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THE ECONOMIC BENEFITS OF PHARMACEUTICAL INNOVATIONS:

THE CASE OF COX-2 INHIBITORS

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Despite dramatic improvements in medical technology, little attention has been paid to the role of these innovations in improving economic outcomes. This study estimates the labor supply effects of Cox-2 inhibitors, a widely prescribed class of pharmaceuticals used for the treatment of chronic pain and inflammation and primarily marketed under the brand names Vioxx, Celebrex, and Bextra. This paper exploits the removal of Vioxx from the market in 2004 as an exogenous change in drug use. This removal was associated with a 0.35 percentage point decrease in overall labor force participation and $19 billion in lost wages.

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Physical and mental health is a primary determinant of labor supply (Currie and Madrian, 1999). This is particularly true among older Americans for whom negative health shocks are an important cause of labor force exits (Haider and Loughran, 2001). In recent years, the prevalence of chronic conditions among all Americans has grown (Wu and Green, 2000; Hoffman and Schwartz, 2008). Given that the incidence of chronic conditions rises with age, it is reasonable to expect the labor force participation of elderly individuals would have decreased. Instead, the last two decades have seen dramatic increases in the labor force participation of older Americans. Figure 1 reports the change in labor force participation from the Current Population Survey between 1987 and 2007 for males and females grouped in five-year age ranges. Both males and females over the age of 60 increased their labor force participation over this time period far more than their younger counterparts. As a result of greater overall labor force participation trends, the change for females was consistently larger than the change for males. Importantly, the increase was still largest for older women compared to younger women.

To explain these labor supply increases, economists have examined factors such as mandatory retirement law changes, Social Security reforms, and shifts from defined benefit to defined contribution pensions (Quinn, 1999). However, the labor supply effects of improved medical technology have been largely ignored. The dearth of research concerning the economic effects of medical innovation is remarkable, given that the large increases in both absolute and per-capita United States health spending are the result of these technological advancements (Newhouse, 1992; Cutler, 2004). These cost increases have been particularly apparent in the pharmaceutical sector. Between 1980 and 2005, the percentage of medical spending on prescription drugs doubled (Caitlin et al., 2007). The majority of the increased spending in the early 2000s came from higher utilization and the development of new drugs, as opposed to increased

prices (Smith, 2004).

Hirth et al. (2003) noted that few authors in health economics have "[a]nalyzed how the choice among available medical treatments or the change in available treatments over time can mediate the effects of health on outcomes such as labor force participation, wages, earnings, and hours" (Hirth et al., 2003: 168). The few studies addressing the economic benefits of advancements in medical technology have focused primarily on the developing world. For example, Thirumuthy et al. (2008) examined the changes in labor supply produced by the use of antiretrovirals for the treatment of HIV/AIDS. Studies of the developed world have been limited to the economic benefits of treatments for mental health disorders (Timbie et al., 2006; Berndt et al., 1998; and Berndt et al., 2000).

This literature is thin because it is difficult to identify exogenous variation in the use of medical technology. In this paper, I overcome this challenge by using the unexpected removal of a popular drug from the market as a source of exogenous variation in the use of an innovation. Specifically, I focus on the relationship between the use of anti-inflammatory Cox-2 inhibitors and the labor supply of people with chronic joint conditions.

Previous research has found that joint conditions such as osteoarthritis reduce wages and labor force participation (Bartel and Taubman, 1979; Mitchell and Burkhauser, 1990; Mitchell, 1991). Prior to the development of Cox-2 inhibitors, many patients were prescribed anti-inflammatory medications. These drugs increased mobility and functioning, allowing users to more fully participate in everyday activities. However, many existing anti-inflammatories were known to cause dangerous gastro-intestinal bleeding in some patients. In contrast, the newly-developed Cox-2 inhibitors did not cause this side effect and, as a result, were widely prescribed. By 2002, four years after their introduction, Cox-2

inhibitors had nearly $6 billion in global sales.[1]

In 2004, Vioxx, one of the mostly widely prescribed Cox-2 inhibitors, was suddenly removed from the market in response to concerns over negative side effects. At the time, an estimated 1.3 million Americans were actively taking the medication—making Merck's decision the largest voluntary recall of a prescription drug in American history (Kaufman, 2004). Since the removal was unexpected[2], it is reasonable to assume that post-removal changes in the use of Cox-2 inhibitors were unrelated to other factors correlated with changes in economic outcomes.

I use data from the Medical Expenditure Panel Survey (MEPS) to estimate the effect of Vioxx's removal on the labor supply of individuals with chronic joint conditions. The preferred specification finds that the Vioxx's removal, along with the subsequent reduction in the use of all Cox-2 inhibitors, decreased the probability of working for an affected individual by 22 percentage points. These estimates suggest that $19 billion in wages were lost in the year following the removal.

I. What are Cox-2 Inhibitors?

Cox-2 inhibitors are a type of non-steroidal anti-inflammatory drug (NSAID) commonly described as "selective NSAIDs." Generally, they work by blocking the cyclooxygenase-2 (Cox-2) enzyme and are intended primarily for individuals with chronic conditions requiring nearly continual use of anti-inflammatories. Prior to the introduction of these medications, individuals with such conditions were limited to "non-selective NSAIDs" such as ibuprofen

[1] Cox-2 inhibitors were sold under several brand-names, including Vioxx, Celebrex, and Bextra. In 2002, global sales of Celebrex were $3 billion, Vioxx were $2.5 billion, and Bextra were $470 million.

[2] The day following the announcement, Merck's stock price fell 27 percent (Rubin, 2004).

(commonly marketed under the brand names Motrin and Advil) or naproxen (commonly marketed under the brand name Aleve) that block both the Cox-1 and Cox-2 enzymes. However, these existing options came with dangerous side effects. One function of the Cox-1 enzyme is protecting the stomach lining. By blocking the stomach's protective enzyme, non-selective NSAIDs increase the chance of gastrointestinal (GI) bleeding. Each year, an estimated 16,500 individuals die from non-selective NSAID-related gastrointestinal complications, amounting to 1 death for every 1,200 patients taking these drugs for two months or longer (Schmidt et al., 2004). Prior to the development of Cox-2 inhibitors, many individuals susceptible to GI bleeding had no therapeutic options and often their only choice was to cope with chronic pain.

The three primary Cox-2 inhibitors sold in the United States were very popular. Examining medical claims data from 19 affiliated managed care plans covering 300,000 physicians and more than four million enrollees, Harley and Wagner (2003) found that users of Cox-2 inhibitors were approximately 57 percent less likely to discontinue medication and 60 percent less likely to switch medications than were users of non-selective NSAIDs. Such persistent use is often interpreted as an indication of high patient satisfaction (Chan and Hamilton, 2006). Patients also experienced a lower rate of treatment discontinuation due to lack of efficacy or adverse GI events (Schmidt et al., 2004; Mamdani et al., 2002). As a result, these medications were recommended as a first line therapy for individuals with joint conditions and potential GI vulnerability (Schnitzer and Hochberg, 2003).

Table 1 contains data from the MEPS detailing the five most common conditions for individuals reporting a Vioxx prescription. Nearly 70 percent of Vioxx recipients reported some type of joint condition or arthropathy, making such individuals the largest category by far using the medication. This statistic should not be surprising, given that the Food and Drug Administration (FDA)

approved the drug primarily for joint conditions and there were relatively few safe therapeutic substitutes for many of these individuals. For these reasons, this study focuses on individuals with joint conditions.

