicians and other health care professionals for the American Heart Association and Centers for Disease Control.

A copy of my curriculum vitae is attached for additional detail.

B. Brief Overview of Principles of Epidemiology

Randomized, double-masked, placebo-controlled clinical trials are the optimal design for testing a hypothesized association between an exposure (or treatment) and disease because such studies offer the best control for confounding (i.e., variables that are associated with the disease and associated with the exposure) and provide for the optimal test for temporality (i.e., exposure precedes disease). Placebo controlled studies are the gold standard for evaluating the risks and benefits of a new treatment. During a clinical trial, four general reasons could explain clinical improvement in a

participant's condition: (1) natural history of the disease; (2) specific effects of the treatment under investigation; (3) regression to the mean; and (4) placebo effect. A study without a placebo control cannot differentiate amongst the prior 3 conditions. Active comparator randomized clinical trials are frequently used once a known treatment is available since withholding treatment from a diseased group could be unethical; however, there are methodological limitations of trials that use an active control. For example, there can be variable responses to drugs in some populations, unpredictable and small effects, and spontaneous improvements which with an active (rather than a placebo) control may mask the full effect of the drug under investigation.

Many epidemiological studies are observational and provide an assessment of a relation between an exposure and disease. Because of the observational nature of these studies, exposures are not "randomly-assigned" to study volunteers, and hence, factors that may be associated with the exposure of interest, and also independent predictors of the disease, may confound the observed relation between the exposure and disease. The best observational design to test a hypothesized association between exposure and disease is a cohort study. Cohort studies can be conducted either prospectively or retrospectively. Cohort studies are similar conceptually to clinical trials in that subjects are followed for the occurrence of endpoints. Therefore, temporality between the exposure and the endpoint can be conclusively evaluated. The availability of large administrative databases has prompted a number of cohort studies to evaluate adverse exposures, including pharmacological exposures, in relation to disease. The benefits of these types of cohort studies include their cost efficiency and ease of implementation. For example, pharmacy records can be linked to clinical records to assess a hypothesized association between a particular drug exposure and disease.

Case-control studies are also hypothesis-testing studies, and they rely on design qualities that, if done correctly, provide for an estimation of the exposure-disease relationship in a cost-efficient way. In a case-control study, diseased individuals are sampled (i.e., cases) as are non-diseased individuals (i.e., controls), and subjects are classified with respect to exposure. The effect measure used is the ratio of the exposure odds in cases compared to the exposure odds in controls. Conceptually, the case-control study can be thought of as nested within a population cohort, and if two important criteria are met, provide a valid estimate of the disease odds ratio. For excellent internal validity, a case-control study requires that exposure must measured in all cases (or a representative sample of cases that reflects the true exposure odds of all cases), and that the sample of the non-diseased members of the source population that generated the cases reflect the exposure odds of the population. If these conditions are met, then the exposure odds ratio will be equal to the disease odds ratio that can be calculated from a cohort study. In practice, these conditions are challenging to meet except in the case of the nested case-control studies, where the exposure odds can be accurately measured using previously collected data and/or specimens. Nested case-control studies overcome two other potential biases common to the case-control studies, namely, temporality and recall bias. Temporality is a concern in non-nested case-control studies because exposure ascertainment is

determined after disease onset. Another potential bias unique to non-nested case-control studies is recall bias, where cases are more likely than controls to recall prior exposures because of their disease.

C. Review of the Evidence for Effects of Seroquel on Metabolic Risk, including Weight Gain, Hypertriglyceridemia, Insulin Resistance, and Diabetes

The basis for my opinions expressed herein is derived from my education, training, research, experience, and review of the Seroquel New Drug Application (NDA) to the Food and Drug Administration, internal Astra Zeneca documents, the peer-reviewed medical literature, and other publicly available documents concerning Seroquel and its relationship to weight gain and other metabolic risks. In developing my opinions in this case, I am relying primarily upon the Astra Zeneca NDA application and the related published literature, published cohort and nested case-control studies, and meta-analyses of published studies. I have spent over 80 hours reviewing literature and documents related to Seroquel.

Based upon my review of the above specified documents, I have developed the following opinions in this case: (1) Seroquel leads to clinically significant and relevant metabolic risk, including weight gain and other metabolic complications, including but not limited to hypertriglyceridemia, insulin resistance, and diabetes; (2) the metabolic risks from Seroquel appear shortly after treatment and throughout treatment; (3) Astra Zeneca should have made the data presentation clearer within the New Drug Approval application and included the data regarding metabolic risk within scientific publications of the Phase II and Phase III randomized clinical trials in order to warn the FDA, future patients and physicians about metabolic risks associated with Seroquel; (4) the metabolic risks associated with Seroquel outweigh the benefits of treatment; and (5) Astra Zeneca promoted Seroquel as metabolically neutral when there was insufficient evidence to support this claim but substantial evidence that the drug in fact caused weight gain and other metabolic derangements (6) Astra Zeneca withheld support for studies that could have demonstrated Seroquel's metabolic risk relative to other atypical antipsychotics. I have developed these opinions utilizing the normal methodology that I exercise as an epidemiologist in the ordinary scope of my practice. Further, I state these opinions to a reasonable degree of scientific certainty.

C.1. Overview: The Effect of Seroquel on Weight Gain and Other Metabolic Derangements

Seroquel causes weight gain and other metabolic toxicities through stimulation of the hypothalamic AMP activated protein kinase (AMPK). AMPK is responsible for maintaining energy balance and the regulation of food intake. Seroquel blocks histamine H1 receptors, the receptors responsible for the inflammatory response which then stimulates AMPK. In addition to the effects on H1 receptors, Seroquel affects insulin action and metabolism directly in the cell, leading to insulin resistance

and alterations in lipogenesis and lipolysis, which ultimately cause progressive lipid accumulation.

Weight gain can lead to reductions in patient compliance with the medication which could lead to poor clinical outcomes. Weight gain is an important concern of Seroquel treatment, and in particular among schizophrenic individuals since there is an association between schizophrenia and Type II diabetes mellitus, and weight gain is an important risk factor for diabetes development. Weight gain is also an important determinant of other metabolic toxicities, such as hypertriglyceridemia, hypertension, and insulin resistance, all part of the metabolic syndrome. Moreover, once weight has been gained, it is challenging to lose, and this is a large concern for schizophrenic patients who are not typically capable of undertaking lifestyle management to maintain or to lose weight.

There is unequivocal and consistent evidence that Seroquel treatment leads to clinically and statistically significant increases in weight, that the onset of the weight gain occurs shortly after the beginning of treatment and progresses with increased duration of treatment, and that the weight gain is proportionate to the dose ingested. Significant weight gain was observed during the Phase II and III trials and subsequently demonstrated throughout the developmental program of Seroquel for other treatment indications. In addition, other components of the metabolic syndrome (i.e., hyperinsulinemia, hypertriglyceridemia) were similarly observed during the development of Seroquel, and increased incidence of diabetes has been observed with Seroquel treatment. The justification for this opinion follows.

C.1.1. Weight Gain in Response to Seroquel Treatment

The New Drug Application for Seroquel was submitted to the FDA in July, 1996. According to the Integrated Safety Report filed as a part of the NDA, weight and vital signs were collected on the same case report form and were summarized together in the safety report to the FDA. In fact, according to the majority of protocols reviewed, weight for the Phase II and III trials was collected at each visit. Results presented in the Integrated Safety Report are restricted to the analysis which required that subjects who were included in the tabulations had both baseline and post-baseline observations available. Clinically significant weight gain was defined by a gain of 7% of the baseline body weight (approximately 10 pounds for a 150 pound individual).

In the Phase II and III trials, the mean age of the trial participants was 38 years, and the mean body weight was normal (76 kg or 168 lbs). A total of 2162 schizophrenic patients were exposed to Seroquel with doses ranging from 50 to 800 mg/day administered between two and four times daily. Of the 2162 subjects, 1710 were from Phase II and III controlled trials and 454 were from new Seroquel exposures from the uncontrolled trials and were available for analysis. As of June 1, 1995, 407 subjects had been exposed to Seroquel for 6 months or longer and only 1 subject for 2 years or longer; 110 subjects were treated for one year or longer. As stated on page

119 of the report, "In the Phase II and III placebo-controlled trials, Seroquel was associated with a statistically significant weight gain (p=0.0471)." Additionally, from the short term placebo-controlled trials, Astra Zeneca stated that the mean weight gain for Seroquel-treated patients was 2.2 kg (4.85 pounds) greater than the mean weight increase for placebo-treated patients. The range of weight gain was markedly higher for the Seroquel treated than the placebo treated patients, indicating that the distribution of weight gain was non-normal. Therefore, median weight change would have been the optimal measure of central tendency, but median weight change was not provided (in contrast to other vital sign measures that were provided as medians). Had the median, rather than the mean, been reported, the findings regarding the differences between Seroquel and placebo would have been even more dramatic. More detail regarding individual studies is provided below.

The following table describes the studies included in the NDA, and the status of vital signs collected in each. Placebo controlled trials are indicated by **bold** type. Uncontrolled trials are indicated by *italics*. Active comparator trials are indicated by underlined text. Trial 0012 was a low dose Seroquel study and limited data were provided in the Integrated Safety report for this study, although the data provided were indicative of weight increases with treatment.

Vital signs and weight assessments by trial (integrated Phase II-III trials)

	0004	*0005*	**0006**	0007	**0008**	0012	**0013**	0014	0015	*0048*	*LTE*
Pulse	X	X	X	X	X	X	X	X	X	X	X
Blood Pressure*		X	X	X	X	X	X	X	X	X	X
Respiratory	X	X	X		X						
Temperature		X	X	X	X	X		X		X	US
Weight	X	X	X	X	X	X	X	X	X	X	X

* All measures were taken while subjects were seated.
* Unless otherwise noted, readings were taken for both supine and standing systolic and diastolic blood pressures.
+ Only supine readings were taken for Trial 0007.
** Respiration readings were taken while subjects were in the supine position unless otherwise noted.

Data for studies 0004, 0006, 0008, and 0013 were only provided in summary form. In these trials combined, 89/391 (23%) of Seroquel treated subjects had clinically significant weight gain compared to 11/178 (6%) of placebo-treated subjects. This resulted in a relative risk for clinically significant weight gain with treatment of **3.68** (p<.0001, 95% CI 2.1-6.7).

For Study 13 alone, clinically significant weight gain was observed in 2/51 (6%) for placebo, 2/52 (4%) for haldoperidol, 6/53 (11%), 8/48 (17%), 5/52 (10%), 8/51 (16%), 7/54 (13%) for Seroquel 75 mg, 150 mg, 300 mg, 600 mg, and 750 mg, respectively. In comparing low dose Seroquel (75 or 150 mg) versus placebo, the relative risk of weight gain was **3.54** (p=.06, 95% CI .95-16.1), and contrasting high dose (the dose recommended for schizophrenia), the relative risk of weight gain versus placebo was **4.77** (p=.012, 95% CI 1.34-18.2). This provides strong evidence

for dose response, a criterion frequently invoked to determine causation, and also indicates that Seroquel results in increased risk of clinically significant weight gain.

For Study 0013 and 0014 combined, clinically significant weight gain occurred in 70/354 (19.8%) in the Seroquel treated subjects versus 18/236 (7.6%) in the haloperidol treated subjects (relative risk **2.61**; 95% confidence interval 1.61 – 2.42, p<.0001).

For Study 0007, clinically significant weight gain occurred in 28/100 Seroquel treated subjects compared to 19/99 of the chlorpromazine treated subjects (**RR=1.47**, p=-0.14, 95% CI 0.88-2.44). This active comparator study indicated that Seroquel's weight gain was greater than that of another atypical antipsychotic. This active comparator was not used again in subsequent trials presented in the NDA.

In summary, for these short-term placebo trials, the relative risk for a clinically significant increase in weight ranged from 2.61 to 4.77, indicating a strong and consistent increased risk, and for the active comparisons, a modest to strong increased risk for weight gain compared to chlorpromazine and haldoperidol.

Study 0015 was the long-term, 52-week study, implemented to evaluate the long-term efficacy and safety of Seroquel compared to haldoperidol for treatment of schizophrenia. In this study, Seroquel was associated with a statistically significant increase in weight gain that was dose-dependent and time-dependent (i.e., the longer the treatment, the greater the weight gain). The difference in the mean weight gain was 3.0 kg between treatment groups (+1.6 kg for Seroquel versus -1.4 kg for haldoperidol). Clinically significant weight gain occurred in 50/209 (23.9%) of the Seroquel participants compared to 4/38 (10.5%) of the haldoperidol-treated subjects (relative risk=2.27, p=0.066, 95% CI=0.94-7.55). As stated in the Integrated Safety Report "In general, mean weight increases from baseline for quetiapine-treated subjects were greater at Week 52 for subjects completing the trial (ranging from 2.05 to 8.52 kg) compared with the increases seen at final evaluation (Week 52 or withdrawal), suggesting a trend for subjects to continue gaining weight over time." Also stated in the Integrated Safety Report "The percentage of subjects with clinically significant increases from baseline in weight increased as the dose level of quetiapine increased (for the 75-, 300-, and 600-mg dose groups, 15.2%, 22.9%, and 32.9% of subjects had significantly high changes)." This dose-response was statistically significant. The findings from this long-term study confirm findings of the short-term studies and also suggest that weight gain continues with treatment duration.

In the uncontrolled trials (0005, 0048, and OLE), 27.5% of Seroquel-treated subjects had a clinically significant high weight gain, comparable to the findings in the controlled trials and the long-term controlled trial for Seroquel-exposed participants (Study 0015 cited previously, i.e., 23.9%).

In addition to these controlled and uncontrolled trials included in the NDA application, there were indications from the long-term extensions of the trials that weight gain was persistent throughout follow-up and increased with time, indicating

that prolonged treatment with Seroquel could lead to substantially increased risk of metabolic toxicity. With increased follow up, data later presented during the observed long-term extensions showed that 37.2% of Seroquel-exposed patients had clinically significant weight gain at some point during follow up. Weight gain increased with increased exposure duration: mean weight change compared to baseline weight increased by 3.8 (± 9.0) kg at week 65, 4.4 (± 9.6) kg at week 104, 5.7 (± 10.9) kg at week 156, and 6.7 to 7.3 (± 9.9-13.1) kg at weeks 208 - 260. If presented as median weight gain, this substantial weight gain would have undoubtedly been much larger.

There are two methodological concerns that, with a degree of scientific certainty, resulted in underestimates of the true effect of Seroquel on weight gain in these studies. First, the studies provided in the NDA had consistently high drop-out rates for Seroquel. This is an important characteristic to define the internal validity of a study. Among the 2162 subjects randomized to (n=1710) or treated in uncontrolled trials (n=454), 80.1% withdrew, and the rate was much higher than the 42% for the active comparators or 61.2% for placebo. This has important implications for the interpretation of results related to weight gain or other metabolic abnormalities. Weight gain is a major contributor to non-compliance, and in aggregate in the Phase II and III program, weight gain was associated with greater drop-outs. Therefore, the result reported from these studies almost surely underestimates the true impact of Seroquel on weight gain. Second, many of the studies conducted restricted weight as an inclusion criterion, generally between 100 and 230 pounds. Had heavier subjects been included, it is likely that the weight gain would have been even greater. Since these subjects were excluded, it is unclear whether Seroquel would have been safe in overweight and obese subjects (i.e., the studies are not generalizeable to these subjects).