The initial popularity of Cox-2 inhibitors was soon replaced by controversy over their safety. Prior to Vioxx's introduction to the market, the potential for increased cardiac risks was noted in the Vioxx GI Outcomes Research (VIGOR) study. VIGOR revealed a fourfold increase in cardiac events for patients taking Vioxx compared to those taking naproxen (Bombardier et al., 2000).[3] In 2001, the FDA held an advisory meeting on the results of the VIGOR study and published data on all cardiac events related to Vioxx, including those initially withheld under questionable circumstances (Prakash and Valentine, 2007). This resulted in a mandated warning label for Vioxx beginning in April 2002. This warning appears to have decreased the medication's attractiveness and the number of Vioxx prescriptions fell in each year following 2002. The use of Celebrex and Bextra also fell, albeit to a lesser extent.

A subsequent study confirmed previous findings that the drug's benefits—patient satisfaction and decreased intestinal toxicity—came at the expense of an increased relative risk of cardiac events (Bresalier et al., 2005). These findings, combined with the earlier studies, caused Merck to voluntarily remove Vioxx from the market on September 30, 2004. Following Vioxx's removal, Pfizer, the manufacturer of Bextra and Celebrex, issued a warning about Bextra's potential cardiac risks. Unsatisfied, the FDA requested that Pfizer remove Bextra from the market and Pfizer complied on April 7, 2005. At this time, Pfizer also added a warning label to Celebrex describing the potentially negative cardiac effects of the medication. Together, these events led to a

[3] Vioxx was found to generate a large increase the *relative* risk of a negative cardiac event. It is important to note that the *absolute* risk of such a negative health event remained low.

decrease in the use of all Cox-2 inhibitors.

II. Data.

The data for this study come from the MEPS—a series of surveys administered since 1996 by the Agency for Healthcare Quality Research and the National Center for Health Statistics. The survey is completed by households, medical providers, and insurance companies. This study uses the household component of the MEPS, which is comprised of a sample drawn from the previous year's National Health Interview Survey (NHIS) respondents. The survey asks individuals questions over a series of five interview rounds, detailing two years of medical expenditures and services utilization.

The MEPS full-year Consolidated Data File contains socio-demographic information for respondents including age, sex, race, and basic economic characteristics. During each MEPS round respondents are asked about their labor force participation status. In addition to the Consolidated Data File, this study uses data from the MEPS Prescribed Medicines File and the Medical Conditions File. The Prescribed Medicines File details all prescription drugs purchased by respondents. In the relevant time period, approximately 60 percent of individuals report taking prescriptions. The Medical Conditions File data describe all medical conditions as well as information about the onset and treatment attempts. These conditions are reported by the MEPS respondents, and approximately 20 percent report no medical conditions throughout the year.

Recall from above, this study focuses on individuals with joint conditions. Given that the probability of developing such a condition increases with age, this analysis sample will contain elderly individuals between the ages of 55 and 75. In addition to increasing the number of respondents in the sample with a joint condition, this age range creates the most reasonable comparison group of non-joint condition respondents for the identification strategy proposed below.

Within this age range, approximately 27 percent of the sample reports a joint condition[4], 20 percent reports a back condition, and 41 percent reports either of these two conditions.

In selecting the appropriate time period for this analysis, I consider both the benefits of increased sample size and the costs of events other than the removal of Vioxx biasing the results. Throughout Vioxx's time on the market and during the period following its removal, there were other notable events that should differentially affect individuals with and without joint conditions. In particular, in 2002 the FDA required Merck to include a "black box" warning label on the packaging and marketing of Vioxx. In each subsequent year the number of prescriptions declined, suggesting the warning label decreased the attractiveness of the drug to both physicians and patients. A second concerning event is the return of Pfizer's active marketing of Celebrex in 2006 (approximately 2 years after the removal of Vioxx from the market).

Any sample period that includes these additional events will provide a biased reduced form and IV estimate of the removal decision's labor supply effects. Due to this fact, the longest time period used in this analysis is 2003 through 2006 (covered by MEPS panels 8 through 10). This use of multiple

[4] For the purposes of this analysis, individuals are classified as having a joint condition if they report such a condition during any MEPS interview round. There could be some concern that individuals developing a joint condition after Vioxx is removed from the market may generate a bias in the estimated effect of the removal. Tin this analysis this is not a concern for the following reasons. First, the MEPS queries respondents about the year the reported condition began. In the sample for the instrumental variable results below, approximately 80 percent of the joint condition respondents report a start date for their condition prior to the removal of Vioxx. Re-estimating the IV results with individuals classified as having a joint condition only if they report a condition start date before Vioxx's removal generates point estimates of similar magnitude and precision. Second, if the development of arthritis in later rounds of a MEPS panel was the source of the labor supply results below in a manner that is unrelated to Vioxx's removal, this effect should also be seen in earlier MEPS panels (when Vioxx is still available). For example, this could be the case if individuals are endogenously reporting arthritis to justify their lack of labor force participation during later rounds of the MEPS panel. However, this pattern is *not* seen in these earlier panels. These facts suggest that the method of classifying joint conditions in this analysis is not generating an artificial relationship between Cox-2 inhibitors and labor supply.

MEPS panels limits the ability to include individual level fixed effects for estimates from the longer time period. Therefore, the main IV results will focus on MEPS data from 2004 to 2005. These data come from MEPS Panel 9 and contain responses from the same individuals before and after the removal. [5]

The MEPS is uniquely suited for this study as it is the only dataset that contains information on labor force status, detailed prescription medicine activity, and medical conditions. The National Health Interview Survey (NHIS) has the advantage of larger samples, but contains no prescription data. Similarly, the Behavioral Risk Factor Surveillance System (BRFSS) contains data on arthritis status for some (but not all) years, but does not have information on the use of prescription medications. However, the MEPS does have drawbacks. Within any individual panel, the MEPS has relatively small sample sizes—decreasing the power and precision of estimates using these data. Furthermore, any individual panel only contains two years of observations, limiting the ability to estimate the long term effects of the removal.

III. The Reduced Form Relationship

This study asks: What was the effect of Cox-2 inhibitors on labor supply? A naïve approach to this question might examine the cross-sectional relationship between working and the use of Cox-2 inhibitors using ordinary least squares analysis. However, even with a rich set of covariates, this approach would not identify the causal effect of medications on labor supply because of the likely presence of latent confounds. For example, individuals who take the medication

[5] This panel of the MEPS is the only one that includes observations for individuals in the time period both before and after the removal of Vioxx from the market. Another conceivable event for an IV strategy is the introduction of Vioxx in 1999. Unfortunately, Vioxx slowly penetrated the market during its first year with fewer than 100 participants in the overlapping MEPS Panel (Panel 3) taking Vioxx.

may also have a greater desire to work, imparting upward bias to estimates of the drug's effect. Alternatively, due to their intense chronic pain, individuals with more severe joint conditions may be both less likely to work and more likely to seek out a prescription for a Cox-2 inhibitor, generating a downward bias to the estimates.

In order to overcome potential endogeneity in drug choice, I propose an instrumental variables estimation strategy that exploits the removal of Vioxx from the market in September 2004 as an exogenous change in use of all Cox-2 inhibitors.[6] Because the removal of Vioxx was unexpected, differences in the use of the drug in the post-removal time periods should be uncorrelated with any factors generating a bias in OLS estimates.