A metabolic cause for concern regarding the weight data presented in the NDA is the consistent pattern for reductions in thyroid hormone levels that occurred with Seroquel treatment. Low levels of thyroid hormone are associated with greater body weight. Each trial presented in the Table above collected at least one measure of thyroid function. As stated in the Integrated Safety Report, "Consistent laboratory data suggest that quetiapine treatment tends to reduce thyroid hormone plasma levels, primarily total T4 and free T4 with smaller decreases seen in total T3 and reverse T3... Both total T4 and free T4 mean values are reduced and the incidence of significantly low values is increased in quetiapine-treated subjects compared both to placebo- and haloperidol-treated subjects. Results from Trials 0013 and 0015 indicate that the reductions in thyroid hormone levels are dose-related, that the onset of the reductions may occur within the first few days of treatment." Note that the definition of abnormalities for any of the thyroid hormone levels was less than 0.8 times the lower limits of normal or greater than 1.2 times the upper limit of normal. The Integrated Safety Report dismisses these thyroid changes as clinically irrelevant since the thyroid stimulating hormone did not significantly increase. However, because most of the studies were short term, the design may have precluded the development of an increased TSH.

Finally, weight was measured at almost every visit along with the vital signs. Yet detailed week-by-week data could not be found in the Integrated Safety Results. No data were provided in the published literature across the time course of the studies. This is particularly important given the very large drop-out rates that occurred consistently throughout the studies provided in the NDA. It is likely, given the consistent weight increases seen in every Phase II and III study conducted and summarized in the NDA that weight increased among those that subsequently dropped out, and therefore, findings that included subjects who dropped out could have made the findings even less favorable for Seroquel.

Additional studies from the AZ website conducted after the NDA was submitted were evaluated for weight change (based on data provided only on the AstraZeneca website) and showed the consistent pattern of weight increase seen with studies included in the NDA. Data are only tabulated for the first 11 studies listed on the website since the results were consistent with those observed as part of the NDA.

Table 1. Weight Change in AstraZeneca Studies

Study Number	Start – End Date	Results for Metabolic Risk Factors
0039	03/16/98 – 02/03/00	Clinically significant weight gain in 6% of Seroquel, 5% of haldoperidol, and 2% of placebo treated subjects.
0050	05/02/96 - 05/21/99	6 subjects with hypothyroidism on Seroquel; none on haldoperidol
0099	08/09/00 - 11/26/01	Seroquel-treated patients exhibited a statistically significant (p=0.0031) mean increase of 1.60 kg more than the placebo treated group.
0100	11/08/00 – 01/25/02	Clinically significant weight gain in 10.4% of Seroquel subjects versus 3.9% of placebo subjects (relative risk=2.67)
0104	01/07/01 – 04/25/02	Seroquel subjects gained 2.1 kg versus a loss of 0.1 kg in placebo subjects and a gain of 0.2 kg in haldoperidol subjects
0105	04/03/01 – 05/27/02	Weight gain 3.3 kg in Seroquel vs. 0.3 kg in placebo; clinically significant weight gain in 15% versus 1%, respectively (relative risk=15)
0043	06/28/01 – 09/04/02	Both weight gain and glucose significantly increased (no data provided)
0046	No dates provided	Clinically significant weight gain occurred in 12-15% of Seroquel treated subjects (100-200 mg) versus 15% of placebo treated subjects (relative risk = 0.8 to 1.0)
0049	09/30/02 - 09/17/03	Weight increased 1.7% and 6.1% in 300 and 600 mg Seroquel, respectively, vs. 0.6% in placebo (relative risk 2.8 and 10.2, respectively)
D1447C-0001	08/31/05 - 05/24/07	Seroquel mean weight gain ranged from 0.4 to

		1.3 kg across the doses used compared to placebo (-0.4 kg). Clinically significant weight gain occurred in 12.0 to 15.4% of Seroquel groups compared to 2.9% in the placebo group (relative risk 4.2 – 5.3).
D1447C-0135	06/30/04 – 08/26/05	Weight increased 4.1 kg and 5.4 kg in Seroquel 300 mg and 600 mg treated subjects vs. 1.8 kg in placebo subjects

In aggregate, the evidence from the studies presented in the NDA and the follow-up long-term extensions demonstrate a large effect of Seroquel on weight gain. Based on the placebo-controlled studies using doses recommended for schizophrenia, as much as 90% of the weight gain in Seroquel-treated subjects was caused by the drug.

C.1.2. Glucose Abnormalities and Insulin Resistance in Response to Seroquel Treatment

Increased weight is a major risk factor for elevated glucose, hyperinsulinemia, and Type II diabetes mellitus. Glucose measures were collected in most studies and in every US study completed as part of the NDA. Clinically significant increased glucose was defined to be greater than 13.9 mmol/L or 250 mg/dl. However, limited data were provided in the NDA related to glucose, insulin, or other biochemical indices of metabolic risk.

Studies 126 and 127 were conducted with secondary aims to evaluate more detailed measures of glucose homeostasis. In these two trials, there were 5 cases of diabetes in the Seroquel group (n=646) compared to one in the placebo group (n=689). The difference between Seroquel- and placebo-treated patients was pronounced for glucose values > 200 mg (2.9% and 0.5%, respectively). Among Seroquel-treated subjects, 12.2% of them had at least one glucose value greater than 250 mg/dl compared to only 8.1% of placebo treated subjects. Analyses adjusted for length of follow up and restricted to participants who had fasted for at least 8 hours showed even greater treatment differences with respect to glucose. Seroquel patients had a greater mean increase (5.0 mg/dL) in glucose relative to participants randomized to placebo (-0.05 mg/dL). Elevated HbaIC (> 7.5), a longer term marker of glucose elevation, occurred in 2.1 vs. 0.8 percent of Seroquel versus placebo participants. In aggregate, these data clearly show the excess of glucose abnormalities in subjects randomized to Seroquel.

At the request of the Food and Drug Administration in May, 2000, Astra Zeneca evaluated disturbances in glucose regulation in their Phase I-III program as well as post-marketing surveillance. In the short-term (i.e., less than 6 weeks duration) placebo-controlled studies, only 230 Seroquel treated subjects and 143 placebo-treated subjects had glucose measurements analyzed, and Seroquel treated subjects had higher values of glucose than their placebo counterparts (3.6 (1.52 SE) vs. -0.26 (1.93), p=.12, respectively). Additionally, 3.4% of 323 Seroquel treated subjects

versus 0.7% of 143 placebo-treated subjects had a glucose value in excess of 200 mg/dl during the short term trials (relative risk 4.87, 95% confidence interval 0.83-29.30, p=0.116). In June, 2007, a clinical overview was conducted for the purpose of providing data to support changes to the Core Data Sheet. In that analysis, glucose, insulin, HOMA, and HbA1C were evaluated in the composite of studies that had been conducted. The data indicate that Seroquel is associated with metabolic abnormalities with respect to glucose, insulin resistance, and diabetes. Among the 11,013 Seroquel treated subjects, the mean increase in blood glucose was 0.2 (1.62) mmol/L compared to 0.059 (1.46) mmol/L in 1,592 placebo treated subjects. Differences were much larger for HOMA, a measure of insulin resistance that is sensitive to weight (i.e., subjects who gain weight become more insulin resistant): the difference in means was five fold greater for Seroquel versus placebo [1.26 (9.5) in 2265 Seroquel subjects versus 0.37 (10.83) in 640 placebo subjects]. Not unexpectedly, given these differences in glucose and insulin resistance, the relative risk for diabetes was 2.02 (p=0.49, 95% CI 0.31-12.04).

Since most of the participants in the randomized clinical trials were treated for a short period of time, the actual person-time contributed is small, and may have not yielded sufficient power to detect the excess risk of diabetes associated with Seroquel. However, as early as 1999, Dr. J. Small indicated in her draft for a book chapter for Psychopharmacology of Schizophrenia that "as...quetiapine cause the most weight gain, these drugs may be the most likely to induce diabetes." Once Seroquel was approved by the FDA and administered to large numbers of patients, there was early evidence of an increased risk of diabetes with Seroquel treatment. In 2003, Koller et al published a report using data derived from the FDA Medwatch, a surveillance program for spontaneously reported adverse events. During the period 1/1/97 through 8/15/02, they showed that Seroquel use unmasked or precipitated diabetes, the onset was rapid and severe, and removal of the drug resolved the condition in some cases.

Subsequent observational studies (cohort and case-control) confirmed the excess risk of diabetes with Seroquel. For example, Guo et al, using an integrated, seven-state, Medicaid-managed, care claims database from 1/1/98 through 12/31/02, reported the relative risk of diabetes was 2.5 (95% CI 1.4-4.3) in Seroquel users compared to users of conventional antipsychotics. Other studies have suggested that the diabetes risk increases with greater exposure time. For example, Dr. Lambert and colleagues reported from the Veteran's Affairs database that Seroquel was associated with an increased risk for diabetes compared to conventional antipsychotics (RR 1.67, 95% CI 1.01-2.76) and that the risk increased with greater treatment duration (RR for 52 weeks of treatment 1.82, 95% CI 1.32 – 2.49). Other studies have found relative risks for quetiapine versus conventional antipsychotics to range from 1.17 (95% CI 1.06 – 1.30; Ollendorf et al, 2004) to 3.15 (95% CI 1.63 – 6.09; Citrone et al, 2004), with other studies by Sernyak, Leslie, Lambert, and Guo showing relative risks between these two extremes (see Table 2). However, all studies used conventional treatment as the comparison group rather than non-treatment, which could result in a confounding effect, i.e., attenuation of the effect size of Seroquel, if these treatments also were causally related to diabetes. For example, compared to non-treatment,

Sacchetti et al reported a relative risk of 33.7 (95% CI 9.2 – 123.6) for Seroquel. Most studies reported also have a very limited time window of exposure and a small number of subjects exposed to Seroquel.

Table 2: Observational Studies reporting Relative Risks of Seroquel compared to Conventional Antipsychotic Treatments		
First Author	Year	Relative Risk (95% Confidence Interval))
Sernyak	2002	1.31 (1.11 - 1.55)
Citrone*	2004	3.15 (1.63 – 6.09)
Feldman*	2004	NR (1.3 – 2.9)
Ollendorf *	2004	1.17 (1.06 – 1.30)
Leslie*	2004	1.20 (0.99 – 1.44)
Lambert*	2005	1.2 (0.80 – 1.70)
Guo*	2005	1.8 (1.4 – 2.4)
Lambert*	2006	1.67 (1.01 – 2.76)
Guo*	2007	2.5 (1.4 – 4.3)
* indicates industry support among investigative team members, NR=not reported		

C.1.3. The Effect of Seroquel on Triglycerides and Cholesterol

Seroquel has consistent and detrimental effects on triglyceride values which is congruent with its effects on weight and glucose / insulin abnormalities. As stated in the Integrated Safety Report, clinically significant increased triglycerides were defined as a doubling of triglycerides above the upper limit of normal. In aggregate in the Phase II and III placebo-controlled studies summarized in the Integrated Safety Report, the relative risk for increased triglycerides above the normal range at the end of the treatment was 2.7 (22.3% of Seroquel users versus 8.2% of placebo users). The percentage of participants who had a clinically significantly high triglyceride value at any time during these studies was even greater in Seroquel versus placebo users (26.3% versus 8.2%). Cholesterol values showed a similar pattern.

D. Metabolic Derangements associated with Seroquel outweigh Benefits of Treatment

Given the totality of evidence regarding the increased metabolic risk with Seroquel treatment, the relative benefit of Seroquel compared to other antipsychotic agents is debatable. In fac, in 1997, Dr. L. Arvanitis questioned the competitive advantage of Seroquel. In her review of the data regarding weight gain, she stated "I was really struck by how consistent the data was across pools…across parameters / measures…across cohorts." In her summary, she stated that the weight gain was rapid but continued to increase with continued treatment and that the weight gain was 45% at 52 weeks of treatment. She concluded that she did not see a "competitive opportunity" no matter how weak. Subsequent studies confirmed Dr. Arvantis' concern that Seroquel's benefit / risk profile is not superior to other drugs in the class. In aggregate, the drop out rate in the Phase II and III studies was consistently highest

for Seroquel compared to haloperidol or chlorpromazine. The largest and most carefully done study to address the overall effectiveness across drugs in this class was conducted by the National Institutes of Health, specifically, the National Institute of Mental Health. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study randomized 1493 patients with schizophrenia at 57 U.S. sites to receive olanzapine (7.5 to 30 mg per day), perphenazine (8 to 32 mg per day), quetiapine (200 to 800 mg per day), or risperidone (1.5 to 6.0 mg per day) for up to 18 months; ziprasidone (40 to 160 mg per day) was included after its FDA approval. The primary outcome measured used to define effectiveness was withdrawal from the study for any reason. That study found that the time to the discontinuation of treatment for any cause (i.e., the primary outcome measure) was longer in the olanzapine treated subjects than in the Seroquel treated subjects (hazard ratio, 0.63; $P<0.001$). Additionally, the time to the discontinuation of treatment for lack of efficacy was longer, and the total duration of successful treatment longer, in the olanzapine treated subjects than in the quetiapine treated subjects (hazard ratio, 0.41; $P<0.001$ and 0.53; $P<0.001$, respectively). Finally, another indicator of poorer efficacy is the proportion of patients who take the maximal dose of a drug: a higher proportion of patients assigned to quetiapine received the maximal dose allowed in the study.

E. Astra Zeneca Failed to Warn Future Patients and Physicians about the Metabolic Risk associated with Seroquel

Despite the consistent clinically and statistically significant increases in weight and other metabolic parameters noted in all Phase II and III studies presented in the Integrated Safety Report, none of the weight or metabolic factors were listed in the summary of the risks and benefits provided at the conclusion of that report. Publications of the Phase II and III studies never mentioned increased weight or other metabolic abnormalities in the abstract of the publication (i.e., the summary of a scientific publication that is publicly available through various search engines such as PubMed). Within publications, the weight data were listed at the end of results sections, and in the discussion section, dismissed as expected complication of treatment.

F. Astra Zeneca Promoted Seroquel as Metabolically Neutral

Early publications of Seroquel Phase II and III randomized clinical studies promoted Seroquel as metabolically safe despite the large, consistent, and statistically significant findings of weight gain, reduced T4, and hypertriglyceridemia in the clinical trials included in the NDA application in 1996. Even as late as 5/22/99, Astra Zeneca produced a news release from the APA meeting in Washington stating Seroquel "reduces weight gain" and that the "potential to gain weight and develop diabetes.....can be minimized with Seroquel." This data --- for which a news release was created --- were based on retrospective chart review of a case series of 60 patients. This design is the weakest of all designs in epidemiologic research, and the results from this study were in sharp contrast to the totality of evidence from the gold

standard of research designs, namely, the placebo-controlled randomized clinical trials that comprised much of the data submitted with the NDA.

In 2000, publications supported by the company by Breecher et al; describe Seroquel as having a 'favorable weight profile", consistent with the "recommended vocabulary". In 2003, Seroquel's management team created "key messages" to be used in publication. And again, Seroquel's "favorable weight profile" was a key message of Astra Zeneca. In February, 2005, a document created by Astra Zeneca entitled "Seroquel Vocabulary and Descriptors Summary Document" was finalized. Its purpose was to communicate accepted vocabulary to be used in all publications from Seroquel as well as language to be avoided or not used. With respect to weight, the "recommended" vocabulary to be used in publications was "favorable weight profile" and "minimal weight gain". For diabetes, recommended statements generally highlighted either the increased risk of diabetes in schizophrenic patients or the weaknesses of epidemiological studies and confounding as likely reasons of excess diabetes risk associated with Seroquel treatment. In 2006, the Division of Drug Marketing, Advertising, and Communications of the U.S. Food and Drug Administration ordered Astra Zeneca to "cease the dissemination of violative promotional materials for Seroquel" because of false or misleading statements that minimized the risk of hyperglycemia and diabetes mellitus.

In aggregate, this brief and non-exhaustive list of examples point to a concerted effort to promote Seroquel as safe and metabolically neutral in the context of compelling placebo and active comparator controlled clinical trials indicating the drug was associated with substantial metabolic risk.

G. Astra Zeneca withheld Support for Studies Regarding Seroquel's Metabolic Risk

Astra Zeneca consistently withheld support for studies which could demonstrate Seroquel's lack of safety relative to other antipsychotic agents. As evidenced by an email from Dr. Goldstein, July 18, 2002, an investigator requesting 3 grams of Seroquel to study diabetogenic and hyperlipidemia side effects of Seroquel and other atypical antipsychotics was denied by Astra Zeneca. Dr. Goldstein stated "This would be an interesting study but carries substantial risks that we do not differentiate from olanzapine or clozapine. This would be damaging.....I would not want to enter into a study that could provide any data that could influence regulatory authorities against us." Additional internal communications from Dr. Goldstein reinforce the stance of Astra Zeneca with regard to initiating studies. For example, Dr. Goldstein states in another email "they don't want to introduce studies that could potentially damage Seroquel's comparison against other atypical's."

In 2005, Astra Zeneca promoted a policy that gave "green" or "red lights" to make funding decisions for research proposals brought forward from independent investigators. A "red light" was given for glucose and/or metabolism investigator sponsored studies. Specifically, Astra Zeneca's stated policy for glucose or metabolism studies was "don't bother for red". In light of the totality of data within

their own studies indicating the metabolic derangements associated with Seroquel treatment, and subsequent observational epidemiological studies indicating the diabetes risk associated with treatment, this was an unreasonable approach with respect of patient safety.

As medical literature is consistently being published and new evidence from other sources is emerging in reference to this subject I reserve the right to supplement this

I have participated in two trials involving Vioxx.

Donna K. Arnett, Ph.D., M.S.P.H.

CURRICULUM VITAE

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Formal Education

1981	B.S.	College of Nursing, University of South Florida, Tampa, FL.
1987	M.S.P.H.	Epidemiology, College of Public Health, University of South Florida, Tampa, FL.
1991	Ph.D.	Epidemiology, School of Public Health, University of North Carolina, School of Public Health, Chapel Hill, NC.

Professional Experience

1992 - 1994	American Heart Association Postdoctoral Fellow Department of Epidemiology School of Public Health University of North Carolina
1994 - 1998	Assistant Professor of Epidemiology Division of Epidemiology School of Public Health University of Minnesota
1998 - 2003	Associate Professor of Epidemiology Division of Epidemiology School of Public Health University of Minnesota
2003 – 2004	Mayo Professor of Epidemiology Division of Epidemiology School of Public Health University of Minnesota

2004 – Present	Chair and Professor of Epidemiology Department of Epidemiology School of Public Health University of Alabama at Birmingham

Societies and Organizations

1990 - Present	Fellow, American Heart Association, Council on Epidemiology and Prevention
1992 - Present	Society for Epidemiologic Research
1992 - Present	American Public Health Association
1996 - Present	Minnesota Public Health Association
1996 - Present	The American Society of Human Genetics
1998 - Present	International Genetic Epidemiology Society
2002 - Present	American Society of Hypertension
2004 – Present	Senior Scientist, UAB Comprehensive Cancer Center
2004 – Present	Senior Scientist, UAB Clinical Nutrition Research Center
2005 – Present	Internal Advisor, UAB Center for AIDS Research

Awards and Honors

1981	Graduated magna cum laude
1987	Outstanding Student Faculty Scholarship, College of Public Health, Department of Epidemiology, University of South Florida
1988 - 1991	U.S. Public Health Service Traineeship Award, University of North Carolina, Chapel Hill
1989	Alumni Student Faculty Award for Outstanding Service, School of Public Health, University of North Carolina
1990	Biomedical Research Service Award, University of North Carolina
1992	Delta Omega, Honor Society for Public Health, Theta Chapter
2000	Finalist, Roger Williams Award, American Heart Association, Council on Epidemiology and Prevention, March, 2001
2004	Award of Meritorious Achievement of the American Heart Association

Grant and Contract Support

Title:	GenHAT - Genetics of Antihypertensive Treatments
Funding source/type:	NIH/NHLBI 5 R01 HL63082 $5,263,486
Summary:	Ancillary to the Antihypertension and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), we are investigating whether common polymorphisms of several hypertension candidate genes modify the effect of antihypertensives on long-term outcomes, including mortality, coronary heart disease and stroke.
Period:	8/1/99-7/31/05
Role:	Principal Investigator

Title:	HyperGEN: Genetics of Left Ventricular Hypertrophy
Funding source/type:	NIH/NHLBI 2 R01 HL55673, $3,303,849
Summary:	This 5 year project is recruiting family members with left ventricular hypertrophy and/or hypertension. Genetic analysis will be conducted to identify genomic regions contributing to variation in cardiac size and structure.
Period:	8/1/00-7/31/05
Role:	Principal Investigator

Title:	NHLBI Family Blood Pressure Program-HyperGEN
Funding source/type:	NIH/NHLBI 2 U01 HL54496, $3,558,679
Summary:	This project addresses the genetics of two major complications of hypertension (hypertensive heart disease and hypertension-associated kidney disease). It is a continuation of the first cycle of the NHLBI-FBPP.
Period:	9/16/00-6/30/05
Role:	Co-Investigator

Title:	FHS SCAN
Funding source/type:	NIH/NHLBI, 1 U01 HL67901, $1,171,497
Summary:	As an extension of the NHLBI Family Heart Study, we will re-recruit participants and characterize coronary calcification and inflammatory markers. The goal is to identify genomic regions contributing to inter-individual variation in these traits.
Period:	7/1/01-6/30/05
Role:	Co-Investigator

Title:	Genetic and Environmental Determinants of Triglycerides
Funding source/type:	NIH/NHLBI, U 01 HL72524, $10,147,893
Summary:	This study is characterizing the genetic basis of the variable response of triglycerides (TGs) to two environmental contexts, one that raises TGs (dietary fat), and one that lowers TGs (fenofibrate treatment).
Period:	9/30/02–8/31/06
Role:	Principal Investigator

Title:	Genes and Environmental Determinants of Triglycerides Administrative Supplement
Funding source/type:	NIH/NHLBI, 3 U01 HL72524-0181, $1,000,000
Summary:	The University of Minnesota serves as the Program Administrative Center for the 5 networks participating in the Gene-Environment Collaborative Studies.
Period:	9/30/02-8/31/06
Role:	Principal Investigator

Title:	MESA Family Study
Funding source/type:	NIH/NHLBI, 1 R01 HL071251-01A1, $723,209
Summary:	The goal of this study is to determine the extent of genetic contribution to variation in coronary calcium (EBCT and CT scan) and carotid artery wall thickness (B-mode ultrasound) in non-majority populations.
Period:	8/1/03-6/30/08
Role:	Co-Principal Investigator

Submitted Grants

Status:	Resubmitted
Title:	Identifying Susceptibility Genes for Metabolic Syndrome
Funding source/type:	NIH/NIDDK, $1,651,855
Summary:	The overall goal of this 3-year project is to characterize a 19.5 Mb region on chromosome 2q35-2q37 using linkage disequilibrium (LD) mapping to identify genes influencing susceptibility to the MS.
Period:	4/1/05-3/31/08
Role:	Co-Investigator
Status:	To be resubmitted November, 2005

Title:	Pharmacogenomics of HAART – Induced Lipoatrophy in HIV Patients
Funding source/type:	NIH/HHS/PHS, $5,186,437.00
Summary:	We will use a whole-genome association study to identify loci that predict lipoatrophy among HIV+ patients undergoing highly active antiretroviral therapy (HAART)
Period:	07/01/05-06/30/10
Role:	PI
Status:	To be resubmitted September 2005

Title:	Delta States Center for Genomics and Public Health: A Four-State Partnership
Funding source/type:	CDC/HHS/PHS, $500,000.00
Summary:	Established to develop a strong regional educational and technical assistance program network directed to state and local health departments, K-12 school systems, and the general public.
Period:	09/01/04-08/31/08
Role:	PI
Status:	Not funded; Agency withdrew program

Former Grants

Completed Research

Title:	Colliding Categories: Haplotypes, Race & Ethnicity
Funding source/type:	NIH

Summary:	The aim of this project is to explore the ethical and legal ramifications of the impending collision between biological and regulatory classifications of population subgroups in American society.
Period:	7/1/04-6/30/06
Role:	Consultant

Title:	FHS: Molecular Genetics and Genetic Epidemiology MN
Funding source/type:	NIH/NHLBI, 2 R01 HL56567, $182,025
Summary:	This extends the genome-wide analysis for NHLBI FHS conducted during the initial funding period.
Period:	10/23/01-8/31/04
Role:	Principal Investigator

Title:	Training Grant in CVD Genetic Epidemiology
Funding source/type:	NIH/NHLBI, 1 T32 HI07972, $694,879
Summary:	This proposal funded 3 pre-doctoral and 1 post-doctoral trainees in CVD genetic epidemiology at the University of Minnesota
Period:	7/16/01-7/15/06
Role:	Principal Investigator

Title:	Community Surveillance of Cardiovascular Disease -- Risk Factor Survey (MHS)
Funding source/type:	NIH/NHLBI 5 R01 HL23727, $4,576,444
Summary:	A survey of 5,000 adults, ages 25-74 years, and children ages 8-17 years will be conducted using methodology identical to prior MHS surveys done in 1980-82, 1985-87, 1990-92, and 1995-97.
Period:	3/01/00-2/28/04
Role:	Principal Investigator

Bibliography

Peer-reviewed senior & co-authored articles (formerly published under Koehn)

1. Koehn DK, Glasser SP. The impact of antianginal drug therapy on the incidence of asymptomatic myocardial ischemia. J Clin Pharmacol 1989;29:722.

2. Glasser SP, Bittar N, Kinhal V, Bennet WT, Koehn DK. The efficacy and safety of dilevalol in patients with chronic stable angina pectoris. J Clin Pharmacol 1989;29:983.

3. Glasser SP, Koehn DK, Powell R. Regression of left ventricular hypertrophy in treated hypertensive patients with dilevalol and metoprolol-a double blind randomized study. J Clin Pharmacol 1989;29(9):791.

4. Glasser SP, Chrysant SG, Graves J, Rofman B, Koehn DK. Safety and efficacy of amlodipine added to hydrochlorothiazide therapy in essential hypertension. Am J Hypertens 1989;2(3):154.

5. Glasser SP, Koehn DK. Predictors of left ventricular hypertrophy in patients with essential hypertension. Clin Cardiol 1989;12:129.

6. Glasser SP, Arnett DK. Reexamination of tolerance issues and efficacy endpoints of long-acting products. Hospital Formulary 1990;25(1):42.

7. Arnett DK, Glasser SP. The risk factor profile for patients with asymptomatic myocardial ischemia. Journal of Applied Cardiology 1990;5:239-244.

8. Rinde-Hoffman D, Glasser SP, Arnett DK. Update on nitrate therapy. J Clin Pharmacol 1991;31(8):697.

9. Arnett DK, Strogatz DS, Ephross SA, Hames CG, Tyroler HA. Greater incidence of electrocardiographic left ventricular hypertrophy in black men than white men at seven year follow-up in Evans County, Georgia. Ethn Dis 1992;2(1):10-17.

10. Howard G, Burke GL, Evans GW, Crouse JR, Riley W, Arnett D, deLacy R, Heiss G. Relations of intimal-medial thickness among sites within the carotid artery as evaluated by B-mode ultrasound. Stroke 1994;25:1581-1587.

11. Arnett DK, Rautaharju P, Crow R, Folsom AR, Ekelund LG, Hutchinson R, Tyroler HA, Heiss G. Black-white differences in electrocardiographic left ventricular mass and the impact of antihypertensive therapy: The ARIC study. Am J Cardiol 1994;74:247-252.

12. Arnett DK, Evans GW, Riley WA. Arterial Stiffness: A New Cardiovascular Disease Risk Factor? Am J Epidemiol 1994;140: 669-682.

13. Arnett DK, Tyroler HA, Burke G, Hutchinson R, Howard G, Heiss G. Hypertension and Subclinical Carotid Artery Atherosclerosis in Blacks and Whites (The ARIC Study). Arch Intern Med 1996;156:1983-1989.

14. Bright PE, Arnett DK, Blair C, Bayona M. Gender and ethnic differences in survival in a cohort of HIV positive clients. Ethn Dis 1996;1(1):77-85.

15. Chambless LE, Zhong M, Arnett DK, Folsom A, Riley W, Heiss G. Variability in B-mode ultrasound in the Atherosclerosis Risk in Communities Study (ARIC). Ultrasound Med Biol 1996;22(5):545-554.

16. Arnett DK, Rautaharju P, Sutherland S, Keil J. The Validity of Electrocardiographic Estimates of Left Ventricular Hypertrophy and Mass in African Americans. The Charleston Heart Study. Am J Cardiol 1997;79:1289-1292.

17. Iribarren C, Luepker RV, McGovern PG, Arnett DK, Blackburn H. Twelve-Year Trends in Cardiovascular Disease Risk Factors in The Minnesota Heart Survey, Are Socioeconomic Differences Widening? Arch Intern Med 1997;157:873-881.

18. Pankow JS, Vachon CM, Kuni CC, King RA, Arnett DA, Grabrick DM, Rich SS, Anderson VE, Sellers TA. Genetic Analysis of Mammographic Breast Density in Adult Women: Evidence of a Gene Effect. J Natl Cancer Inst 1997;89(8):549-556.

19. Pieper RM, Arnett DK, McGovern PG, Shahar E, Blackburn H, Luepker RV. Trends in Cholesterol Knowledge and Screening and Hypercholesterolemia Awareness and Treatment, 1980-1992: The Minnesota Heart Survey. Arch Intern Med 1997;157:2326-2332.

20. Arnett DK, Pankow JS, Atwood LD, Sellers TA. Impact of Adjustments for Intermediate Phenotypes on the Power to Detect Linkage. Genet Epidemiol 1997;14:749-754.

21. Folsom AR, Arnett DK, Hutchinson RG, Liao F, Clegg L, Cooper LS. Physical activity and incidence of coronary heart disease in middle-aged women and men. Med Sci Sports Exerc 1997;29(7):901-909.