As is seen in the first stage estimates below, the removal of Vioxx from the global market caused an unambiguous and unsurprising decrease in use of Cox-2 inhibitors. Therefore, the proposed IV strategy primarily depends on the magnitude and precision of the reduced form relationship between the drug removal decision and the labor supply of individuals with joint conditions. I identify this relationship using a differences-in-differences framework that compares the labor supply of individuals with joint conditions to those without joint conditions before and after the removal of Vioxx from the market. The key identifying assumption is that in the absence of the removal decision, the

[6] I also attempted a similar strategy using the "black box" warning label placed on Vioxx in April 2002. This warning label reflected the newly discovered increased cardiac risk. The warning label did appear to lower usage of Vioxx, reflected by both the downward trend in Figure 2 and a negative and statistically significant coefficient on Vioxx in a specification of equation (2) estimated using data from MEPS Panel 7. There is no corresponding decrease in labor supply. This could be evidence that individuals who stopped taking Vioxx following the warning did not require the medication to work. A common criticism of Vioxx was that it was over prescribed, potentially as a result of a large amount of direct-to-consumer advertising (Dai et al., 2005). The lack of an effect on labor supply from this earlier warning may suggest that researchers require a complete removal of a drug from the market as an exogenous source of variation in utilization. Without a complete removal there can be large amounts of selection bias affecting those who choose to continue or stop taking the medication.

percentage of those working in the two groups would follow similar trends. One method of evaluating this assumption is to compare descriptive statistics from the two groups. Table 2 contains statistics for MEPS respondents aged 55 to 75 in the time period just prior to the removal. Respondents are grouped by whether they report a joint condition, no joint condition, or a back condition (but not a joint condition). The numbers in bold indicate results that are statistically different from individuals reporting joint conditions at a p-value of 0.05.

Individuals reporting joint conditions are older than those with either no joint condition or a back condition. This reflects the fact that arthritis is a disorder that presents itself most often in older patients. For example, nearly 65 percent of MEPS respondents in the sample who reported an arthropathy during at least one MEPS round are 55 years of age or older. Individuals with joint conditions were also more likely to be female and less likely to have graduated from high school or college than individuals who report no joint condition.

As would be expected, individuals without a joint condition have better self-reported health than those with either a back condition or a joint condition. This difference in health status can also be seen in other outcomes in the MEPS data that are not reported in the table. For example, MEPS respondents with an arthropathy report a higher rate of "activity limitations" than similarly aged individuals without these conditions.[7]

Importantly, the two groups exhibit comparable pre-removal trends in their probability of working. Using data from 2003 through 2006, Figure 2 presents the percentage of MEPS respondents between 55 and 75 years of age according to their joint condition status. Prior to the removal of Vioxx from the

[7] These limitations include: work limitations, school limitations, or house limitations as defined in the MEPS. Individuals are classified as limited if: they report difficulty completed tasks such as lifting 10 pounds, walking ten steps, using fingers to grasp, and difficulty bending or stooping. Questions on activity limitations are only asked in the 1st, 3rd, and 5th MEPS rounds, limiting the ability to use them as an outcome variable.

market, the labor supply of these two groups followed a similar trend. After the removal, the labor supply of individuals with joint conditions decreases and remains depressed, while individuals without joint conditions continued the increase in senior labor supply observed in Figure 1.

Individuals with joint conditions are older than those without these conditions. This may make it difficult to visually compare the pre-removal trends in Figure 2. To address this issue, I also include the fitted values from an OLS regression of working on a full set of indicator variables for age and interaction terms between a joint condition status indicator variable and time effects for MEPS respondents between the ages of 55 and 75. The omitted time period is immediately prior to Vioxx's removal. These estimates confirm the trend in the percentage working in the same figure. In the pre-removal period, there is little difference between the two groups of MEPS respondents. Following the removal, individuals with joint conditions worked at a consistently lower rate than those without these conditions. Using the data from the pre-removal time period, a test of whether the point estimates for these interaction terms are jointly different from zero cannot reject the null hypothesis at a p-value of 0.10. Together, the evidence suggests that, in this age range, individuals without a joint condition serve as a reasonable comparison group for the labor supply responses of those with a joint condition.

To estimate the relationship across the several MEPS panels reported in Figure 2, I treat the data as a series of repeated cross sections and estimate the following OLS equation:

$$WORKING_i = \tau_0 + \sum \lambda_j AGE_i + \tau_1 JOINT_i + \tau_2 REMOVE_i * JOINT_i + \eta X_i + \phi_i + \varepsilon_i \qquad (1)$$

where $WORKING_i$ is an indicator variable equal to one if an individual reports they are working at any point in the MEPS round, AGE_i is a series of indicator variables for reported age, $JOINT_i$ is equal to one if an individual reports a joint

condition during any MEPS round[8], $REMOVE_i$ is an indicator variable equal to one for observations following Merck's removal decision, $\mathbf{X_i}$ is a vector of demographic variables including race, sex, education, and MEPS region, ϕ_i is an indicator variable for each interview time period, and ε_i is an idiosyncratic error term. Standard errors are clustered at the individual level. The difference-in-differences coefficient of interest is τ_2 which represents the change in the percentage of individuals with joint conditions who work following the removal of Vioxx from the market compared to individuals without joint conditions.

Table 3 reports the OLS estimates from equation (1) for a number different samples of 55 to 75 year old MEPS respondents. The first estimate is for the full sample, and shows that the removal decreased the labor supply of individuals with joint conditions by a statistically significant 3.9 percentage points. In the pre-removal time period, approximately 40 percent of individuals in this age range with joint conditions were working, suggesting that the removal decreased the labor supply of those with joint conditions by 10 percent.

The removal of Vioxx was unanticipated—indeed, the suddenness of the announcement did not allow individuals to stockpile the medications. While some patients may have recently filled multi-month prescriptions that allowed them to ration their remaining medication, others were quickly deprived of access to the drug. Therefore, in the relatively short time period following the removal considered in this analysis, the estimated adverse effect on working should increase. This growth may also be partially due to the typical progression of arthritic symptoms—some patients may have left their Cox-2 prescriptions unfilled while their initial symptoms were less severe and then faced the new limits on treatment once their symptoms increased enough to require medication.

[8] Includes individuals who report "osteoarthritis," "other and unspecified arthropathies," or "other and unspecified disorders of joint" (ICD-9 codes 715, 716, and 719).

Figure 3 presents the parameter estimates and 95 percent confidence intervals from a specification of equation (1) with five interaction terms between indicator variables for each MEPS interview round after the removal decision and the indicator variable for a reported joint condition. As reported in Figure 3, the time path of the estimated effect grows during the two years following the removal. In the final round, the labor supply of those with joint conditions is approximately seven percentage points lower than the labor supply of those without these conditions. It is important to note that over a much longer time period than is considered in this analysis, individuals with joint conditions may be able to make adjustments to their lives or jobs that allow them to more fully participate in the labor force. In addition, physicians and their patients may successfully adopt alternative treatments that limit the longer term effects of the removal decision. This is discussed in more detail in Section 6 below.

The second and third columns of Table 3 provide estimates by gender. The estimate for males shows a statistically significant seven percentage point reduction in labor supply. Over 50 percent of males in this age range report working during the pre-removal time period, suggesting that the removal decreased labor supply by approximately 14 percent. The effect for females is smaller than the full sample estimate and is not statistically significant at conventional levels.