22. Glasser SP, Arnett DK, McVeigh GE, Finkelstein SM, Bank AJ, Morgan DJ, Cohn JN. Vascular Compliance and Cardiovascular Disease: A Risk Factor or a Marker? Am J Hypertens 1997;10:1175-1189.

23. Smith MA, Shahar E, Doliszny KM, McGovern PG, Arnett DK, Luepker RV. Trends in Medical Care of Hospitalized Stroke Patients Between 1980 and 1990: The Minnesota Stroke Study. J Stroke and Cerebrovascular Disease 1998;7(1):76-84.

24. Glasser SP, Arnett DK, McVeigh GE, Finkelstein SM, Bank AJ, Morgan DJ, Cohn JN. The Importance of Arterial Compliance in Cardiovascular Drug Therapy. J Clin Pharmacol 1998;38:202-212.

25. Garg UC, Arnett DK, Folsom AR, Province MA, Williams RR, Eckfeldt JH. Lack of Association Between Platelet Glycoprotein IIb/IIIa Receptor PI^A Polymorphism and Coronary Artery Disease or Carotid Intima-Media Thickness. Thromb Res 1998;89:85-89.

26. Arnett DK, Sprafka JM, McGovern PG, Shahar E, McCarty M, Luepker RV. Trends in Cigarette Smoking: The Minnesota Heart Survey, 1980-1992. Am J Public Health 1998;88(8):1230-1233.

27. Arnett DK, Borecki IB, Ludwig EH, Pankow JS, Myers R, Evans G, Folsom AR, Heiss G, Higgins M. Angiotensin Converting Enzyme Genotypes and Carotid Atherosclerosis: The Atherosclerosis Risk in Communities and the NHLBI Family Heart Studies. Atherosclerosis 1998;138(1):111-116.

28. Garg U, Arnett DK, Evans G, Eckfeldt JH. No Association between Factor V Leiden Mutation and Coronary Heart Disease or Carotid Intima Media Thickness. Thromb Res 1998;89:289-293.

29. Borecki IB, Higgins M, Schreiner PJ, Arnett DK, Mayer-Davis E, Hunt S, Province MA. Evidence for multiple determinants of the body mass index: the Family Heart Study. Obes Res 1998;6:107-114.

30. Djousse L, Ellison C, Zhang Y, Arnett DK, Sholinsky P, Borecki I. Relation between dietary fiber consumption and fibrinogen and plasminogen activator inhibitor type-1: The National Health, Lung, and Blood Institute (NHLBI) Family Heart Study. Am J Clin Nutr 1998;68:568-575.

31. Smith MA, Doliszny KM, Shahar E, McGovern PG, Arnett DK, Luepker RV. Delayed Hospital Arrival for Acute Stroke: The Minnesota Stroke Survey. Ann Intern Med 1998;129(3):190-196.

32. Zheng ZJ, Folsom AR, Arnett DK, McGovern P, Eckfeldt J. Plasma Fatty Acid Composition and 6-Year Incidence of Hypertension in Middle-Aged Adults: The Atherosclerosis Risk in Communities (ARIC) Study. Am J Epidemiol 1999;150(5);492-500.

33. Pereira MA, McGovern PG, Arnett DK, Hutchinson RG, Szklo M, Carpenter M, Folsom AR. Physical activity and incident hypertension in black and white adults: The Atherosclerosis Risk in Communities Study (ARIC). Prev Med 1999;28:304-312.

34. Peacock JM, Folsom AR, Arnett DK, Eckfeldt JH, Chambless LE, Szklo M. Relationship of Serum and Dietary Magnesium to Incident Hypertension. The Atherosclerosis Risk in Communities (ARIC) Study. Ann Epidemiol 1999;3:159-165.

35. Arnett DK, Chambless LE, Kim H, Evans GW, Riley W. Variability in Ultrasonic Measurements of Arterial Stiffness in the Atherosclerosis Risk in Communities Study. Ultrasound Med Biol 1999;25(2):175-180.

36. Liao D, Arnett DK, Tyroler HA, Riley WA, Chambless LE, Szklo M. Arterial Stiffness and the Development of Hypertension. The ARIC Study. Hypertension 1999;34(2):201-206.

37. Rose KM, Newman B, Tyroler HA, Szklo M, Arnett DK, Srivastava N. Women, Employment Status, and Hypertension: Cross-Sectional and Prospective Findings From the Atherosclerosis Risk in Communities Study. Ann Epidemiol 1999;6:374-382.

38. Smith MA, Shahar E, McGovern PG, Doliszny KD, Arnett DK, Luepker RV. HMO Membership, Patient Age and the Use of Specialty Care for Acute Hospitalized Stroke: The Minnesota Stroke Survey. Med Care 1999;37(12):1186-1198.

39. Kronenberg F, Rich SS, Sholinsky P, Arnett DK, Province ME, Myers RH, Eckfeldt JH, Williams RR, Hunt SC. Insulin and Hypertension in the NHLBI Family Heart Study: A sibpair approach to a controversial issue. Am J Hypertens 2000;13(3):240-250.

40. Djoussé L, Ellison RC, Pankow JS, Arnett DK, Zhang Y, Hong, Y, Province M. Alcohol consumption and plasminogen activator inhibitor type-1: the NHLBI Family Heart Study. Am Heart J 2000;139:704-709.

41. Wilk JB, Djousse L, Arnett D, Rich S, Province M, Hunt S, Crapo R, Higgins M, Myers RH. Evidence for Major Genes Influencing Pulmonary Function in the NHLBI Family Heart Study. Genet Epidemiol 2000;19(1):81-94.

42. Coon H, Leppert M, Hunt S, Province M, Myers R, Arnett DK, Eckfeldt J, Heiss G, Kronenberg F. Evidence for a major gene accounting for mild elevation in LDL cholesterol: The NHLBI Family Heart Study. Ann Hum Genet 1999;63(pt 5):401-412.

43. Arnett DK, Williams R, Folsom AR, Rao DC, Heiss G. Dyslipidemic Hypertension as a Screening Tool for Excess Familial Risk of Coronary Heart Disease: The Atherosclerosis Risk in Communities (ARIC) and the NHLBI Family Heart Study. CVD Prevention 1999;2:180-186.

44. Luoto R, Sharrett R, Arnett D, Sorlie P, Schreiner P, Ephross. Blood pressure and menopausal transition - The ARIC Study 1987-1995. J Hypertens 2000;18(1):27-33.

45. Arnett DK, Xiong B, McGovern PG, Blackburn H, Luepker RV. Secular Trends in Dietary Macronutrient Intake in Minneapolis-St. Paul, 1980-1992. Am J Epidemiol 2000;152:868-873.

46. Arnett DK, Boland LL, Evans GW, Riley W, Barnes R, Tyroler HA, Heiss G. Hypertension and Arterial Stiffness: The Atherosclerosis Risk in Communities Study. Am J Hypertens 2000;13:317-323.

47. Rose K, Tyroler HA, Nardo CJ, Arnett DK, Light KC, Rosamond W, Sharrett AR, Szklo M. Orthostatic Hypotension and Incident Coronary Heart Disease in the ARIC Study. Am J Hypertens 2000;13:571-578.

48. Pankow JS, Arnett DK, Borecki I, Hunt S, Eckfeldt J, Folsom AR, Djousse L. Lack of association between the angiotensin converting enzyme insertion/deletion polymorphism and plasminogen activator inhibitor-1 antigen levels in the NHLBI Family Heart Study. Blood Coagul Fibrinolysis 2000;11:551-558.

49. Phillips ELR, Arnett DK, Himes JH, McGovern PG, Luepker RV. Differences and Trends in Antioxidant Dietary Intake in Smokers and Non-smokers, 1980-1992. The Minnesota Heart Survey. Ann Epidemiol 2000;10:417-423.

50. al'Absi M, Arnett DK. Adrenocortical Responses to Stress and Risk for Hypertension. Biomed & Pharmacother 2000;54:234-244.

51. Kronenberg F, Pereira MA, Schmitz MKH, Arnett DK, Evenson KR, Crapo RO, Jensen RL, Burke G, Sholinsky P, Ellison RC, Hunt SC: Influence of leisure time physical activity and television watching on atherosclerosis risk factors in the NHLBI Family Heart Study. Atherosclerosis 2000;153:433-443.

52. Arnett DK. Genetic contributions to left ventricular hypertrophy. Current Hypertension Reports, Pathogenesis of Hypertension: Genetic and Environmental Factors 2000;2:50-55.

53. Tsai MY, Arnett DK, Eckfeldt JH, Williams RR, Ellison RC. Plasma Homocysteine and its Association with Carotid Intimal-Medial Wall Thickness and Prevalent Coronary Artery Disease: NHLBI Family Heart Study. Atherosclerosis 2000;151:519-524.

54. Rose KM, Nardo CJ, Tyroler HA, Rosamond WD, Light KC, Sharrett AR, Arnett D, Szklo M. Postural Change in Blood Pressure and Incident CHD in the Atherosclerosis Risk in Communities (ARIC) Study. In press, Am J Epidemiol.

55. Williams RR, Rao DC, Ellison RC, Arnett DK, Heiss G, Oberman A, Eckfeldt JH, Leppert MF, Province MA, Mockrin SC, Hunt SC. NHLBI Family Blood Pressure Program: Methodology and Recruitment in the HyperGEN Network. Ann Epidemiol 2000;10(6):389-400.

56. Hong Y, Leppert MF, Lin J, Hunt SC, Rich SS, Arnett DK, Myers R, Eckfeldt J, Williams RR, Province MA. No evidence of linkage between VLDL receptor gene and fasting serum insulin or HOMA insulin resistance index: The NHLBI Family Heart Study. Metabolism 2000;49:293-297.

57. Wilk JB, Djousse L, Borecki I, Atwood L, Hunt SC, Rich SS, Eckfeldt JH, Arnett DK, Rao DC, Myers RH. Segregation Analysis of Serum Uric Acid in the NHLBI Family Heart Study. Hum Genet 2000;106(3)355-359.

58. Weinert CR, Arnett D, Jacobs D Jr, Kane RL. The relationship between persistence of abdominal symptoms and a successful outcome after cholecystectomy. Arch Intern Med 2000;160:989-995.

59. Rose KM, Arnett DK, Ellison RC, Heiss G. Skip Patterns in DINAMAP-Measured Blood Pressure in 3 Epidemiological Studies. Hypertension 2000;35:1032-1036.

60. Coon H, Myers RH, Borecki IB, Arnett DK, Hunt SC, Province MA, Djousse L, Leppert MF. Replication of linkage of familial combined hyperlipidemia to chromosome 1q with an additional heterogeneous effect of the apolipoprotein AI/CIII/AIV locus: The NHLBI Family Heart Study. Arterioscler Thromb Vasc Biol 2000;20(10):2275-2280.

61. Arnett DK, Glasser SP, McVeigh G, Prineas R, Donahue R, Cohn JN, Sinaiko A. Blood Pressure and Arterial Compliance in Young Adults: The Minnesota Children's Blood Pressure Study. Am J Hypertens 2001;14:200-205.

62. Djousse L, Myers RH, Coon H, Arnett DK, Province MA, Ellison RC. Smoking Influences the Association Between Apolipoprotein E and Lipids: The National Heart, Lung, and Blood Institute Family Heart Study. Lipids 2000;35:827-831.

63. DeWan AT, Arnett DK, Atwood LD, Province MA, Lewis CE, Hunt SC, Eckfeldt J. A Genome Scan for Renal Function Among Hypertensive: The HyperGEN Study. Am J Hum Genet 2001;68:136-144.

64. Hong Y, Rautaharju PM, Hopkins PN, Arnett DK, Djousse L, Pankow JS, Sholinsky P, Rao DC, Province MA. Familial aggregation of QT interval variability in a general population: results from the NHLBI Family Heart Study. Clin Genet 2001;59:171-177.

65. Folsom AR, Pankow JS, Tracy RP, Arnett DK, Peacock JM, Hong Y, Djousse L, Eckfeldt JH. Association of C-reactive Protein with Markers of Prevalent Atherosclerotic Disease. Am J Cardiol 2001;88:112-117.

66. Palmieri V, Bella JN, Arnett DK, Roman MJ, Oberman A, Kitzman DW, Hopkins PN, Paranicas M, Rao DC, Devereux RB. Aortic Root Dilatation at Sinuses of Valsalva and Aortic Regurgitation in Hypertensive Normotensive Subjects. The Hypertension Genetic Epidemiology Network (HyperGEN) Study. Hypertension 2001;37(5):1229-1135.

67. Bella JN, Palmieri V, Liu JE, Kitzman DW, Oberman A, Hunt SC, Hopkins PN, Rao DC, Arnett DK, Devereux RB. Relationship Between Left Ventricular Diastolic Relaxation and Systolic Function in Hypertension: The HyperGEN Study. Hypertension 2001;38:424-428.

68. Devereux RB, Bella JN, Palmieri V, Oberman A, Kitzman DW, Hopkins PN, Rao DC, Morgan D, Paranicas M, Fishman D, Arnett DK. Left Ventricular Systolic Dysfunction in a Bi-Racial Sample of Hypertensive Adults: The HyperGEN Study. Hypertension 2001;38:417-423.

69. Arnett DK, Devereux RB, Kitzman D, Oberman A, Hopkins PN, Atwood LA, Dewan A, Rao DC. Linkage of Left Ventricular Contractility to Chromosome 11 in Humans: The HyperGEN Study. Hypertension 2001;38:767-772.

70. Schmitz MKH, Arnett DK, Bank A, Liao Duanping, Evans GW, Evenson KR, Stevens J, Sorlie P, Folsom AR. Arterial Distensibility and Physical Activity in the ARIC Study. Med Sci Sports Exerc 2001;33(12):2065-2071.

71. McGovern PG, Jacobs DR JR, Shahar E, Arnett DK, Folsom AR, Blackburn H, Luepker RV. Trends in Acute Coronary Heart Disease Mortality, Morbidity, and Medical Care From 1985 Through 1997: The Minnesota Heart Survey. Circulation 2001;104:19-24.

72. Province MA, Arnett DK, Hunt SC, Leiendecker-Foster C, Eckfeldt JH, Oberman A, Ellison RC, Heiss G, Mockrin SC, Williams RR. Association between the alpha-adducin gene and hypertension in the HyperGEN Study. Am J Hypertens 2000;13(6 pt 1):710-718.

73. Palmieri V, Bella JN, Liu JE, Oberman A, Schuck MY, Kitzman D, Hopkins P, Rao DC, Morgan D, Arnett D, Devereux RB. Effect of Type 2 Diabetes Mellitus on Left Ventricular Geometry and Systolic Function in Hypertensive Subjects: Hypertension Genetic Epidemiology Network (HyperGEN) Study. Circulation 2001;103:102-107.

74. Feitosa MF, Borecki I, Hunt SC, Arnett DK, Rao DC, Province M. Inheritance of the waist-to-hip ratio in the National Heart, Lung, and Blood Institute Family Heart Study. Obes Res 2000;8(4):294-301.

75. Diez Roux AV, Stein Merkin S, Arnett D, Chambless L, Massing M, Nieto FJ, Sorlie, P, Szklo M, Tyroler HA, Watson RL. Neighborhood of residence and incidence of coronary heart disease. N Engl J Med 2001;345(2):99-106.

76. Arnett DK, Hong Y, Bella J, Oberman A, Kitzman DW, Hopkins PN, Rao DC, Devereux RB. Sibling Correlation of Left Ventricular Mass and Geometry in Hypertensive Blacks and Whites: The HyperGEN Study. Am J Hypertens 2001;14:1226-1230.

77. The FBPP Investigators. A Multi-Center Genetic Study of Hypertension: The Family Blood Pressure Program (FBPP). Hypertension 2002;39(1):3-9.

78. Palmieri V, de Simone G, Arnett DK, Bella JN, Kitzman DW, Oberman A, Hopkins PN, Province MA, Devereux RB. Relation of Various Degrees of Body Mass Index in Patients with Systemic Hypertension to Left Ventricular Mass, Cardiac Output, and Peripheral Resistance (The Hypertension Genetic Epidemiology Network Study). Circulation. 2001;88:1163-1168.

79. Peacock JM, Arnett DK, Atwood LD, Myers RH, Coon H, Rich SS, Province MA, Heiss. Genome Scan for Quantitative trait Loci Linked to High-Density Lipoprotein Cholesterol. The NHLBI Family Heart Study. Arterioscler Thromb Vasc Biol 2001;21:1823-1828.

80. Feitosa MF, Borecki IB, Rich SS, Arnett DK, Sholinsky P, Myers RH, Leppert M, Province MA. A quantitative trait locus influencing body mass index resides on chromosome 7: The NHLBI FHS. Am J Hum Genet 2002;70:72-82.

81. Arnett DK, Black H, Boerwinkle E, Davis B, Eckfeldt J, Ford C. Pharmacogenetic Approaches to Hypertension Treatment: The Genetics of Hypertension Associated Treatment (GenHAT). Pharmacogenomics Journal 2002;2:309-317.

82. al'Absi M, Devereux RB, Lewis C, Kitzman D, Rao DC, Hopkins P, Markovitz J, Arnett DK. Blood Pressure Responses to Acute Stress and Left Ventricular Mass (The Hypertension Genetic Epidemiology Network Study). Am J Cardiol 2002;89:536-540.

83. Tang W, Arnett DK, Devereux R, Province MA, Oberman A, Hopkins P, Kitzman D. Associations between angiotensinogen gene variants and left ventricular mass and functions in HyperGEN Study. Am Heart J 2002;143:854-860.

84. Knox SS, Adelman A, Ellison RC, Arnett D, Siegmund K, Weidner G, Province M. Hostility, Social Support, and Carotid Artery Atherosclerosis in the NHLBI Family Heart Study. Am J Cardiol 2000;86(10):1086-1089.

85. de Simone G, Palmieri V, Bella J, Celentano A, Hong Y, Oberman A, Kitzman DW, Hopkins PN, Arnett DK, Devereux RB. Association of Left Ventricular Hypertrophy with Metabolic Risk Factors: The HyperGEN Study. J Hypertens 2002;20:1-9.

86. Juhaeri, Stevens J, Chambless LE, Tyroler HA, Rosamond W, Nieto FJ, Schreiner P, Jones SW, Arnett D. Association between weight gain and hypertension in a bi-ethnic cohort: The Atherosclerosis Risk in Communities Study. Int J Obesity 2002;26:58-64.

87. Palmieri V, Arnett DK, Roman MJ, Liu JE, Bella JN, Oberman A, Kitzman DW, Hopkins PN, Morgan D, de Simone G, Devereux RB. Appetite Suppressants and Valvular Heart Disease in a Population-Based Sample. The HyperGEN Study. Am J Med 2002;112(9):710-715.

88. DeWan AT, Arnett DK, Miller MB, Peacock JM, Atwood LD, Province MA, Lewis CE, Hunt SC, Eckfeldt JH. Refined Mapping of Suggestive Linkage to Renal Function in African Americans: The HyperGEN Study. Am J Hum Genet 2002;71:204-205.

89. Austin M, Arnett D, Beaty T, Durfy S, Fineman R, Gettig E, Lochner-Doyle D, Peyser P, Sorenson J, Thompson J, Watts C. Opportunities for Public Health Genetics Trainees: Results of an Employer/Workplace Survey. Community Genetics 2001;4:143-147.

90. Bella JN, Palmieri V, Kitzman DW, Liu JE, Oberman A, Hunt SC, Hopkins PN, Rao DC, Arnett DK, Devereux RB. Gender Difference in Diastolic Function in Hypertension: The HyperGEN Study. Am J Cardiol 2002;89:1052-1056.

91. Tang W, Arnett DK, Devereux RB, Atwood L, Kitzman DW, Rao DC. Linkage of Left Ventricular Early Diastolic Peak Filling Parameters to Chromosome 5 in Hypertensive African-Americans: The HyperGEN Echocardiography Study. Am J Hypertens 2002;5:621-627

92. Kronenberg F, Pereira MA, Schmitz MKH, Arnett DK, Evenson KR, Crapo RO, Jensen RL, Burke G, Sholinsky P, Ellison RC, Hunt SC: Influence of leisure time physical activity and television watching on atherosclerosis risk factors in the NHLBI Family Heart Study. Compendium Series: Obesity 2002;153:433-443.

93. Kronenberg F, Coon H, Ellison RC, Borecki I, Arnett DK, Tyroler A, Province MA, Eckfeldt JH, Hopkins PN, Hunt SC. Segregation analysis of HDL cholesterol in the NHLBI Family Heart Study and in Utah pedigrees. European Journal of Human Genetics 2002;10:367-374.

94. Coon H, Eckfeldt JH, Leppert MF, Myers RH, Arnett DK, Heiss G, Province MA, Hunt SC. A genome-wide screen reveals evidence for a locus on chromosome 11 influencing variation in LDL cholesterol in the NHLBI Family Heart Study. Human Genetics 2002;111(3):263-269.

95. Arnett DK, McGovern PG, Jacobs DR, Shahar E, Duval S, Blackburn H, Luepker RV. Fifteen-Year Trends in Cardiovascular Risk Factors (1980-82 through 1995-97): The Minnesota Heart Survey. Amer J Epidemiol 2002;156:929-935.

96. Diez Roux AV, Chambless L, Stein Merkin S, Arnett D, Eigenbrodt M, Nieto FJ, Szklo M, Sorlie P. Socioeconomic disadvantage and change in blood pressure associated with aging. Circulation 2002;106:703-710.

97. Luoto R, Sharrett R, Arnett D, Eigenbrodt M. Pulse Pressure and Age at Menopause - the ARIC Study. Biomed Central Women's Health 2002;2:6.

98. Tang W, Arnett DK, Devereux RB, Province MA, Atwood LD, Oberman A, Hopkins PN, Kitzman DW. Sibling resemblance for left ventricular structure, contractility and diastolic filling. Hypertension 2002;40(3):233-238.

99. Djoussé L, Rothman KJ, Cupples LA, Arnett DK, Ellison RC. Relation between serum albumin and carotid atherosclerosis: the NHLBI Family Heart Study. Stroke, 2003;34:53-57.

100. Pankow JS, Province MA, Hunt SC, Arnett DK. Regarding "Testing for Population Subdivision and Association in Four Case-Control Studies". Letter to the Editor, Am J Hum Genet 2002;71(6):1478-1480.

101. Skelton TN, Andrew ME, Arnett DK, Burchfiel CM, Garrison RJ, Taylor HA. Echocardiographic Left Ventricular Mass in African-Americans. The Jackson Cohort of the Atherosclerosis Risk in Communities Study. Echocardiography 2003;20(2):111-120.

102. Devereux RB, Hopkins PN, Kitzman DW, Rao DC, Arnett DK. Relation of Insulin to Left Ventricular Geometry and Function in African-American and White Hypertensive Adults: The HyperGEN Study. Am Heart J 2002;15(12):1029-1035.

103. Juhaeri, Stevens J, Chambless LE, Tyroler HA, Harp J, Jones D, Arnett D. Weight change among self-reported dieters and non-dieters in white and African American men and women. European Journal of Epidemiology 2001;17:917-923.

104. Mosca L, Arnett DK, Dracup K, Hansen BC, Labarthe DR, Marks JS, Matthews KA, Pearson TA, Weintraub W, Wilson W. Task Force on Strategic Research Direction: Population/Outcomes/Epidemiology/Social Science Subgroup key science topics report. Circulation. 2002;106(20):e167-172.

105. Rao DC, Province MA, Leppert MF, Oberman A, Heiss G, Ellison RC, Arnett DK, Eckfeldt JH, Schwander K, Mockrin SC, Hunt SC. A Genome-Wide Affected Sibpair Linkage Analysis of Hypertension: The HyperGEN Network. American Journal of Hypertension 2003;16:148-150.

106. Harnack L, Lee S, Schakel SF, Duval S, Luepker RV, Arnett DK. Trends in the trans fatty acid composition of the diet in a metropolitan area: The Minnesota Heart Survey. Journal of the American Dietetic Association 2003;103:1160-1166.

107. Palmieri V, Bella JN, Arnett DK, Oberman A, Kitzman DW, Hopkins PN, Rao DC, Roman MJ, Devereux RB. Associations of aortic and mitral regurgitation with body composition and myocardial energy expenditure in adults with hypertension: The Hypertension Genetic Epidemiology Network study. Am Heart J 2003;145(6):1071-1077.

108. Wilk JB, DeStefano AL, Arnett DK, Rich SS, Djousse L, Crapo RO, Leppert MF, Province MA, Cupples LA, Gottlieb DJ, Myers RH. A genome wide scan of pulmonary function measures in the NHLBI Family Heart Study. Am J Respiratory and Critical Care Medicine 2003;167:1528-1533.

109. Grizzard WS, Arnett D, Haag SL. Twin Study of Age Related Macular Degeneration. Ophthalmic Epidemiology 2003;5:315-322.

110. Juhaeri, Stevens J, Jones DW, Arnett D. Associations of aging and birth cohorts with body mass index in a biethnic cohort. Obesity Research 2003;11:426-433.

111. Arnett DK, Skelton T, Liebson PR, Benjamin E, Hutchinson RG. Comparison of M-Mode Echocardiographic Left Ventricular Mass Measured Using Digital and Strip Chart Readings: The ARIC Study. Cardiovascular Ultrasound 2003;1(1):8.

112. Juhaeri, Stevens J, Chambless LE, Nieto FJ, Jones D, Schreiner P, Arnett D, Cai J. Associations of weight loss and changes in fat distribution with the remission of hypertension in a bi-ethnic cohort: the Atherosclerosis Risk in Communities Study. Preventive Medicine 2003;36:330-339.

113. Tang W, Devereux RB, Kitzman DW, Province MA, Leppert M, Oberman A, Hopkins PN, Arnett, DK. ARG16Gly Polymorphism of the ß2-Adrenergic Receptor and Left Ventricular Systolic Function. American Journal of Hypertension 2003;16:945-951.

114. de Simone G, Devereux RB, Palmieri V, Bella JN, Oberman A, Kitzman DW, Hopkins PN, Rao DC, Arnett DK. Influence of fat-free mass on detection of appropriateness of left ventricular mass: The HyperGEN study. J Hypertens 2003;21:1747-1752.

115. Freedman BI, Beck SR, Rich SS, Heiss G, Lewis CE, Turner S, Province MA, Schwander KL, Arnett DK, Mellen BG. A Genome-Wide Scan for Urinary Albumin Excretion in Hypertensive Families. Hypertension 2003;42:291-296.

116. Djoussé L, Hunt SC, Arnett DK, Province MA, Eckfeldt JH, Ellison RC. Dietary linolenic acid is inversely associated with plasma triacylglycerol: the NHLBI Family Heart Study. Am J Clin Nutr 2003;79(6):1098-1102.

117. Tang W, Arnett DK, Rich SS, North KE, Pankow JS, Miller MB, Borecki IB, Hopkins PN, Leppert M, Myers RH. Linkage analysis of a composite factor for multiple metabolic syndrome (MMS): The NHLBI Family Heart Study. Diabetes 2003;52:2840-2847.

118. Djousse L, Arnett DK, Coon H, Province MA, Moore LL, Ellison RC. Fruit and Vegetable Consumption and LDL-cholesterol: The NHLBI Family Heart Study. Am J Clin Nutr 2004;79(2):213-217.

119. Ellison RC, Zhang Y, Qureshi MM, Knox S, Arnett DK, Province MA. Lifestyle determinants of HDL-cholesterol: the NHLBI Family Heart Study. American Heart Journal 2004;147(3):529-535.

120. Rose K, North KE. Arnett DK, Ellison RC, Hunt SC, Lewis CE, Tyroler HA. Blood pressure and pulse responses to three stressors: Associations with sociodemographic characteristics and cardiovascular risk factors. J Hum Hypertens 2004;18:333-341.

121. Arnett DK, Des Fuentes L, Broeckel U. Genes for left ventricular hypertrophy. Current Hypertension Reports Feb 2004;6(1):36-41.

122. Astor BC, Arnett DK, Brown A, Coresh J. Association of Kidney Function and Hemoglobin with Left Ventricular Morphology Among African Americans: The Atherosclerosis Risk in Communities (ARIC) Study. American Journal of Kidney Disease 2004;43:836-845.

123. Din-Dzietham R, Heiss G, Couper D, Evans G, Arnett D, Jones D, Tyroler HA. Arterial Stiffness is Greater in African Americans Than in European Americans. The ARIC Study. American Journal of Hypertension 2004;17:304-313.

124. De Simone G, Kitzman DW, Palmieri V, Liu JE, Oberman A, Hopkins PN, Bella JN, Rao DC, Arnett DK, Devereux RB. Association of inappropriate left ventricular mass with systolic and diastolic dysfunction: The HyperGEN Study. In press, American Heart Journal.

125. Arnett, DK; Claas, SA. Pharmacogenetics of Antihypertensive Treatment. Drug Development Research 2004; 62:191-199.

126. Nkomo VT, Arnett DK. Benjamin EJ, Liebson PR, Hutchinson RG, Skelton TN. Left ventricular structure and systolic function in African Americans: The Atherosclerosis Risk in Communities (ARIC) Study. Ethnicity & Disease 2004;14(483-88):

127. Kizer JR, Arnett DK, Bella JN, Paranicas M, Rao DC, Province MA, Oberman A, Kitzman DW, Hopkins PN, Liu JE, Roman MJ, Devereux RB. Racial-Ethnic Differences in Left Ventricular Structure in Hypertensive Adults. The Hypertension Genetic Epidemiology Network (HyperGEN) Study. In press, Hypertension.

128. Barkley RA, Chakravarti A, Cooper RS, Ellison RC, Hunt SC, Province MA, Turner sT, Weder AB, Boerwinkle, on behalf of the Family Bloood Pressure Program. Positional Identification of Hypertension Susceptibility Genes on Chromosome 2. Hypertension 2004;43(part 2):477-482.