In addition to gender, it is possible that the effect of the removal decision varied by occupation. Specifically, individuals with joint conditions who work in jobs requiring more physical activity may have a differential response to Vioxx's removal from the market. The fourth and fifth columns of Table 3 report the results for MEPS respondents who reported a physical occupation during at least one round in the MEPS.[9] The estimate for males in non-physically demanding

[9] In the MEPS, current main jobs are coded at the 4 digit level using the Census Industry and

jobs is slightly larger and more precisely estimated than the estimate for those reporting physically demanding occupations. Two points are important to consider. First, very few males in this age group actually work in these physical occupations. Second, there may also be unobservable differences between these two groups that influenced how they respond to the removal, as is discussed in more detail below.

Despite the pre-trend test regarding the comparability of individuals in the 55 to 75 age group with and without joint conditions, there could be some lingering concerns about this assumption. The descriptive statistics in Table 2 suggests that individuals with a back condition but no joint condition are more similar in levels to people with joint conditions on many dimensions. Vioxx's removal affected back conditions sufferers to a less degree than individuals with joint conditions. In the MEPS data prior to the drug's removal, individuals with back conditions report the use of Cox-2 inhibitors at half the rate of those with joint conditions. Furthermore, these back condition sufferers had a greater number of available therapeutic alternatives. This suggests that back condition sufferers may serve as a suitable supplementary comparison group to the main results. However, restricting the comparison group to only individuals with back conditions comes at some cost; the group is relatively small in number and these individuals were still affected, albeit to a lesser degree, by the removal decision.

The sixth column of Table 3 contains the difference-in-differences estimates using only individuals with back conditions as a comparison group. Although not statistically significant at conventional levels, the estimate is very similar in magnitude to the effect in the main sample. The imprecision of the

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Occupation coding schemes. For confidentiality reasons, these codes are condensed into more general categories. Individuals were classified as having physical jobs if they reported working in farming, fishery and forestry; construction, extraction, and maintenance; production, transportation, and moving; or military specific occupations.

estimate may be a result of a smaller sample size or it may be caused by the inability to control for unobservable time invariant differences between those with joint and back conditions. The role of these time-invariant differences is discussed in more detail below.

The results discussed above provide evidence of a relationship between the withdrawal of Vioxx from the market and the percentage of seniors with joint conditions who work. However, these multi-year estimates do not fully exploit the panel nature of the MEPS data. Panel 9 of the MEPS contains observations of the same individuals both before and after the removal. These data allow for the use of individual-level fixed effects to control for time invariant differences across individuals that influence their response to Merck's removal decision. This relationship can be estimated using the following fixed-effects equation:

$$WORKING_{it} = \gamma_0 + \sum \psi_j AGE_{it} + \gamma_1 REMOVE_t * JOINT_i + \mu_i + \nu_t + \varepsilon_{it} \qquad (2)$$

where μ_i is an individual-level fixed effect, ν_t is an indicator variable for each interview time period, and all other variables are defined as in equation (1). The coefficient of interest, $\gamma_{1,}$ is the within-estimate of the change in extensive margin labor supply. In this context, this estimate is driven by the change in labor supply for a MEPS respondent with a joint condition compared to the change (or lack thereof) for similar individuals without joint conditions before and after Vioxx's removal.

As in equation (1), the difference-in-difference identification strategy in equation (2) rests on the assumption that individuals in Panel 9 without joint conditions are an appropriate comparison group. Figure 4 reports the labor supply by joint conditions status for Panel 9 MEPS respondents aged 55 to 75. Similar to Figure 2, the labor supply of individuals with and without joint conditions follows a similar pattern in the pre-removal time period. Following Merck's removal decision, the two groups exhibit different labor supply trends—individuals

without joint conditions continue the upward trend in labor force participation, while individuals suffering from joint conditions decrease their labor supply.[10] Over the entire panel, the percentage of individuals with joint conditions who are working never exceeds the level in the final interview of the pre-removal period. Figure 5 contains a similar analysis for individuals reporting only joint and back conditions. The pre-removal trends presented in Figures 2, 4, and 5 are remarkably similar, suggesting that respondents in Panel 9 are not noticeably different from those in the larger sample.

Table 4 contains estimates from the 9th panel of the MEPS. To ensure comparability with the earlier results from Panels 8 to 10, the first column reports the estimate of equation (1) using only Panel 9 data. The point estimate is nearly identical to the earlier estimate and is statistically significant at a p-value of 0.01. The second column contains the estimate for equation (2) using Panel 9 data. This estimate is approximately 40 percent smaller than the corresponding estimate without fixed effects and is significant at a p-value of 0.10. This suggests that time invariant differences among those with joint conditions generate an upward bias in estimates without fixed effects.

The final column of Table 4 contains the fixed effect estimate for a sample of Panel 9 respondents reporting either a joint or back condition. Following the removal of Vioxx, individuals with joint conditions were 2.7 percentage points less likely to work than individuals reporting a back condition. In contrast to the corresponding estimate without fixed effects, this coefficient is statistically significant at a p-value of 0.10.

[10] The increase in senior labor supply over this time period has been documented in other data sources. According to the Bureau of Labor Statistics, the labor force participation rate for individuals older than aged 55 increased steadily from 2004 to 2005, for a total increase of approximately 2 percentage points. The large increase in Figure 2 should be expected, given that the sample includes only the healthier group of elderly individuals reporting no joint conditions. In addition, the MEPS sampling frame only includes the non-institutional population, which should be healthier on average than the overall population.

In unreported results of the reduced form in Panel 9, the estimated effect (standard error) for males is -0.0263 (0.024) and the estimate for females is -0.0202 (0.014). Neither of these estimates is statistically significant at conventional levels and their magnitude generally follows the same pattern as above. However, it is important to note that the difference between the gender-specific reduced form estimates is smaller with the inclusion of fixed effects. In contrast, unreported results by occupation type are not statistically significant in the smaller sample, but the estimates suggest a much larger gap between individuals with physical and non-physical occupations. The Panel 9 reduced form fixed effects estimate (standard error) for those in physical jobs is -0.0456 (0.0528), compared to an estimate of -0.018 (0.0126) for those not in these occupations.

The fixed-effects results suggest that the estimates from the broader sample are upwardly biased by unobservable time-invariant factors. Therefore, the IV analysis below will be limited to the fixed-effect reduced form estimates from Panel 9.

IV. Instrumental Variables Estimates

The reduced form estimates provide evidence that Vioxx's removal from the market decreased the labor supply of individuals with joint conditions compared to similarly aged individuals without these conditions. Estimating the causal impact of Cox-2 inhibitors on this change in working requires an instrumental variables estimation strategy that accounts for the effect of the removal decision on the use of Cox-2 inhibitors. Figure 6 presents the reported prescription drug activity for individuals with joint conditions aged 55 to 75 in the 9th MEPS Panel. As expected, Merck's removal decision led to the end of Vioxx use.

The removal of Vioxx had far-reaching implications on the use of other

medication such a Celebrex. Clearly, any IV analysis that uses drug removal as an instrument must account for this spillover effect. Failure to consider the overall impact on the drug class underestimates the first-stage effect. Since the IV coefficient in an exactly identified model is the ratio of the reduced form and first stage coefficients, underestimating the first stage relationship will generate, by construction, an upward bias in the IV estimate.[11] For illustration, two sets of results are presented below: one specification considers only Vioxx, while the preferred specification accounts for the use of all Cox-2 inhibitors.

Table 5 reports the first stage and IV estimates. The first stage estimate comes from a specification of equation (2) with an indicator variable for a reported prescription as the dependent variable. The first column presents results of a specification examining the effect of the removal decision on the use of only Vioxx. The first row contains the first stage estimate, which shows that individuals with joint conditions decreased their use of Vioxx by 5.8 percentage points following the removal—an amount approximately equal to the percentage of MEPS respondents with joint conditions who reported using Vioxx immediately prior to the removal. The F-test for the instrument is 39.7, limiting concerns of bias from a weak instrument.