129. Smith SC Jr, Milani RV, Arnett DK, Crouse JR III, McGrae McDermott M, Ridker PM, Rosenson RS, Taubert KA, Wilson PWF. Atherosclerotic Vascular Disease Conference. Writing Group II: Risk Factors. AHA Conference Proceedings. Circulation 2004;109:2613-2616.

130. Davis BR, Ford CE, Boerwinkle E, Arnett D, Eckfeldt J, Black H. Imputing Gene-Treatment Interactions When the Genotype Distribution is Unknown Using Case-Only and Putative Placebo Analyses – A New Method for the Genetics of Hypertension Associated treatment (GenHAT) Study. Statistics in Medicine 2004;23(15):

131. Harnack L, Steffen L, Arnett DK, Gau S, Luepker RV. Accuracy of estimation of large food protions. Journal of the American Dietetic Association 2004;104(5):804-806.

132. Tsai MY, Georgopoulos A, Otvos JD, Ordovas JM, Hanson NQ, Peacock JM, Arnett DK. Comparison of ultracentrifugation and nuclear magnetic resonance spectroscopy in the quantification of triglyceride-rich lipoproteins after oral fat load. Clin Chem 2004:50:1201-1204.

133. Djousse L, Arnett DK, Eckfeldt JH, Province MA, Singer MR, Ellison RC. Alcohol Consumption and Metabolic Syndrome in the NHLBI Family Heart Study: Does the Type of Beverage Matter? Obesity Research 2004; 12:1375-1385.

134. Djoussé L, Pankow JS, Arnett DK, Eckfeldt JH, Myers RH, Ellison RC. Apolipoprotein E polymorphism modifies the alcohol-HDL association in the NHLBI Family Heart Study, Am J Clin Nutr. 2004; 80:1639-44

135. Wilk JB, Djousse L, Arnett DK, Hunt SC, Province MA, Heiss G, Myers RH. Genome-wide linkage analyses for age at diagnosis of hypertension and

early-onset hypertension in the HyperGEN Study. Am J Hypertens 2004;17:839-844.

136. Taylor HA, Benjamin EB; Ding J; Liebson P; Arnett DK; Skelton TK. Left Ventricular Mass Indexed to Height and Prevalent Magnetic Resonance Imaging Cerebrovascular Disease in an African American Cohort: The Atherosclerotic Risk In Communities Study. Stroke 2004/416545

137. Djousse L, Arnett DK, Eckfeldt JH, Province MA, Singer MR, Ellison, RC. Alcohol Consumption and Metabolic Syndrome: Does the Type of Beverage Matter? Obesity Research, Vol. 12 No. 9 September 2004:1375-85

138. Nunez E; Arnett D; Benjamin EJ; Liebson PR; Skelton TN; Tyroler HA; Taylor H; Andrew M. Optimal Threshold Value for Left Ventricular Hypertrophy in African-Americans: The ARIC Study. Hypertension; 2005; 45(1):58-63.

139. Djousse L; Arnett DK; Pankow JS; Hopkins PN, Province MA: Dietary linolenic acid is associated with a lower prevalence of hypertension in the NHLBI Family Heart Study: Hypertension 2005;45:368-373.

140. Barber CA, Margolis K, Luepker RV, Arnett DK. The Impact of the Women's Health Initiative on Discontinuation of Postmenopausal Hormone Therapy: The Minnesota Heart Survey (2000-2002). Journal of Women's Health Vol. 13, No. 9, 2004:975-85

141. Avery CL, Freedman BI, Heiss G, Kraja A, Rice T, Arnett D, Miller MB, Pankow JS, Lewis CE, Myers RH, Hunt SC, Almasy L, North KE. Linkage Analysis of Diabetes Status Among Hypertensive Families. Diabetes Vol. 53, Dec 2004:3307-12

142. Arnett DK; Miller MB; Coon H; Ellison RC; North KE; Province M; Leppert M; Eckfeldt JH: Genome-wide linkage analysis replicates susceptibility locus for fasting plasma triglycerides: NHLBI Family Heart Study. Human Genetics 2004; 115; 468-74

143. Taylor HA; Clark BL; Garrison RJ; Andrew ME; Han H; Fox ER; Arnett DK; Samdarshi T; Jones DW: Relation of Aortic Valve Sclerosis to Risk of Coronary Heart Disease in African-Americans. Am J Cardiol 2005;95:401-404

144. Wu J; Kraja AT; Oberman A; Lewis CE; Ellison RC; Arnett DK; Heiss G; Lalouel JM; Turner ST; Hunt SC; Province MA; Rao DC: A Summary of Antihypertensive Medication Effects on Measured Blood Pressure American Journal of Hypertension in press 2005

145. Lewis CE, North KE, Arnett D, Borecki IB, Coon H, Ellison RC, Hunt SC, Oberman A, Rich SS, Province MA, Miller MB. Sex-specific findings from a genome-wide linkage analysis of human fatness in non-Hispanic white and African Americans: The HyperGEN Study. International Journal of Obesity, in press 2005

146. Agno FS, Chinali M, Bella JN, Liu JE, Arnett DK, Kitzman DW, Oberman A, Hopkins PN, Rao DC, Devereux EB: Aortic valve sclerosis is associated with preclinical

cardiovascular disease in hypertensive adults: The Hypertension Genetic Epidemiology Network Study. J Hypertens 2005; 23(4):867-73.

147. Arnett DK, Tang W, Province MA, Oberman A, Ellison RC, Morgan D, Eckfeldt JH, Hunt SC: Interarm differences in seated systolic and diastolic blood pressure: The HyperGEN Study. J Hypertens 2005; 23(6):1141-1147.

148. Wu J, Kraja AT, Oberman A, Lewis CE, Ellison RC, Arnett DK, Heiss G, Lalouel J, Turner ST, Hunt SC, Province MA, Rao DC: A Summary of Antihypertensive Medication Effects on Measured Blood Pressure; American Journal of Hypertension 2005 (in press).

149. Lin JP, Myers RH, Almasy L, Coon HH, Arnett DK, Hong Y, Hunt SC. Linkage of the cholesterol 7alpha-hydroxylase gene and low-density lipoprotein cholesterol conditional on apolipoprotein E association: the National Heart, Lung, and Blood Institute Family Heart Study. Chin Med J (Engl). 2005;118(5):362-9.

150. North KE, Miller MB, Coon H, Martin LJ, Peacock JM, Arnett DK, Zhang B, Province M, Oberman A, Blangero J, Almasy L, Ellison RC, Heiss G. Evidence for a gene influencing fasting LDL cholesterol and triglyceride levels on chromosome 21q. Atherosclerosis 2005; 179:119-125

151. de Simone G, Devereux R, Kizer JR, Chinali M, Bella JN, Oberman A, Kitzman DW, Hopkins PN Rao DC , Arnett DK. Body composition and fat distribution influence systemic hemodynamics in the absence of obesity:the HyperGEN Study. Am J Clin Nutr 2005;81:757–61.

152. Lynch Amy I., Arnett Donna K., Atwood Larry D., Devereux Richard B., Kitzman Dalane W., Hopkins Paul N., Oberman Albert, Rao Dabeeru C. A Genome Scan for Linkage With Aortic Root Diameter in Hypertensive African Americans and Whites in the Hypertension Genetic Epidemiology Network (HyperGEN) Study. Am J Hypert 2005; 18:627-632

153. Daniels SR, Arnett DK, Eckel RH, Gidding SS, Hayman LL, Kumanyika S, Robinson TN, Scott BJ, St Jeor S, Williams CL. Overweight in children and adolescents: pathophysiology, consequences, prevention, and treatment. Circulation 2005;111(15):1999-2012.

154. Djousse L, Rautaharju PM, Hopkins PN, Whitsel EA, Arnett DK, Eckfeldt JH, Province MA, Ellison RC. Dietary linolenic acid and adjusted QT and JT intervals in the National Heart, Lung, and Blood Institute Family Heart study. J Am Coll Cardiol 2005; 45(10):1716-22.

155. Benjamin IJ, Arnett DK, Loscalzo J; American Heart Association Basic Science Writing Group. Discovering the full spectrum of cardiovascular disease: Minority Health Summit 2003: report of the Basic Science Writing Group. Circulation. 2005;111(10):e120-3.

156. Taylor HA Jr, Clark BL, Garrison RJ, Andrew ME, Han H, Fox ER, Arnett DK, Samdarshi T, Jones DW. Relation of aortic valve sclerosis to risk of coronary heart disease in African-Americans. Am J Cardiol. 2005;95(3):401-4.

157. de Simone G, Kitzman DW, Chinali M, Oberman A, Hopkins PN, Rao DC, Arnett DK, Devereux RB. Left ventricular concentric geometry is associated with impaired relaxation in hypertension: the HyperGEN study. Eur Heart J. 2005; 26(10):1039-45.

158. Nunez E, Arnett DK, Benjamin EJ, Oakes JM, Liebson PR, Skelton TN. Comparison of the prognostic value of left ventricular hypertrophy in African-American men versus women. Am J Cardiol. 2004;94(11):1383-90.

159. Tsai MY, Hanson NQ, Straka RJ, Hoke TR, Ordovas JM, Peacock JM, Arends VL, Arnett DK. Effect of influenza vaccine on markers of inflammation and lipid profile. J Lab Clin Med. 2005;145(6):323-7.

160. Arnett DK, Davis BR, Ford CE, Boerwinkle E, Leiendecker-Foster C, Miller MB, Black H, Eckfeldt JH. Pharmacogenetic association of the angiotensin-converting enzyme insertion/deletion polymorphism on blood pressure and cardiovascular risk in relation to antihypertensive treatment: the Genetics of Hypertension-Associated Treatment (GenHAT) study. Circulation. 2005;111(25):3374-83.

161. Djousse L, Arnett DK, Carr JJ, Eckfeldt JH, Hopkins PN, Province MA, Ellison RC; Investigators of the NHLBI FHS. Dietary linolenic acid is inversely associated with calcified atherosclerotic plaque in the coronary arteries: the National Heart, Lung, and Blood Institute Family Heart Study. Circulation. 2005;111(22):2921-6.

162. Burchfiel CM, Skelton TN, Andrew ME, Garrison RJ, Arnett DK, Jones DW, Taylor HA Jr. Metabolic Syndrome and Echocardiographic Left Ventricular Mass in Blacks. The Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2005 Aug 1; [Epub ahead of print]

163. Wu J, Kraja AT, Oberman A, Lewis CE, Ellison RC, Arnett DK, Heiss G, Lalouel JM, Turner ST, Hunt SC, Province MA, Rao DC. A summary of the effects of antihypertensive medications on measured blood pressure. Am J Hypertens. 2005;18(7):935-42.

164. Chinali M, de Simone G, Liu JE, Bella JN, Oberman A, Hopkins PN, Kitzman DW, Rao DC, Arnett DK, Devereux RB. Left Atrial Systolic Force and Cardiac Markers of Preclinical Disease in Hypertensive Patients The Hypertension Genetic Epidemiology Network (HyperGEN) Study. Am J Hypertens. 2005;18(7):899-905.

165. Laura J. Rasmussen-Torvik, Kari E. North, C. Charles Gu, Cora E. Lewis, Jemma B. Wilk, Aravinda Chakravarti, Yen-Pei C. Chang, Michael B. Miller, Na Li, Richard B. Devereus, and Donna K. Arnett. A Population Association Study of Angiotensinogen

Polymorphisms and Haplotypes With Left Ventricular Phenotypes. Hypertension 2005 46: 1294-1299. (PubMed ID 16286570)

166. Tang, W. Pankow J.S., Arnett D.K. (Mis)use of factor analysis in the study of insulin resistance syndrome. AM J Epidemiol. 2005 Nov 1; 162(9):921-2; author reply 923. Epub 2005 Sep 8.

167. Hsu FC, Zaccaro DJ, Lange LA, Arnett DK, Langefeld CD, Wagenknecht LE, Herrington DM, Beck SR, Freedman BI, Bowden DW, Rich SS The impact of pedigree structure on heritability estimates for pulse pressure in three studies. Hum Hered. 2005;60(2):63-72. Epub 2005 Sep 8.

168. Tang W, Arnett DK, Devereux RB, Panagiotou D, Province MA, Miller MB, de Simone G, Gu C, Ferrell RE. Identification of a novel 5-base pair deletion in calcineurin B (PPP3R1) promoter region and its association with left ventricular hypertrophy. Am Heart J. 2005 Oct; 150 (4):845-51 PMID: 16209992.

169. Wu J, Kraja AT, Oberman A, Lewis CE, Ellison RC, Arnett DK, Heiss G, Lalouel JM, Truner ST, Hunt SC, Province MA, Rao DC. A summary of the effects of antihypertensive medications on measured blood pressure. Am J Hypertens. 2005 Jul; 18(7):935-42. PMID: 16053990.

170. Chinali M, de Simone G, Liu JE, Bella JN, Oberman A, Hopkins PN, Kitzman DW, Rao DC, Arnett DK, Devereux RB. Left atrial systolic force and cardiac markers of preclinical disease in hypertensive patients: the Hypertension Genetic Epidemiology Network (HyperGEN) Study. Am J Hypetens. 2005 jul; 18(7):899:905. PMID: 16053984.

171. Bielinski SJ, Lynch Al, Miller MB, Weder A, Cooper R, Oberman A, Chen YD, Turner St, Forange M, Province M, Arnett DK. Genome-wide linkage analysis for loci affecting pulse pressure: the Family Blood Pressure Program. Hypertension. 2005 Dec; 46(6):1286-93. Epub 2005 Nov 14. PMID: 16286574.

172. Rasmussen-Torvik LJ, North KE, Gu CC, Lewis CE, Wilk JB, Chakravarti A, Chang YP, Miloer MB, Li N, Devereus RB, Arnett DK. A population association study of angiotensinogen polymorphisms and haplotypes with left ventricular phenotypes. Hypertension. 2005 Dec;46(6):1294-9. Epub 2005 Nov 14. PMID: 16286570

173. Tang W, Pankow JS, Arnett DK. Re: "(Mis)use of factor analysis in the study of insulin resistance syndrome". Am J Epidemiol. 2005 Nov 1;162(9):921-21 author reply 923. Epub 2005 Sep 8. No abstract available. PMID 16150887

174. The National Heart, Lung, and Blood Institute Working Group on Future Directions in Hypertension Treatment Trials. Major clinical trials of hypertension: what should be done next? Hypertension. 2005 Jul;46(1):1-6. Epub 2005 May 23.

175. Feitosa M, Miller MB, Heiss G, DK Arnett, Myers R, Pankow JS, Hopkins P. Evidence of QTL on 15q21 for High-Density Lipoprotein Cholesterol: The National Heart, Lung, and Blood Institute Family Heart Study (NHLBI FHS) Atherosclerosis. Ref.: Ms. No. ATH-D-05-00614R1

176. An P, Freedman BI, Rich SS, Mandel SA, Arnett DK, Myers RH, Chen YD, Hunt SC, Rao DC. Quantitative trait loci on chromosome 8q24 for pancreatic beta-cell function and 7q11 for insulin sensitivity in obese nondiabetic white and black families: evidence from genome-wide linkage scans in the NHLBI Hypertension Genetic Epidemiology Network (HyperGEN) study. *Diabetes*. Feb 2006; 55(2):551-558.

177. Arnett DK, Class SA, Glasser SP. Pharmacogenetics of antihypertensive treatment. *Vascul Pharmaol*. Feb 2006; 44(2):107-118.

178. Feitosa MF, Provinice MA, Heiss G, Arnett DK, Myers RH, Pankow JS, Hopkins PN, Borecki IB. Evidence of QTL on 15q21 for high-density lipoprotein cholesterol: The National Heart, Lung, and Blood Institute Family Heart Study (NHLBI FHS). *Atherosclerosis*. Mar 7 2006.

179. Rosen BD, Saad MF, She S, Nasir K, Edvardsen T, Burke G, Jerosch-Herold M, Arnett, DK, Lai S, Bluemke DA, Lima JA. Hypertension and smoking are associated with reduced regional left ventricular function in asymptomatic: individuals the Multi-Ethnic Study of Atherosclerosis. *J Am Coll Cardiol*. Mar 21 2006; 47(6):1150-1158.

180. Tang W, Hong Y, Province MA, Rich SS, Hopkins PN, Arnett DK, Pankow JS, Miller MB, Eckfeldt JH. Familial Clustering for features of the metabolic syndrome: the National Heart, Lund, and Blood Institute (NHLBI) Family Heart Study. *Diabetes Care*. Mar 2006;29(3):631-636.

181. Avery CL, Freedman BI, Kraja AT, Borecki IB, Miller MB, Pankow JS, Arnett DK, Lewis CE, Myers RH, Hunt SC, North KE. "Genotype-by-sex interaction in the aetiology of type 2 diabetes mellitus: support for sex-specific quantitative trait loci in Hypertension Genetic Epidemiology Network participants. Diabetologia DOI 10.1007/s00125-006-0375-4

182. Susan G. Lakoski, Mary Cushman, Roger S. Blumenthal, Richard Kronmal, Donna Arnett, Ralph B. D'Agostino Jr., Robert C. Detrano, David M. Herrington. Implications of C-reactive protein or coronary artery calcium score as an adjunct to global risk assessment for primary prevention of CHD.(2006), doi:10.1016/j.atherosclerosis.2006.07.006.

183. de Simone G, Devereux RB, Chinali M, Palmieri V, Oberman A, Kitzman DW, Hopkins PN, Rao DC, Arnett DK: Body fat distribution influences cardiac output in normotensive and hypertensive overweight individuals: The HyperGEN Study. J Am Coll Cardiol 2004;43:512A.

184. Li ZB, Devereux RB, Liu JE, Kitzman DW, Oberman A, Hopkins P, Gu CC, Arnett DK: Prevalence and correlates of mitral regurgitation in hypertensive patients: The HyperGEN Study. J Am Coll Cardiol 2004;43:429A.

185. Krasikov T, Devereux RB, Arnett DK, Oberman A, Hopkins PN, Kitzman DW, Rao DC: Correlates of high pulse pressure in hypertensive adults from a population-based sample: The HyperGEN study. J Am Coll Cardiol 2005;(in press).

186. Agno FS, Bella JN, Arnett DK, Oberman A, Hopkins PN, Kitzman DW, Rao DC, Devereux RB: Left ventricular mass among hypertensive adults without clinical disease: The HyperGEN study. J Am Coll Cardiol 2005;(in press).

187. Agno FS, Arnett DK, Bella JN, Oberman A, Hopkins PN, Kitzman DW, Rao DC, Devereux RB: Left ventricular mass among offspring of hypertensive adults: The HyperGEN study. *J Am Coll Cardiol* 2005;(in press).

188. Davis BR, Arnett D, Boerwinkle E, Ford CE, Leiendecker-Foster C, Miller M, Black H, Eckfeldt J. Absence of an Interaction Between the Alpha Adducin Polymorphism and Antihypertensive Treatment on Cardiovascular Risk in High-Risk Hypertensives: The GENHAT Study. Pharmacogenomics J. 2006 May 16; [Epub ahead of print] PMID: 16702981 [PubMed - as supplied by publisher]

189. B.Rosen, T.Edvardsen, S.Lai, E.Castillo, L.Pan, M.Jerosch-Herold, S.Sinha, R.Kronmal, D.Arnett, J.Crouse III, S. Heckbert, D. Bluemke, J.Lima. Left Ventricular Concentric Remodeling Is Associated With Decreased Global and Regional Systolic Function The Multi-Ethic Study of Atherosclerosis. Circulation. 2005 Aug 16;112(7):984-91. PMID: 16103253 [PubMed - indexed for MEDLINE]

190. Tang W, Hong Y, Province MA, Rich SS, Hopkins PN, Arnett DK, Pankow JS, Miller MB, Eckfeldt JH., Familial clustering for features of the metabolic syndrome: the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study. Diabetes Care. 2006 Mar;29(3):631-6. PMID: 16505518 [PubMed - indexed for MEDLINE]

191. Artz MB, Harnack LJ, Duval SJ, Armstrong C, Arnett DK, Luepker RV. Use of nonprescription medications for perceived cardiovascular health. Am J Prev Med. 2006 Jan;30(1):78-81

192. Arnett DK, Class SA, Glasser SP. Phamacogenetics of antihypertensive treatment Vascul Pharmacol. 2006 Feb;44(2):107-18. Epub 2005 Dec 13. PMID: 16356784

193. Arnett DK, Jacobs DR Jr, Luepker RV, Blackburn H, Armstrong C, Class SA. Twenty-year trends in serum cholesterol, hypercholesterolemia, and cholesterol medication use: the Minnesota Heart Survey, 1980-1982 to 2000-2002.Circulation. 2005 Dec 20; 112(25):3884-91. Epub 2005 Dec 12. PMID: 16344385

194. C.Charles Gu, Yen-Pei C. Chang, Steven C. Hunt, Karen Schwander, Donna Arnett, Luc Djousse, Gerardo Heiss, Al Oberman, Jean-Marc Lalouel, Mike Province, Aravinda Chakravarti, D.C. Rao. Haplotype Association Analysis of AGT Variants with Hypertension-Related Traits: The HyperGEN Study. Hum Hered 2005;60:164-176 DOI:10.1159/000090118

195. Ping An, Barry I. Freedman, Stephen S. Rich, Stehpen A. Mandel, Donna K. Arnett, Richard H. Myers, Yii-Der I. Chen, Steven C. Hunt, and D.C. Rao. Quantitative Trait Loci on Chromosome 8q24 for Pancreatic β-Cell Function and 7q11 for Insulin Sensitivity in Obese Nondiabetic White and Black Families. Evidence From Genome-Wide Linkage Scans in the NHLBI Hypertension Genetic Epidemiology Network (HyperGEN) Study. Diabetes, Vol 55, February 2006. 551-558

196. Li ZB, de Simone G, Bella NJ, Cai L, Kitzman DW, Oberman A, Hopkins P, Rao DC, Arnett DK, Devereux RB Relation of Left Ventricular Geometry and Isovolumeric Relaxation Time in Hypertensive Patients: The HyperGEN study.

197. Lakoski SG, Cushman M, Blumenthal RS, Kronmal R, Arnett D, D'Agostino RB Jr, Detrano RC, Herrington DM. Implications of C-reactive protein or coronary artery calcium score as an adjunct to global risk assessment for primary prevention of CHD. Atherosclerosis. 2006 Aug 14; [Epub ahead of print] PMID: 16914155

Non-Peer Reviewed Articles

1. Arnett DK. Multiple Risk Factor Approaches. "Optimizing Antianginal Therapy. The Role of the Nurse in Clinical Practice." Ischemic Heart Disease: A Comprehensive Review for Nurse Clinicians, Monograph, University of South Florida, Tampa, FL, 1994, 5-12.

Book Chapters

1. Mulla Z, Arnett DK. Gender Differences in the Rates of Therapeutic Cardiac Procedures and Associated Mortality Among elderly Patients Hospitalized for Acute Myocardial Infarction. In: *Facts and Research in Gerontology.* JM Ribera, D Carrie, J Puel, J Serro-Azul, B Vellas, L Albarede, PJ Garry (ed.). Paris: Serdi Publisher, 1997:104-119.

Presentations & Abstracts (formerly published under Koehn)

1. Glasser SP, Koehn DK. Lack of LVH regression in hypertensive subjects treated alone or in combination with amlodipine. American College of Pharmacology, 1988, Orlando, FL.

2. Glasser SP, Koehn DK. The effect of dilevalol, a new beta blocker with ISA, on asymptomatic myocardial ischemia. American College of Pharmacology, 1988, Orlando, FL.

3. Glasser SP, Koehn DK. The effect of antianginal therapy upon the exercise test's ability to predict the presence of asymptomatic ischemia. American College of Pharmacology, 1988, Orlando, FL.

4. Glasser SP, Koehn DK. Impact of Antianginal Drug Therapy on the Incidence of Asymptomatic Ischemia. American College of Pharmacology, 1988, Orlando, FL.

5. Arnett DK, Ephross SA, Strogatz DS, Hames CG, Tyroler HA. Differences in mortality associated with left ventricular hypertrophy in black and white men at thirteen year follow-up in Evans County, Georgia. Fifth International Interdisciplinary Conference of Hypertension in Blacks, 1990, Chicago, IL.

6. Arnett DK, Riley W, Rautaharju P, Tyroler HA, Heiss G. Electrocardiographic left ventricular mass and its association with arterial stiffness and menopause. The ARIC Study. American Heart Association 64th Scientific Sessions, November 1991, Anaheim, CA. Circulation 1991;84(4):548.

7. Arnett DK, Tyroler HA, Chambless LE, Heiss G. Are target organ manifestations of elevated blood pressure different in blacks and whites? The ARIC Study. American Heart Association 32nd Annual Conference on Cardiovascular Disease Epidemiology, March, 1992, Memphis, TN.

8. Arnett DK, Ephross SA, Riley WA, Tyroler HA, Heiss G. Is hormone replacement therapy among surgically or naturally postmenopausal women associated with lower arterial stiffness? The ARIC Study. American Heart Association 65th Scientific Sessions, November, 1992, Anaheim, CA. Circulation 1992;86(4):674.

9. Evans GW, Riley WA, Arnett DK, Barnes RW, Burke GL. Statistical issues in the use of arterial distensibility as a surrogate endpoint in clinical trials. 14th Annual Meeting of the Society for Clinical Trials, 1993, Orlando, FL.

10. Arnett DK, Evans GW, Riley WA, Barnes RW, Heiss G. Differences in arterial elasticity by antihypertensive medication, gender, and ethnicity. The ARIC Study. American Heart Association 33rd Annual Conference on Cardiovascular Disease Epidemiology, March, 1993, Santa Fe, NM.

11. Arnett DK. Risk factor clustering in the Atherosclerosis Risk in Communities Study. National Heart, Lung, and Blood Institute, 1993, Bethesda, MD.

12. Hutchinson RG, Arnett DK, Watson RL, Barnes RA, Brown S, Davis CE, Tyroler HA. Gender differences in multiple risk factor clustering among Blacks and Whites. American Heart Association 66th Scientific Sessions, November, 1993, Atlanta, GA. Circulation 1993;88(4 Pt 2):357.

13. Bright P, Arnett DK, Blair C, Bayona M. Ethnic and Gender Differences in Survival among an HIV Positive Cohort. Society for Epidemiologic Research Meeting, 27th Annual Meeting, 1994, Miami, FL.

14. Brancati FL, Folsom AR, Watson RL, Tyroler HA, Cai J, Arnett D, Szklo M. Race, physical activity, and diabetes mellitus: The ARIC Study. Society of General Internal Medicine, National Meeting, 1994, Chicago, IL.

15. Arnett DK, Rautaharju PM, Sutherland SE, Keil JE. The validity of electrocardiographic estimates of left ventricular mass in African-Americans. The Charleston Heart Study. American Heart Association 34th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1994, Tampa, FL.

16. Arnett DK. Cardiology Update '95, January, 1995. Estrogen Replacement Therapy in Postmenopausal Women. 1995, Orlando, FL.

17. Mulla ZD, Arnett DK, Straumford JV, Leaverton PE. Sex Differences in the Outcomes of Myocardial Infarction: An Analysis of 262,105 Patient Records. Society for Epidemiologic Research, 28th Annual Meeting. 1995, Snowbird, UT.

18. Arnett DK, Tyroler HA, Hutchinson RG, Howard G, Heiss G. The paradoxical effect of hypertension and its association with subclinical atherosclerosis in African Americans: The ARIC Study. American Heart Association 35th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1995, San Antonio, TX.

19. Arnett DK, Province MA, Williams RR, Pankow JS, Heiss G, Folsom AR. Dyslipidemic Hypertension is Associated with Familial Aggregation of Coronary Heart Disease. The Atherosclerosis Risk in Communities (ARIC) Study. American Heart Association 68th Scientific Sessions, November, 1995, Anaheim, CA. Circulation 1995;92(8):800.

20. Arnett DK, McGovern PG, Peterson DM, Shahar E, Luepker RV. Ten Year Trends in Leisure Time Physical Activity: The Minnesota Heart Survey. American Heart Association 68th Scientific Sessions, November, 1995, Anaheim, CA. Circulation 1995;92(8):311.

21. Peterson DM, Arnett DK, McGovern PG, Shahar E, Luepker RV. Leisure-Time Physical Activity Trends in the Minnesota Heart Survey, 1980-1992. American Heart Association 68th Scientific Sessions, November, 1995, Anaheim, CA. Circulation 1995;92(8):617.

22. Iribarren C, Luepker RV, McGovern PG, Arnett DK, Peterson DM, Blackburn H. Twelve-year trends in cardiovascular disease risk factors: Are socioeconomic differences widening? The Minnesota Heart Survey. American Heart Association 68th Scientific Sessions, November, 1995, Anaheim, CA.

23. Rose K, Newman B, Tyroler HA, Arnett D, Szklo M. A Comparison of Employment Status-Hypertension Associations in Women Based on Prevalence and Incidence Data. Society of Epidemiologic Research, 1996, Boston, MA.

24. Arnett DK, Skelton T, Vitelli L, Ephross S, Hutchinson R. Hormone Replacement Therapy and Echocardiographic Left Ventricular Mass in Most-Menopausal African American Women: The ARIC Study. American Heart Association 36th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1996, San Francisco, CA.

25. Pieper RM, Arnett DK, Shahar E, McGovern PG, Luepker RV. Trends in Knowledge, Awareness, and Treatment of Hypercholesterolemia: The Minnesota Heart Survey. American Heart Association 36th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1996, San Francisco, CA.

26. Howard G, Wagenknecht LE, Nieto FJ, Arnett D, Burke GL, for the ARIC Investigators. Passive and Active Smoking are Related to Progression of Atherosclerosis. American Heart Association 36th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1996, San Francisco, CA.

27. Xiong B, Arnett DK, McGovern PG, Blackburn H, Luepker RV. Secular Trends in Dietary Macronutrient Intake in the Minnesota Heart Survey, 1980-1992. American Heart Association 69th Scientific Sessions, November, 1996, New Orleans, LA. Circulation 196;94(8):578.

28. Falkner N, Arnett DK, McGovern PG, Blackburn H, Luepker RV. Twelve Year in Obesity, Systolic Blood Pressure, and Cholesterol: The Minnesota Heart Survey. American Heart Association 69th Scientific Sessions, November, 1996, New Orleans, LA. Circulation 1996;94(8):738.