Empirical evidence demonstrates that Vioxx's removal also reduced the use of other Cox-2 inhibitors. Specifications of the first stage equation with a dependent variable equal to either Celebrex or Bextra use return statistically significant estimates (standard error) of -0.0158 (0.0095) and -0.0313 (0.008), respectively.[12] The magnitude and significance of these estimates show that

[11] This is equivalent to considering the use of other Cox-2 inhibitors as an omitted independent variable in the structural equation. Failure to account for the relationship between the instrument and this omitted variable will bias the IV estimate.

[12] The estimated effect for Bextra may be relatively large as a result of the FDA removal decision in April 2005.

changes in the use of all three Cox-2 inhibitors contributed to the economic impact of the withdrawal. The second column of Table 5 reports the estimated effect of removing all three drugs. Following Merck's decision, the use of these drugs by individuals with joint conditions dropped by 10.23 percentage points. In the first round of the 9th MEPS panel, 19.32 percent of individuals with joint conditions between the ages of 55 and 75 reported use of a Cox-2 inhibitor. In short, Merck's removal decision decreased the use of all Cox-2 inhibitors by 50 percent. The F-test statistic on the instrument is 55.61.

The final estimate in first column of Table 5 is the IV estimate of Vioxx's effect on the labor supply of individuals with joint conditions. The use of Vioxx is associated with a 38.95 percentage point increase in the percentage of individuals with joint conditions who work. In the first two interview rounds in Panel 9, approximately 40 percent of 55 to 75 years olds with a reported joint condition work—as expected the estimate from this Vioxx-only specification is implausibly large.

This magnitude of the effect results from a failure to consider the role of reductions in the use of other Cox-2 inhibitors on the labor supply of individuals with joint conditions. This can be seen in the IV coefficient for a specification considering the use of *any* Cox-2 inhibitor and not simply Vioxx, reported in the second column. The estimate suggests that Cox-2 inhibitors were responsible for a 22.07 percentage point increase in the percentage of working individuals with joint conditions.

The second and third columns of Table 5 contain the first stage and IV estimates for Panel 9 respondents divided by gender. While the small sample size decreases the precision of the estimates, the IV point estimate for males is nearly twice the magnitude of the estimate for females. This follows the pattern of reduced form results discussed above.

The last column of Table 5 presents the estimates for a sample containing only those individuals with joint and back conditions. The IV estimate suggests that Cox-2 inhibitors are associated with a 26.82 percentage point increase in labor supply for individuals with joint conditions compared to those with back conditions. This estimate has a p-value of 0.119 and is similar in magnitude to the IV estimate from the full sample, suggesting that the use of all individuals without joint conditions as a comparison group does not bias the main result.

One potential concern with the results is that secular changes in the ability or desire of individuals with any chronic condition to participate in the labor force are driving the IV results. If this were the case, then similar results to those in Table 5 should appear for individuals with other chronic conditions that are not treatable with Cox-2 inhibitors. I re-estimate the IV model for individuals suffering from chronic conditions that should not have been directly affected by the removal of Vioxx—individuals with heart conditions[13] and respiratory conditions.[14] These conditions are associated with increased rates of short-term disability insurance and SSDI receipts, but are not treated with Cox-2 inhibitors (Wagner et al., 2000). In unreported results, neither group exhibits a negative labor supply response during the post-removal period. Overall, I find no evidence that secular changes in the ability of individuals with chronic conditions to work are responsible for the observed effect of Vioxx's removal on working.

V. Economic Magnitude of the Effect of Cox-2 Inhibitors on Labor Supply

The estimates described above represent local average treatment effects (LATE) for individuals whose use of Cox-2 inhibitors was affected by Merck's removal decision. Recall that, in 2002, the FDA required Merck to place a "black

[13] ICD-9 codes 410, 411, 413, 414, 427, 428, and 436.
[14] ICD-9 codes 466, 486, 490, 493, and 496.

box" warning on Vioxx detailing its potential negative cardiac effects. From that point forward, sales of all three Cox-2 inhibitors declined. Therefore, individuals still taking these drugs in late 2004 may not be representative of the average individual with a joint condition or the average Cox-2 user prior to the warning. Instead, they may be individuals who received a particularly large benefit from the medication. This sample selection helps to explain the size of the estimates above. The selected sample, however, could be of great interest. Policymakers attempting to understand the costs and benefits of pharmaceuticals may be interested in the individuals receiving the largest benefits from the medication.

To understand the magnitude of the effect in a broader economic context, I consider both the overall use of Cox-2 inhibitors at the time of Merck's decision and the distribution of individuals with joint conditions in the labor market. At the time of Merck's approval decision, Cox-2 inhibitors were a widely used class of pharmaceuticals. In the last full year on the market, Vioxx was the 16th highest grossing prescribed pharmaceutical, Celebrex was the 25th highest, and Bextra ranked 116th. Combined, these medications had nearly $6 billion in sales.

Given these sales data, it is not surprising that many individuals with joint conditions reported they were taking these drugs. In the first round of the 9th Panel of the MEPS, 19.32 percent of Americans between the ages of 55 and 75 with joint conditions reported filling a prescription for one of the three Cox-2 inhibitors. The IV results show that the removal of Vioxx from the market decreased the labor supply of affected individuals by 22.07 percentage points. Given that 40.61 percent of MEPS respondents with joint conditions between the ages of 55 and 75 were working, the estimate suggests the removal of Vioxx from the market was associated with a 54 percent reduction in the probability of working for individuals with joint conditions who were still taking a Cox-2 inhibitor immediately prior to the removal of Vioxx.

Two "back of the envelope" calculations help to place these estimates in a

broader economic context. The first considers the size of the effect with respect to the entire labor force. According to the 2004 Current Population Survey, individuals between the ages of 55 and 75 make up 13.6 percent of the labor force. Approximately one quarter of the MEPS respondents in this age group report the presence of a joint condition and approximately 19 percent of those individuals reported having filled a prescription for a Cox-2 inhibitor. Together, these estimates suggest that, in the period before Vioxx's removal from the U.S. market, 0.63 percent of the overall labor force was between the ages of 55 and 75 and using a Cox-2 inhibitor to manage the chronic pain caused by their joint condition. Therefore, the IV estimate above suggests that Merck's removal decision resulted in a 0.35 percentage point (90% CI: 0.01% - 0.69%) decline in the overall labor force during the first year. The large magnitude of this effect is driven both by the size of the point estimate and the sheer number of individuals with joint conditions taking these drugs.

A second way to understand the magnitude of the estimate is to consider lost wages—the first order monetary effect of the decision to stop working. In the first round of the 9th MEPS Panel, the average annual income of an individual between the ages of 55 and 75 with a joint condition, conditional on working, was approximately $37,530. Merck's removal decision was responsible for approximately $19 billion (90% CI: $521 million to $38 billion) in lost wages in the first year after removal. For perspective, recall that in the last full year of availability Cox-2 inhibitors had sales of nearly $6 billion.

Certainly, this foregone wages estimate represents only the estimated lost income resulting from a decrease in working for individuals affected by the 2004 removal decision. It is not a net calculation of the costs and benefits of the medication, which is outside the scope of this analysis. Among other considerations, such an exercise would need to account for the lost utility from increased pain and the increased utility from more leisure enjoyed by individuals

outside of the labor force. Importantly, that broad analysis would need to account for the primary reason that Vioxx was removed from the market—an increased relative risk of a negative cardiac outcome. This unintended side effect adds an expected cost to taking Vioxx.