29. Tsai M, Arnett DK. Homocysteine and MTHFR, Carotid Intima Media Thickness and CHD. The NHLBI Family Heart Study. February, 1997, Bethesda, MD.

30. Norman J, Arnett DK. Electrocardiographic Determinants of Echocardiographic Left Ventricular Mass. National Heart, Lung, and Blood Institute, June, 1997, Bethesda, MD.

31. Zheng ZJ, Folsom AR, Ma J, Arnett D, McGovern PG, Eckfeldt JH. Plasma Fatty Acid Composition and 6-Year Incidence of Hypertension in Middle-Aged Adults: The ARIC Study. The 4th International Conference on Preventive Cardiology, June, 1997, Montreal, Quebec.

32. Arnett DK, Vitelli LL, Chambless LE, Howard G, Hutchinson RG, Tyroler HA, Heiss G. Pulse Pressure, Diastolic Blood Pressure and Progression of Carotid Artery Atherosclerosis: The Atherosclerosis Risk in Communities Study. The 4th International Conference on Preventive Cardiology, June, 1997, Montreal, Quebec.

33. Hutchinson RG, Skelton TN, Arnett DK, Benjamin EJ, Liebson PR, Eigenbrodt ML. Left Ventricular Hypertrophy by Echocardiogram in African-Americans: The ARIC Study. The 4th International Conference on Preventive Cardiology, June, 1997, Montreal, Quebec.

34. Robinson EL, Arnett DK, Himes JH, McGovern PG, Luepker RV. Differences and Trends in Antioxidant Dietary Intake in Smokers and Non-Smokers, 1980-1992: The Minnesota Heart Survey. The 4th International Conference on Preventive Cardiology, June 1997, Montreal, Quebec.

35. Rose KM, Nardo C, Tyroler HA, Rosamond W, Light KC, Arnett D, Sharrett AR, Szklo M. Postural Change in Blood Pressure and Incident Coronary Heart Disease in the Atherosclerosis Risk in Communities Study. The 4th International Conference on Preventive Cardiology, June, 1997, Montreal, Quebec.

36. Pereira M, Arnett D, Hutchinson R, Szklo M, Carpenter M, Folsom A. Physical Activity and Incidence of Hypertension in Middle-Aged Adults. The 4th International Conference on Preventive Cardiology, June, 1997, Montreal, Quebec.

37. Hutchinson RG, Skelton TN, Arnett DK, Benjamin EJ, Liebson PR, Eigenbrodt ML. Echocardiographic Left Ventricular Hypertrophy in African-Americans: The ARIC Study. College of Chest Physician's Meeting, October, 1997. Chest Supplement, 1997;112(3):38S.

38. Arnett DK, Tsai MY, Evans GW, Williams RR, Province MA, Heiss G. Homocysteine is Associated with Arterial Stiffness in Current Smokers: The NHLBI Family Heart Study. American Heart Association 38th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1998, Santa Fe, NM.

39. McGovern PG, Shahar E, Doliszny KM, Arnett DK, Luepker RV. Trends in congestive heart failure among Twin Cities residents aged 30-84 years, 1980- 1996. American Heart Association 38th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1998, Santa Fe, NM.

40. Liao D, Arnett D, Tyroler HA, Riley W, Chambless LE, Brown A, Szklo M. Arterial stiffness and the development of hypertension-The ARIC Study. American Heart Association 38th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1998, Santa Fe, NM.

41. Liao D, Evans G, Arnett D, Pankow J, Liese A, Davis CE, Salomma V, Heiss G. Multiple metabolic syndrome is associated with increased arterial stiffness-The ARIC Study. American Heart Association 38th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1998, Santa Fe, NM.

42. Peacock JM, Folsom AR, Arnett DK, Eckfeldt JH, Szklo M. Relationship of Serum and Dietary Magnesium to Incident Hypertension: The Atherosclerosis Risk in Communities

(ARIC) Study. American Heart Association 38th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1998, Santa Fe, NM.

43. Davis BR, Ford CE, Boerwinkle E, Atwood L, Arnett D. Design and Analysis Considerations for Assessing Gene-Treatment Interactions in a Clinical Trial. The Joint Statistical Meetings, August, 1998, Dallas, TX.

44. Knox S, Adelman A, Ellison RC, Weidner G, Siegmund K, Arnett D. Hostility, Social Support & Carotid Artery Atherosclerosis in the NHLBI Family Heart Study. Society of Behavioral Medicine, August, 1998.

45. Arnett DK, Devereux RB, Hong Y, Rao DC, Oberman A, Kitzman DW, Hopkins PN. Strong heritability of left ventricular mass in hypertensive African Americans and wall thickness in hypertensive whites: The HyperGEN Echocardiography Study. American Heart Association 71st Scientific Sessions, November, 1998. Circulation 1998;98(17):I-658.

46. Arnett DK, Paranicas M, Bella JN, Rao DC, Oberman A, Kitzman DW, Hopkins PN. Differences between African American and whites in left ventricular mass and geometry. The HyperGEN Echocardiography Study. American Heart Association 71st Scientific Sessions, November, 1998. Circulation 1998;98(17):I-204.

47. Liao D, Simpson R, Jr., Arnett DK, Manolio T, Szklo M, Evans G, Heiss G. Association of arterial stiffness and left ventricular hypertrophy. American Heart Association 71st Scientific Sessions, November, 1998. Circulation 1998;98(17):I-721.

48. Luepker RV, McGovern PG, Shahar E, Arnett DK, Jacobs DR, Blackburn H. Trends in blood pressure control and stroke in a metropolitan area: The Minnesota Heart Survey. American Heart Association 71st Scientific Sessions, November, 1998. Circulation 1998;98(17):I-657.

49. Palmieri V, Bella JN, Liu J, Oberman A, Kitzman D, Hopkins P, Rao DC, Morgan D, Fishman D, Arnett D, Devereux RB. Does Diabetes Affect LV Structure and Systolic Function Independent of Blood Pressure, Age and Gender? A Population Sample-based Study from the Hypertension Genetic Epidemiology Network (HyperGEN) Study. American College of Cardiology, 1999.

50. Bella JN, Palmieri V, Schuck MY, Kitzman D, Hopkins P, Rao DC, Oberman A, Arnett D, Devereux RB. Impaired Diastolic Relaxation and Left Ventricular Systolic Function. The Hypertension Genetic Epidemiology Network (HyperGEN) Study. American College of Cardiology, 1999.

51. Devereux RB, Bella JN, Palmieri V, Oberman A, Kitzman D, Hopkins P, Rao DC, Morgan D, Paranicas M, Arnett D. Prevalence and Correlates of Mild and Moderate/Severe Left Ventricular Dysfunction in Hypertension Patients in a Population Sample: The HyperGEN Study. American College of Cardiology, 1999.

52. Tang W, Arnett D, Devereux R, Rao DC, Oberman A, Hopkins P, Kitzman D. Associations between angiotensinogen gene polymorphism and left ventricular mass and geometric pattern. American Heart Association 39th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1999, Orlando, FL. Circulation 1999;99(8):1109-1125.

53. McGovern PG, Arnett DK, Shahar E, Luepker RV. Trends in serum cholesterol levels, 1980-1997: The Minnesota Heart Survey. American Heart Association 39th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1999, Orlando, FL. Circulation 1999;99(8):1109-1125.

54. Arnett DK, McGovern PG, Jacobs DR, Luepker RV. Continued declines in cigarette smoking: The Minnesota Heart Survey. American Heart Association 39th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1999, Orlando, FL. Circulation 1999;99(8):1109-1125.

55. Pankow J, Arnett D, Ellison C, Hopkins P, Tracy R, Eckfeldt J. Familial Aggregation of Systemic Inflammatory Markers: The NHLBI Family Heart Study. American Heart Association 39th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1999, Orlando, FL. Circulation 1999;99(8):1109-1125.

56. Hong Y, Province MA, Rich SS, Hopkins PN, Williams RR, Arnett DK, Pankow J, Rao DC. Familial clustering of features of multiple metabolic syndrome with special reference to plasminogen activator inhibitor-1: The NHLBI Family Heart Study. American Heart Association 39th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1999, Orlando, FL. Circulation 1999;99(8):1109-1125.

57. Rose KM, Tyroler HA, Ephross SA, Arnett DK, Couper D, Light KC, Skelton TN. Blood Pressure Decreases in Response to a Change in Posture: Variations by menopausal Status and Use of Hormone Replacement Therapy among Women in the ARIC Study. American Heart Association 39th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1999, Orlando, FL. Circulation 1999;99(8):1109-1125.

58. Gross M, Schmitz KH, Jacobs DR, Luepker RV, Arnett DK, Wessman J. The Age-Associated Distribution of Serum Alpha-Tocopherol in an Adult Population: The Minnesota Heart Survey. American Heart Association 39th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1999, Orlando, FL. Circulation 1999;99(8):1109-1125.

59. Ellison RC, Zhang Y, Knox S, Arnett DK, Province MA. Lifestyle Determinants of HDL-Cholesterol: The NHLBI Family Heart Study. American Heart Association 39th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1999, Orlando, FL. Circulation 1999;99(8):1109-1125.

60. Djousse L, Ellison RC, Pankow S, Arnett DK, Zhang Y, Hong Y, Province M. Alcohol consumption and plasminogen activator inhibitor type-1 in the NHLBI Family Heart Study. American Heart Association 39th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1999, Orlando, FL. Circulation 1999;99(8):1109-1125.

61. Schmitz K, Arnett D, Folsom A, Liao D, Evans G, Evenson K, Stevens J, Sorlie P. Physical Activity and Arterial Stiffness in the ARIC Study. American Heart Association 39th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, March, 1999, Orlando, FL. Circulation 1999;99(8):1109-1125.

62. Din-Dzietham R, Heiss G, Couper D, Jones D, Liao D, Arnett D, Evans G, Tyroler H. African-Americans have stiffer common carotid arteries (CCA) than European-Americans: The ARIC Study 1987-1992. Society for Epidemiologic Research, June, 1999.

63. Feitosa M, Borecki I, Hunt S, Arnett D, Schreiner P, Rao DC, Province M. The genetics of regional fat distribution phenotypes in the population-based National Heart, Lung, and Blood Institute Family Heart Study (NHLBI-FHS). International Genetic Epidemiology Society, September, 1999, St. Louis, MO.

64. Tang W, Devereux R, Province M, Atwood L, Arnett D. Sibling Correlations of Echocardiographic Left Ventricular (LV) Measurements Derived from Factor Models: The HyperGEN Study. International Genetic Epidemiology Society, September, 1999, St. Louis, MO.

65. Arnett DK, Devereux RB, Oberman A, Kitzman DW, Province MA, Rao DC. Comparison of linkage using simple echocardiographic left ventricular (LV) mass versus factor analysis of LV mass in African Americans: The HyperGEN Study. American Society of Human Genetics 49th Annual Meeting, October, 1999, San Francisco, CA.

67. Leppert MF, Coon H, Borecki I, Arnett DK, Hunt SC, Province MA, Djousse L, Myers RH. Analysis of Familial Combined Hyperlipidemia with chromosome 1q21-q23 markers and the APOAI/CIII/AIV gene cluster in the NHLBI Family Heart Study. American Society of Human Genetics 49th Annual Meeting, October, 1999, San Francisco, CA.

68. Lewis CE, Arnett D, Borecki I, Coon H, Ellison RC, Hunt S, Oberman A, Rich S, Province MA. Genome-wide linkage analysis of human fatness: The HyperGEN Blood Pressure Study. American Society of Human Genetics 49th Annual Meeting, October, 1999, San Francisco, CA.

69. Fisher K, Arnett DK, Atwood L, Hunt S, Coon H, Province M, Rao DC, Myers R, Oberman A, Lewis CE, Heiss G. A Genome-Wide Linkage Analysis in Hypertensive African American and White Siblings for Loci that Influence Variation in Pulse Pressure: The HyperGEN Network of the Family Blood Pressure Program. American Society of Human Genetics 49th Annual Meeting, October, 1999, San Francisco, CA.

70. Dewan AT, Eckfeldt J, Rao DC, Hunt S, Lewis CE, Rich S, Arnett DK. A genome scan for creatinine clearance among hypertensive siblings: The HyperGEN Network of the NHLBI Family Blood Pressure Program. American Society of Human Genetics 49th Annual Meeting, October, 1999, San Francisco, CA.

71. Juhaeri, Stevens J, Chambless LE, Tyroler HA, Rosamond W, Nieto FJ, Arnett D, Jones D, Schreiner P. Associations between weight change and hypertension in a bi-ethnic cohort: The ARIC Study. NAASO (North American Association for the Study of Obesity), November, 1999.

72. Taylor HA, Brown A, Burchfiel C, Clemons T, Arnett D, Skelton T, Garrison R, UNC Coord Ctr Rep, Jones D. Pulse pressure: Potent predictor of coronary disease risk in a biracial cohort of normo- and hypertensives. American Heart Association 72nd Scientific Sessions, November, 1999, Atlanta, GA. Circulation 1999;100(18):I-230.

73. Arnett DK, Devereux RB, Rao DC, Kitzman D, Oberman A, Hopkins P. A Genome Search in Hypertensive African American and White Siblings Detects a Locus Mapping to Chromosome 7 that Influences Variation in Left Ventricular Mass: The HyperGEN Study. American Heart Association 72nd Scientific Sessions, Atlanta, GA, November, 1999, Atlanta, GA. Circulation 1999;100(18):I-193.

74. Palmieri V, de Simone G, Arnett DK, Bella JN, Liu JE, Kitzman DW, Oberman A, Hopkins PN, Fishman D, Devereux RB. Impact of Lean Body Mass on Left Ventricular Mass and Hemodynamics in Obese and Non-Obese Hypertensives: The HyperGEN Study. American Heart Association 72nd Scientific Sessions, November, 1999, Atlanta, GA. Circulation 1999;100(18):I-741.

75. Liao D, Sloan R, Simpson R, Massing MW, Evans G, Arnett DK, Heiss G. Left Ventricular Mass is Associated with Poor Cardiac Autonomic Control: The ARIC Study. American Heart Association 72nd Scientific Sessions, November, 1999, Atlanta, GA. Circulation 1999;100(18):I-157.

76. Bella JN, Arnett DK, Kitzman D, Oberman A, Hopkins P, Rao DC, Palmieri V, Devereux R. Gender Difference in Diastolic Function in a Population-Based Sample of Hypertensive Adults: The HyperGEN Study. American College of Cardiology Scientific Sessions, March, 2000, Anaheim, CA.

77. Rose KM, Arnett DK, Ellison RC, Heiss G. Skip Patterns in Automated Blood Pressure Measurements from Three National Heart, Lung, and Blood Institute-Sponsored Studies. American Heart Association 40th Conference on Cardiovascular Disease Epidemiology and Prevention, March, 2000, San Diego, CA.

78. Peacock JM, Atwood LD, Arnett DK, Borecki IB, Hunt SC, Myers RH, Pankow JS, Hong Y. Gene-environment interactions in the prediction of HDL cholesterol: Influence of waist-hip ratio. American Heart Association 40th Conference on Cardiovascular