These effects should be interpreted cautiously. Due to data constraints, this study cannot comment on the long run economic effects of Vioxx's removal from the market. Over a longer period of time, some portion of individuals who previously used Vioxx may have identified effective ways to manage pain, reducing the removal's economic effect. To illustrate this potential long term substitution, I estimate a version of equation (2) with Celebrex use as the dependent variable and the interaction of indicator variables for the removal period and any reported Vioxx use prior to the removal as an explanatory variable. Estimating this model on a sample of individuals reporting joint conditions, the point estimate of interest (standard error) was 0.0858 (0.0309) and statistically significant at a p-value of 0.05. This suggests that, in the relatively short post-removal time period in the MEPS, individuals with joint conditions who had previously used Vioxx were approximately 8.8 percentage points more likely to report a Celebrex prescription than individuals with joint conditions who had not used Vioxx.[15] Over a longer time period than can be considered in this analysis, other individuals may have developed strategies to cope with the loss of their medication, and this may have reduced their long-term economic losses.

This last point is particularly important given the advanced age of the individuals primarily affected by Vioxx's removal. Since these individuals were already nearing the end of the working years, a portion of the estimated effect may represent a retiming of retirement decisions. This potential retiming may

[15] Importantly, this is only a measure the amount of short term switching in medications and not a measure of patient satisfaction with the new medication. A longer time period that is available in these data is necessary to answer that question.

help explain the magnitude of the IV estimates above. It also affects the applicability of this estimate to younger populations who rather than retiring might seek out accommodations that allow them to remain in the labor force following the removal of other medical technologies. In considering this question of external validity, it is important to note that a large number of medications are aimed at individuals in these older age ranges who may similarly change retirement decisions in response to the development or removal of a medical innovation.

VI. Conclusion

Cox-2 inhibitors had an economically and statistically significant impact on labor supply in the United States. These medications are only one example of a medical advancement that has a demonstrable economic impact. Other technological advancements have contributed to the improved economic life of individuals, such as more effective treatments for heart attack victims and joint replacements. Further research is needed to determine the impact of these innovations on economic outcomes, including labor supply.

This study also speaks to a broader point—the importance of accounting for economic effects in regulatory decision-making and comparative effectiveness research. In the United States, firms currently use random assignment clinical trials to demonstrate to the FDA that new pharmaceuticals are both safe and efficacious. These trials traditionally focus on objective medical outcomes. For example, in evaluating cancer medications, both mortality and tumor size are used to measure efficacy. However, many new drugs are aimed at increasing the quality of life rather than simply its length (Bren, 2007). Quality of life medications typically provide benefits—improved pain, depression, and energy levels—that are best described by patient reported outcomes (PROs) rather than objective medical criteria. Additionally, patients may enjoy economic benefits

from these medications. Beyond the FDA, in the United States and several European countries, there are increasing calls for evidence-based medicine that uses cost effectiveness research to determine which treatments will be covered by insurance plans.[16] Failing to consider the full scope of benefits will lead to a variety of erroneous decisions in both of these regulatory contexts.

Finally, researchers who have previously evaluated the net health benefits of advancements in medical and pharmaceutical technology have generally not included economic effects in their estimated benefits profile. Cutler and McClellan (2001) found that technology-driven cost increases were smaller than their benefits. Lichtenberg (2001) found that individuals consuming newer drugs had lower mortality and non-drug medical spending. Duggan (2005) analyzed the cost-effectiveness of second generation anti-psychotics and found that the drugs failed to pay for themselves. However, nearly all studies addressing this question (including those above) fail to consider non-medical outcomes such as increased productivity, wages, or labor supply. Accounting for the economic benefits of medical innovations broadens the discussion of the net benefits of health spending. Historically, this discussion has focused on the growth in the absolute amount of spending and a rather coarse series of health outcome statistics. Failure to account for the wide range of economic benefits leads to an overstatement of the net costs of healthcare.

[16] For example, $1.1 billion of the recent American Recovery and Reinvestment Act, signed into law on February 19, 2009, was earmarked for comparative-effectiveness research.

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Tables

Table 1
Reported ICD-9 Codes for Vioxx Prescriptions

	Condition	Percent of Vioxx Recipients
1.	Other and unspecified arthropathies	43.2
2.	Other and unspecified disorders of back	20.9
3.	Other and unspecified disorders of joint	14.7
4.	Intervertebral disc disorders	8.4
5.	Osteoarthrosis and allied disorders	6.2

Source: Medical Expenditure Panel Survey 1998-2004

Table 2
Descriptive Statistics for Individuals Aged 55-75, MEPS Panel 9

	Joint Condition	No Joint Condition	Back Condition
Age	64.2	**62.9**	**63.0**
% Female	63.0	**48.3**	58.1
% HS Grad	76.7	80.2	79.3
% Bachelors	20.9	**27.1**	24.8
% White	77.7	76.9	76.2
% Black	9.6	9.6	10.2
Health Status	2.9	**2.5**	2.8
% Working	39.3	**47.1**	39.5
% Physical Job	10.3	12.7	12.1
% of Overall Sample	27.2	41.6	20.5
Wage Income Condition on Employment	$37,530	$38,652	$37,334

Numbers in bold are different from those reporting a joint condition at a p-value < 0.05.
Source: Round 1, Panel 9, 2004 Medical Expenditure Panel Survey

Table 3
OLS Reduced Form Estimates of the Effect of Vioxx's Removal on Labor Supply
MEPS Respondents, 2003-2006, Aged 55 to 75

	Full Sample	Males	Females	Physical Job, Males	No Physical Job, Males	Joint and Back
Remove*Joint	-0.039**	-0.07**	-0.018	-0.06*	-0.073**	-0.031
	(0.017)	(0.027)	*(0.0227)*	*(0.034)*	*(0.023)*	*(0.029)*
N	37,299	16,767	20,532	3,614	13,153	15,273

Entries represent the estimated difference-in-differences coefficients (standard errors) from a linear probability model of the effect of the removal of Vioxx from the market on the labor supply of individuals with joint conditions between the ages of 55 and 75. Unreported covariates include indicator variables for age, MEPS round, census region, sex, race, Hispanic ethnicity, and education. All specifications are weighted using MEPS longitudinal weights. Standard errors are clustered at the individual level.

* p-value<0.1

** p-value<0.05

*** p-value<0.001

Table 4
OLS and Fixed Effect Reduced Form Estimates of the Effect of Vioxx's Removal on Labor Supply
Panel 9MEPS Respondents, 2004-2005, Aged 55 to 75

	Panel 9	Panel 9	Panel 9 Joint and Back
Remove*Joint	-0.039**	-0.023*	-0.027*
	(0.02)	*(0.0128)*	*(0.0165)*
N	12,231	12,231	5,223
Fixed Effects	No	Yes	Yes

Entries represent the estimated difference-in-differences coefficients (standard errors) from a linear probability model of the effect of the removal of Vioxx from the market on the labor supply of individuals with joint conditions between the ages of 55 and 75. For the non-fixed effects regression in the first column the unreported covariates include indicator variables for age, MEPS round, census region, sex, race, Hispanic ethnicity, and education. For the fixed effect results in the last two columns, unreported covariates include indicator variables for age, MEPS round, and census region. All specifications are weighted using MEPS longitudinal weights. Standard errors are clustered at the individual level.

* p-value<0.1
** p-value<0.05
*** p-value<0.001

Table 5
Fixed Effects and IV Estimates of Effect of Cox-2 Inhibitors on Labor Supply
MEPS, Panel 9, 2004-05, Age 55-75

	Vioxx Prescriptions	All Cox-2 Prescriptions	Males, Cox-2 Prescriptions	Females, Cox-2 Prescriptions	Joint and Back, Cox-2 Prescriptions
			First Stage Estimates		
$Remove_t * Joint_i$	-0.058***	-0.1023***	-0.0813***	-0.1122***	-0.0999***
	(0.0092)	(0.0137)	*(0.0195)*	*(0.0183)*	(0.0164)
1st stage F-test	39.7	55.6	17.33	37.5	37.19
			2SLS Estimates		
$COX2_{it}$	0.3895*	0.2207*	0.324	0.1805	0.2682
	(0.2306)	(0.1304)	*(0.3096)*	*(0.1302)*	(0.1723)
N	2,725	2,725	1,179	1,546	1,099
*N*T*	12,321	12,321	5,514	6,807	5,233

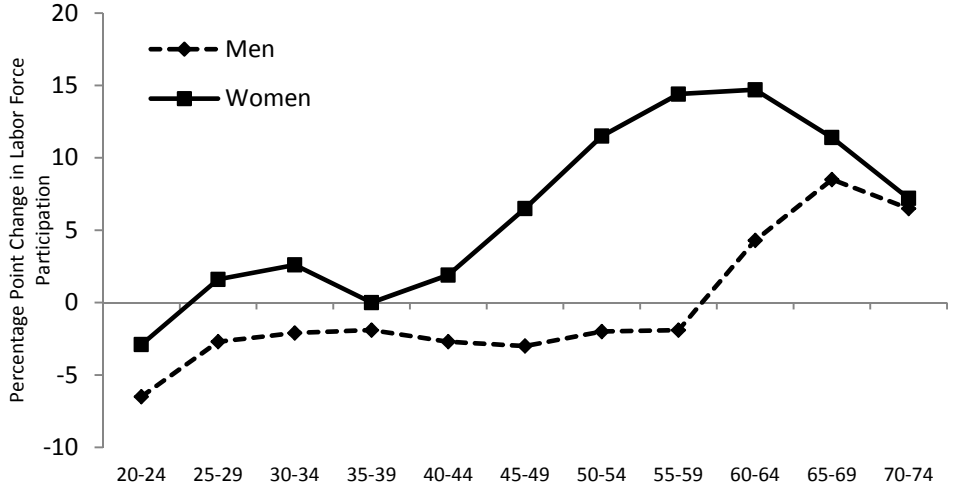
Entries in the first row represent the estimated coefficients (standard errors) from a linear probability model of the first stage relationship between Vioxx's removal from the market and the use of Cox-2 inhibitors. Those in third row represent the estimated coefficients from the linear probability IV model using the interaction term between being in the removal time period and joint condition as an instrument for the use of Cox-2 inhibitors. Unreported covariates also include indicator variables for age, MEPS round, and census region. The first column only considers the use of Vioxx, while the remaining columns consider the use of all three Cox-2 inhibitors. Regressions are weighted using MEPS longitudinal weights. Standard errors are clustered at the individual level

* p-value<0.1

** p-value<0.05

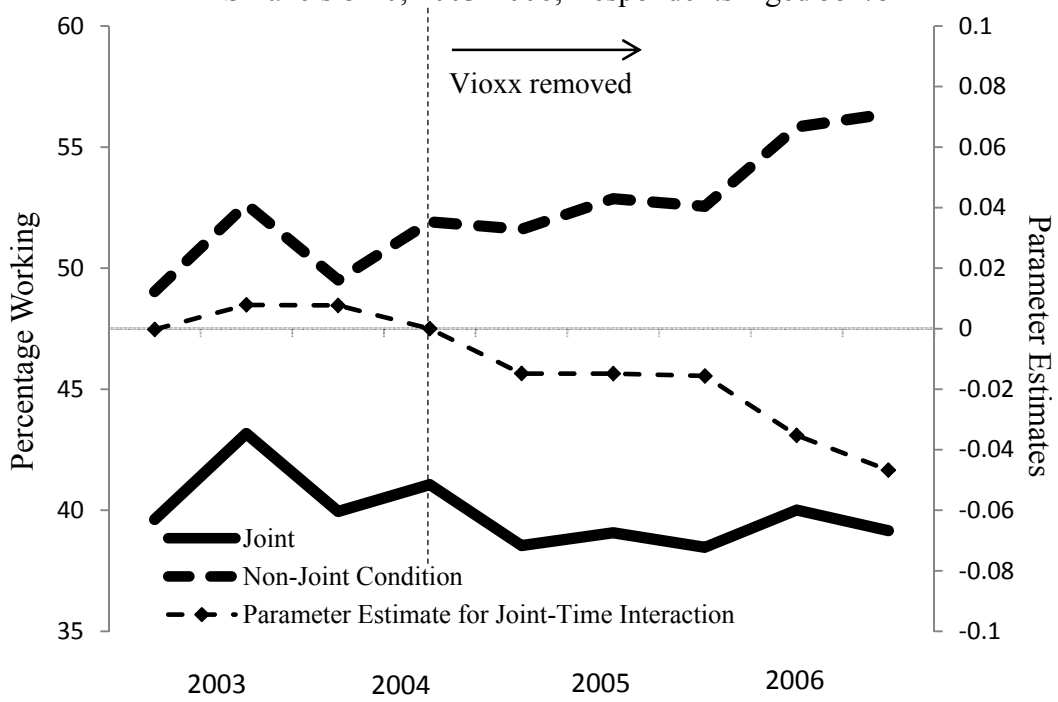
*** p-value<0.001

Figure 1
Change in Labor Force Participation Rates by Age and Sex, 1987-2007



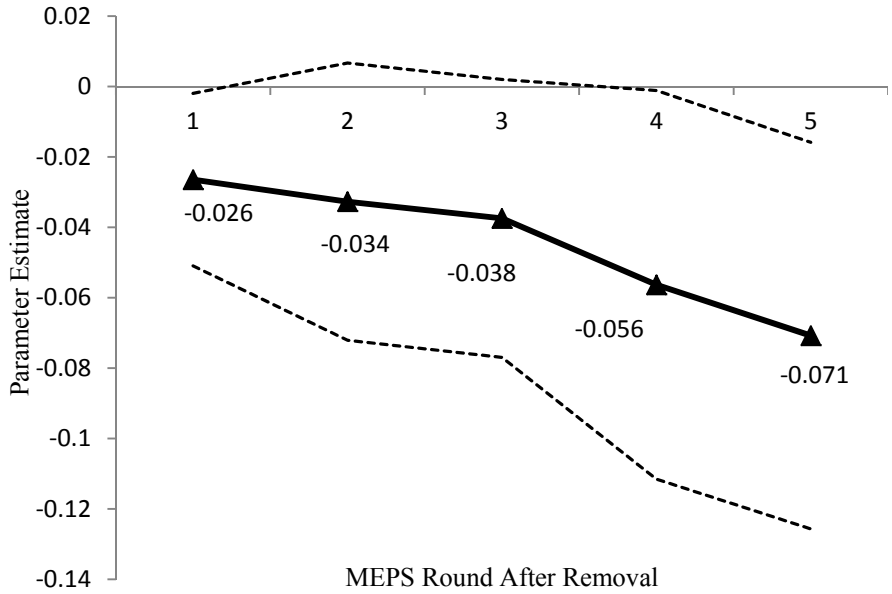
Note: Data in the chart represents the change in labor force participation from 1987 to 2007 by 5 year age group for males and females from the Bureau of Labor Statistics.

Figure 2
Percentage Working by Joint Condition Status
MEPS Panels 8-10, 2003-2006, Respondents Aged 55-75



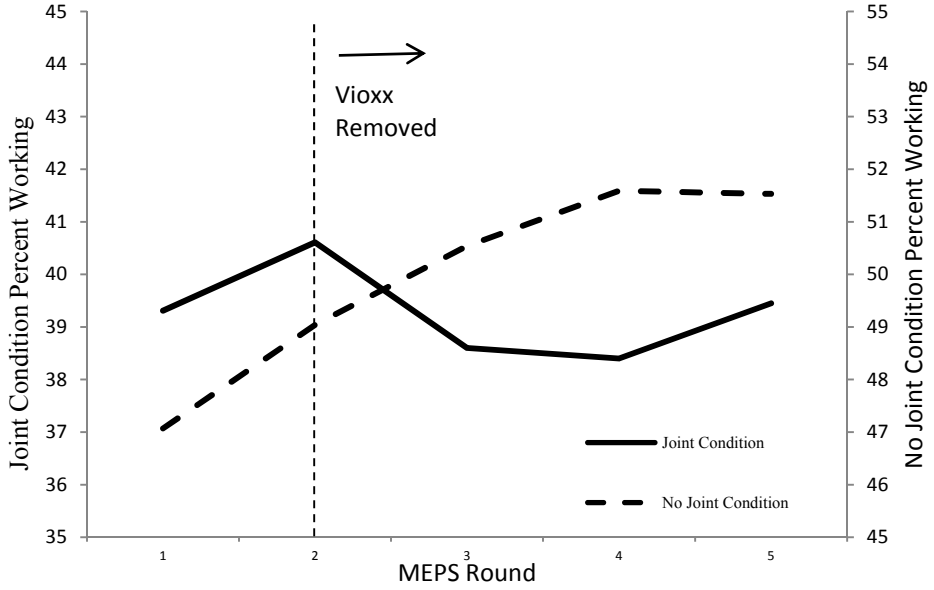
Note: Data in the chart shows the percentage of individuals reporting they are working during the MEPS round based on whether they report a joint condition during any MEPS round. The dashed line in the middle of the figure represents the parameter estimates for the interaction terms from an OLS regression of working on a set of age effects and a full set of indicator variables for joint condition status and time period.

Figure 3
Reduced Form Parameter Estimates and 95% Confidence Interval
MEPS 1987-2007, Respondents Aged 55-75



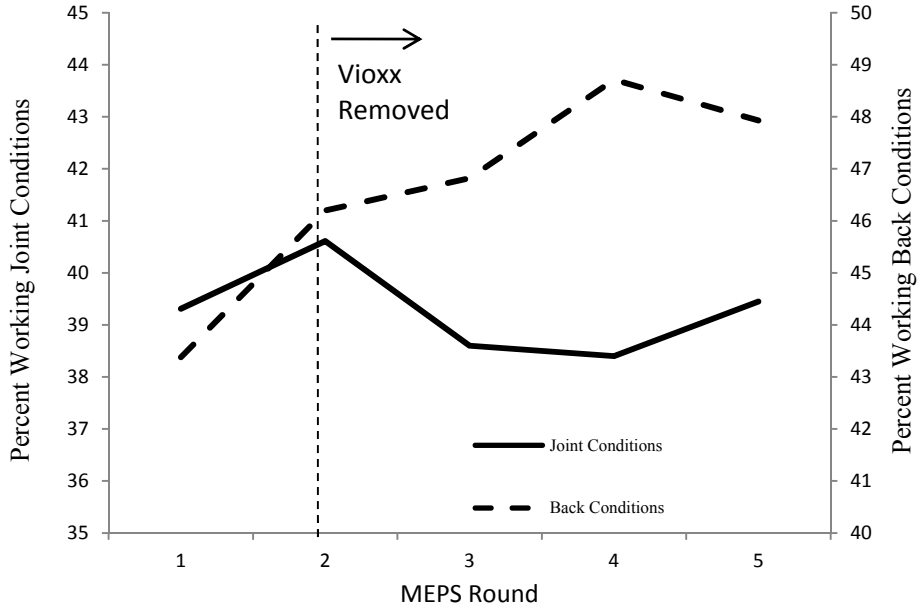
Note: Entries in the chart represent the reduced form parameter estimates and 95 percent confidence intervals for the interaction term between an indicator variable for the MEPS round after the removal and a reported joint condition.

Figure 4
Percentage Working by Joint Condition Status
MEPS Panels 9, 2004-2005, Respondents Aged 55-75



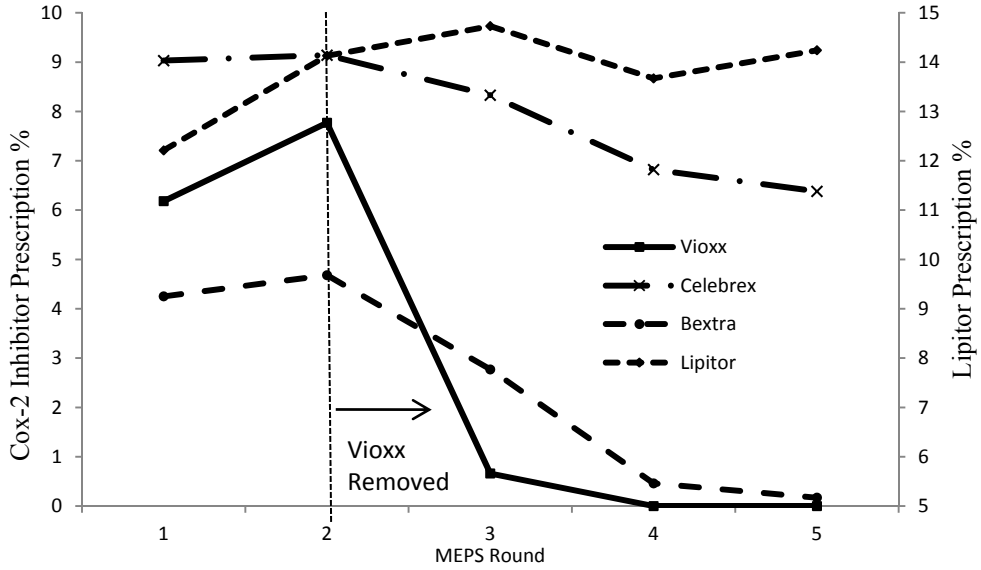
Note: Data in the chart shows the percentage of individuals reporting they are working during the MEPS round based on whether they report a joint condition during any MEPS round. Entries for those without a joint condition correspond to the right vertical axis.

Figure 5
Percentage Working by Joint Condition Status
MEPS Panel 9, 2004-2005, Respondents Aged 55-75 with Reported Back or Joint Condition



Note: Data in the chart shows the percentage of individuals reporting they are working during the MEPS round based on whether they report a joint condition or a back condition during any MEPS round. Entries for those with a back condition correspond to the right vertical axis.

Figure 6
Prescription Drug Rates, 2004-05
Age 55-75 with Reported Joint Condition, MEPS Panel 9



Note: Data in the chart shows the percentage of individuals reporting a particular prescription in the a MEPS round. Lipitor prescriptions correspond to the right vertical axis.